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New possibilities for ST analysis – A post-hoc analysis on the Dutch STAN RCT

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Aims: Determine the optimal cut-off for relative ST events in fECG to detect fetal metabolic acidosis.

Keywords:
Fetal electrocardiography
Fetal monitoring
ST event
Metabolic acidosis
T/QRS

ABSTRACT

Background: The diagnostic value of ST analysis of the fetal electrocardiogram (fECG) during labor is uncertain. False alarms (ST events) may be explained by physiological variation of the fetal electrical heart axis. Adjusted ST events, based on a relative rather than an absolute rise from baseline, correct for this variation and may improve the diagnostic accuracy of ST analysis.

Aims: Determine the optimal cut-off for relative ST events in fECG to detect fetal metabolic acidosis.

Study design: Post-hoc analysis on fECG tracings from the Dutch STAN trial (STAN+CTG branch).

Subjects: 1328 term singleton fetuses with scalp ECG tracing during labor, including 10 cases of metabolic acidosis.

Outcome measures: Cut-off value for relative ST events at the point closest to (0,1) in the receiver operating characteristic (ROC) curve with corresponding sensitivity and specificity.

Results: Relative baseline ST events had an optimal cut-off at an increment of 85% from baseline. Relative ST events had a sensitivity of 90% and specificity of 80%.

Conclusions: Adjusting the current definition of ST events may improve ST analysis, making it independent of CTG interpretation.

1. Introduction

ST analysis of the fetal electrocardiogram (fECG) seemed to be a very promising method for fetal monitoring during labor, as the technique would provide an objective addition to subjective fetal monitoring with cardiotocography (CTG) [1]. However, multiple randomized controlled trials and meta-analyses showed contradictory results in fetal asphyxia or operative delivery rates when CTG was combined with ST analysis compared to solely CTG [2–9]. The method of ST analysis combines CTG information with alarms (ST events) that arise in case of specific changes in the ST interval of the fECG during fetal hypoxia (Fig. 1). ST analysis determines three types of...
ST events: episodic, baseline and biphasic ST events. Both episodic and baseline ST events reflect an absolute increase of the T/QRS value compared to a median T/QRS value in the preceding registration (the so-called T/QRS baseline). The combination of a suboptimal or abnormal CTG and one or more of these ST events, may reflect fetal hypoxia. However, Kwee et al. showed that ST events are also reported in 50% of normal CTG tracings [10]. Clinicians can ignore these ST events when they interpret the CTG as normal. CTG interpretation is known to be subjective and has a high intra- and inter-observer variability [11,12]. Therefore, ST events may potentially be erroneously interpreted. This might partly explain the disappointing results of ST analysis to detect metabolic acidosis or reduce operative delivery rates [2–9]. Adjusted ST alarms, independent from CTG interpretation, might improve the diagnostic accuracy of the ST analysis technique.

Becker et al. showed that the T/QRS baseline itself is independent of the fetal condition [13]. On the contrary, the T/QRS baseline depends on the position of the scalp electrode compared to the fetal electrical heart axis. As the fetal electrical heart axis varies between individuals and the fetal electrocardiogram is recorded from one single scalp electrode, this can influence fECG amplitudes and waveform [14]. In accordance to this, we found more ST events in fetuses with a higher T/QRS baseline [15].

The current method of ST analysis does not take into account how the fetal electrical heart axis affects the amplitudes and waveform of the fECG. When the current definition is used, some fetuses are more prone to ST events than others, due to the alignment between the scalp electrode and the electrical heart axis regardless of fetal condition [15].

Previously, we explored the value of adjusted ST events in a case controlled study [16]. These adjusted ST events were based on relative rises from T/QRS baseline – so-called ‘relative’ ST analysis. We found that the diagnostic accuracy of the adjusted ST analysis to detect an arterial cord pH <7.05 improved. Both sensitivity and specificity of relative ST events (without CTG) were higher compared to conventional ST analysis plus CTG (absolute ST analysis). However, this study was limited to two groups of fetuses, at the extremes of neonatal arterial cord pH; umbilical cord pH below 7.05 and above 7.20.

