A beat-by-beat analysis of electrocardiograms from cardiac transplant recipients


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ABSTRACT

A software system is described for producing a beat-by-beat analysis of the electrocardiograms from patients after heart transplantation. Pacemaker spikes are automatically detected and eliminated from the signals. R waves are located by a robust and accurate two-step algorithm. Based on the variable length of single heartbeats, the Fourier coefficients of three orthogonal surface leads and of two intracardiac leads are calculated beat-by-beat. Power spectra are then obtained by combining contributions from the variable fundamental frequency and its multiples (harmonics) into fixed frequency classes of 1 Hz width and averaging over 60–120 cardiac cycles. Additionally, averaged beat-by-beat power spectra are calculated for windowed QRS complexes and T waves. As by-products, single beat quantities, such as R–R and R–T intervals, averaged signals for all leads, and the orientational autocorrelation function of the electrical vector of the heart, are obtained. Following beat-by-beat evaluation, mean values and standard deviations are obtained for all quantities.

Keywords: Signal acquisition, signal analysis, cardiac transplantation, electrocardiogram, Fourier analysis

INTRODUCTION

Transvenous endomyocardial biopsy has until recently provided the only reliable means to detect episodes of acute graft rejection in cardiac transplant recipients. Since the procedure is invasive and inconvenient for the patient, numerous alternative diagnostic methods have been investigated, among others the analysis of the electrocardiogram (ECG)✓. In comparison with previous approaches, which in several respects fail to offer convincing reliability, our system introduces two new aspects:

- Intracardiac leads (A, B) are recorded together with surface leads.
- Fourier analysis is performed on the raw data of single heart beats, and spectra are averaged afterwards.

The beat-by-beat Fourier analysis necessitates the concept of frequency-locked spectral averaging as described below.

Signals from intracardiac leads are very sensitive to changes in catheter location, and hence do not lend themselves to consistent triggering. Even a trigger derived from conventional surface leads would shift within the cardiac cycle if, e.g. between successive follow-ups of a patient, the orientation of the electrical axis should change. We therefore decided to acquire an orthogonal vector ECG (Frank lead system), which would be triggered by the modulus \( R = (X^2 + Y^2 + Z^2)^{1/2} \) of the vector itself (R wave of the vector). The interval (representing a cardiac cycle) obtained in this way was then used as a basis for the analysis of all single lead signals.

SIGNAL ACQUISITION (Figure 1)

Analogue amplification and orthogonal decomposition of signals

ECG amplification was accomplished by five totally independent amplifier channels for bipolar leads. Three input channels were connected to an isolated, active Frank lead module in order to generate three orthogonal signal components from eight surface leads. Two bipolar inputs were connected to the intracardiac leads, derived between the electrodes 3–2 and 4–2 on a four-lead USCI catheter, whose tip was transmurally positioned close to the apex within the right ventricle. Electrode 1, which is likely to receive injury currents, remained unused.

Each amplifier channel was designed for wide bandwidth (~3 dB points: 0.5 and 1100 Hz) and low noise (10\( \mu V \) pp, multiplied by amplification of the channel). A selectable low-pass filter at 400 Hz was provided. The gain set at each module (100, 200, 500 and 1000 x) was automatically passed to the evaluation software. The IEC 601 CF guidelines were fulfilled concerning leakage currents through the

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the amplifier gains from the calibration signal (separately for each channel), rescaled data to millivolts (at the amplifier input), and wrote a separate direct access file of rescaled voltages to a RAM disk. A special technique was developed to access these data conveniently from FORTRAN (for details see the Appendix).

Detection of R waves using the ECG vector length

From each triplet \((X_i, Y_i, Z_i)\) of orthogonal signals, the length \(R_i\) of the vector was calculated, written to an additional direct access file, and considered to be a sixth data channel. R wave detection was then performed by a two-pass procedure (Figure 2).

Pass 1: Robust detection of QRS complexes. The time derivatives of the three orthogonal components

\[
\frac{d}{dt} X, \quad \frac{d}{dt} Y, \quad \frac{d}{dt} Z
\]

for each record \(i\) were calculated from the slopes of linear regression lines over \(N_d(=4\) ms) points. Derivatives were squared, added and summed over a window of \(N_E + 1\) successive data points to obtain an ‘energy collector’ at record \(k\):

\[
E_k = \frac{1}{N_E + 1} \sum_i \left[ \left( \frac{d}{dt} X \right)_i^2 + \left( \frac{d}{dt} Y \right)_i^2 + \left( \frac{d}{dt} Z \right)_i^2 \right]
\]

\(k \leq i \leq k + N_E\) (1)

\(N_E\) was chosen to span an 80 ms window at a given sampling rate. (Note that all lengths of windows are primarily specified in milliseconds, and the program automatically evaluated the number of points in the window according to sampling rate. In the following description we refer to ‘number of points’ for reasons of simplicity.) \(E_k\) was re-evaluated for successive values of \(k\) in a (first in/first out FIFO) ring buffer utilizing the method described in the Appendix.

