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AN ANALYSIS OF THE REGULATORY MECHANISMS IN FETAL HEART RATE CHANGES, USING A MATHEMATICAL ANALYSIS-MODEL

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Synopsis To elucidate the effects of regulatory mechanisms on heart rate changes in the human fetus in utero, we devised a mathematical model involving factor analysis, a type of multivariate analysis.

From the viewpoint of mathematics, a set of fetal heart rate (FHR) values has two different properties, scalar and vector.

We studied the instantaneous FHR values for 96, 704 beats in sequence, obtained from a normal fetus at 33 weeks of gestation.

The scalar components of the FHR changes appear to be composed of around 4,000 beats, among which a few isolated properties may be present.

These findings indicate the underlying baseline heart rates, which differ in biological origin.

The distribution of the beat-to-beat differences included the "core fluctuation" ranging up to ± 3 beats per minute.

According to the factor analysis for the vectorial components, it has also become evident that there were at least two different characteristics in FHR changes, indicating the existence of acceleration and deceleration mechanisms.

Key words: Fetal heart rate • Regulatory mechanisms • Computer simulation • Mathematical model

Introduction

Intrapartum cardiotocography (CTG) has greatly contributed to the diagnosis of fetal distress¹⁾¹²⁾¹⁶⁾¹⁷⁾²¹⁾²⁶⁾.

The deceleration of the fetal heart rate (FHR) is indicative of the applicable information for assessment of the fetus, since it would be associated with fetal hypoxia in response to the uterine contraction during labor.

Antenatal application of CTG has also proven to be useful in evaluating the fetal well-being and in predicting the fetal outcome¹⁰⁾²³⁾.

Such is known clinically as the non-stress test $(NST)^{7(19)25(28)29)}$ and contraction stress test $(CST)^{2(9)11(24)27)}$.

NST enables estimation of a fetus at risk, based upon the cardiographic findings; reduced FHR variability and the absence of the concordant acceleration of FHR with fetal movement, while CST is based mainly on the deceleration related to the oxytocin-induced uterine contraction.

However, it is extremely difficult to isolate external criteria on the cardiotocograms, for example, the uterine contraction, which would account for all the biological features of FHR changes throughout pregnancy.

We designed a mathematical model, and used a computer system to quantitatively assess the fundamental properties of instantaneous FHR changes.

Material and methods

The process-flow chart of this experimental system is illustrated in Fig. 1. A normal fetus at 33 weeks of gestation was chosen as the candidate for the study. Original heart sounds were collected for 12 continuous hours using a highly sensitive microphone placed on the maternal abdomen. During this time, the mother was in either the supine or semi-recumbent position. The sounds were then processed to calculate the instantaneous FHR values on the unit of beats per minute (bpm), employing the cardiotocograph (Toitu MT-810). These values were directly entered into the microcomputer system and were stored in memory on the floppy disc, in a real-time manner, thereby forming a set of data-file with the instantaneous FHR's of 96,704 beats in sequence. The investigation was thus made on this file. The on-line processing was usually used to analyze the data with the

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Fig. 1. Flow chart of the experiment.





**∆FHR: FHR_{n+1}−FHR_n (bpm)

aid of the microcomputer system. In addition, we used a large general purpose computer system (FACOM OS IV/F4 M200) in the Computer Center of Kyushu University, when there were particular needs in processing the data.

Fig. 2. represents the methodology used.

Since the actual set of the instantaneous FHR values is considered to be no more than a sequence of numbers, it can be divided into two kinds of properties in terms of mathematics; permutation and combination. In other words, the former could be called vector and the latter scalar.

The scalar components are thought to express the particular differences on the configuration of the histogram as being coincident with each set of data. The vectorial components could be expressed on a matrix (FHR/ Δ FHR matrix) with the absolute FHR values (bpm) and the corresponding beat-to-beat differences (bpm), respectively in columns and rows (Fig. 2).

The factor analysis, one form of multivariate analysis, was attempted according to the steps in order of processing, as shown in Fig. 3; (1) calculation of FHR/ Δ FHR matrix, (2) preparatory process





for factor analysis, where correlation matrix $(\Delta FHR/\Delta FHR \text{ matrix})$ with beat-to-beat differences (bpm) in both elements of columns and rows could be achieved, and (3) each procedure of factor analysis to compute the factor loading matrix on the basis of this correlation matrix.

Results

I. An analysis of the scalar components :

Fig. 4 shows the histogram, obtained from the first 90,000 beats of the sequential FHR values where the horizontal and vertical axes indicate the FHR values in every one bpm and corresponding incidence rates, respectively.

