Frequency analysis of the surface electrocardiogram for recognition of acute rejection after orthotopic cardiac transplantation in man

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ABSTRACT Recognition of acute rejection after heart transplantation has been based mainly on invasive methods until now. In this study we analyzed two well-defined surface electrocardiographic recordings by fast Fourier transform (FFT) (Blackman Harris window, 512 points) after low-noise, high-gain amplification (filter setting 0.5 to 300 Hz) each day for 4 weeks after cardiac transplantation in 27 patients. Twenty acute rejection crises requiring treatment were diagnosed by cytoimmunologic monitoring and endomyocardial biopsy. Single-beat analysis of the QRS complex by FFT revealed a progressive change of the spectral morphology (increase of the frequency content between 70 and 110 Hz) on the days of rejection in 19 of 20 patients. At that time there were no visible changes on the electrocardiogram in the time domain in most patients. At the same time, the frequency content of the ST segment decreased between 10 and 30 Hz in 16 of 20 patients. After successful treatment, the frequency spectra of the QRS complex and ST segment returned to control within 1 to 2 weeks in most patients. One false-positive result was seen in a patient with mediastinitis and large pericardial effusion. A drop in QRS amplitude (> 20%) occurred in 10 of 20 rejection crises and in 10 patients without rejection. Nine patients after cardiac transplantation without rejection and seven control patients after cardiac surgery (not transplantation) showed stable frequency plots from one day to the other after the first postoperative day, but with considerable changes in QRS amplitude. Our results offer promise that frequency analysis, but not QRS amplitude, of low-noise electrocardiographic recordings can be used for the noninvasive, early detection of acute rejection after cardiac transplantation.


THE TWO MAJOR complications after cardiac transplantation are acute rejection and infection. Until now the diagnosis of rejection has been based mainly on invasive endomyocardial biopsy, which cannot be done on a daily basis and is of potential risk for the immunocompromised patient. Reliable, noninvasive diagnostic tests to identify the beginning of rejection episodes are still necessary. Changes in the immune systems of recipients have proved to be sensitive for acute rejection but lack specificity.1 Hemodynamic alterations are absent in the initial stages of rejection, when therapy should be started. Electrophysiologic changes, such as reduction of QRS amplitude, have been shown not to correlate reliably with acute rejection2 and are too variable for therapeutic decisions.

As a new approach for the noninvasive detection of acute rejection, we analyzed the frequency content of the QRS complex and ST segment of surface electrocardiograms (ECGs) by fast Fourier transform (FFT), a powerful analytic algorithm that reveals changes in the surface ECG that are invisible in the standard ECG.

Methods Two bipolar electrocardiograms were recorded simultaneously each day for 4 weeks after cardiac transplantation with a special, low-noise, high-gain amplifier. The recording sites (fourth intercostal space in right and left midaxillary line, first and fifth intercostal spaces in left midclavicular line) were marked with India ink. A preamplifier was placed in the sterile intensive care unit close to the patient's chest to reduce noise interferences from the environment (figure 1). The patient's skin was cautiously but thoroughly cleaned with gasoline and acetone (electrode impedance < 2 kΩ), and self-adhesive Ag/AgCl electrodes were applied with moderate pressure.
A long, shielded cable connected the preamplifier with the main amplifier outside the sterile unit. The filter setting was 0.5 to 300 Hz (analog Butterworth filter, 24 dB/octave). Analog-to-digital conversion was performed at an accuracy of 12 bits and at a sampling rate of 1000 Hz. The amplification of the analog signal was adjusted to ±10 V to take full advantage of the 12-bit analog-to-digital converter's input range. Data acquisition, analysis, and storage of the signals was done with a Hewlett Packard system (computer Model 9836 and Multiprogrammer 6944A). In addition to a 6 sec period of single-beat recording, on-line signal averaging of 100 consecutive beats was performed. The trigger point was evaluated automatically by the system by determining the peak with the steepest slopes at both sides within the QRS complex regardless of absolute voltage (usually the R peak). A DC shift of the signal did not influence detection of the trigger point and was corrected before averaging. Trigger jitter was ±1 msec. A beat was accepted for averaging if at a point-by-point comparison the difference between the signal and a template was less than 1%, thereby eliminating extrasystoles and overtly noisy signals. Signal averaging reduced the inherent noise level from 8 ± 3 μV (± SD) to 1.8 ± 0.7 μV.

