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Evaluation of the fetal QT interval using non-invasive fetal ECG technology

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Abstract

Non-invasive fetal electrocardiography (NI-FECG) is a promising alternative continuous fetal monitoring method that has the potential to allow morphological analysis of the FECG. However, there are a number of challenges associated with the evaluation of morphological parameters from the NI-FECG, including low signal to noise ratio of the NI-FECG and methodological challenges for getting reference annotations and evaluating the accuracy of segmentation algorithms. This work aims to validate the measurement of the fetal QT interval in term laboring women using a NI-FECG electrocardiogram monitor. Fetal electrocardiogram data were recorded from 22 laboring women at term using the NI-FECG and an invasive fetal scalp electrode simultaneously. A total of 105 one-minute epochs were selected for analysis. Three pediatric electrophysiologists independently annotated individual waveforms and averaged waveforms from each epoch. The intervals measured on the averaged cycles taken from the NI-FECG and the fetal scalp electrode showed a close agreement; the root mean square error between all corresponding averaged NI-FECG and fetal scalp electrode beats

was 13.6 ms, which is lower than the lowest adult root mean square error of 16.1 ms observed in related adult QT studies. These results provide evidence that NI-FECG technology enables accurate extraction of the fetal QT interval.

Keywords: non-invasive FECG, ECG morphological analysis, crowd-sourcing, medical annotations

(Some figures may appear in colour only in the online journal)

Introduction

Continuous fetal heart rate monitoring is the standard of care for intrapartum management in the United States and in many other countries (American College of Obstetricians and Gynecologists 2005). The limitations of this technology—particularly the very low specificity—are well known, along with the association between the use of continuous fetal heart rate monitoring and an increase in operative vaginal deliveries and cesareans (American College of Obstetricians and Gynecologists 2005). Obstetricians, however, have few alternatives due to the difficulty in monitoring other physiologic signals from the fetus during pregnancy and labor.

The one fetal signal that has generated the most interest is the fetal ECG waveform, which can be reliably obtained during labor with the use of an invasive fetal scalp electrode (FSE), and less reliably using non-invasive adhesive electrodes attached to the maternal abdomen (Wolfberg and Norwitz 2009, Sameni and Clifford 2010, Behar *et al* 2016).

Most studied is the ratio between the *T*-wave and the *R*-wave, a metric analyzed and reported by the STAN monitor (Neoventa Medical, Goteborg, Sweden) as a proxy for the ST segment. There is a reasonable physiologic basis for monitoring the ST segment during labor as a marker for hypoxia or ischemia (Greene 1987, Greene and Rosen 1989). Although a large American study failed to find improved newborn outcomes or reduced cesarean rates when the STAN monitor was used (Belfort *et al* 2015), multiple independent trials in Europe have demonstrated significant improvements in newborn outcome when the STAN monitor was used (Amer-Wahlin *et al* 2001, Doret *et al* 2011, Kessler *et al* 2013).

Less research has been conducted on the association between the fetal QT interval and newborn outcome, even though many studies link QT-interval abnormalities during the fetal and newborn period with serious events, including sudden infant death syndrome (Crotti *et al* 2013). Oudijk and colleagues used the STAN monitor to measure the QT interval and demonstrated that during severe intrapartum hypoxia and metabolic acidosis, there was a significant shortening of the QT and corrected QT interval (Oudijk *et al* 2004). More recently one group identified a fetus as having long QT syndrome using QT measurement performed on the non-invasive fetal ECG (NI-FECG) (Fujimoto *et al* 2009). In adults, the QT interval has been of high interest in a number of conditions including the Romano–Ward and Jervell–Lange-Neilson syndromes, drug toxicity, and to predict prognosis following acute myocardial infarction (Campbell *et al* 1985).

Other pathologic conditions linked to an abnormal QT interval include an association between a prolonged QT interval in newborns and the use of selective serotonin reuptake inhibitors (SSRI) during pregnancy (Dubnov *et al* 2005, Dubnov-Raz *et al* 2008). These observations suggest the potential to screen for adverse events using the fetal QT interval during pregnancy and labor.