This would be considered to include all the variances, accompanying the characteristics of the scalar components in FHR changes, because it comprised such the large numbers of the samples. Therefore, this histogram was termed "standard histogram" and is a basic reference for further analysis, as shown in Fig. 5. We used here the "random numbers", as having the uniform distribution from one to 90,000, and which could be freely generated by the built-in mathematical function in the computer system. If these random numbers were assigned to each order of 90,000 beats in the actual sequence, any optional set of the samples with the complete random sequence of the FHR values can be obtained and the corresponding histogram; "sample histogram" can be made.

The concreate procedures are illustrated on the encircled area in Fig. 5. There can be seen two





Fig. 5. Quantitative analysis of the scalar components in the FHR changes, using random numers.



numbers of FHR values and the corresponding congruence rate, respectively.

histograms of "a" plus "c" and "b" plus "c", each being indicative of the standard histogram and sample histogram, respectively.

These abbreviations; "a", "b" and "c" also indicate the numbers of the FHR's included in each area. A given "sample histogram" was then magnified so as to contain the equal numbers of the samples to those in the standard histogram. This can be accomplished by multiplying "k" into the real numbers of the samples in every FHR values (bpm), where "k" means the magnifying rate ; "k" = 90,000/total numbers of the FHR's in the sample histogram. At this time, "a" become equivalent to "b", so that "c" can be quantified on the unit of per cent, namely "C", according to the formula, presented in the figure. Instead of "a" or "b", "x"; ("a"+ "b")/2 was here used for the actual processing, because it was more feasible for assembling computer program.

This "C" is named "congruence rate" and can be used as a parameter to compare the congruences of 988

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the patterns between the sample and standard histograms. The results of this analysis are demonstrated on the graphic representation in Fig. 5. The numbers on the horizontal axis indicate those of the FHR values when sampled from the original set of 90,000 beats, while the vertical axis shows the corresponding "congruence rate".

In addition, the same procedures of the analysis were repeated independently nine times, the result being a series compatible with a group of the asterisk's interpolated by the solid lines. Herein, the congruence rates get monotoneously increased with the expansion of the sample-size up to around four thousand, where they rapidly converge upon a certain point as the arrow indicates in the figure, and there is little growth in the values, namely "plateau phenomenon", irrespective of the additional numbers of the samples as well. The congruence rate when converging is estimated to be about 93 per cent. This suggests that these 4,000 beats are, indeed, the constituents of the definite entity, demonstrable of the outstanding peculiarity

Fig. 6. Sample histogram obtained from a given set of randomized 4,000 beats of the FHR values.



Fig. 7. A series of the procedures where the sample histogram is decomposed into the normal distributions.



I. II. III and IV in the figure show the extracted normal distributions, each having the values of mean (bpm) and SD (bpm); 132 and 4.2, 141 and 3.3, 161 and 7.9, and 149 and 3.5, respectively. Among 4,000 beats of FHR's in the sample histogram in Fig. 6, these I, II, III and IV possess 1,498, 873, 440 and 314 beats, respectively.

in the scalar components of the FHR changes, since the vectorial properties ought to be eliminated in the process of randomizing the chronological order of the FHR sequence.

The "sample histogram" exhibited in Fig. 6 offers an example as taken from a given set of these FHR values. Thus, an attempt was made on this histogram to analyze the scalar components. This is analogous on the configuration to the "standard histogram" (Fig. 4). Such was characterized as follows ; there were a few prominences along the ridges of the histogram, as the arrows point out in the figure, and this may be a compound histogram, composed of the certain types of the distribution. Now, assuming that so called "normal distribution"

would be used for the analysis, this histogram can be decomposed into at least four different kinds of "normal distribution", depending on a series of the procedures, as shown in Fig. 7. Herein, taking account such special features as the prominences and ridges on the distribution, arbitrarily estimated were the initial values of both mean and standard deviation (SD), such being the basic parameters of the normal distribution. The primary distribution thus obtained was developed one after another in the process of an inductive method until the best fit to the original was obtained. The refined normal distribution was then subtracted from the original, resulting in a residue which could be applied for the next step of the analysis. These procedures were successfully completed, using a method of questions and answers dialogue on the on-line microcomputer system.

Conversely, the original histogram can also be



Fig. 8. The original histogram can be restored by the extracted normal distributions; I, II, III and IV, as shown in Fig.7. restored up to a considerable extent by these extracted normal distributions; I, II, III, and IV, each having the values of mean (bpm) and SD (bpm); 132 and 4.2, 141 and 3.3, 161 and 7.9, and 149 and 3.5, respectively, as documented in Fig. 8.

However, the FHR values ranging from less than 110 and over 190 bpm were excluded, because these were confirmed to relate to artifacts mainly when the fetus moved vigorously. Furthermore, the unusually large incidence rates which can be seen in some FHR values were neglected in the processing. These seem to be accidentally caused by rounding the measured values of beat-to-beat interval into the instantaneous FHR values.

