Supplementary information

Software design

The program for STV calculation was written in Python version 3.6 (Python software foundation) using literature by Dawes[1–5]. Two later publications were consulted additionally[6, 7]. We intended to follow the methods used by Dawes, but particular details for baseline construction, detailed below, could not be determined from literature.

FHR registration

CTG's were registered using Philips series 50A or M1350A machines (Philips Healthcare, Amsterdam, the Netherlands). These machines use a pulsed wave Doppler probe and register the frequency shift between the emitted signal and the reflected echo-signal. Moving tissue (like fetal heart or blood vessels) within the ultrasound beam causes a frequency shift of the reflected signal. The signal is filtered to register fetal cardiovascular movements and exclude other movements (like fetal or maternal body movements). Beat-to-beat (R-R) intervals can never be calculated exactly due to beat-to-beat variation of the signal. Timing of a heart beat is improved in modern CTG monitors by autocorrelation, where the wave pattern of previous beats is used to determine the timing of the current beat[8]. Each R-R interval is inverted to a FHR value (beats / minute). FHR values are exported with a sampling interval of 250 ms (4 Hz). If no new FHR value is available at sampling time then the same FHR value will be exported again. This data sampling method results in a large number of double values, as the sampling frequency is approximately twice the average FHR. For calculation of FHR variability mathematical processing of the data is necessary. There are two possible approaches. Cesarelli at al developed an algorithm for recovery of the true uneven FHR series from the sampled monitor data[9]. On evaluation of this algorithm using artificially generated FHR series they observed an exact reconstruction of the original signal. However, it remains questionable if this algorithm works with similar accuracy with patient data, where gaps in the registration often occur. Another solution is averaging FHR values over a small window. Dawes decided for computing reasons on a window of 1/16 minute (3.75 seconds) for averaging the original valid heart periods[1]. The suitability of this window was later tested and found acceptable as the largest period of time which could be used without serious attenuation of the peaks and troughs of the principal variations likely to be of physiologic or clinical interest. Others decided to use a shorter interval (2.5 sec), which resulted in a higher FHR variability than with windows of 3.75 sec[10].

Signal processing

To eliminate noise from errors in the signal reception of the CTG-hardware, all samples with extreme values (more than 200 beats per minute (bpm) and less than 30 bpm) were rejected. Furthermore all samples with an inter-beat interval (IBI)less than 0.6 or more than 1.55 times the average of the three previous samples were considered invalid and were also rejected. Rejected values were excluded from calculations, but because they remained in the data array the original time order of the data points was preserved. IBI was calculated from the FHR (IBI = 60.000 / FHR) and is expressed in milliseconds (ms). The next step was to calculate averages of IBI for time periods of 3.75 seconds (epochs), containing 15 exported CTG values, which resulted in 16 epochs per minute. We decided on a window of 3.75 sec, similar to FetalCare, as it was our intention to make a comparison with this application. If an

epoch contained less than 3 valid IBI values than the epoch value was set to missing. All further calculations were performed with these epoch values.

Baseline

Baseline calculation is of the utmost importance, as all further calculations depend on this. Baseline calculation consists of four intermediate steps. First a reference value is calculated that is used to set upper and lower constraints for the baseline calculation. Then an initial baseline level is calculated. Starting with this initial baseline level, the baseline calculation continues using the average of IBI values that are within the constraints in a moving window of one minute duration. Lastly a filter is used to smooth the baseline. These processing steps are detailed below.

Baseline reference value

For calculation of the reference value a frequency analysis was made of IBI in steps of one millisecond. The histogram was analysed from long to short IBI (right to left), to determine the first peak of IBI (Figure 1). This was usually the mode of the distribution, but sometimes an earlier peak with longer IBI was detected. This could happen In CTG's with many accelerations, where the frequency of short IBI's was so high that these formed the mode of the distribution, while an earlier peak would represent the basal fetal heart rate better. The validity of this earlier peak was determined by criteria published by Pardey in his description of the FetalCare system[7].

An earlier peak was only used if the following four criteria were met:

1) the reference value of this peak had a higher count than the 5 following shorter IBI's,
2) the frequency of samples with this IBI peak was at least 0.5% of the total number of samples (excluding missing values), to exclude outliers
3) more than 12.5% of the samples had a longer IBI, to exclude the tail of the distribution that may represent decelerations
4) the difference of this peak IBI with the mode of the IBI frequency distribution was less than 30 ms, to prevent a reference value far from the mode .