Hampering research is the requirement that a wire electrode be directly attached to the fetal scalp in order to obtain a reliable signal. Placement of the FSE requires ruptured membranes

and a dilated cervix and thus this modality is limited to monitoring during labor. Furthermore, the FSE does not allow for monitoring of the fetus prior to labor, and because the FSE has only one electrode on the fetal scalp, it does not cover the 3D electrical field emanating from the fetal heart. In contrast, the NI-FECG monitor could be used for antepartum (as well as intrapartum) fetal monitoring and it provides a 3D electrical representation of the electrical field emanating from the fetal heart. Thus, there is a strong motivation for developing a non-invasive method for measuring the FECG obtained from multiple abdominal ECG sensors. Indeed, NI-FECG is a non-invasive monitoring method that allows to estimate the FHR, as well as information on the electrical activity of the heart which is embedded in the ECG morphology.

Accurate extraction of the FHR from the NI-FECG has been demonstrated (Behar *et al* 2014, Clifford *et al* 2014). Our group previously has described the accurate measurement of the ST segment from the external fetal ECG recordings (Clifford *et al* 2011). However, accurate QT interval estimation from NI-FECG has not been previously demonstrated.

To be clinically useful, the fetal QT interval measured using abdominal ECG technology must be reliably identical to the fetal QT interval measured using a direct ECG measurement. We sought to validate the non-invasive measurement of the fetal QT interval in order to allow for additional research to be conducted without the need for a FSE. This paper describes the method for rigorously comparing the fetal QT intervals extracted from the NI-FECG and FSE, and demonstrates the feasibility of fetal QT measurement from the NI-FECG signal.

Materials and methods

The study was approved by the Institutional Review Boards at the institutions where data were collected: Brigham and Women's: 2010-P-00278/1, Cleveland Clinic Fairview: 12–154, Newton Wellesley: N08-445 and Tufts Medical Center: 7863 20. Fetal ECG data were recorded from 22 term laboring women with singleton fetuses. Data were recorded simultaneously using a 28 NI-FECG monitor (Mindchild Medical, North Andover, MA) and a single lead invasive FSE (GE Corometrics). Data were recorded at a sampling frequency of 1 kHz with 16-bit accuracy. All women delivered newborns with five-minute Apgar scores above six, and none of the fetuses were exposed to SSRI medication in-utero. There were no prolonged QT intervals noted by the three independent reviewers of the data or any indications for long QT syndrome from the clinical data.

Each recording period was divided into one-minute segments for the analysis. Segments were selected that had a relatively stable fetal heart rate based on determination that the baseline heart rate did not change by more than 20 bpm during the one-minute period (Silva *et al* 2013). In segments that contained accelerations or decelerations (defined as changes from baseline of more than 20 bpm lasting more than 15 s) the corresponding sub-segments (generally lasting between 10–15 s) were replaced by random noise to ensure the annotators were not annotating in areas with large changes in heart rate. This procedure was implemented to ensure that the fetal QT interval was approximately stable over each one-minute segment, which is necessary when computing averages of ECG cycles (Christov and Simova 2006). Indeed, a relationship between the QT length and the heart rate has been established in adults (Bazett 1920) and although such a relationship has not been studied in fetuses, it is reasonable to assume that the QT length be modulated by the fetal heart rate (even if differently than for adults).

The QT interval is defined as the time interval between the Q wave onset and the end of the T wave in the heart's electrical cycle. Three pediatric cardiologists independently annotated the data using the modified Physionet Lightwave interface (Zhu *et al* 2014) (example in

