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Detection of T-wave Alternans in Fetal Magnetocardiography Using the Generalized Likelihood Ratio Test

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Abstract

T-wave alternans (TWA) is an indicator of cardiac instability and is associated with life-threatening ventricular arrhythmias. Detection of TWA in the adult has been widely investigated and is used routinely for cardiac risk assessment. Detection of TWA in the fetus, however, is much more difficult due to the low amplitude and variable configuration of the signal, the presence of strong interferences, and the brevity of fetal TWA episodes. In this paper we present a statistical detector based on the generalized likelihood ratio test that is designed for detection of TWA in the fetus. The performance of the detector is evaluated by constructing receiver-operator characteristic curves, using simulated data and real data from subjects with macroscopic TWA. The detector is capable of detecting TWA episodes as brief as 20 beats. The detection performance is improved significantly by modeling the fetal T-wave as a low rank, low bandwidth signal, and using maximum likelihood estimation to estimate the model parameters. This approach enables all of the data to be used to estimate the noise statistics, providing highly effective suppression of interference, including maternal interference. The method is suitable for routine use because it can be applied to raw, unprocessed recordings, allowing automated analysis of extended fetal magnetocardiography recordings.

Keywords

T-wave alternans; long QT syndrome; repolarization abnormalities; fetal magnetocardiography; maximum likelihood estimation; generalized likelihood ratio

I. Introduction

ABNORMAL cardiac repolarization, which manifests as T-wave abnormalities on the electrocardiogram and magnetocardiogram, is strongly associated with channelopathies, cardiomyopathies, and sudden death at all ages [1], [2], [3], [4]. T-wave abnormalities can take on a number of different forms, such as QTc prolongation, ST segment depression or elevation, T-wave axis deviations, and T-wave alternans (TWA). While several of these abnormalities are markers of serious cardiovascular disease, TWA has received considerable

recent attention due to its association with sudden cardiac death. Currently, there is an urgent need for improved, noninvasive methods of predicting sudden cardiac death, following the publication of two large clinical trials that greatly expanded the indications for implantable cardiac defibrillators [5] [6].

TWA is an alternation in T-wave amplitude or morphology, often occurring in a beat-to-beat, or ABAB, pattern. The degree of TWA can vary widely. In extreme cases, TWA is among the most striking of all ECG patterns, exhibiting a dramatic reversal of T-wave polarity in alternating beats. Such forms of visually apparent, or macroscopic, TWA are an indicator of severe cardiac instability, but even low levels of TWA are clinically significant [7]. Using computer methods, it is possible to detect very low amplitude TWA conforming to an ABAB pattern, known as microvolt TWA (MTWA). Over the last decade, detection of MTWA has developed into a routine procedure for cardiac risk assessment [8].

A number of detection methods have been devised to detect MTWA in the adult ECG, and their methodological principles have been reviewed by Martinez and Olmos [9]. The two most widely used methods of detecting MTWA are the spectral method of Cohen and coworkers [10], and the modified moving average method of Vernier and coworkers [11]. Although MTWA may be present at rest [12], the spectral method is applied to stress ECGs and the moving average method was developed for ambulatory monitoring. The spectral method detects the TWA component of the power spectrum, corresponding to a frequency of 0.5 cycles per beat, over a 128 beat segment of the recording. The modified moving average method detects TWA based on differences in the averaged waveforms of the odd-numbered and even-numbered beats, computed over 15 second time windows. A recent review of clinical TWA studies has shown that the two methods generate approximately the same hazard ratios when applied to patients with low ejection fraction and/or hypertrophic cardiomyopathy [13].

Repolarization abnormalities have not been extensively studied in the fetus because the fetal ECG is difficult to record during pregnancy. Only in the last few years, owing to the increased utilization of fetal magnetocardiography (fMCG), have such studies been possible, but already there is strong evidence for the clinical significance of fetal TWA. In the setting of fetal long QT syndrome (LQTS), macroscopic TWA is clearly a critical finding due its association with torsade de pointes (TdP). Based on study of 13 LQTS fetuses, Cuneo and coworkers showed that QTc duration exceeding 580 ms was predictive of TWA, second-degree block, and TdP [14]. Three of the 4 subjects with TdP had macroscopic TWA. Zhao and coworkers demonstrated repolarization abnormalities [15] in fetuses with various forms of arrhythmia and congenital heart disease. Seven fetuses showed TWA. They had such suboptimal outcomes as in utero demise, hydrops, ventricular tachycardia, and neonatal pacing. These results corroborate that TWA is associated with cardiac instability in the fetus, as it is in the adult, and puts the fetus at increased risk of ventricular tachycardia. Detection of fetal TWA calls for an evaluation of family history for evidence of ion channelopathies, as well as testing and correction of maternal magnesium, calcium, and vitamin D levels. If fetal LQTS is suspected, drugs that prolong repolarization are contraindicated and vigilance for the onset of TdP and other arrhythmias should be increased. These measures can be life-saving because TdP, while highly lethal, can be effectively treated in utero using drug therapy [16],[17].