Two segments were analyzed: the total QRS, centered in a segment of 120 msec, and the ST segment (300 msec). The segments were determined by the computer after manual definition of the beginning and end of the QRS complex with a movable cursor. Interobserver difference of the segment limits was less than 5 msec and did not change the frequency plots. Frequency resolution was constant throughout the recording period (QRS ~ 22 Hz, ST ~ 9 Hz), since segment size and window function are fixed variables.

The course of the analysis is shown in figure 2. The segment, here the entire QRS complex (top panel), was multiplied point by point with a special window function (four-term Blackman-Harris window) (broken line in top panel) to avoid edge discontinuities (beginning and end of the segment are set to 0, middle panel). The data points were set at the beginning of an array of 512 elements, and the remaining points were set to zero. Then the frequency content of the signal was calculated by the computer by applying FFT of 512 points according to the Cooley-Tukey algorithm. The frequency plot was normalized for different input amplitudes by setting the predominant frequency equal to one. Since the power spectrum rapidly declines at frequencies above 45 Hz, the scaling in the range from 45 to 200 Hz was expanded 10-fold (bottom panel) (ST segment × 50).

For comparison from one day to the other, the area under the frequency plot was calculated in the range of 70 to 110 Hz (shaded area). The signal-averaged QRS complex was analyzed in the same way.

For analysis of the ST segment, which has a much lower frequency content than the QRS complex, the area from 10 to 30 Hz was determined. Daily cytoimmunologic monitoring was performed as described elsewhere.², ³

Endomyocardial biopsy specimens were analyzed according to the method of Billingham.² Acute rejection requiring treatment was assumed in stage 2 (myocyte necrosis) and stage 3 (hemorrhage in addition to myocyte necrosis).

Twenty-seven cardiac transplant recipients were studied since November 1985. The primary diagnoses leading to transplantation were cardiomyopathy (n = 24) and coronary artery disease (n = 3). The mean age of the recipients was 40 ± 10 years (± SD). Seven patients were studied after coronary artery bypass grafting by Fourier analysis for 8 days as a control group.

Statistical evaluation was done by the Wilcoxon signed-rank test for paired data.

Results

Analysis of test signal. Figure 3 shows the analysis of a test signal by FFT. A symmetric ramp (duration 80 msec, amplitude 1 mV [top left panel]) is superim-

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**FIGURE 1.** Scheme of the recording set-up. The patient and the preamplifier are within the sterile intensive care unit. After amplification and filtering, the signals are analog-to-digital converted (ADC) and processed by the computer.
posed by a small sinus burst (frequency 90 Hz, amplitude 0.01 mV). In the time domain, the small signal can no longer be recognized without complex filtering (bottom left panel). In the frequency domain, the contribution of the sinus burst is clearly demonstrated by a peak at 90 Hz (bottom right panel). By FFT it is possible to detect high-frequency signals in the ramp up to an amplitude ratio of 1:0.001.

**Analysis of control groups.** Seven patients were analyzed for 8 days after coronary artery bypass surgery. Figure 4 shows the frequency plot of the QRS complex of one representative patient on consecutive days. There was no change in the frequency content in the range from 0 to 45 Hz from one day to the other. In the 10-fold extended frequency plot from 45 to 200 Hz, the variations between consecutive days were also minimal after the first postoperative day. The area under the frequency plot in the range from 70 to 110 Hz was constant (range of changes ± 8% compared with postoperative day 2). The QRS amplitude in this patient, however, showed considerable changes from one day to the other (drop > 20% on 2 days). The frequency spectrum of the ST segment (not shown) after signal averaging was also very constant (changes of area less than ± 7%).