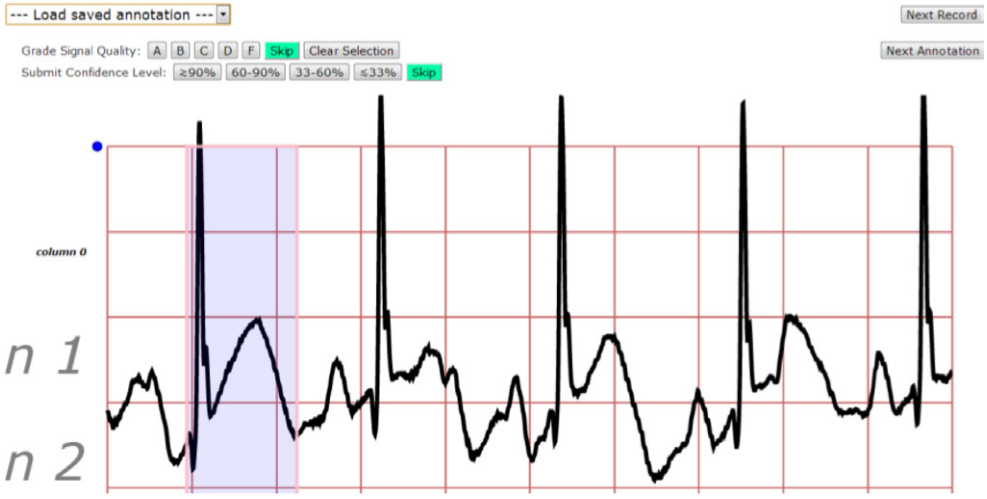

Figure 1. Annotation interface. A fetal QT interval was annotated by dragging a mouse across the interface from left to right (shaded area). The signal in this illustration is a FSE segment. The procedure was also repeated for the ECG derived from the non-invasive FECG.

figure 1). This online system either presented the cardiologists with a rhythm strip one minute long, or presented them with a single ECG waveform created by automatically averaging a series of ECG waveforms. Each cardiologist was trained on the interface individually during an online training session. The precision of the annotation interface was 1 ms.

The first set of annotations, denoted SET1, contained 210 one-minute segments (105 recorded using abdominal electrodes and the corresponding 105 segments recorded using a FSE). Each cardiologist was instructed to annotate five QT intervals per one-minute segment, and was told that they were free to choose the five cycles to annotate, a methodology similar to prior manual QT annotation exercises (Moody *et al* 2006). The next set, denoted SET2, included 210 averaged fetal ECG cycles (105 abdominal and 105 corresponding FSE). One annotation per waveform was requested. Cardiologists were blinded to signal source (i.e. whether the signal to annotate was FSE or NI-FECG) and the waveforms were presented at random.

In each set, the data were randomized so that two consecutive waveforms were not extracted from the same patient. An example of an annotation made on a rhythm strip segment is demonstrated in figure 1. Examples of signals used in SET1-2 are shown in figure 2.

We analyzed the variation between paired measurements of the QT segment (measured on the NI-FECG and FSE). For that purpose the root meant square error (RMSE) and absolute error (AE) were computed. We also evaluated the RMSE95 and AE95 defined as the RMSE and AE evaluated while excluding the extreme 5% values. This was done to make sure that no outliers in the sample size were biasing the estimation of the RMSE and AE. Three methods for fusing the annotations were investigated: mean, median and an expectation maximization (EM) algorithm (Zhu *et al* 2014)—see description in the following paragraph. In addition Wilcoxon signed rank test was applied to test the hypothesis that the difference between scalp and abdominal annotations were samples from continuous distributions with zero median for both SET1 and SET2. The EM algorithm used for fusing the annotations is described in the context of QT annotation in Zhu *et al* (2014). It is assumed that R annotators have annotated a series of N, QT observations. The true QT annotation for each individual record is written

