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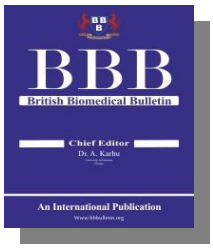

Original

Application of Symbolic Dynamics in Fetus to Study Placental Insufficiency and Metabolic Acidosis

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ABSTRACT

Objective
To assess the possibility to diagnose placental insufficiency and metabolic acidosis by analysing the fetal heart rate (FHR) variability by using non-linear methods; symbolic dynamics or traditional linear stochastic theory.

Study design
The recorded FHR signal sets from the last hour of delivery in 21 live born fetuses were analysed. The complexity of the FHR variability was described by an entropy parameter using symbolic dynamics as well as by standard deviation of each FHR. Cases with placental insufficiency and metabolic acidosis were identified from cord artery blood gas analyses.

Results
No significant correlation was found between the entropy parameter and the arterial pH or between the standard deviation and the arterial pH. Results are improving when combining the two (entropy parameter and standard deviation) in a multiple regression analysis.
Only one of the analysed cases was identified with metabolic acidosis (cord artery pH < 7,0 and Base Deficit > 12,0 mmol/L).

Conclusion
To know if it is possible to diagnose placental insufficiency and metabolic acidosis by analysing the FHR variability by using non-linear methods, symbolic dynamics or traditional linear stochastic theory, a study with FHR not influenced by uterine contractions during labour is needed to conclude if the lack of correlation is caused by uterine contractions or insufficient mathematical methodology.

Introduction

Placental insufficiency is a condition that can be fatal to the fetus. The decrease in oxygen may lead to fetal hypoxia and metabolic acidosis. Placental insufficiency and fetal hypoxia may be suspected by typical changes in the CTG in terms of baseline fetal heart rate, variability, accelerations and decelerations. However, CTG is an unreliable method and a Doppler ultrasound examination of the umbilical arteries and the vessels in the fetal brain is needed to further confirm fetal hypoxia. These procedures are both time consuming and requires experienced midwifes to recognise the CTG patterns and a special trained obstetrician to perform the ultrasound examination.

Several studies show that the use of non-linear dynamics (chaos theory) is better than ordinary linear stochastic theory, when trying to detect pathology in the human organs.

One study reported that chaos theory measures a decrease in heart rate variability in those patients who are in high risk of developing ventricular fibrillation ($p<0.001$, sensitivity 91%, specificity 85%). The patients' heart frequencies standard deviation (SD) could not tell whom of the patients that would experience ventricular fibrillation[1].

Using non-linear dynamics has shown good correlation between reduced heart beat complexity and death rate in pigs with myocardial ischema inflicted on them[2].

Moreover, one study have examined sheep fetuses and found that fetuses exposed to long-term hypoxia are associated with a reduction in fetal heart rate (FHR) variability compared to normal fetuses. This is possibly due to a delay in the normal maturational changes of the autonomic control of FHR. The acute reaction (until 20 hours past the first hypoxic event) was a transitory increased FHR variability. The FHR variability is normally increasing with advancing gestational age and hypoxemia seems to delay the normal maturation of the autonomic control[3].

Another study showed no decrease in FHR variation when healthy women at term pregnancy were exposed to short-term hypoxia. However, in a group of women with pregnancy-related complications (severe pre-eclampsia and/or severe growth retardation), a reduced FHR variation was found in relation to increasing resistance in the placenta[4].

This change in FHR variability will possibly vary depending on what caused the hypoxia and its duration, e.g. a sudden event during labour or placental insufficiency.

Chronic hypoxia in the fetus will lead to a decrease in the natural variations in the fetus heart rate.

Labour is a potential threat to fetal wellbeing. Most fetuses will have sufficient metabolic reserve to withstand the effect of reduced oxygen supply during uterus contractions. A distressed fetus could be due to limited oxygen reserves caused by placental insufficiency. We are searching a way to predict placental insufficiency in advance of delivery by use of symbolic dynamics.

The purpose of this study is to apply the symbolic dynamic model on the fetus heart rates and test the hypothesis that symbolic dynamics can be used to indicate which fetuses suffer from hypoxia due to placental insufficiency.

We also want compare the use of symbolic dynamics with the standard deviation as a predictor of hypoxia when analyzing the FHR variability.

Materials and Methods

Materials

We analysed FHR signal sets from the last hour of delivery in 35 live born fetuses.

The recordings were collected from three Norwegian and Swedish delivery units from June 1998 to January 1999 as a part of a Nordic observational multi-centre study.