For several reasons, detection of TWA is much more difficult in the fetus than in the adult. First, TWA in the fetus occurs spontaneously and is highly variable in duration and frequency of occurrence. Although it may be present continually in severe cases, most often it is transient, appearing in episodes as brief as 10 seconds or less. In the adult, TWA may be present at rest [12], but during clinical testing it is induced by increasing heart rate and,

when present, is relatively persistent and stationary. Second, the fMCG suffers from low signal amplitude, variable configuration, and strong interferences, which confound TWA detection. The signal amplitude and configuration depend strongly on fetal lie, which can differ substantially between subjects. In addition, the recordings are contaminated by interference from various environmental and biological sources. The most important of these is interference from the maternal MCG, which closely resembles the fMCG but typically shows higher amplitude and lower heart rate. These difficulties, which are minimal or absent for detection of TWA in adults, can be partly overcome through the use of large sensor arrays, which are able to characterize the covariance of the signal and interference. This underscores the need for a detection method specific to fMCG, which is able to fully exploit the spatial and temporal information available in the recordings.

The goal of this study is to develop a statistical detector for the challenging task of detecting TWA in the fetus. In section II we motivate and describe the use of the generalized likelihood ratio test (GLRT) for this application. In addition, we present a low-rank, low bandwidth model of the fMCG, which is subsequently shown to improve estimation of the signal and the noise statistics required for implementation of the GLRT. In section III we summarize the results of several assessments of detector performance. Receiver operating characteristic (ROC) curves are used to evaluate the performance of the detector and the efficacy of the signal model when applied to simulated data and to real data from subjects with macroscopic TWA. The detector is then applied to data from at-risk subjects in whom ground truth is not known, in order to demonstrate practical use of the detector. In Section IV we identify key attributes of the method that make it well suited for fetal application. We also discuss the performance improvements that result from use of the low-rank, low bandwidth signal model in conjunction with maximum likelihood estimation. Our notation uses lowercase and bold uppercase symbols to denote vectors and matrices, respectively. Superscripts T and -1 denotes matrix transpose and inverse, respectively.

II. Methods

The problem of detecting TWA in the fetus is a composite hypothesis test since parameters such as the T-wave shape are unknown. Optimal procedures generally do not exist for composite hypothesis tests [18], so we used the generalized likelihood ratio test (GLRT). Martinez and coworkers have previously applied the GLRT to TWA detection in adults [19], [20]. The GLRT performs detection using a likelihood ratio in which unknown parameters are replaced by their maximum likelihood estimates (MLE). The asymptotic or large data record performance of the GLRT is known [18]. MLE has been applied to estimation of evoked responses in electro- and magneto-encephalography (EEG / MEG) [21], [22]. In particular, we have previously shown that MLE is effective at estimating spatially low rank, low bandwidth, repeated MEG signals [23]. Our approach is motivated by this experience and the fact that the signal and noise characteristics of T-waves and evoked brain signals are very similar.

A. TWA identification method based on the generalized likelihood ratio test

Assume there are M spatial channels and N time samples, and a total of $2J$ data epochs, where each epoch corresponds to one beat. The data for the j^{th} epoch is represented by the M by N matrix $\mathbf{X}_j = \mathbf{S}_j + \mathbf{N}_j$, where $\mathbf{S}_j$ is the $M \times N$ matrix of signal (T-wave) samples and $\mathbf{N}_j$ is the $M \times N$ matrix of noise samples in the j^{th} epoch. The noise is assumed to be temporally white (independent from sample to sample) and Gaussian distributed with unknown spatial covariance matrix. The m^{th} row of $\mathbf{X}_j$ corresponds to the signal recorded in the m^{th} channel. The T wave is assumed to have limited bandwidth and lie in a low-dimensional spatial

subspace, so the signal matrix for an arbitrary epoch is approximated using the representation [23]

$$\mathbf{S} = \mathbf{H}\mathbf{\Theta}\mathbf{C}^T \quad (1)$$

where $\mathbf{H}$ is an unknown $M \times P$ matrix whose columns are a basis for the P -dimensional spatial subspace spanning the columns of the signal matrix $\mathbf{S}$, $\mathbf{C}$ is a known $N \times L$ matrix whose columns are a basis for the L dimensional temporal subspace spanning the rows of $\mathbf{S}$, and $\mathbf{\Theta}$ is a $P \times L$ unknown signal amplitude matrix. We assume $\mathbf{C}$ is determined based on the assumed bandwidth of the T waves following the procedure described in the appendix of [23]. $\mathbf{H}$ and $\mathbf{\Theta}$ are estimated from the data.