This study aims to determine the optimal cut-off for adjusted, so-called relative ST events in a cohort of fetuses within the full range of arterial cord pH values, in order to classify neonatal metabolic acidosis at birth.

2. Material and methods

We performed a post-hoc analysis on a prospectively collected cohort. Patients were included from the index group (CTG + ST analysis) from the Dutch STAN trial [3]. Inclusion criteria were women aged 18 years and older, during labor, pregnant of a singleton in cephalic position, with a gestational age above 36 weeks. We refer to the publication by Westerhuis et al. [3] for detailed information about the selected patients in the original trial. Additional exclusion criteria for the current study were: missing postpartum umbilical cord blood gas results, missing STAN tracings (Neoventa, Mölndal, Sweden), signal quality <50% in the last hour before birth, maternal fever during labor (>38 degrees Celsius), use of tocolytics, and fetal cardiac malformations or arrhythmia.

All patients in the CTG + ST arm of the original study were connected to a S21 or S31 STAN® monitor with a Goldtrace scalp electrode (Neoventa Medical, Mölndal, Sweden) applied to the fetal head. Both monitors used the same algorithm for ST analysis and stored the T/QRS values on the monitor. We extracted this original T/QRS information from the STAN® monitors. At first, we determined the medians of the T/QRS values in shifting windows of 10 and 20 min. Then, T/QRS baseline was defined the same way as in conventional ST analysis: the lowest median T/QRS value in a twenty-minute window in the registration up to maximally three hours ago. Additionally, we determined the T/QRS baseline without this three-hour restriction, including the entire

![ECG parameters](image)

Fig. 1. ECG parameters. The T/QRS value is the quotient of the T wave amplitude and the QRS amplitude.
registration done so far. Conventional ST analysis applies a restricted memory for three hours for the T/QRS baseline. We would argue that the baseline should be set at the best fetal condition, probably at the beginning of the measurement. This should logically not be restricted to the preceding three hours of registration. Therefore, we also examined the effect of ST events without the three-hour baseline memory restriction.

Finally, the relative differences between the T/QRS median and T/QRS baseline values were computed with Matlab2015b® (The Mathworks; Natick, MA). As such, we computed episodic as well as baseline relative ST events, in analogy of the conventional absolute episodic and baseline ST events. In conventional ST analysis, episodic events reflect a single T/QRS value that exceeds 0.10 compared to the median T/QRS value of the preceding 10 min. Conventional baseline events occur in case the median T/QRS value of the last 10 min exceeds at least 0.05 compared to the T/QRS baseline.

We explored two concepts for relative episodic and baseline ST events:

1) Episodic and baseline median length definitions with restricted baseline memory up to three hours. Relative episodic ST events represent the relative difference between the most recent T/QRS value and the median of T/QRS values over the last 10 min. Relative baseline ST events represent the difference between the median T/QRS values over the last 10 min compared to the T/QRS baseline (lowest 20 min median so far, restricted to last the three hours).

2) Episodic and baseline median length definitions with unrestricted baseline memory. In parallel with the previous concept, relative episodic ST events compare the most recent T/QRS value with the median T/QRS value over the last 10 min. Relative baseline ST events compare the median T/QRS value over the last 10 min with the T/QRS baseline (lowest 20 min median so far, since the start of the registration).

To determine sensitivity and specificity to detect metabolic acidosis for relative ST analysis, we defined a positive test for relative ST analysis as at least one relative ST event within the last hour of registration. Metabolic acidosis was defined as cord artery pH $<$ 7.05 and base deficit in the extracellular fluid (BD$_{ecf}$) $>$ 12 mmol/L directly after birth. The definition was set as pH $<$ 7.10 and BD$_{ecf}$ $>$ 12 mmol/L in cases with only an umbilical vein sample (one available blood gas sample or the pH difference between two samples below 0.03). [17]

Clinical data were obtained from the original dataset of the Westerhuis trial (3). In case variables were missing or unclear in the dataset, they were verified in the original patient files. Baseline characteristics were presented as medians with corresponding interquartile range (continuous variables) and number with corresponding percentage (categorical variables). The baseline characteristics were compared between the group with metabolic acidosis and the group without metabolic acidosis with a Mann-Whitney U test for continuous variables and a Fisher’s exact test for categorical variables.