II. An anaylsis of the vectorial components :

A given set of the two successive FHR values can be converted into a pair of the values; one is the present FHR value itself, and another the beatto-beat difference (bpm) with either a positive or negative sign. Employing these parameters among all the sets of data, the FHR/ Δ FHR matrix could be calculated where the results indicate the cumulative incidence rates in each element of the matrix.

Fig. 9 represents these results in a form of a three dimensional image. The pattern is mound-shaped, spreading symmetrically around the points that the beat-to-beat differences equal zero, whereas the absolute FHR values range from approximately 116 to 160 bpm or more. Refering to the incidence

"Fig. 9. FHR/∆FHR (DFHR in the figure) matrix with the results of the cumulative incidence rates shown as the three dimensional image.



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rates, the "core" can be identified as varying within \pm 3 bpm of the beat-to-beat differences along with the summit of the distribution.

We prefer to define this finding as "core fluctuation", because this possesses the characteristics of the symmetry around the zero bpm of beat-to-beat difference, thereby implicating that a given instantaneous FHR could have an equal opportunity in proportion to the individual incidence rate to increase or decrease, at the time when shifting.

By multiplying this FHR/ Δ FHR matrix into its transpose matrix (Δ FHR/FHR matrix), the inner products can be obtained and here referred to as the correlation matrix (Δ FHR/ Δ FHR matrix). This matrix will include the interactions between the various combinations of the beat-to-beat differences.

A factor analysis was now applied on this correlation matrix in accordance with each step of the procedures, as minutely illustrated in Fig. 3.

Final results of the factor analysis were summed up into as many couples of eigenvalue and eigenvector (mathematical terms) as required.

Herein, the eigenvector is given another name; factor axis, which could contribute to all the net variances, to what extent the corresponding eigenvalue indicates. The values in each element of the eigenvector, factor loadings, represent the correlation coefficients to the respective factor axis. In this study, the numbers of factor axes adopted were confined to ten. Among these, the major two (I and II) were presented in a form of the factor loading matrix, as seen in Table 1. Considering the magnitude of contributions (eigenvalues), both of these axes show higher values than the remainder, respectively, that the sum of these values reaches about 60 per cent of all. Encircled were the loading values over 0.5, to which the corresponding variables were thought to be representative to each factor axis. The variables are here equivalent to the levels of beat-to-beat differences (bpm), as shown in left column of the Table.

Accordingly, it has been pointed out that factor I and II may have the properties, characterized by the beat-to-beat differences ranging from-4 to +8 bpm and from-11 to-2 bpm, respectively. Since one factor axis has no connection with another, there seem to be two underlying principles in the vectorial components of the FHR changes, related to the

Table	1.	Factor	loading	matrix	by
fact	or	analysis.			

	Factor axes	I	II
-15		0.342	0.100
-14		0.052	0.166
-13		0.034	0.312
-12	-	-0.199	0.290
-11		-0.216	0.607
-10		-0.159	0.450
- 9		0.124	0.700
- 8		0.238	0.703
\overline{c} - 7		0.298	0.726
ud – 6		0.379	0.764
. <u></u>		0.474	0.741
8 - 4		0.692	0.478
u – 3		0.536	0.679
2		0.868	0.324
- 1- tr		0.963	0.089
0 pea		0.915	0.226
<u>ģ</u> 1		0.902	0.057
2 eat		0.909	0.044
d s 3		0.823	0.390
ald. 4		0.809	0.079
5 aria		0.863	0.261
⇒ 6		0.827	0.209
. 7		0.525	0.101
8		0.710	-0.057
.9		0.333	0.085
10		0.322	0.008
11		0.290	0.051 ,
12		0.172	-0.053
13		0.388	-0.117
14		0.333	-0.005
Contributio	ons	9.818	4.001

acceleration and the deceleration.

Discussion

Cardiotocography is now in widespread use and is a great aid in monitoring the fetus in obstetric practice. The conventional analysis, however, are usually dependent on the distinctive patterns of the cardiotocograms, based upon visual recognition. Such gives rise to the conflicting problem that the cardiotocographic findings are often at unexpected variance with the individual examiners, even though the same FHR record might be subjected to assessment. In a similar context, there is also a problem that the paper-speed fed by the motor affects the configurations of the pattern in the cardiotocographic tracing.

To avoid these difficulties, characteristics of FHR changes were identified by reference to some external criteria, such as the uterine contraction in relation to the deceleration.

Many authors have made vigorous efforts to precisely describe the FHR changes, either in a quantitative fashion^(1)13/14/22/34) or by means of the scoring system^(3)15/20).

The purpose of these attempts would necessarily be directed toward investigation of the biological features inherent in FHR changes, irrespective of the presence or absence of external references.

The reports of Laros et al.¹⁸⁾ and Detwiler et al.⁵⁾ are most pertinent.