The signal (T-wave) alternates shape between even and odd beats in the presence of TWA. We denote $\mathbf{S}^o = \mathbf{H}^o\mathbf{\Theta}^o\mathbf{C}^T$ as the signal for the odd beats and $\mathbf{S}^e = \mathbf{H}^e\mathbf{\Theta}^e\mathbf{C}^T$ as the signal for the even beats. These definitions assume the spatial ($\mathbf{H}$) and temporal ($\mathbf{\Theta}$) shapes of the T wave may change between beats, while the bandwidth of the T wave, and thus $\mathbf{C}$, remains constant. Let $\mathbf{X}^o = [\mathbf{X}_1 \ \mathbf{X}_3 \dots \mathbf{X}_{2J-1}]$ and $\mathbf{X}^e = [\mathbf{X}_2 \ \mathbf{X}_4 \dots \mathbf{X}_{2J}]$ be data matrices formed from the even and odd epochs, respectively, and define the complete collection of $2J$ epochs of data as

$$\mathbf{X} = [\mathbf{X}^o \ \mathbf{X}^e] \quad (2)$$

Hence, we have

$$\mathbf{X}^o = [\mathbf{S}^o \ \mathbf{S}^o \ \dots \ \mathbf{S}^o] + [\mathbf{N}_1 \ \mathbf{N}_3 \ \dots \ \mathbf{N}_{2J-1}] \quad (3)$$

$$\mathbf{X}^e = [\mathbf{S}^e \ \mathbf{S}^e \ \dots \ \mathbf{S}^e] + [\mathbf{N}_2 \ \mathbf{N}_4 \ \dots \ \mathbf{N}_{2J}] \quad (4)$$

The hypothesis test for detecting TWA is to decide whether $H_0 : \mathbf{S}^o = \mathbf{S}^e$ or $H_1 : \mathbf{S}^o \neq \mathbf{S}^e$. The GLRT for these hypotheses is expressed as

$$\frac{p_{H_1}(\mathbf{X}; \widehat{\mathbf{H}}^o, \widehat{\mathbf{\Theta}}^o, \widehat{\mathbf{H}}^e, \widehat{\mathbf{\Theta}}^e)}{p_{H_0}(\mathbf{X}; \widehat{\mathbf{H}}, \widehat{\mathbf{\Theta}})} > t \quad (5)$$

where $p(\cdot)$ denotes the probability density function (PDF) of the data and $\widehat{\mathbf{H}}^o, \widehat{\mathbf{\Theta}}^o, \widehat{\mathbf{H}}^e, \widehat{\mathbf{\Theta}}^e, \widehat{\mathbf{H}}$ and $\widehat{\mathbf{\Theta}}$ are the MLEs of $\mathbf{H}^o, \mathbf{\Theta}^o, \mathbf{H}^e, \mathbf{\Theta}^e, \mathbf{H}$ and $\mathbf{\Theta}$ under the corresponding PDFs, respectively. The numerator is the PDF of the data when H_1 is assumed true ($\mathbf{H}^o \neq \mathbf{H}^e, \mathbf{\Theta}^o \neq \mathbf{\Theta}^e$) while the denominator is the PDF when H_0 is assumed true ($\mathbf{H}^o = \mathbf{H}^e = \mathbf{H}, \mathbf{\Theta}^o = \mathbf{\Theta}^e = \mathbf{\Theta}$). Hence, we decide H_1 if the ratio of PDFs is greater than the threshold t .

The PDF of the data under hypothesis H_0 is expressed as

$$p_{H_0}(\mathbf{X}; \mathbf{R}_0, \mathbf{H}, \mathbf{\Theta}) = (2\pi)^{-MNJ} (\det \mathbf{R}_0)^{-NJ} \exp \left\{ -\frac{1}{2} \text{tr} \left(\mathbf{R}_0^{-1} (\mathbf{X} - \mathbf{H}\mathbf{\Theta}\mathbf{D}_0^T) (\mathbf{X} - \mathbf{H}\mathbf{\Theta}\mathbf{D}_0^T)^T \right) \right\} \quad (6)$$

where $\mathbf{D}_0^T = [\mathbf{C}^T \ \mathbf{C}^T \dots \mathbf{C}^T]$ is an L by $2JN$ matrix representing the temporal bases concatenated across all epochs and $\mathbf{R}_0$, the spatial covariance matrix of the noise, is unknown. The MLEs for the unknown noise covariance and T-wave parameters are well-known under H_0 [21], [22], [23], [24]. The MLE for $\mathbf{R}_0$ is expressed as a function of the unknown $\widehat{\mathbf{H}}$ and $\widehat{\mathbf{\Theta}}$

$$\widehat{\mathbf{R}}_0 = \frac{1}{2NJ} \left\{ \sum_{i=1}^{2J} \left((\mathbf{x}_i - \widehat{\mathbf{H}}\widehat{\Theta}\mathbf{C}^T)(\mathbf{x}_i - \widehat{\mathbf{H}}\widehat{\Theta}\mathbf{C}^T)^T \right) \right\} \quad (7)$$