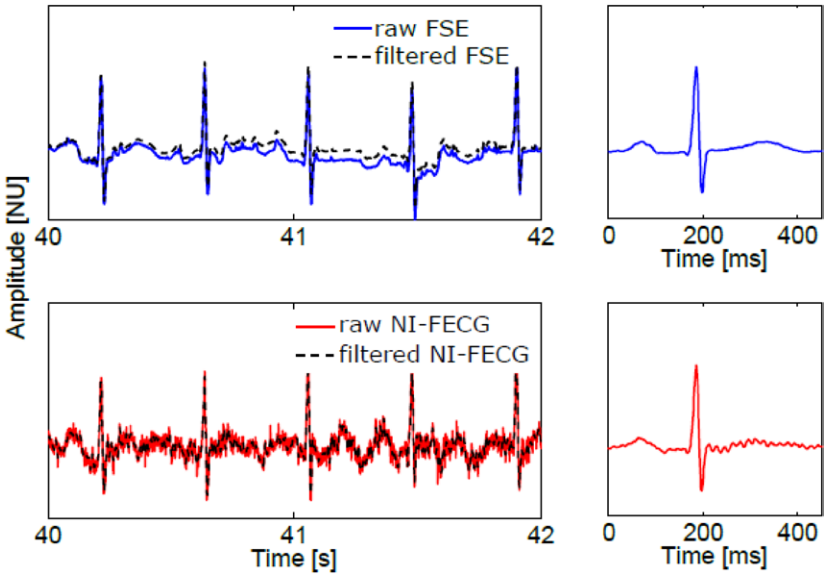

Figure 2. Example of signal used for SET1 and SET2. Top left: raw (solid line) and filtered (dashed) FECG from FSE; Top right: corresponding average ECG; Bottom left: raw (solid line) and filtered (dashed) abdominal NI-ECG; Right: corresponding average ECG templates constructed from the raw ECG signal.

z_i, $i \in [1;N]$ and the annotation from annotator j and which was performed on record i is denoted y_i^j. In addition, it is assumed that z_i can be predicted using a linear regression model: $z_i = \underline{w}^T \cdot \underline{x}_i + \epsilon$, where $\underline{w}$ is the regression vector and ϵ is a zero-mean Gaussian noise with precision γ and $\underline{x}$ is a feature vector. No features were used in the approach detailed here and thus $\underline{x}$ is a unity vector. The EM algorithm can be summarized as follows:

(1) E-step: the E-step estimates the expected true annotations for all records, $\underline{\hat{z}}$, as a weighted sum of the provided annotations with their precision λ^j.

$$\underline{\hat{z}} = \frac{\sum_{j=1}^{R} \lambda^j \cdot \underline{y}^j}{\sum_{j=1}^{R} \lambda^j}$$

(2) The M-step is based on the current estimate of $\underline{\hat{z}}$ and given the dataset written D. The model parameters such as the regression coefficient $\underline{\hat{w}}$ and precision $\underline{\hat{\lambda}}$ can be updated using the following equations:

$$\frac{1}{\hat{\lambda}^j} = \frac{1}{N}\sum_{i=1}^{N}(y_i^j - \underline{\hat{w}}^T \cdot \underline{x_i})^2$$

$$\underline{\hat{w}} = \left(\sum_{i=1}^{N} \underline{x_i} \cdot \underline{x_i}^T\right)^{-1} \sum_{i=1}^{N} \underline{x}_i \cdot \hat{z}_i$$

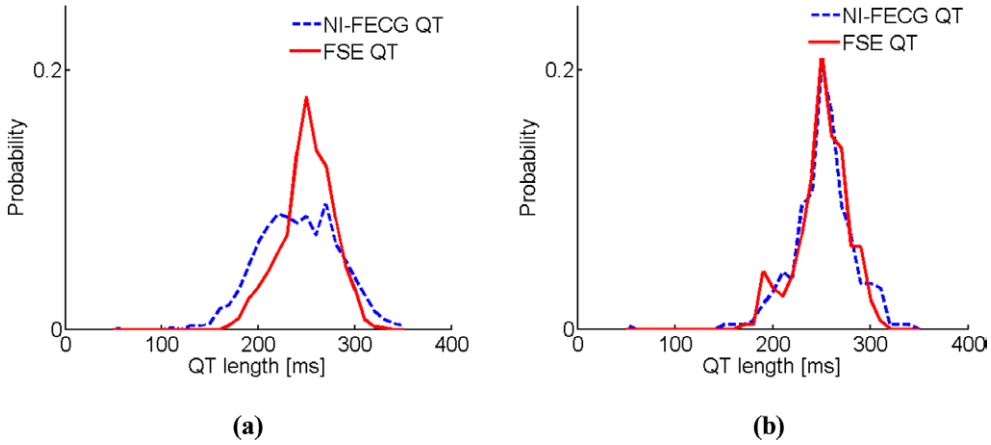

Figure 3. Empirical probability density function for the median FSE QT interval annotated by the three annotators for: (a) SET1 (i.e. annotation on the raw signals), 3150 annotations, and (b) SET2 (annotation on the averaged heart beat cycles) 630 annotations. For SET2, the two distributions (NI-FECG QT and FSE QT) superimpose closely, while the NI-FECG QT distribution has a lower median and is more platykurtic (broader) than the FSE QT distributions for SET1, indicating more extreme values.