Those eligible for the study were women in active labour at more than 36 completed gestational weeks, and for whom a clinical decision had been made to apply a fetal scalp electrode for continuous internal CTG recording[5].

The multi-centre study originally recorded FHR from 573 cases. The acid-base status of the cord artery and vein was recorded to assess the condition of the child at birth. Thirty-three non-hypoxic fetuses were randomly picked from the Nordic database to form our material in this study. None of the fetuses had major cardiac anomalies. The ethics committees of the participating hospitals approved the study and all mothers gave informed consent.

In our material we have information about umbilical cord blood gas in 35 fetuses. However only 21 of those were from the cord artery limiting our population to 21.

Umbilical cord blood gas

Umbilical cord blood gas analyses have been used to evaluate fetal oxygenation.

Both arterial pH and Pco_2/Base Deficit are essential values.

The Pco_2 /Base Deficit are used to differentiate between respiratory or metabolic acidosis.

The umbilical cord PO_2 or O_2 saturation is not useful, as many normal new-borns are initially hypoxemic until normal extrauterine respiration is established.

Respiratory acidosis is not predictive of newborn injury or long-term injury.

According to the Nordic multi-centre study[5] we have used a cut-off for metabolic acidosis: cord artery pH<7.00 and Base Deficit >12.0 mmol/l[6] or in case of cord vein sample only pH<7.10 and Base Deficit >12.0 mmol/l.

These limits should identify if a fetus was clinically affected from intrapartum hypoxia.

Data acquisition and signal processing

The fetal ECG was recorded during delivery with an intrauterine scalp electrode using a STAN®S 21 monitor (Neoventa Medical, Gothenburg, Sweden). The fetal unipolar ECG lead configuration consisted of a single helix scalp electrode and a maternal skin electrode. The R-peaks were detected and R-R intervals were measured and digitised (sampling rate 500 Hz). The R-R interval data sets were stored on a PC hard disc.

Calculation of a symbolic dynamics estimate of the heart rate variability

We have calculated a symbolic dynamics estimate for the fetal heart rate variability. We used the procedure below to analyse the ECG time series (fig.1a):

The control of the autonomic regulation of the heart rate is done by the sinus node. The sinus rhythm should be derived from the onsets of the P-waves. However, the P-wave signal cannot always be extracted and the intervals between the R-peaks are chosen for further analysis.

Step 1. Find the sequence of the R-R interval (length between two R-peaks)

$$\{x_i\}_{i=1}^{n}$$

This is shown in fig.1b with the interval number along the x-axis and the interval duration in milliseconds along the y-axis.

At this stage it is often possible to recognize the classic differences between healthy fetus and patient with a normal and a reduced variability.

Step 2. Calculate the first derivative, y_i (fig.1c) of the R-R interval

$$\{y_i\}_{i=1}^{n-1} = x_{i+1} - x_i$$

The reason for calculating the first derivative is to omit longer periods of the same symbols, as a result of T drift in the R-R interval.

Step 3. Detect the two levels, which divide the data into three equally numbered data sets[1] (fig.1c).

Step 4. Transform y_i into the time series of symbol s_i sequences, (fig.1d)

The transformation into symbols refers to the two levels identified in the step above and the symbols are as follows:

$$\{s_i\}_{i=1}^{n-1} = \begin{cases} C: & y_i > level\ 2 \\ B: level\ 1 > & y_i \le level\ 2 \\ A: & y_i \le level\ 1 \end{cases}$$

Step 5. Find the word sequence (word length = 3), w_i (fig.1e)

$$\{w_i\}_{i=1}^{n-1-2} = s_i s_{i+1} s_{i+2}$$

Step 6. Compute the probability density distribution, p_k, of words length three

$$\left(\sum_{k=1}^{\#bins} p_k = 1, where\ \_\#bins = \#symbols^{(\#wordlength)} = 27 \right)$$

(fig.1f)

Step 7. Calculate the normalised entropy, E, of the probability distribution

$$I = -\frac{1}{Log\,(27)} \sum_{k=1}^{27} p_k Log\,(p_k) \quad 0 \le E \le 1$$

This procedure was applied to the 35 recorded ECG and each case got an entropy parameter, E, which is a value between 0 and 1. This entropy parameter is further used in the statistical analyses as an estimate for the variability in the heart beat rate.

We have used the first 9000 data points in the FHR signal sets to calculate the E-parameter.