Substitution of $\widehat{\mathbf{R}}_0$ into the PDF reveals that the MLEs $\widehat{\mathbf{H}}$ and $\widehat{\Theta}$ are obtained by minimizing the determinant of the $\widehat{\mathbf{R}}_0$. Define $\bar{\mathbf{D}}_0$ as an orthonormal set of vectors spanning the null space of $\mathbf{D}_0$ and let $\mathbf{X}_{\bar{\mathbf{D}}_0} = \mathbf{X}\mathbf{D}_0(\mathbf{D}_0^T\mathbf{D}_0)^{-1/2}$, $\mathbf{X}_{\bar{\mathbf{D}}_0} = \mathbf{X}\bar{\mathbf{D}}_0$, and $\mathbf{Q}_{\bar{\mathbf{D}}_0} = \mathbf{X}_{\bar{\mathbf{D}}_0} \mathbf{X}_{\bar{\mathbf{D}}_0}^T$. Following [23], the product $\widehat{\mathbf{H}}\widehat{\Theta}$ is given by

$$\widehat{\mathbf{H}}\widehat{\Theta} = \mathbf{Q}_{\bar{\mathbf{D}}_0}^{1/2} \tilde{\mathbf{H}} \tilde{\mathbf{H}}^T \mathbf{Q}_{\bar{\mathbf{D}}_0}^{-1/2} \mathbf{X}_{\bar{\mathbf{D}}_0} (\mathbf{D}_0^T \mathbf{D}_0)^{-1/2} \quad (8)$$

where $\tilde{\mathbf{H}}$ is given by the P eigenvectors of $\mathbf{Q}_{\bar{\mathbf{D}}_0}^{-1/2} \mathbf{X}_{\bar{\mathbf{D}}_0} \left(\mathbf{I} + \mathbf{X}_{\bar{\mathbf{D}}_0}^T \mathbf{Q}_{\bar{\mathbf{D}}_0}^{-1} \mathbf{X}_{\bar{\mathbf{D}}_0} \right)^{-1} \mathbf{X}_{\bar{\mathbf{D}}_0}^T \mathbf{Q}_{\bar{\mathbf{D}}_0}^{-1/2}$ corresponding to the P largest eigenvalues.

The respective PDFs under hypothesis H_1 may be written

$$p_{H_1}(\mathbf{X}; \widehat{\mathbf{H}}^o, \widehat{\Theta}^o, \widehat{\mathbf{H}}^e, \widehat{\Theta}^e) = p_o(\mathbf{X}^o; \mathbf{R}_1, \mathbf{H}^o, \Theta^o) p_e(\mathbf{X}^e; \mathbf{R}_1, \mathbf{H}^e, \Theta^e) \quad (9)$$

with

$$p_{o,e}(\mathbf{X}^{o,e}; \mathbf{R}_1, \mathbf{H}^{o,e}, \Theta^{o,e}) = (2\pi)^{-\frac{MN}{2}} (\det \mathbf{R}_1)^{-\frac{NJ}{2}} \exp \left\{ -\frac{1}{2} \text{tr} \left(\mathbf{R}_1^{-1} (\mathbf{X}^{o,e} - \mathbf{H}^{o,e} \Theta^{o,e} \mathbf{D}_1^T) (\mathbf{X}^{o,e} - \mathbf{H}^{o,e} \Theta^{o,e} \mathbf{D}_1^T)^T \right) \right\} \quad (10)$$

The superscripts o, e refer to the odd and even beats, respectively, as the same equation applies to both cases. $\mathbf{D}_1^T = [\mathbf{C}^T \quad \mathbf{C}^T \cdots \mathbf{C}^T]$ is an L by JN matrix representing the temporal bases across the odd or even epochs. This formulation assumes samples of the noise are identically distributed in even and odd epochs. The MLE of the noise covariance matrix is given as a function of the unknown $\widehat{\mathbf{H}}^o, \widehat{\mathbf{H}}^e, \widehat{\Theta}^o$, and $\widehat{\Theta}^e$ as

$$\widehat{\mathbf{R}}_1 = \frac{1}{2NJ} \left\{ \sum_{i=\text{odd}}^{2J-1} (\mathbf{x}_i - \widehat{\mathbf{H}}^o \widehat{\Theta}^o \mathbf{C}^T)(\mathbf{x}_i - \widehat{\mathbf{H}}^o \widehat{\Theta}^o \mathbf{C}^T)^T + \sum_{i=\text{even}}^{2J} (\mathbf{x}_i - \widehat{\mathbf{H}}^e \widehat{\Theta}^e \mathbf{C}^T)(\mathbf{x}_i - \widehat{\mathbf{H}}^e \widehat{\Theta}^e \mathbf{C}^T)^T \right\} \quad (11)$$