Otherwise the mode of the distribution was chosen.

Initial baseline value

The initial CTG baseline level might differ slightly from the reference value because the heart rate is changing continuously. The initial CTG baseline level was therefore estimated from the average of IBI epoch values during the first 4 minutes that were within 20 ms of the reference value. If less than 10 values could be obtained within these constraints then the constraints were increased to 40 ms in steps of 10 ms. If the first 4 minutes contained insufficient signal then the calculation was repeated over the next 4 minutes. If the initial CTG baseline level could still not be calculated or if the initial CTG baseline level differed more than 20 ms from the reference value, then the reference value was used for the start of the baseline calculation. This methodology was described by Dawes and Pardey[2, 7].

Baseline calculation

Although it was clear from the descriptions by Dawes and Pardey that baseline values should remain within a fixed distance from the reference value, it was not clear how to calculate continuation of the baseline after the initial CTG baseline level. We decided to calculate for each point the mean of the previous 8, the current and the next 7 epoch IBI values that were within 30 ms of the reference value. In this way baseline points were calculated from a moving window of one minute duration. For the first 8 samples the initial baseline level was used. In case no valid epoch values were available, the previous baseline value was used.

FetalCare used larger constraints of 60 ms. We preferred to use a smaller value for the constraints and change these to larger limits if necessary, as described below in the paragraph on baseline validation.

Baseline filter

After calculation of all baseline points for the complete registration the baseline was filtered using a low-pass infinite impulse response (IIR) filter. The IIR filter is configured as a two-way exponential smoothing filter using the equation:

$TE_f(i) = C \times TE(i) + (1 - C) \times TE_f(i-1)$, with $i = [1 \ldots N]$

where TE(i) is the average IBI of epoch number i, $TE_f(i)$ is the filtered heart interval of epoch number i, N is the number of epochs of the registration and C is the filter coefficient. Dawes chose C = 0.05 (personal communication between Dobbe and Dawes)[6]. This procedure was repeated backwards to prevent a phase difference. The resulting time constant of about 75 s guarantees a slowly varying baseline from which prominent heart rate changes can be clearly distinguished[6].

Baseline validation

Normally the FHR varies around the baseline. In rare cases (0.01% according to Pardey) a rapid shift of the FHR might occur which falls outside the constraints around the reference value and therefore cannot be followed by the baseline calculation[7]. If anywhere in the cCTG the FHR remained higher or lower than the fitted baseline and did not cross the baseline within 10 minutes then the complete baseline calculation procedure was repeated with wider constraints in steps of 10 ms with a maximum of 100 ms.

Decelerations, accelerations and outliers

Following baseline calculation all epochs with an IBI that differed more than 75 ms from the baseline (upwards or downwards) were marked as outliers[7]. Decelerations were defined by periods of 60 s or more with FHR below the baseline and a largest difference from the baseline of more than 10 bpm, or of 30 seconds or more with a largest deviation of more than 20 bpm. Accelerations were defined by a period of 15 seconds or more with a FHR above the baseline and a peak value at least more than 10 bpm above baseline.

These definitions, used by Dawes for FetalCare, differ from several professional guidelines[5, 7, 11]. Notwithstanding this, we decided to use these definitions because the definition of decelerations affects STV calculation, as decelerations are excluded from STV calculation, and it was our intention to make a comparison with FetalCare.

Outlier epochs that were not part of an acceleration were, together with a neighboring epoch on each side, excluded from further calculations.

Short term variation

Short term variation (STV) was calculated for each minute by averaging the absolute difference of the IBI of consecutive epochs. If a minute contained less than 50% valid epochs or if it was part of a deceleration then this minute was rejected. Additionally all minute averages that were larger than 4 x the mean of all minute STV values were rejected. STV for the complete cCTG was calculated as the average of all valid one-minute STV values.