With

$$\hat{z}_i = \frac{\sum_{j=1}^{R} y_i^j \lambda^{\mathrm{j}}}{\sum_{j=1}^{R} \lambda^{\mathrm{j}}}$$

The precision is initialized as being equal for all annotators (i.e. at the initial step of the algorithm). The initial precision can thus be written as: $\underline{\hat{z}} = \frac{1}{R}\sum_{j=1}^{R} \underline{y}^j$.

Results

Cycles with high correlation were retained to build the averaged cycles and a minimum of 20 cycles per 1 min segment were required to form a valid template. The QT interval measured using the FSE was 0.3 ms shorter, on average, than the QT interval measured using NI-FECG when averaged cycles were annotated and 8.7 ms longer when individual cycles were annotated. Figure 3 shows the probability density function for the fetal QT interval annotated by the three annotators for SET1 and SET2. On this plot, NI-FECG QT refers to the QT annotated on the NI-FECG extracted using the MindChild monitor and FSE QT refers to the QT annotated on the FSE by the reviewers. For SET2, the two distributions (NI-FECG QT and FSE QT) superimpose almost perfectly (without a significant difference between the distributions), while the NI-FECG QT distribution has a lower median and is more platykurtic (broader) for SET1. For SET1, the null hypothesis of the Wilcoxon signed rank test was rejected under the 5% significance level whereas the null hypothesis could not be rejected for SET2. This statistical test confirms that the distributions for scalp and abdominal annotations only matched (i.e. were not significantly different) when using the averaged cycles of the NI-FECG and FSE.

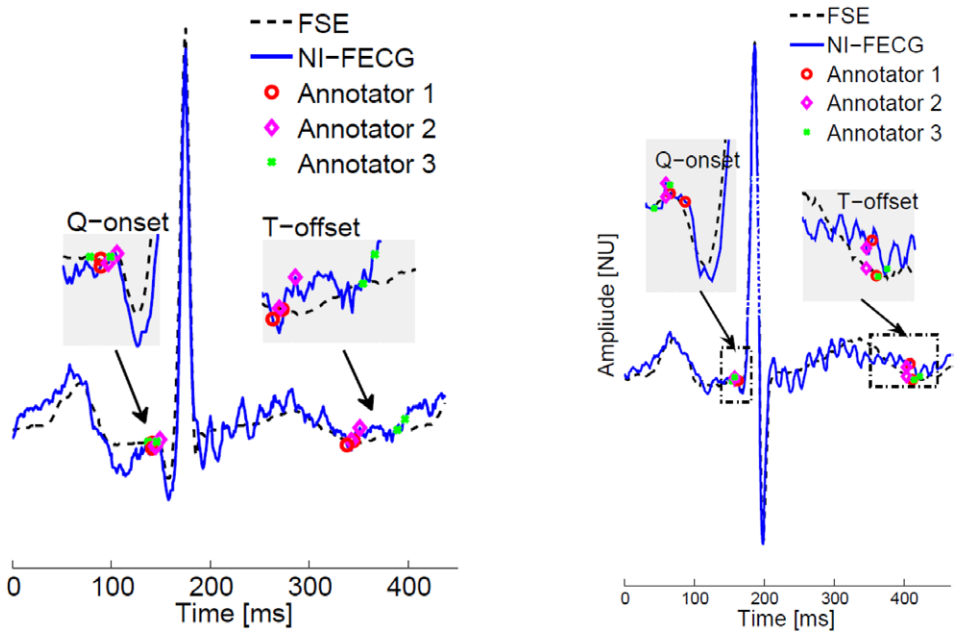

Figure 4. Comparison of annotations performed on average FECG waveforms from both the FSE and the NI-FECG monitor by three experts. (a) Note the close correspondence between experts on both the FSE and NI-FECG signal. (b) Note the disagreement between annotator 3 and the other two experts. This last example illustrates the importance of combining annotators to improve the reliability of results.