The aim of this study is to determine the optimal cut-off value for relative ST events and the corresponding sensitivity and specificity for metabolic acidosis. The abovementioned definitions were used to calculate an area under receiver operator characteristic (ROC) curve (AUC) and to determine the cut-off value closest to (0,1) in this curve. The point closest to (0,1) was defined as the minimum square of distance.

Besides, we performed a leave-one-positive-case-out cross validation, performing the same analysis for each metabolic acidosis patient: we defined the testing set as that single metabolic acidosis case, and the training set as all the rest (both metabolic acidosis and the other patients). We fitted the model on the training set, obtaining the optimal cut-off value and corresponding AUC. We then evaluated the diagnostic accuracy of each of the so-obtained 10 thresholds via sensitivity, specificity and diagnostic accuracy (percentage of correctly classified cases). All statistical analyses were performed in SPSS Statistics 22 for Mac (IBM, Armonk, NY).

3. Results

We included 1328 patients out of 2827 from the CTG + ST intention-to-treat branch from the Dutch STAN trial (Fig. 2). Patient characteristics are presented in Table 1. The total duration of scalp ECG registration varied from 34 to 1352 min. In the group of cases with metabolic acidosis 3 (30%) registrations were shorter than 3 h, in the group without metabolic acidosis this was the case in 457 (34.7%) subjects.

Metabolic acidosis was defined as cord artery pH $<$ 7.05 and base deficit in the extracellular fluid (BD$_{ecf}$) $>$ 12 mmol/L directly after birth. Abbreviations: FBS, fetal blood sampling; HIE, hypoxic ischemic encephalopathy; IQR, interquartile range; NICU, Neonatal Intensive Care Unit; SD, standard deviation. Groups were compared with Fisher’s exact test for categorical variables and Mann-Whitney U test for continuous variables.

Table 2 shows AUC values for different relative ST events. Differences depend on event definition and memory restrictions. Relative episodic ST events were not statistically significant to detect metabolic acidosis; therefore we did not determine cut-off values for this type of events. Overall, ST events with unrestricted baseline memory had better AUC values compared to ST events with restricted memory. These differences were not statistically significant. Fig. 3 shows the ROC curve for both relative ST events with and without memory restrictions.

The optimal cut-off value of a relative baseline event with restricted memory based on the value closest to (0,1) was set at an increment of 85% from baseline. At this cut-off value, sensitivity was 80.0% and specificity was 85.7%. The optimal cut-off value for relative baseline ST events with unrestricted memory was also found at 85%, with a respective sensitivity of 90.0% and specificity of 79.7%.

To explore the classification performance of the relative baseline events within this dataset, we repeated the same analysis on the data leaving out one metabolic acidosis case at a time (n = 10). For events with restricted memory we found a mean sensitivity of 80.0% (range 77.8–88.9%), mean specificity of 85.8% (range 85.7–86.3%) in the training set, and a diagnostic accuracy of 80% in the testing set. For events with unrestricted memory we found a mean sensitivity of 90.0% (range 88.9–100.0%), mean specificity of 79.9% (range 79.7–81.2%) in the training set, and a diagnostic accuracy of 90% in the testing set. Details are presented in Tables S1 and S2 of the supplementary materials.

4. Discussion

We found that relative ST analysis has an area under the ROC curve of 0.85, with a sensitivity of 90%, and specificity of nearly 80% at the optimal cut-off value. In our previously published case control study, we found better diagnostic characteristics (AUC 0.99, sensitivity of 90% and
pretation, which is known for its high intra- and inter-observer variability[12,19].