Similarly to the hypothesis H_0 case, the MLEs $\widehat{\mathbf{H}}^o, \widehat{\Theta}^o, \widehat{\mathbf{H}}^e$ and $\widehat{\Theta}^e$ are obtained by minimizing the determinant of $\widehat{\mathbf{R}}_1$. This minimization is equivalent to

$$\underset{\tilde{\Theta}^o, \mathbf{H}^o, \tilde{\Theta}^e, \mathbf{H}^e}{\text{minimize}} \left| \mathbf{Q}_{\bar{\mathbf{D}}_1} + (\mathbf{X}_{\bar{\mathbf{D}}_1}^o - \mathbf{H}^o \tilde{\Theta}^o) (\mathbf{X}_{\bar{\mathbf{D}}_1}^o - \mathbf{H}^o \tilde{\Theta}^o)^T + (\mathbf{X}_{\bar{\mathbf{D}}_1}^e - \mathbf{H}^e \tilde{\Theta}^e) (\mathbf{X}_{\bar{\mathbf{D}}_1}^e - \mathbf{H}^e \tilde{\Theta}^e)^T \right| \quad (12)$$

where we define $\bar{\mathbf{D}}_1$ as a matrix whose columns are an orthonormal basis spanning the null space of $\mathbf{D}_1$, and

$$\mathbf{X}_{\mathbf{D}_1}^o = \mathbf{X}^o \bar{\mathbf{D}}_1, \mathbf{X}_{\mathbf{D}_1}^e = \mathbf{X}^e \bar{\mathbf{D}}_1 \quad (13)$$

$$\mathbf{Q}_{\mathbf{D}_1} = \mathbf{X}_{\mathbf{D}_1}^o \mathbf{X}_{\mathbf{D}_1}^{oT} + \mathbf{X}_{\mathbf{D}_1}^e \mathbf{X}_{\mathbf{D}_1}^{eT} \quad (14)$$

$$\tilde{\Theta}^o = \Theta^o (\mathbf{D}_1^T \mathbf{D}_1)^{1/2}, \tilde{\Theta}^e = \Theta^e (\mathbf{D}_1^T \mathbf{D}_1)^{1/2} \quad (15)$$

It can be shown that separate minimization of the even and odd epoch components of (12) results in the minimization of the whole term. Therefore, the MLEs of $\mathbf{H}^o \Theta^o$, and $\mathbf{H}^e \Theta^e$ can be obtained similarly to the H_0 case. That is,

$$\widehat{\mathbf{H}}^{o,e} \widehat{\Theta}^{o,e} = \mathbf{Q}_{\mathbf{D}_1}^{1/2} \tilde{\mathbf{H}}^{o,e} \tilde{\mathbf{H}}^{o,eT} \mathbf{Q}_{\mathbf{D}_1}^{-1/2} \mathbf{X}_{\mathbf{D}_1}^{o,e} (\mathbf{D}_1^T \mathbf{D}_1)^{-1/2} \quad (16)$$

where $\tilde{\mathbf{H}}^{o,e}$ is given by the P eigenvectors corresponding to the P largest eigenvalues of

$$\mathbf{Q}_{\mathbf{D}_1}^{-1/2} \mathbf{X}_{\mathbf{D}_1}^{o,e} \left(\mathbf{I} + \mathbf{X}_{\mathbf{D}_1}^{o,eT} \mathbf{Q}_{\mathbf{D}_1}^{-1} \mathbf{X}_{\mathbf{D}_1}^{o,e} \right)^{-1} \mathbf{X}_{\mathbf{D}_1}^{o,eT} \mathbf{Q}_{\mathbf{D}_1}^{-1/2}.$$

Substituting the sample covariance matrix estimates into the exponential in each probability density function in (5) results in the exponential terms being independent of the data, and the GLRT is expressed as :

$$H_1: \frac{|\widehat{\mathbf{R}}_0|}{|\widehat{\mathbf{R}}_1|} > t \quad (17)$$

The GLRT derived above assumes a low rank spatio-temporal structure for the T waves. A simpler, more general model is to assume the T wave has no temporal and spatial structure, but instead is represented by an arbitrary rank unstructured matrix $\mathbf{S}$. In this case the MLE of $\mathbf{S}$ is given by the sample average from the respective set of epochs, denoted as $\mathbf{S}_{avg}$, $\mathbf{S}_{avg}^o$, $\mathbf{S}_{avg}^e$, respectively. The corresponding GLRT decides H_1 if

$$\frac{p_{H_1}(\mathbf{X}; \mathbf{S}_{avg}^o, \mathbf{S}_{avg}^e, \widehat{\mathbf{R}}_1)}{p_{H_0}(\mathbf{X}; \mathbf{S}_{avg}, \widehat{\mathbf{R}}_0)} > r \quad (18)$$