Including all seven patients, the frequency content of the QRS complex decreased consistently, whereas the frequency content of the ST segment increased between postoperative day 1 and 2. Thereafter the
TABLE 1
Frequency analysis of ECG after cardiac transplantation in patients without rejection on endomyocardial biopsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Control period (days)</th>
<th>QRS complex</th>
<th>ST segment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amplitude (%)</td>
<td>Changed morphology of spectrum</td>
</tr>
<tr>
<td>1</td>
<td>45/M</td>
<td>6</td>
<td>-35</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>11</td>
<td>-30</td>
<td>0</td>
</tr>
<tr>
<td>3*</td>
<td>49/M</td>
<td>20</td>
<td>-30</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>44/M</td>
<td>19</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>47/M</td>
<td>7</td>
<td>-25</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>48/F</td>
<td>11</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>21/M</td>
<td>10</td>
<td>-10</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>21/M</td>
<td>16</td>
<td>+10</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>35/M</td>
<td>9</td>
<td>-55</td>
<td>+</td>
</tr>
</tbody>
</table>

*Same as patient 17 in table 2. He was free of rejection for 21 days.

spectral changes of both segments were very small (changes of the area < 20% compared with postoperative day 2). The QRS amplitude, however, varied considerably (at least one drop > 20% in six of seven patients).

Another control group consisted on nine patients who had undergone transplantation but had not suffered rejection (table 1). None of these patients showed signs of rejection on the endomyocardial biopsy. There were considerable changes in the QRS voltage (-55% to +10%). In all patients except one (No. 9), the frequency content of the QRS complex remained constant or even decreased in the range from 70 to 110 Hz. The frequency spectra of the ST segment also showed only minor changes (no drop > 20%) except in patients 8 and 9.

Patient 9 (table 1) presented with acute mediastinitis and large pericardial effusion. He showed a prominent change of the frequency spectra with an increase in the area of the QRS complex and a marked fall in the area of the ST segment.

Analysis of rejection after cardiac transplantation. Representative data for a transplant patient (patient 1 in table 2) are shown in figures 5 and 6. The QRS amplitude (figure 5) was constant during the first week after transplantation. On postoperative day 8 there was a dramatic fall of QRS amplitude in recording B (-43%), whereas the QRS amplitude in recording A was unchanged. On the seventh day, cytoimmunologic monitoring was activated for the first time. The frequency spectrum of the QRS complex (figure 6, top left panel) was constant up to postoperative day 6 but then showed a progressive increase of the frequency content in the range from 70 to 110 Hz. The area under the frequency plot of the QRS complex (bottom left panel) increased with a peak value at postoperative day 8. Endomyocardial biopsy on the eighth day revealed stage 2 rejection. The frequency representation of the ST segment (figure 6, right) was very low (<30 Hz). On the days of rejection the frequency content decreased, and the area between 10 and 30 Hz declined by 40% (figure 6, bottom right panel). The changes of the frequency spectrum were present in recording A and B, although QRS amplitude and morphology were constant in recording A. The spectral changes were most pronounced on days 8 (QRS complex) and 9 (ST segment).

After treatment of this patient with three 1 g doses of methylprednisolone, the QRS amplitude of recording B remained at a low level; however, the frequency spectrum of the QRS complex and ST segment and the corresponding areas returned to control values within 1 week (figure 6, middle left and right panels).

Twenty-seven patients were analyzed by FFT for a period of 26 ± 13 days (range 4 to 79). Six of 27 patients died, four during the recording period. One patient died because of rejection. Twenty rejection crises were diagnosed by endomyocardial biopsy.