Besides changing the ST event definition from an absolute to a relative rise from baseline, we examined ST events that omit the T/QRS baseline reset after three hours. In the original STAN® method the last 10 min over the lowest 20 min in the last three hours of a recording are used. In the current study, we used the lowest baseline T/QRS value of the individual fetus as a reference without the three hour restriction. Assuming that fetal condition will most likely worsen during labor, the lowest T/QRS value represents the most optimal fetal condition. It is unclear why the reference is adjusted every three hours in the original STAN method.

We chose to use the registration from the last hour before time of birth, to ascertain the relation between T/QRS value and metabolic acidosis (the closest moment between the ECG and a reliable marker of neonatal wellbeing). In theory, an early event could indicate fetal compromise, which returned to a normal condition after successful interventions, such as stopping oxytocin infusion. As this is a retrospective study, no clinical decisions could have been made on potential relative ST events. Therefore, when examining the total time of registration instead of mere the last hour of registration, the relation between ST events and metabolic acidosis would be less reliable.

The here presented test characteristics for relative ST events only reflect an estimation of the sensitivity and specificity of metabolic acidosis as no actual clinical decision was made on these relative ST events. Instead of mere the last hour of registration, the relation between ST events and metabolic acidosis would be less reliable.

Moreover, the new relative ST analysis is independent of CTG interpretation, which is known for its high intra- and inter-observer variability[12,19].

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics of included women.</th>
<th>Included women (n = 1328)</th>
<th>Metabolic acidosis group (n = 10)</th>
<th>No metabolic acidosis group (n = 1318)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median [IQR] or n (%)</td>
<td>Median [IQR] or n (%)</td>
<td>Median [IQR] or n (%)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age at delivery - years</td>
<td>32.2 [28.9–35.3]</td>
<td>32.2 [28.0–38.9]</td>
<td>32.2 [28.9–35.3]</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>722 (54.4)</td>
<td>7 (70.0)</td>
<td>715 (54.2)</td>
</tr>
<tr>
<td>Prolonged pregnancy &gt;42 weeks</td>
<td>156 (11.7)</td>
<td>1 (10.0)</td>
<td>155 (11.8)</td>
</tr>
<tr>
<td>Small for gestational age (≤&lt;p&gt;10)</td>
<td>110 (8.3)</td>
<td>1 (10.0)</td>
<td>109 (8.3)</td>
</tr>
<tr>
<td>Fetal sex - male</td>
<td>724 (54.5)</td>
<td>5 (50.0)</td>
<td>719 (54.6)</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>537 (40.4)</td>
<td>3 (30.0)</td>
<td>534 (40.5)</td>
</tr>
<tr>
<td>Epidural analgesia</td>
<td>481 (36.2)</td>
<td>5 (50.0)</td>
<td>476 (36.1)</td>
</tr>
<tr>
<td>Meconium stained amniotic fluid</td>
<td>326 (24.5)</td>
<td>3 (30.0)</td>
<td>323 (24.5)</td>
</tr>
<tr>
<td>Oxytocin augmentation</td>
<td>924 (69.6)</td>
<td>6 (60.0)</td>
<td>918 (69.7)</td>
</tr>
<tr>
<td>FBS</td>
<td>84 (6.3)</td>
<td>3 (30.0)</td>
<td>81 (6.1)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>35 (2.6)</td>
<td>1 (10.0)</td>
<td>34 (2.6)</td>
</tr>
<tr>
<td>Failure to progress</td>
<td>12 (33.4)</td>
<td>1 (100.0)</td>
<td>11 (33.4)</td>
</tr>
<tr>
<td>Combination</td>
<td>17 (48.6)</td>
<td>0 (0.0)</td>
<td>17 (50.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (5.8)</td>
<td>0 (0.0)</td>
<td>2 (5.8)</td>
</tr>
<tr>
<td>Instrumental vaginal delivery</td>
<td>35 (12)</td>
<td>6 (60.0)</td>
<td>35 (12)</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>77 (48.4)</td>
<td>6 (100.0)</td>
<td>71 (46.4)</td>
</tr>
<tr>
<td>Failure to progress</td>
<td>68 (42.8)</td>
<td>0 (0.0)</td>
<td>68 (44.4)</td>
</tr>
<tr>
<td>Combination</td>
<td>11 (6.9)</td>
<td>0 (0.0)</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.9)</td>
<td>0 (0.0)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Umbilical cord artery pH</td>
<td>7.22 [7.18–7.28]</td>
<td>7.02 [6.95–7.03]</td>
<td>7.23 [7.18–7.28]</td>
</tr>
<tr>
<td>Apgar Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 at 1 min</td>
<td>17 (1.3)</td>
<td>4 (40.0)</td>
<td>13 (1.0)</td>
</tr>
<tr>
<td>&lt;7 at 5 min</td>
<td>14 (1.1)</td>
<td>4 (40.0)</td>
<td>10 (0.8)</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>129 (9.6)</td>
<td>5 (50.0)</td>
<td>124 (9.4)</td>
</tr>
<tr>
<td>NICU</td>
<td>11 (0.8)</td>
<td>1 (10.0)</td>
<td>10 (0.8)</td>
</tr>
<tr>
<td>Medium Care</td>
<td>118 (8.9)</td>
<td>4 (40.0)</td>
<td>114 (8.6)</td>
</tr>
<tr>
<td>HIE Sarnat 2 or 3 at discharge</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Not determined; 95%CI, 95% confidence interval.