Figure 4 shows two examples of averaged cycles (FSE and NI-FECG) being annotated by the three experts. The figure shows the close agreement between the expert annotations on the FSE and on the NI-FECG. A total of 3150 annotations were performed for SET1 (1050 per annotator) and 630 for event 2 (210 per annotator). Tables 1 and 2 presents the results for SET1 and SET2 when considering each individual annotator and all the annotators combined. The AE of 14.2 ms and 10.4 ms for SET1 and SET2 respectively when combining all the annotators compares favorably to AEs reported in the literature when adult data are annotated in a similar fashion.

Figure 5 shows that combining the annotations from the three experts resulted in a lower bias, a slope closer to one and higher goodness of fit ($R^2 = 0.61$) than any of the three annotators taken individually. The intraclass correlation coefficient (ICC) was also computed between each individual annotator annotations on the SQT and AQT to quantify how much the two sets of annotations resembled each other. ICC of 0.522, 0.613, 0.616 for annotators 1–3 were obtained. The relative ranking between the three annotators is in accordance with the χ^2 evaluated (see figure 5).

Discussion and conclusion

This is the first paper to demonstrate that the fetal QT interval can be reliably measured from ECG data recorded non-invasively using electrodes on the maternal abdomen. Although we note that no pathologically long or short QT intervals were present in the data available, we

Table 1. Individual annotators (A1)–(A3) and annotations for SET1 and SET2.

Method/stats	RMSE	AE	RMSE95	AE95
A1-EVENT1	27.5	22.5	25.0	20.7
A2-EVENT1	41.3	32.8	35.9	29.5
A3-EVENT1	21.6	17.1	19.2	15.5
A1-EVENT2	33.2	20.3	22.0	16.3
A2-EVENT2	22.7	16.6	17.8	14.1
A3-EVENT2	18.3	14.8	16.2	13.4

Note: Reference: FSE QT obtained from annotator A. Measure: non-invasive fetal ECG QT obtained from annotator A. RMSE95 and AE95: RMSE and AE when removing the 5% extreme values. All values are expressed in ms. The lowest AE is underlined and also corresponds to the lowest RMSE.

Table 2. Combining cardiologists' annotations to get FSE QT and non-invasive fetal ECG QT for SET1 and SET2.

Method/stats	RMSE	AE	RMSE95	AE95
Mean-EVENT1	17.9	14.1	15.1	12.4
Median-EVENT1	21.3	17.1	18.7	15.5
EM-EVENT1	18.0	14.2	15.3	12.7
Mean-EVENT2	15.4	11.5	12.1	9.9
Median-EVENT2	18.8	14.2	15.8	12.5
EM-EVENT2	13.6	10.4	11.4	9.2

Note: The error is assessed for the mean/median/EM non-invasive fetal ECG QT against mean/median/EM FSE QT approaches for fusing the annotations. RMSE95 and AE95: RMSE and AE when removing the 5% extreme values. All values are expressed in ms. The lowest AE is underlined and also corresponds to the lowest RMSE.

do not see any significant reason to believe the signal processing of our FECG would lead to significant distortions, since we have shown in earlier work that low frequency components of the FECG are not distorted by our extraction process (Clifford *et al* 2011). However, definitely proving this remains a topic for future studies with a significant prevalence of fetuses with short or long QT intervals.