QRS amplitude increased by a mean of 23 ± 19% within the first 3 postoperative days (p < .05). A drop of QRS amplitude (>20%) occurred at least once in 20 of 27 patients during the recording period. When acute rejection was detected by endomyocardial biopsy, the QRS amplitude fell (>20%) in 10 of 20 patients (table 2). There was even an increase of amplitude (>20%) in five of 20 patients at the time of rejection (table 2). Thus sensitivity of the QRS amplitude to detect rejection was 50% (table 2), and specificity was 44% (table 2).
TABLE 2
Frequency analysis of ECG after cardiac transplantation in patients with rejection on endomyocardial biopsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>CIM (days of activation po)</th>
<th>ECG (days of changes po)</th>
<th>QRS complex</th>
<th>ST segment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amplitude (%)</td>
<td>Changed morphology of spectrum</td>
</tr>
<tr>
<td>1</td>
<td>43/M</td>
<td>6-11</td>
<td>7-11</td>
<td>-40</td>
<td>+100</td>
</tr>
<tr>
<td>2</td>
<td>23/M</td>
<td>6-13</td>
<td>7-12</td>
<td>+10</td>
<td>+60</td>
</tr>
<tr>
<td>3</td>
<td>40/F</td>
<td>8-12</td>
<td>11-12</td>
<td>-60</td>
<td>+100</td>
</tr>
<tr>
<td>4</td>
<td>35/M</td>
<td>4-20</td>
<td>6-10, 13-20</td>
<td>-40</td>
<td>+40</td>
</tr>
<tr>
<td>5</td>
<td>24/M</td>
<td>3-15</td>
<td>4-10, 14-17</td>
<td>+140</td>
<td>-30</td>
</tr>
<tr>
<td>6</td>
<td>29/F</td>
<td>5-7</td>
<td>5-8</td>
<td>+70</td>
<td>+200</td>
</tr>
<tr>
<td>7</td>
<td>52/M</td>
<td>6-12</td>
<td>7-12</td>
<td>-40</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>33/M</td>
<td>6-10</td>
<td>7-9</td>
<td>-20</td>
<td>+40</td>
</tr>
<tr>
<td>9</td>
<td>53/M</td>
<td>6-9</td>
<td>6-8</td>
<td>-45</td>
<td>+70</td>
</tr>
<tr>
<td>10</td>
<td>41/M</td>
<td>5-14</td>
<td>5-14</td>
<td>-60</td>
<td>+90</td>
</tr>
<tr>
<td>11</td>
<td>54/M</td>
<td>5-8</td>
<td>6-7</td>
<td>+10</td>
<td>+130</td>
</tr>
<tr>
<td>12</td>
<td>42/M</td>
<td>8-9</td>
<td>8-14</td>
<td>+45</td>
<td>+90</td>
</tr>
<tr>
<td>13</td>
<td>35/F</td>
<td>4-8</td>
<td>5-15</td>
<td>-45</td>
<td>+60</td>
</tr>
<tr>
<td>14</td>
<td>46/M</td>
<td>5-8</td>
<td>6-9</td>
<td>-20</td>
<td>+30</td>
</tr>
<tr>
<td>15</td>
<td>48/M</td>
<td>6-9</td>
<td>6-8</td>
<td>+25</td>
<td>+30</td>
</tr>
<tr>
<td>16</td>
<td>49/M</td>
<td>7</td>
<td>-</td>
<td>+25</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>49/M</td>
<td>21-79</td>
<td>21-53</td>
<td>-40</td>
<td>+10</td>
</tr>
<tr>
<td>18</td>
<td>35/F</td>
<td>7-12</td>
<td>10-13</td>
<td>+15</td>
<td>+40</td>
</tr>
</tbody>
</table>
| 19      | 38/M         | 5-13                        | 9-13                     | -40          | +130      | +130       | -

Changes of QRS amplitude and frequency spectrum compared with postoperative day 2. See text for definitions. po = postoperative.

1). Furthermore, a drop of QRS amplitude (> 20%) not related to rejection occurred in 10 of 27 patients (table 2). The correlation between change in QRS voltage and rejection was not statistically significant.

QRS duration did not show characteristic changes after cardiac transplantation or during rejection episodes. Bundle branch block was present in three patients.

The frequency spectrum usually showed major changes in the immediate postoperative period: the frequency content of the total QRS complex decreased, but that of the ST segment increased on postoperative days 1 and 2; thereafter, the spectrum was constant from one day to the other, as in the control group. A changed morphology of the frequency plot of the total QRS complex similar to that in figure 6 could be seen in 19 of 20 patients when endomyocardial biopsy revealed acute rejection crisis (table 2). Activation of cytoimmunologic monitoring correlated closely in time (difference 1 to 2 days) with the appearance of changes of the frequency spectrum. The spectral changes of the QRS complex during the time of rejection consisted of an increase of the frequency content within the range of 60 to 150 Hz. We saw no changes in the frequency spectrum between 0 and 45 Hz. In most cases, there was no visible alteration of the QRS complex in the time domain even at high amplification. The increase of the frequency content could be expressed as the area under the frequency plot between 70 and 110 Hz (table 2). However, the spectral range, which changed during rejection, varied slightly between the patients; hence the area between 70 and 110
Hz was less sensitive for detection of rejection crises than judging the spectral morphology of the QRS complex over the whole frequency range (increase of area \( > 20\% \) in 15 of 20 rejection crises; \( p < .001 \)). Frequency analysis of the QRS complex beat by beat or after signal averaging revealed identical results.