Table 2

<table>
<thead>
<tr>
<th>Diagnostic characteristics of both episodic and baseline relative ST events at optimal cut-off.</th>
<th>Relative ST event</th>
<th>Area under ROC curve</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic event, restricted memory</td>
<td>0.62</td>
<td>0.47–0.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline event, restricted memory</td>
<td>0.82</td>
<td>0.85</td>
<td>0.80</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Episodic event, unrestricted memory</td>
<td>0.62</td>
<td>0.47–0.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline event, unrestricted memory</td>
<td>0.85</td>
<td>0.85</td>
<td>0.90</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

A specificity of 0.63 and a specificity of 0.66 of significant ST events.[18] Furthermore, the new relative ST analysis is independent of CTG interpretation, which is known for its high intra- and inter-observer
method that is independent of CTG interpretation. If so, it thereby expands more objective methods for fetal monitoring. Before this method could be implemented, relative ST analysis needs external validation.

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CRediT authorship contribution statement

A.D.J. Hulsenboom: Conceptualization, Methodology, Investigation, Project administration, Formal analysis, Writing – original; M.B. Van der Hout-van der Jagt: Investigation, Formal analysis, Writing - review & editing; E.S.A. van den Akker: Investigation, Writing - review & editing; P.C.A.M. Bakker: Investigation, Writing - review & editing; E. van Beek: Investigation, Writing - review & editing; A.P. Drogtrop: Investigation, Writing - review & editing; A. Kwee: Investigation, Writing - review & editing; M.E.M.H. Westerhuis: Investigation, Writing - review & editing; R.J.P. Rijnders: Investigation, Writing - review & editing; N.W.E. Schuitemaker: Investigation, Writing - review & editing; C. Willekes: Investigation, Writing - review & editing; R. Vullings: Conceptualization, Methodology, Writing - review & editing; S.G. Oei: Investigation, Conceptualization, Methodology, Writing - review & editing; J.O.E.H. van Laar: Conceptualization, Methodology, Writing - original draft, Writing - review & editing.

Declaration of competing interest

R. Vullings is a shareholder in Nemo Healthcare BV, the Netherlands. S.G. Oei initiated the scientific research from which Nemo Healthcare originated, there is no financial relationship between Nemo Healthcare and S.G. Oei. All other authors have declared that no competing interests exist.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2021.105537.

References


![Fig. 3. Receiver operating characteristic (ROC) curve of relative baseline ST events.](https://doi.org/10.1016/j.earlhumdev.2021.105537)
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