Our annotators, who were blinded to the source of the waveform they were annotating, generated QT intervals with excellent correlation between abdominal data and corresponding FSE signal when averaged waveforms were used. In contrast, when individual waveforms were annotated, the distortion inherent to the waveforms led the annotators to generally identify shorter QT intervals when annotating the abdominal signals than the FSE signals (see figure 3). These findings, suggest that the most accurate approach to fetal QT annotation will be to use a waveform created from a running average of several heartbeats. This was confirmed by the quantitative analysis presented in tables 1 and 2 where the results for the experiment on SET2 were consistently better. Combining the annotations from the three electrophysiologists resulted in a lowering of the RMSE (from 18.3 ms to 13.6 ms, SET2) and AE (14.8 ms to 10.4 ms, SET2) compared to using any individual annotator. This is in accordance with the finding of Zhu *et al* (2014) for adult QT annotation aggregation. In the case of the experiment on SET2 the expectation maximization algorithm gave the best results.

The magnitude of the fetal QT estimation error obtained in this study (17.9 ms RMSE for SET1 and 13.6 ms RMSE for SET2) compare to the RMSE obtained when combining QT

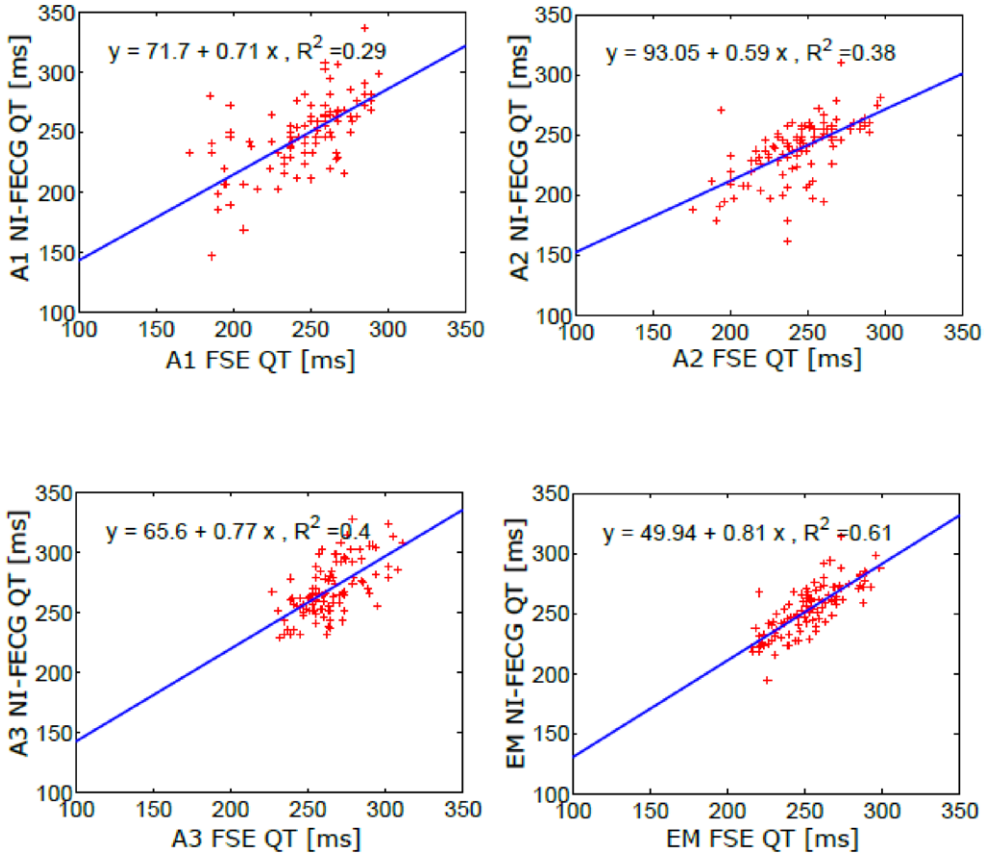

Figure 5. Plot of QT annotations from the extracted NI-FECG obtained using the NI-FECG monitor (denoted NI-FECG QT) against QT annotations from the FSE signal (denoted FSE QT), 22 fetuses (105, 1 min segments). A: annotator. (e.g. A1 NI-FECG QT refers to the QT annotated by annotator one on the NI-FEGC output from by the Meridian monitor). EM: crowd sourced annotations from the three clinicians using the EM algorithm (e.g. EM FSE QT refers to the scalp QT annotations merged using the EM algorithm). Line fit is given by: $y =$ intercept $+$ gradient x, R^2 is the corresponding coefficient of determination (goodness of fit).

annotations from three annotators on adult ECG (RMSE of 16.07 ms found previously) (Zhu *et al* 2014).