First, a hysteresis \((E_{on} - E_{off})\) was constructed from the initial 5000 data points \([E_{on} = 0.7 \max(E_0), E_{off} = 0.7 \min(E_0)]\). Then the energy collector was re-evaluated for successive values of \(k\) until \(E_k > E_{on}\) (at record \(k_{on}\)). For \(k > k_{on}\), \(E_k\) was scanned for maximum until \(E_k\) declined below \(E_{off}\). The record \(k_{max}\), at which \(E_k\) was maximum, was considered to be the onset of the QRS complex. (Note that the length of the energy collector, 80 ms, corresponds approximately to the length of a QRS complex.) The record \(k_{max} + N_E\) was assumed to represent the end of the QRS complex. The procedure was repeated to locate successively all QRS complexes in a file. Following each detection of a QRS complex, the running averages for \(E_{on}\) and \(E_{off}\) were updated.

This method proved to be robust under various circumstances, as encountered in about 100 data files.

Pass 2: High accuracy location of R wave. Starting at the onset of the QRS complex at record \(k_{max}\), two linear regression lines (each extending over \(N_R, \text{part2}\) data points, \(\equiv 16\) ms) were fitted to the calculated channel R. The first one was intended to locate the descending slope of the R wave. The second regression line,
large, this is easily achieved by shifting an energy collector (spanning a 3 ms window) over the data. When a spike was found, the data within a 12 ms interval around the spike were replaced by calculated values on a straight line connecting the original data at the endpoints of the interval. Each data file was thus automatically cleared of pacemaker spikes before being analysed.

It should be added that atrial pacing occurs in that phase of a cardiac cycle where the ECG is slowly varying close to baseline, and hence the spikes are easily detected and linear interpolation is sufficient. In one patient with ventricular pacing, the algorithm failed when spikes occurred during the QRS complexes.

**Detection of T waves**

When the QRS complexes had been identified, a running mean \((N_T + 1\) points wide, corresponding to 60 ms) was calculated for channel ‘R’:

\[
S_k = \frac{1}{N_T + 1} \sum_{i} R_i \quad k \leq i \leq k + N_T
\]

and the maximum \(S_k\) was assumed to indicate the onset of the T wave.

Next, a linear regression line \((N_{T, \text{pass2}}\) data points wide, corresponding to 30 ms) was determined at each point, and when its slope’s modulus reached a minimum, this was taken to define the peak of the T wave. Again, these record numbers were stored.

In summary, R waves were found by a high-accuracy two-pass algorithm, while T waves were located between QRS complexes, again using a two-step procedure.

**FREQUENCY DOMAIN ANALYSIS**

**Beat-by-beat Fourier analysis of whole cardiac cycles of non-windowed signals**

For each heart beat the following procedure was carried out. The length of the beat, \(N_{R-R}\), was used to define the fundamental frequency and harmonics (multiples), for which spectral components were calculated. However, since the ECG signal is very steep and sharply peaked in the vicinity of the R wave, severe discontinuities (at the beginning and end of the interval) could result even from near periodic ECGs if a Fourier analysis were actually performed on the interval R–R. (Note that Fourier analysis on a finite interval formally assumes a periodic continuation of the signal outside the interval. Data unequal at the beginning and end of the interval therefore produce a ‘discontinuity step’ (at the interval boundary). In the spectrum, this step gives rise to high-frequency components, which are not contained in the otherwise smooth data (artefacts due to imperfect periodicity)). We therefore moved the interval backward in time by a certain fraction, \(N_{\text{back}}\), of the interval length, \(N_{R-R}\) (leaving the interval’s length unchanged). At the boundaries of the displaced interval the signal was close to the isoelectric line, and discontinuities were minimized. The
original data were then Fourier analysed within this displaced interval (separately for all three surface Frank leads and R) in order to obtain the power spectra for the non-windowed whole beats.

**Beat-by-beat Fourier analysis of QRS complexes and T waves**

QRS complexes were separated from the rest of the cardiac cycle by multiplying the original data by a four-term Blackman–Harris window, centered on the R wave and NW,QRS records wide (correspond to 120 ms). All data were thus forced to zero outside the window. Windowed data were then passed on for Fourier analysis, yielding spectral components at the same frequencies as the whole beat analysis (i.e. for multiples of the R–R fundamental frequency).