No concern has been given to the interpretation of the FHR pattern with respect to uterus contractions or if the fetus is asleep.

Statistical analysis

The statistical analyses are all performed by use of the program SPSS 11.

We wanted to test for statistical association between the entropy parameter and the umbilical cord artery pH.

The Pearson's correlation coefficient (n=21) was calculated in the analyses.

As only one case analyzed had acid-base status that was compatible with metabolic acidosis, we removed this case from the statistical analysis, and checked for statistical correlation between pH and entropy parameter for the remaining 20 cases with "normal" pH (n=20).

Furthermore we calculated the normal standard deviation for the FHR recordings (n=21) and checked for statistical correlation.

Moreover we performed a multiple linear regression analysis where the combination of both entropy parameter and standard deviation was checked for statistical correlation with arterial pH (n=21). In this combination analysis we constructed a linear multiple regression equation of the general form:

$$[pH] = b_0 + [entropy] \cdot b_1 + [SD] \cdot b_2$$

P-values <0.05 were considered significant.

[1] It is not always possible to divide the data into three equally numbered data sets. Practically the solution is to find the levels with the best match.

Results

We calculated entropy parameter and SD and these are listed along with blood gas values in table 1.

The correlation analysis of entropy parameter and the arterial pH gave r =-0.142 (p=0.54, n=21) (fig.2). The regression analysis reported no cases with an absolute residual greater than 3 standard deviation. This implies that there are no outliers that should be eliminated.

The correlation analysis of the standard deviation of the FHR variation and the arterial pH gave r = -0.325 (p=0.15, n=21) (fig.3).

From table 1 it can be seen that only case 13, fulfilled the criteria for metabolic acidosis. This infant is also reported in the multi-centre study[5] to have a high asphyxia score. Case 34 also reported a high asphyxia score, but is not included in our analysis as we do not have the artery pH for this child. When removing case 13, we got the following result: r= 0,005 (p=0.984, n=20).

The multiple regression analysis gave r=0.513 (p=0.064, n=21). Still not statistically significant, but result are improving in the combination.

Discussion

We wanted to test if non-linear methods symbolic dynamics could be used to predict hypoxia from the FHR recordings only in fetuses suffering from hypoxia due to placental insufficiency. An entropy parameter was calculated to describe the complexity in the FHR variability. Furthermore we tested the SD of the FHR as a predictor of hypoxia.

We found no such statistical significant correlation.

We have used the umbilical cord arterial pH to measure if the child is suffering from hypoxia/metabolic acidosis or not. There are different opinions of which level of arterial pH value that indicate a fetal acidosis. One study that compared 5 min. Apgar score with arterial pH, concluded that pH=7.20 as a limit for acidosis is too high[7].

Another study established the normal range of umbilical cord artery blood gases in a labour ward to pH=7.21±0.08 for vaginal deliveries and pH=7.22±0.07 for Caesarean sections, respectively[8]. This study concluded that pH = 7.00 was a reliable lower cut-off indicating perinatal metabolic acidosis[6].

The Nordic multi-centre study[5] used umbilical artery pH ≤ 7.05 along with a Base Deficit > 12 mmol/l as a marker of intrapartum metabolic acidosis.

We used this as our guideline to differentiate between metabolic acidosis or not.

Our material included only one infant that fulfils the criteria for asphyxia, but the entropy parameter did not seem to be particular for this case. This could be due to acute hypoxia that could give increase in FHR variability.

The other infants were evaluated to have arterial pH that did not affect them clinically. Is it perhaps possible that a weak acidosis don't lead to a significant change in the FHR variability? Thus, when pH is within the "normal" range (above the limits defined), there is no pathology and no correlation between "normal" arterial pH and the entropy parameter.

These results could also indicate that one parameter is not sensitive to alone discriminate between pathological and non-pathological physiology.

Combination of the entropy parameter and the standard deviation in a regression analysis improve the results. Another function than the linear equation used in the regression analysis may give better result.

The FHR recordings were taken during the last hours of delivery. During uterus contractions, the flow of oxygenated blood through the uterus will

temporarily be reduced. It is a normal reflex in the fetus to have a decrease in heart rate (decelerations) synchronous with the contraction and an increase afterwards (accelerations). Hence, uterus contractions influence on the fetal heart rate and may mask the natural FHR variations.

In order to diagnose placental insufficiency by using symbolic dynamics it may be essential that the FHR is not influenced by uterus contractions. Moreover it is important to examine fetuses at the same gestational age as normal FHR variability will increase with gestational age in well-being fetuses[3]. We may need to optimise the use of the entropy parameter and standard deviation in a mathematical equation, or a combination of the two.