Similarly to the structured T wave case, the GLRT test statistic becomes $|\widehat{\mathbf{R}}_0| / |\widehat{\mathbf{R}}_1|$, with

$$\widehat{\mathbf{R}}_1 = \frac{1}{2NJ} \left\{ \sum_{i=odd}^{2J-1} (\mathbf{X}_i - \mathbf{S}_{avg}^o)(\mathbf{X}_i - \mathbf{S}_{avg}^o)^T + \sum_{i=even}^{2J} (\mathbf{X}_i - \mathbf{S}_{avg}^e)(\mathbf{X}_i - \mathbf{S}_{avg}^e)^T \right\} \quad (19)$$

$$\widehat{\mathbf{R}}_0 = \frac{1}{2NJ} \left\{ \sum_{i=1}^{2J} (\mathbf{X}_i - \mathbf{S}_{avg})(\mathbf{X}_i - \mathbf{S}_{avg})^T \right\} \quad (20)$$

where

$$\mathbf{S}_{avg} = \frac{1}{2J} \sum_{i=1}^{2J} \mathbf{x}_i, \mathbf{S}_{avg}^o = \frac{1}{J} \sum_{i=odd}^{2J-1} \mathbf{x}_i, \mathbf{S}_{avg}^e = \frac{1}{J} \sum_{i=even}^{2J} \mathbf{x}_i \quad (21)$$

The performance of the structured and unstructured T wave detectors is compared in the Results section.

We demonstrate the effectiveness of the detector using both synthetic and real fMCG data. The data is digitized at 520.8 Hz after analog filtering with a passband of 0.1-200 Hz. The performance of the detectors is evaluated by ROC curves. An ROC curve plots true positive rate (sensitivity) vs. false positive rate (1-specificity), where sensitivity is the probability that the test is positive for a patient who truly has the disease (TWA), and specificity is the probability that the test result is negative for a patient who truly does not have TWA.

B. Synthetic data

We generate synthetic data assuming the sensor configuration of the 37-channel superconducting quantum interference (SQUID) magnetometer (Magnes, 4D Neuroimaging, Inc., San Diego, CA) in our lab in order to facilitate the comparison between the simulated and real data. The synthetic data was obtained by superimposing a repeated, high SNR T-wave on a background of realistic noise. The T-wave signal was obtained from a high-SNR averaged fMCG waveform, taken from a fetal LQTS patient at 34 weeks' gestation. The noise was from a normal pregnant patient at 11 6/7 weeks' gestation; which contained only environment noise and maternal interference. TWA is simulated by varying the amplitude of even/odd beats. Since the duration of TWA can be short as 10 seconds, we choose $2J = 20$ beats of data for each TWA case. We generated 200 TWA cases and 200 cases with identical even and odd beat T-waves, which were used as a control to evaluate the probability of false detection. The fMCG signal is commonly modeled as an equivalent current dipole. In this model, the spatial matrix $\mathbf{H}$ is rank $P = 2$. In a typical fMCG signal, the T-wave has the majority of its energy in the frequency band 0-20 Hz. We chose the temporal bases ($\mathbf{C}$) to model this frequency range as described in [23].

We also examine the detector performance as a function of the TWA SNR when sensitivity or specificity is fixed. If the false positive rate is fixed, the true positive rate will be low when SNR is low, and will increase as SNR increases. Our goal is to identify the SNR required for reliable detection at clinically acceptable false positive rates. We simulated multiple SNRs by fixing the odd beats, and varying the amplitude of even beats. This has the effect of varying the size of the change between even and odd beats and consequently varies the signal component of the SNR.

Variation of the signal amplitude is common in real data. For example, maternal breathing movements typically produce a 10-20% variation in fetal signal amplitude. Consequently, we also assessed the influence of variance in the even and odd beat T-wave amplitudes. We chose an SNR of 0.158, which corresponds to a 50% amplitude difference between the mean even and mean odd epochs in the TWA data. Typically, the signal variance is proportional to the mean signal. Thus, we introduced variance into the amplitudes by setting the standard deviation of the amplitudes for the even and odd beats equal to 20% and 40% of their means.

C. Real data

We retrospectively reviewed the data from 11 patients with confirmed LQTS. Subjects with LQTS typically have large T-waves, and macroscopic TWA can often be identified visually.

Four of the eleven LQTS patients were found to have intermittent macroscopic TWA. Figure 1 shows examples of fMCG tracings during TWA. For visual clarity, maternal interference was removed from the recordings depicted in Fig. 1 using the method described in [25]. The data from these four patients is assumed to be positive for TWA when constructing ROC curves. Data from normal control patients is assumed to be negative for TWA. The input data for the detectors is the raw fMCG recording, which includes noise and maternal interference. The T-wave is assumed to be located within the interval from the end of the QRS complex to the beginning of the next P-wave. The data was inspected to exclude artifacts and verify that the TWA subjects follow an ABAB pattern for at least 10 beats. This criterion yielded 101 episodes of TWA. Another 261 20-beat segments were selected from six normal patients. For the structured model, we assume the same spatial rank $P = 2$ and temporal frequency band 0-20 Hz as in the simulations.