However, it should be kept in mind that the quantification technique is not always of higher diagnostic value than visual recognition, when assessing the FHR variability, as documented by Escarcena et al.⁶.

On the basis of these current investigations, we designed the mathematical model described above.

Electrocardiography provides a better measurement of beat-to-beat intervals than phono- or ultrasound-cardiography³³). Nevertheless, the noise could be almost completely randomized in distribution, when taken from the large-scale samples, so that increase in signal/noise (S/N) ratio would ensue.

For this reason, we used here the phonocardiograph (Toitu MT-810) with a built-in autocorrelometer to calculate the instantaneous FHR values.

The S/N ratio of this autocorrelation method limits the accuracy of approximately ± 0.5 per cent for each FHR value, when tested in in-vitro experiments (data not shown).

As a consequence of an analysis for the scalar components, it become evident that a set of the instantaneous FHR's is likely to carry properties on the 4,000 beats, among which there may also be present at least four isolated characteristics differing in the biological origin. This strongly suggests the existence of a distinctive nature of the so-called "baseline heart rates".

For confirmation, it is necessary to ascertain that a certain distribution, compatible with any one of the four shown in Fig. 7, could be obtained repeatedly in a smaller size of the smaples. In addition, it should be investigated whether or not the "normal distribution" is appropriate for the analysis of the histogram. If such can be accomplished, the fetus could be assessed on its own terms, putting a label along on the sequence of heart rates, that is to say, "biological clock"⁽³⁾³⁰⁾³¹.

Conforming to an analysis of the vectorial components, there is a "core fluctuation" within \pm 3 bpm of the beat-to-beat differences along with the arrangement of the absolute FHR values. This result is in good agreement with the findings in both fetal lamb and human fetus, respectively reported by Dalton et al.³⁾, and Wheeler et al.³³⁾.

The beat-to-beat differences of FHR changes are generally accepted to be identical to the short-term variabilities. This phenomenon may thus suggest that short-term variabilities are an undefinite fluctuation, namely "biological randomness", unlikely to be regulated by the nervous system.

This agrees well with the report of Zugaib et al.³⁵⁾, where they suggest that there is an absence of a significant influence of the intrinsic mechanisms of heart rate control on the genesis of beat-to-beat variability, based on the results of the experiments in newborn lambs. This finding also leads to the concept that the baseline FHR has to be recognized, as having such characteristics of properties in FHR changes, together with the results of an analysis of the scalar components.

Furthermore, it was demonstrated by means of the factor analysis that there might be different and independent mechanisms of FHR changes, one acting as the decelerator, and the another as accelerator.

Warner et al.³²⁾ proposed a mathematical model, capable of simulating in part the function of the autonomic nervous system, on the basis of the results obtained from animal experiments.

Nevertheless, it remains to be solved whether or not both mechanisms suggested here correspond to the reactions of either adrenergic or cholinergic systems. Moreover, there are unsolved problems in association with the short- and long-term variabilities, and also the scalar and vectorial components.

Finally, if the experimental system we described could be well attained to simulate the biological properties of the heart rates in the human fetus in utero, such would become comparable to the methodology used for conventional animal experiments. 992

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概要 胎児心拍数を制御する生体メカニズムを解明する目的で,筆者らは因子分析などの多変量解析法 を含めた数理モデルを開発した.元来,一群の瞬時心拍数は計測された観測値の数列にすぎないので, その特徴を「組み合せ」的な要素と「順列」的なそれとに分け,前者についてはヒストグラム表示を, 後者には心拍数値そのものと,それの次の一拍への変化分とを各々,行と列にもつマトリックスを基礎 に因子分析を試みた.なお,実験の対象には妊娠33週の正常胎児の一例を選び,本症例のほぼ連続した 12時間にわたる瞬時心拍数96,704拍をデータとして使用した.その結果,一様乱数を用いたヒストグラ ムの解析から,心拍数の「組み合せ」的な特徴は約4000拍を一単位の要素として成り立つていること, およびこれらの要素から得られる確率分布は,正規分布を仮定すると,4個の分布が混在した状態であ ることが示唆され,生体のなかでのいわゆる Baseline Heart Rate のあるべき姿を解釈する際の手懸り を与える所見であると考えられる.一方,「順列」的な要素の解析から,その変化分が±3bpm 以内のコ アを成す心拍数の存在が示された.これは一拍と次の一拍との関係を重視したマトリックスより求めら れたものであるため,心拍数の有する生物学的な「ゆらぎ」ともいうべき現象と解される.さらに,こ のマトリックスを用いた因子分析の成績から,心拍数の加速と減速を司る相互独立の機序の存在が示さ れた.これらの結果は,将来のコンピュータ・シミュレーションの基礎データになると思われる.