Conclusion

We applied non-linear methods symbolic dynamics to the fetal heartbeat variation during labour in order to try to diagnose placental insufficiency. There was no statistical significant association between the heart beat variation or standard deviation and umbilical cord arterial pH. This could be caused by uterine contractions or insufficient mathematical methodology.

However, the combination of both entropy parameter and standard deviation to predict the pH gave results that approaches statistical significant.

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Table 1. Entropy parameters,SD and blood gas values

Case	Artery pH	Artery pCO_2	Artery Base Deficit	Vein pH	Entropy parameter	SD
1					0,98121	50,3
2	7,27	6,7	3,1	7,35	0,96748	21,27
3	7,14	8,91	5,3	7,27	0,95329	13,28
4					0,967	36,96
5				7,31	0,97981	36,9
6	7,11	7,6		7,16	0,91576	14,64
7	7,34	6,1		7,35	0,86147	34,77
8	7,09	10	5,7	7,18	0,95661	24,65
9				7,4	0,94381	25,09
10	7,26	5,31	8,0	7,3	0,95145	24,55
11	7,31	6,84	0,0	7,37	0,89601	30,99
12					0,91997	53,84
13	6,92	11,67	12,9	7,22	0,97655	60,53
14	7,09	10,83	4,4	7,35	0,97144	22,04
15	7,22	7,61	3,6	7,32	0,94209	22,98
16					0,97199	20,44
17				7,12	0,96493	39,64
18				7,31	0,94246	39,4
19				7,3	0,96091	23,44
20	7,19	6,84	7,5	7,23	0,94685	30,98
21	7,23	7,17	4,2	7,34	0,89888	26,77
22	7,26	7,89	0,1	7,33	0,95285	28,32
23	7,16	8,78	4,4	7,38	0,84435	47,97
24	7,24	8,52	-0,3	7,34	0,94431	54,15
25					0,97918	43,96
26	7,09	9,97	6,1	7,3	0,95891	62,17
27					0,88007	25,39
28					0,93084	31,02
29	7,2	7,32	5,6	7,28	0,92779	36,78
30					0,85485	47,1
31	7,23			7,24	0,92955	56,08
32	7,1	9,91	5,6	7,28	0,9012	63,27
33	7,16	5,13			0,97058	26,29
34				7,11	0,96548	45,46
35	7,11	10,2	4,4		0,7567	100,08