For the other seven LQT patients without identified macroscopic TWA, we applied the detector to investigate possibility of MTWA in these patients. Ten minutes of raw fMCG recordings from each patient was examined. After artifact rejection we had total of 322 20-beat segments. Since we don't know the ground truth of MTWA in these patients, it is not possible to compute ROC curves for this data. Therefore, we choose three false positive ratios, 5%, 3%, and 1% in the control population. With detection thresholds obtained the known macroscopic TWA patients, we compare the detection rate of TWA in these four patients with those in the control population.

III. Results

A. Synthetic data

Figure 2 shows ROC for the two models when there is 40% amplitude difference between the even and odd beats in TWA. We chose to define the SNR for detection of TWA as $\|S^e - S^o\| / \text{RMS}$, where $\|\cdot\|$ is the L2 norm and RMS denotes the root mean square of the noise summed across all channels. This definition measures the difference between even and odd T waves summed across all channels and time samples relative to the noise. The SNR is 0.127 in Fig. 2. The results show that the structured detector (5) performs much better than the non-structured detector (18).

Figure 3 displays the true positive rates as a function of varying SNR when the false positive rate was fixed at 3% in each simulation. The results shows that the true positive increases as SNR increases.

Figure 4 shows that the introduction of amplitude variation with 20% standard deviation results in a slight loss of detectability for true positive rates exceeding 0.9 in the low rank detector. The degradation is greater in the presence of 40% standard deviation amplitude variation, but the low rank detector with 40% variation significantly outperforms the unstructured detector with no amplitude variation.

B. Application to real data

Figure 5 shows that the performance is clearly better for the low spatio-temporal rank model than for the unstructured model.

The performance of rank 1, 2, 3, and 8 structured models was compared in the structured model to confirm the validity of the low rank approximation. Figure 6 shows that the rank 1 model clearly gives inferior results. The performance of rank 2, 3, and 8 models is similar.

We also investigated the effect of using different frequency bands in the structured model with recorded patient data. Figure 7 compares the rank 2 signal model detection

performance for frequency bands $0 \leq f \leq 5$; $0 \leq f \leq 10$; $0 \leq f \leq 20$; $0 \leq f \leq 40$; $4 \leq f \leq 20$, and $8 \leq f \leq 20$ Hz. The detector performs similarly when the frequency band is chosen to be $0 \leq f \leq 5$; $0 \leq f \leq 10$; $0 \leq f \leq 20$, and $0 \leq f \leq 40$ Hz, but degrades markedly when low frequencies are excluded. The results indicate that the low frequency signal components are critical to detection performance.

For the other seven LQT patients without identified macroscopic TWA, the structured model with rank 2 and frequency band $0 \leq f \leq 20$ Hz was applied to a total of 322 20-beat segments. The detection thresholds of the three false positive ratios, 5%, 3%, and 1% in the control population were obtained from the ROC curve in Fig. 5, which was generated from the four known macroscopic TWA patients. TWA is detected in 9.3%, 7.8%, and 6.2%, respectively, of the segments in the other seven LQTS patients. Figure 8 shows one example of MTWA detection. The top panel is a 10 sec rhythm strip of raw and processed fetal signals from one of the 37 channels. It is difficult to visually detect TWA in the raw tracings of individual channel due to the presence of maternal interference and noise, yet the MLE of the T-waves with the structured model shows a clear difference between even and odd beats.

IV. Discussion

In this study we developed and evaluated a new statistical detector for the detection of TWA in the fetus. In addition to its excellent performance, several attributes of the detector make it well suited for fetal application. First, it is capable of detecting brief episodes of TWA, which are common in the fetus. We are able to accurately detect TWA in epochs comprised of just 20 beats, equivalent to about 10 seconds in duration. Second, it is remarkably immune to interference, including maternal interference. Maternal T-wave interference is especially problematic due to its large amplitude and its ability to mimic fetal TWA. The maternal T-wave has morphology similar to that of the fetal T-wave and commonly occurs at a rate approximately half that of the fetal T-wave.