A number of published studies have attempted to extract the fetal QT (and other ECG morphology based quantities) from the NI-FECG or fetal magnetocardiography (Brambati and Pardi 1980, Abboud *et al* 1990, Stinstra *et al* 2002, Taylor *et al* 2005). However, these studies did not validate their measurements with invasive data and thus they did not prove that the algorithms that they used for NI-FECG extraction did not distort the QT length, for example, through the distortion of the *T*-wave by heavy preprocessing of the abdominal data or by moving to the source domain using a blind source separation algorithm (Andreotti *et al* 2016).

Stinstra *et al* (2002) used fetal magnetocardiography (MFCG) recordings from 582 healthy patients at different stages of the pregnancy (gestational age 17–41 weeks) and manually annotated the PR, PQ, QRS and QT intervals, averaging over 100 cardiac cycles per recording.

The QT length was found to be in the interval [149–339] ms ($n = 412$, 16–42 weeks of gestation), but the authors did not have FSE data to validate their measurements. Brambati and Pardi (1980), used NI-FECG to record 421 pregnant women (17–41 weeks) performed a similar set of measurements, averaging 50 cardiac cycles per measurement, again without simultaneous measurement of invasive FECG data. Two other papers performed similar analyses and found the QT to range from 207–338 ms ($n = 21$, 32–41 weeks of gestation) (Abboud *et al* 1990) and 233–329 ms ($n = 11$, 24–41 weeks of gestation) (Taylor *et al* 2005). Although these studies did not validate their measurements with invasive data, the ranges found were similar to the ranges obtained in this paper (see figure 3).

It bears mentioning, however, that there is no gold standard for the fetal QT interval, given the inability to adhere standard electrodes to the fetal precordium. Validation using the FSE is a reasonable approach, however it would be useful to validate the fetal QT interval with ECG data measured immediately after birth. Such data would also provide information on whether the QT interval changes at delivery. Despite the fact that one of the principal advantages of the NI-FECG is its ability to perform antenatal monitoring, the study focused on measurements performed at birth. This is because this is the only alternative for obtaining a QT reference by using the FSE (other than using magnetocardiography, which is expensive and would prohibit the use of the NI-FECG monitor). However, it is important to mention that the accuracy in estimating the FQT from the NI-FECG will likely be lower if the gestational age was significantly lower, since the fetal heart would be smaller and the NI-FECG signal to noise ratio may therefore be lower.

Since the extraction and study of morphological parameters from the NI-FECG is a nascent field, it is difficult to say whether the error reported in this study is low enough to be considered acceptable for fetal QT monitoring. However, it is less than that quoted for adult ECG studies and thus demonstrates a promising application. In addition, it is important to note that recent attempts at estimating fetal QT automatically have provided a root mean square error of over 152 ms, which indicates that our approach provides significant improvements (an order of magnitude reduction in errors) (Silva *et al* 2013, Clifford *et al* 2014).

Similar to prior studies (Silva *et al* 2013), we determined that the QT interval can be most accurately measured by averaging a series of cardiac cycles. Averaging allows the production of quality ECG average cycles by reducing the signal to noise ratio by up to a factor $\sqrt{N}$ (where N is the number of cycles averaged) under certain hypotheses (Rompelman and Ros 1986a, 1986b). However this raises the question of how much `averaging' should be allowed given that the ECG is a non-stationary signal. This question needs further investigation, together with the number of annotators and their associated skill levels needed to create an exact QT estimate (Zhu *et al* 2014).

Despite its relatively small sample size, our study is unique in that we validated the non-invasive fetal ECG QT measurement for each subject against invasive data that is largely absent of potential artifact or error due to the automated extraction process, which is scientifically repeatable. In addition we presented a rigorous protocol for obtaining the fetal QT measurements using an online annotation interface designed by our group and by combining the medical annotations from three expert cardiologists.

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