Long term variation

Similar to STV calculation, minutes with more than 50% signal loss or that were part of a deceleration were excluded from the calculation of long term variation (LTV). IBI range was calculated for each minute by addition of the largest deviation of IBI above the baseline to the largest deviation of IBI below the baseline within a minute. If IBI did not cross the baseline within a minute and remained below the baseline then the difference of largest baseline value and the smallest IBI value within that minute were used. If IBI values

remained above the baseline within a minute then the highest IBI value and the smallest baseline value were used. LTV was calculated as the average of the minute range values over the complete registration. An episode in which 5 of 6 consecutive minutes had an IBI range of more than 31 ms was marked as “High variation”. “Low variation” was defined by 5 of 6 consecutive minutes with IBI range less than 31 ms.

Sinusoidal rhythms.

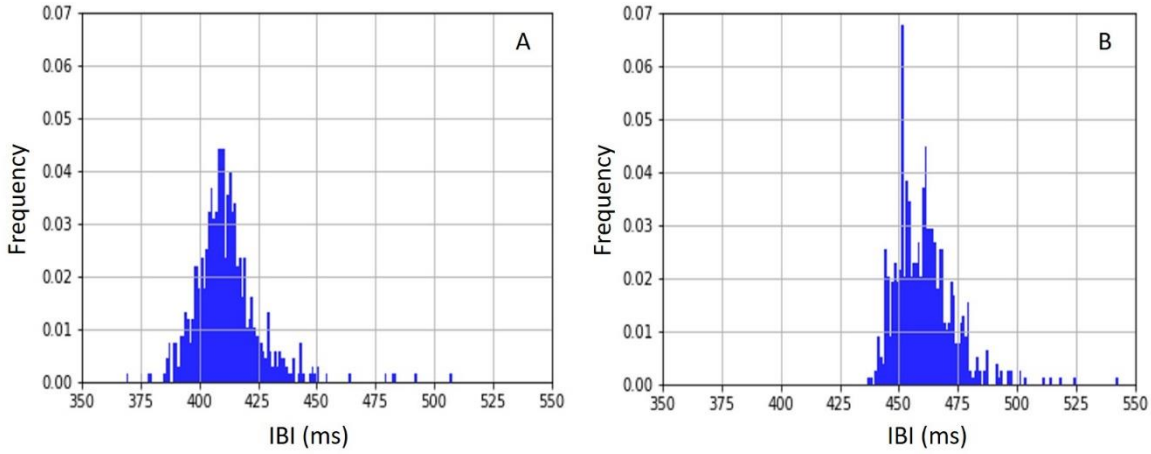
A sinusoidal rhythm is a rare FHR pattern. A low-frequency sinusoidal rhythm (one per 2-5 minutes), superimposed on an otherwise flat FHR tracing, usually signifies disease and poor fetal outcome, whereas a high-frequency sinusoidal rhythm (2-5 per minute) may indicate fetal anemia caused by rhesus alloimmunisation, or fetal hemorrhage[12]. In the absence of a sinusoidal rhythm, STV and LTV are strongly correlated[13]. Street et al observed in a dataset of 73,802 cCTG readings a ratio of STV to LTV of 0.186 ± 0.024 (mean ± SD). A low-frequency sinusoidal rhythm increases the LTV more than the STV and lowers this ratio[13]. If the STV/LTV ratio is more than 2 SDs below the mean, the system alerts the operator that a low-frequency sinusoidal rhythm is likely, similar to Fetalcare. Conversely, a high STV/LTV ratio may be caused by a high-frequency sinusoidal rhythm, but this needs further confirmation. If STV/LTV ratio is more than one SD above the mean then the distribution of peak-to-peak and trough-to-trough intervals in the FHR tracing is calculated over a minimum period of 20 minutes[14]. A high-frequency sinusoidal rhythm can be confirmed by a dominant peak in the distribution at 2 to 5 cycles per minute. A high STV/LTV ratio can also be caused by a baseline error. Similar to FetalCare, STVcalc gives a warning if a sinusoid pattern is suspected.

Software code

The software code of STVcalc is available from GitHub (https://github.com/hwolf46/STVcalc), a repository for freeware and host for collaborating not-for-profit software developers.

Figure 1:

Frequency distribution of all epoch inter-beat interval (IBI) samples for two women. (A) mode and reference point of IBI 410 ms. (B) mode of IBI 451 ms, but reference point set at 461 ms



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