The T waves were windowed (length NW,T, corresponding to 400 ms) and analysed similarly.

**Beat-by-beat Fourier analysis of whole beats of windowed signals**

Intracardiac signals, showing rapidly varying features with unpredictable temporal location (depending on catheter position), were always windowed prior to Fourier analysis. To span the entire cardiac cycle, the Blackman–Harris window length, NW,WH, was chosen to be a constant multiple (NW,WH = 2) of the longest heart beat found as a data file. The window was placed symmetrically around the midpoint of the shifted interval used for whole beat analysis; the frequencies were again taken to be compatible with the current R–R interval.

**Frequency-locked averaging of power spectra**

The fundamental frequency \( f_1 = T^{-1} \), where \( T \) is the cycle length in seconds, and hence all harmonics \( f_j \) vary according to the length of the cardiac cycle. Consequently, one cannot simply average the first Fourier components, \( A(f_j) \), over successive heart beats, since such an average could no longer be attributed to a specific frequency.

The same is true for all harmonics \( f_j \) and also for the power spectrum, \( P(f_j) \). Instead, a grid of 200 frequency bands, each 1 Hz wide in terms of absolute frequency, was set up to average the power spectrum. For each beat, we first evaluated the complex Fourier components:

\[
A(f_j) = \frac{1}{T} \int_0^T dt \, e^{-2\pi i f_j t} \, C(t) \tag{3}
\]

where \( C(t) \) is the ECG data (X, Y, Z, R, A or B). To improve the quality of the spectrum at high frequencies, the data points were joined by a polynomial line, which was then Fourier transformed analytically. Then the power spectrum \( P(f_j) \) was calculated for all harmonics \( f_j \):

\[
P(f_j) = \frac{\text{Re}[A(f_j)]^2 + (\text{Im}[A(f_j)])^2}{1 \leq j \leq j_{\text{max}}} \tag{4}
\]

where \( j_{\text{max}} = 200 \) was the maximum frequency component, which is well below the Nyquist frequency (for a sampling rate of 800 s\(^{-1}\)). According to the heart rate of the respective beat, we then allocated each harmonic frequency, \( f_j \), to a channel number \( k (1 \leq k \leq 200) \) according to:

\[
k - 1 \leq f_j < k \tag{5}
\]

remembering that channel \( k \) holds frequencies between \( k - 1 \) Hz and \( k \) Hz. Then the \( k \)th elements of the three arrays, \( \hat{N_k} \), \( \hat{P_k} \) and \( \hat{P_k}^2 \) were incremented as follows:

- \( \hat{N_k} \) by 1;
- \( \hat{P_k} \) by \( P(f_j) \);
- \( \hat{P_k}^2 \) by \( P^2(f_j) \).

**Figure 3** Frequency-locked power spectra for channel R. Data from 80 beats for a patient paced at 80 bpm. Mean values (solid line), ± standard deviation (— — —) for equidistant frequency bands of 1 Hz width. All values have been divided by the largest mean value found (band 0–1 Hz) and then transformed to a logarithmic scale (dB, left scale). Note that, due to this transformation, the ± standard deviation curves are not symmetric around the mean. The step function curve shows the number of heart beats (right scale), which contributed to each channel by having a harmonic frequency in the respective 1 Hz interval. Due to pacing, heart rate varied only slightly. For the low-order harmonics (≤40 Hz) some bands received contributions from all 80 beats (upper level of step function), others from about 70 beats (second level of step function), while a third set of bands received contributions from only 10 beats. For high-order harmonics the splitting is narrower. For non-paced patients the step function becomes a smooth curve. a, Averaged power spectrum of 80 non-windowed whole beats. b, Averaged power spectrum for the QRS complexes multiplied by a 120 ms four-term Blackman–Harris window centered at the peak of the R wave. c, Averaged power spectrum for the T waves multiplied by a 400 ms four-term Blackman–Harris window centered at the peak of the T wave.
This procedure was carried out for all cardiac cycles within a data file. Since 18 spectra were evaluated per beat (whole beat, QRS complex and T wave for six channels: X, Y, Z, R, A and B), 18 such triplets of arrays were necessary (for simplicity, the discrimination between whole beat, QRS complex, T wave and intracardiac leads was suppressed in the notation). Finally, we calculated the mean and standard error of mean for all bands of each histogram. This procedure ensured a convenient estimate of the statistical spread in the averaged power spectra, which was considered essential in order to assess the statistical significance of intra-individual changes between successive follow-ups of a patient.