A major difference between our methods and those of Martinez and coworkers [19], [20], who also used the GLRT, is that we model the fetal T-wave as a low rank, low bandwidth signal. This spatiotemporal model enables us to use the collective data from all channels to formulate a true multichannel detector, whereas the multi-lead methods proposed by Martinez and co-workers apply preprocessing and transformations to the original leads to isolate the TWA components, and then perform detection one at a time on the transformed leads. A further advantage of our approach is improved estimation of the noise statistics, i.e. sensor covariance, as discussed below. In combination with the spatiotemporal model, this significantly improves detection performance and provides a superior estimate of the T-waveform, compared to estimating the signal by averaging. The detector performs well for models with spatial rank as low as 2. This result is compatible with the expectation that the fMCG can be approximately modeled by a current-dipole since the size of the fetal heart is small compared to the source-to-sensor distance. For models with spatial rank of 2-8 the performance is similar, which suggests that the rank 2 model is capturing all of the useful information in the T wave. We also showed that the very low frequency signal components are the most important for detecting TWA. Detection performance suffers significantly if the model does not include signals extending down to 0.1 Hz. On the other hand, detection performance is notably insensitive to high frequency signals. In practice we typically include signals up to 20 Hz; however, performance is similar even if we includes frequencies only up to 5 Hz.

The GLRT uses maximum likelihood estimation to identify the unknown model parameters, including the noise covariance matrix. A major advantage of the maximum likelihood approach is that it does not require signal-free data to estimate the noise covariance. This

is important because the fMCG is signal-free only during the brief interval from the end of the T-wave to the beginning of the P-wave of the succeeding cardiac cycle. Thus, conventional whitening methods are restricted to using a small fraction of the data vectors to compute the noise covariance, while MLE is able to use all of them. For the brief data segments analyzed in our study it is unlikely that the noise covariance matrix could be accurately estimated using conventional methods. An additional advantage of estimating the noise from data containing the signal is that the whitening is more effective in suppressing nonstationary noise. Traditional whitening relies on an assumption that the noise statistics during the signal-free segments of the recording are the same as those during segments of the recording containing signal. This is relevant to fMCG because the dominant interference, the maternal MCG, is nonstationary.

Detector performance was validated using simulated TWA data and recordings of macroscopic TWA from LQTS subjects. Using simulated data in which the signal conformed exactly to the ABAB pattern, the detector accurately detects very low levels of TWA. In real data, however, the signal amplitude exhibits random variation from beat to beat, which confounds TWA detection. This can be due to a number of causes, such as cycle length changes or axis changes; however, the largest variations are associated with fetal and maternal breathing and body movements. When signal variance is incorporated into the simulation, detector performance degrades as expected. The macroscopic TWA data was used to assess detector performance for the various MLE models, using real data that incorporates the many nonideal characteristics of a real fMCG signal, such as maternal MCG interference, fetal and maternal movement artifact, environmental noise, signal variance, and TWA that does not exactly follow the ABAB pattern. The results corroborate that a low-rank, low bandwidth model is able to accurately represent the real signal and improve detector performance. Our method was then applied to data from LQTS subjects without macroscopic TWA. The detection rate of TWA is approximately five times greater for LQTS subjects than for normal subjects. It is not possible to compute ROC curves for this data because we don't know ground truth, but these results exemplify how our method may be used to detect low amplitude TWA in patients at risk of TWA. Further validation studies are needed in a larger population of at-risk patients.

Our detector addresses a critical need for an objective, automated method of detecting TWA in the fetus. fMCG recordings can be an hour in length, and there is no way to predict when TWA may occur. It is impractical to manually scan through all of the channels of the entire recording to search for TWA; thus an automated method is needed even for detection of macroscopic TWA. Our detector is also very convenient to use because it is applied to the raw data. It does not require the user to remove maternal interference or other artifact. It only requires detection of the fetal QRS complexes, but this is a simple and routine part of fMCG data analysis.

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Fig. 1.
Macroscopic TWA tracings from four confirmed LQTS patients.

Fig. 2. ROC curves obtained using synthetic data for structured rank 2 and unstructured models at SNR=0.127.

Fig. 3. True positive rate for the structured rank 2 and unstructured models as a function of SNR for 3% false positive rate using synthetic data.

Fig. 4.

ROC curves for different levels of variability in the even and odd beat amplitudes for structured rank 2 and unstructured signal models. The standard deviation of the variability introduced into the even and odd beats is expressed as a percentage of the even and odd beat amplitudes, respectively.

Fig. 5. ROC curves for rank 2 structured and unstructured models derived from actual patient recordings.

Fig. 6. ROC curves for the structured model and rank 1, 2, 3, and 8 signal models based on patient recordings.

Fig. 7.
ROC curves for the rank 2 spatial model with different assumed signal bandwidths.

Fig. 8.

a) Raw fMCG tracing for a segment detected to be positive for TWA, taken from the channel in which TWA is most prominent. F: fetal QRS, M:maternal QRS. b) The data shown in a) following removal of maternal interference. Arrows indicate the first odd and even beats c) MLE estimation of the odd epochs using a rank 2 signal model. d) MLE estimation of the even epochs using a rank 2 signal model. The bold line in c) and d) indicates the channel shown in a) and b)