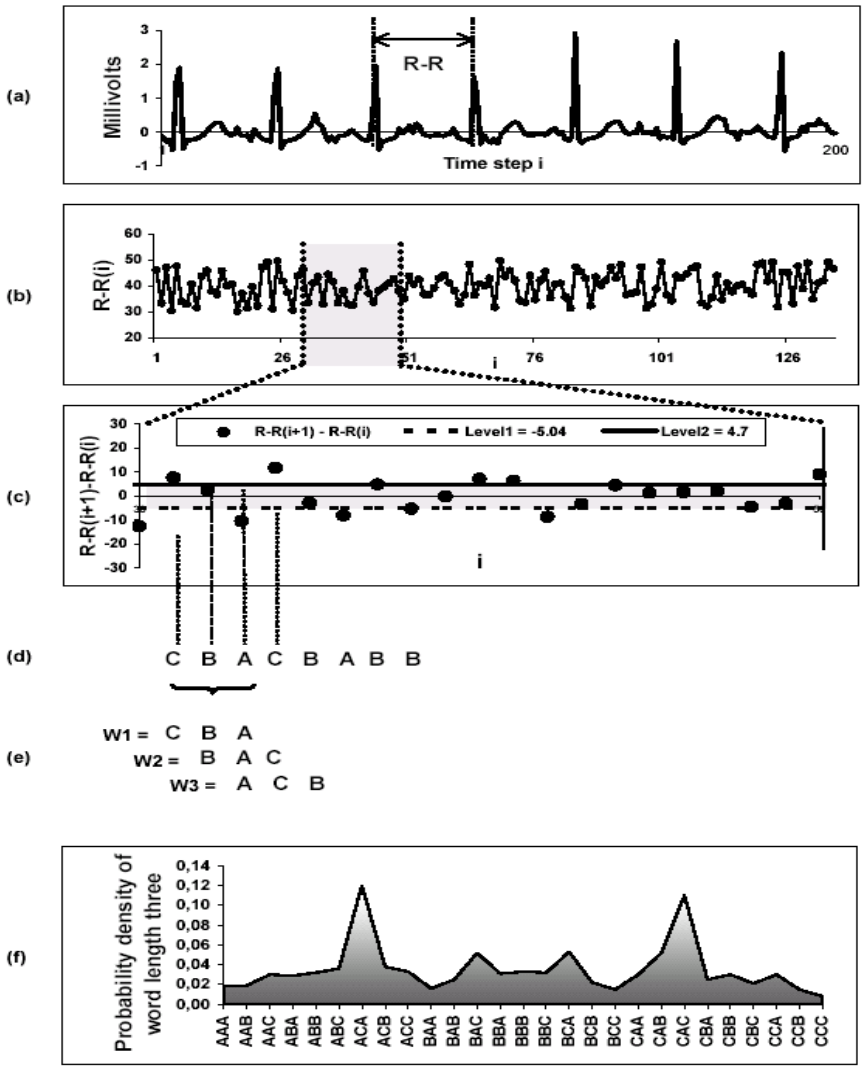

Figure.1. A registration of an ECG time series and the R-R interval is shown (a). In (b), (c) the first derivative of the R-R interval **,** (d) The time series sequence of symbols, (e) the word length three series and (f) shows an example of the probability density distribution of word length three.

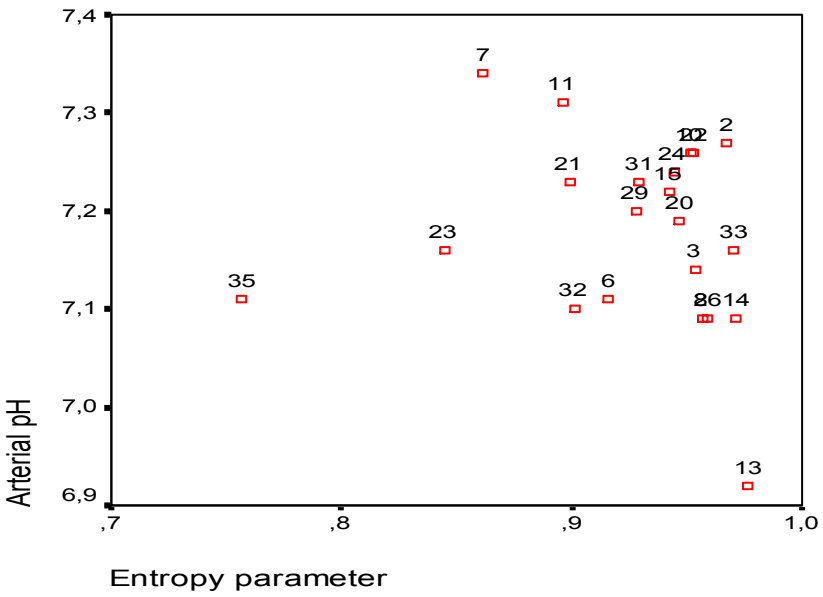

Figure.2. Scatterplot of Entropy parameter against arterial pH

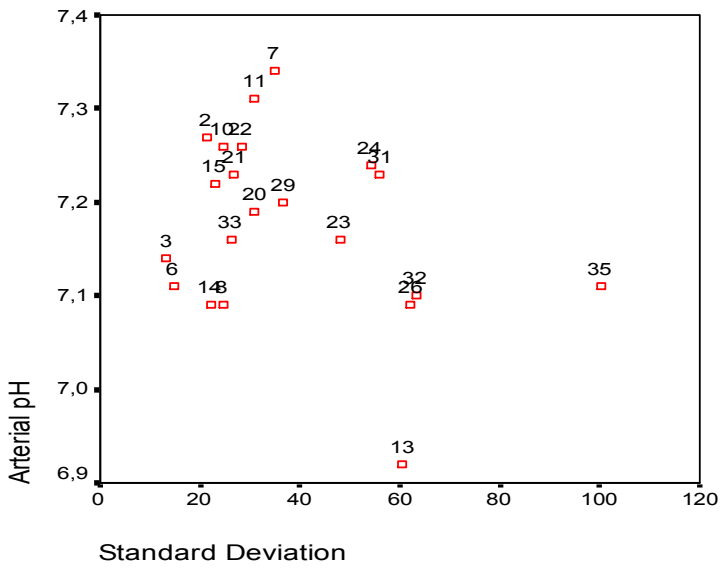

Figure.3. Scatterplot of Standard Deviation against arterial pH

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