TIME DOMAIN ANALYSIS

Quantities calculated for each cardiac cycle

Besides the exact locations of R waves and T waves, the triggering procedure yielded, as by-products, a number of interesting quantities for each heart beat (Figure 4):

- Spatial orientation of the cardiac vector at the peak of the R wave; the corresponding values $X_0$, $Y_0$ and $Z_0$ were stored;
- Maximum energy collector of QRS complex;
- Heights of R wave and T wave;
- Maximum upward and downward slopes;
- Heart rate;
- Duration of R–T segment.

For each heart beat all these quantities were written to a file for subsequent statistical analysis.

Time-locked signal averaging

The location of the R wave, being accurately determined from the vector length (cf. Detection of R waves using the ECG vector length), was used as a unique reference for the time-locked superimposition of signals from successive heart beats (Figure 5). Averages and standard deviations were calculated for 200 data points preceding, and 1000 data points following, the R peak. Usually 60–100 cardiac cycles were used for averaging, separately for each data channel and R; additionally, all channels were also time-locked with respect to the T wave maximum and averaged. While time-locking on the R wave is especially useful to detect irregularities of depolarization (late potentials following the QRS complex), time-locking on the T wave is deemed to be the method of choice for detecting deficiencies in regional repolarization.

Autocorrelation function of vector orientation

For each cardiac cycle, the electrical vector $r_0$ (components $X_0$, $Y_0$, $Z_0$) found at the peak of the R wave was taken as a reference direction. For 200 data
points preceding and 1000 data points following the R peak ($-200 \leq k \leq 1000$), the cosine $C_k$ of the angle $\varphi_k$ between $r_0$ and the electrical vector $r_k$ (components $X_k$, $Y_k$ and $Z_k$) was calculated as a measure of orientational correlation:

$$C_k = \cos(\varphi_k) = \frac{r_k \cdot r_0}{|r_k||r_0|}$$  \hspace{1cm} (6)

Values of $C_k$ close to 1 indicate that both vectors point essentially in the same direction, whereas values close to -1 indicate opposite directions. The oscillations between -1 and +1 reflect the three-dimensional rotation of the electrical vector during a cardiac cycle (cf. Figure 7b). The values of $C_k$ were considered as another 'calculated channel' and were submitted to signal averaging over all beats in a file. The means (± standard deviations) were calculated and displayed versus time, relative to the location of the R wave (Figure 6).

The electrical vector is found to reverse its direction rapidly three times during the QRS complex. Except for two phases (near $t = -0.06$ s and $t = 0.02$ s), standard deviations are small, indicating that the sequence of sarcomere depolarization is an ordered process (during the QRS complex), triggered by the cardiac conduction system. Conversely, large spread during the T wave corresponds to sarcomere repolarization being a stochastic process, in which the uncoordinated activities of single myocytes add up to a total vector whose direction is unpredictable and varies from beat-to-beat at a given time lag behind the R wave.

As with signals from ordinary leads, which are subjected to signal averaging, the clinical relevance of the vector–autocorrelation function is supposed to lie in the detection of myocardial areas showing pathological electrical activity.

**TESTING THE CONCEPT OF FREQUENCY-LOCKED SPECTRUM AVERAGING**

The feasibility of averaging power spectra based on variable fundamental frequencies may be demonstrated clearly in a patient who was deliberately paced at three different frequencies (59, 89 and 119 bpm) during the same routine follow-up. From the various kinds of spectra evaluated, we selected two for the test: (1) the non-windowed analysis of whole beats and (2) the windowed (120 ms) analysis of the QRS complex. Within each beat, Fourier components for both spectra were evaluated at the unique set of harmonics (defined by the duration of the respective beat). The spectra were then averaged over all beats as described in *Frequency-locked averaging of power spectra*.

**Figure 7** shows the averaged power spectra obtained from the whole beat analysis (three pacing frequencies). The differences between these spectra may be compared with the standard deviation of a single spectrum for a fixed pacing frequency, as shown, for example, in **Figure 3a**. Up to approximately 50 Hz, the spectra differ from each other by

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**Figure 6** Autocorrelation function of vector orientation. Cosine of the angle between the reference vector $r_0$ at the R peak (vertical dashed reference line) and a running vector $r_k$ were averaged over all beats. The mean (---) and ± standard deviation (---) are shown. Patient paced at: **a**, 59 bpm (57 beats analysed); **b**, 89 bpm (80 beats analysed)

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**Figure 7** Averaged ECG power spectra for different pacing frequencies. Patient was paced at 59 bpm (--), 89 bpm (---) and 119 bpm (---). **a**, Averaged power spectrum of non-windowed whole beats. For each beat the interval analysed was exactly the length of the R–R interval and was shifted backward in time by 40% of the R–R interval. **b**, QRS complexes were windowed with a 120 ms fourterm Blackman–Harris window centered at the R peaks. The power spectrum was evaluated at exactly the same frequencies as in the whole beat analysis.
Figure 8 Power spectra of QRS complexes for different pacing frequencies. Each of the averaged spectra shown in Figure 7b is displayed together with the standard deviations. Again, due to logarithmic scaling, standard deviations do not appear symmetrical around the mean value. Patient paced at a, 59 bpm; b, 89 bpm; c, 119 bpm.

more than one standard deviation, while for higher frequencies the difference is insignificant. This is to be expected, since even the ordinary ECG tracings change with heart rate, in that, for example, the refractory period is shortened and limited to a diminishing portion of the whole beat as the heart rate increases.

Figure 7b shows the (averaged) power spectra obtained from windowed QRS complexes. The spectra are generally in much closer accord than for the whole beat analysis, and deviate from each other by only one standard deviation over the entire frequency range (cf. Figure 8). This is reasonable, since the QRS complex is almost unaffected so long as heart-rate changes are within physiological limits.

These tests demonstrate the feasibility and consistency (i.e., QRS spectra being independent of heart rate) of results obtained by a beat-by-beat Fourier analysis with subsequent spectrum averaging according to the method described in this work.

INITIAL CLINICAL RESULTS

To demonstrate the applicability of our analysis to rejection diagnosis, we compared the power spectra obtained at three different postoperative follow-ups of one cardiac transplant patient. Since graft rejections require therapy only if they are of histological grade 1–2 or higher, we combined spectra for rejection grades ≤ 1 and displayed a joint bandwidth (High–Low) instead of individual spectra. The spectra obtained under rejection (grade 1.5) were contrasted as single curves (Figure 9). Note that the analysis of whole beats (a), the windowed analysis of the QRS complex (b), as well as the windowed analysis of the T wave (c), all show marked deviations in the spectra under rejection.

SUMMARY

A software system has been developed that is capable of performing a comprehensive analysis of the ECG in cardiac transplant patients. In previous approaches, signal averaging was performed prior to the spectral analysis, and hence only one single spectrum without confidence limits could be obtained. The novel approach in this work lies in reversing the order of procedures.
First the power spectrum of single cardiac cycles (variable in length) was obtained from the original ECG data, implying a variable set of frequencies at which spectral components were evaluated. Then the spectra of all beats were averaged by allocating the spectral components to a histogram whose classes were 1 Hz wide in terms of absolute frequency. This approach also offered the possibility to calculate the standard deviation of the averaged spectrum. All other parts of the evaluation described above are by-products of the high-accuracy software detection of R waves. Only minor additional effort was necessary to calculate: (1) single beat quantities; (2) averaged signals (± standard deviations) for all leads; and (3) the vector autocorrelation function (± standard deviation). Each of these by-products may also be a possible diagnostic tool for detecting acute rejection episodes.

Finally, the additional analysis of intracardiac signals as well as the triggering on orthogonal ECG components are likely to enhance the diagnostic capability of the system.

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REFERENCES


APPENDIX

Syntactic algorithms\(^{10,11}\) locate features of a signal by logical combination of several criteria, and typically have to jump back and forth in the data sequence. If only a part of the data can be loaded into memory at any time, a cumbersome management of buffers is inevitable. We therefore used a FORTRAN function, called $Y(I)$, which simply reads record $I$ from a direct access file on a RAM disc. In the calling program, data may then be accessed as if they were elements of a dimensioned array. However, since no dimension statement appears, the compiler interprets $Y(I)$ as a function. Consider the following example:

```
PROGRAM TEST
C DIMENSION X(100000),Y(100000),Z(100000)
OPEN(UNIT=1,FILE='ECG',ACCESS='DIRECT',RECORDLENGTH=2)
SUM = 0.
DO 1 I=1,100000
   SUM = SUM + Y(I)
1 CONTINUE
STOP
END

C REAL FUNCTION Y(I)
READ(LREC=I) Y
RETURN
END
```

The generalization to several channels, e.g. $X(I)$, $Y(I)$ and $Z(I)$, is straightforward. Moreover, working in arrays can be easily reactivated without any software changes should more memory become available.