Single-beat analysis of the ST segment was often not possible because of artifacts and muscle interference of patients in the immediate postoperative period. However, the frequency evaluation was reproducible after signal averaging. In two patients (Nos. 18 and 19) signal averaging failed because of inconstant trigger point. In 16 of 20 rejection crises we observed a decrease of the frequency content between 10 and 30 Hz resulting in a decline of the area in this range (table 2; \( p < .001 \) compared with postoperative day 2). In all but one patient (No. 17, table 2), frequency changes of the QRS complex correlated well with changes of the ST segment on the days of rejection.

During the course of rejection episodes, the spectral deviation of the QRS complex returned to control values after adequate therapy of rejection in nine of 19 cases, persisted in six of 19 cases, and could not be followed long enough in five patients because of discharge or death.

With regard to the ST segment, spectral changes returned to control in nine of 16 patients, persisted in five, and could not be followed up in two.

The frequency spectra of both the QRS complex and ST segment were not significantly affected by changes in heart rate between 70 and 110 beats/min. In the immediate postoperative period (days 2 to 7), seven patients showed a decrease in heart rate from 110 to 120 beats/min down to 80 beats/min (or lower).
these patients without signs of rejection the frequency spectra did not show changes related to different heart rates. No patient's heart rate was outside the range from 70 to 110 beats/min after the second postoperative day.

Changes in the frequency spectra did not correlate with the time of recording (circadian changes), serum level of potassium within the physiologic limits, creatinine level, or drug therapy, including catecholamines.

Discussion

Recognition of rejection. Recognition of acute rejection at an early stage is of vital interest after cardiac transplantation. Endomyocardial biopsy has been shown to be highly sensitive for detection of rejection, but the procedure cannot be performed on a daily basis and the risks associated with invasive techniques are high in the immunocompromised patient. Activation of the immune system can be demonstrated in the early stage of rejection by noninvasive cytoimmunologic monitoring, but because this monitoring is not specific for changes in the heart muscle, differentiation between acute rejection and infection is sometimes difficult. Magnetic resonance imaging of cardiac allografts has been proposed for detection of increased cellular and interstitial edema, myocardial necrosis, and hemorrhage accompanying acute rejection, but limited availability and the problems with monitoring critically ill patients in a high magnetic field outside the isolation unit are current disadvantages.

The use of the electrocardiogram as a cardiac-specific tool for detection of acute rejection has been disappointing until now. In an early study in dogs with cardiac homografts, a decline in ECG voltage, usually beginning 4 to 5 days before death, occurred in all animals that demonstrated the morphologic changes of acute rejection. In a series of baboons with heterotopic transplants there was a considerable change in QRS voltage from the body surface, ranging from 40% to 138% of the initial value in the recipient’s own heart and from 26% to 158% of the initial voltage in the donor heart. These great variations in QRS voltage could also be demonstrated in clinical studies after cardiac transplantation. Especially since the use of cyclosporine A, which reduces interstitial and intracellular edema during rejection, the ECG amplitude proved to be an unreliable predictor of early acute rejection, even if a persistent 20% decrease is taken as a criterion. With regard to QRS voltage, our results confirm these previous findings. Despite the fact that the precordial recording sites were precisely marked by India ink and the skin was carefully prepared with gasoline and acetone, the decline in ECG voltage occurred only in about 50% of the rejection crises and was equally frequent without rejection. The causes of failure might include changes of skin-electrode impedance, circadian rhythms, deviation of heart axes, pericardial effusion, chest wall edema caused by steroid administration, and development of fibrous scar tissue around the heart.

Frequency analysis of ECG. FFT of the ECG after cardiac transplantation provides a new noninvasive technique with major advantages: the analysis, as applied in this study, is independent of signal amplitude and allows evaluation of changes that are not visible in the routine ECG. Unlike the conventional ECG, in which voltage is plotted against time, the frequency composition of a signal is analyzed. The mathematic algorithm allows the quantification of frequency components of the ECG that are not accessible with conventional analysis in the time domain without complex filtering. Thus frequency analysis by FFT avoids various disadvantages of filtering (a priori appropriate cutoff frequencies unknown, filter ringing, signal distortion).

Although the information of a signal is in principle identical in the time and frequency domain, it may be much easier to detect certain changes in one domain. Another advantage of ECG analysis is that it can be performed quickly (30 min) and within the coronary care unit as a bedside method.

In almost all patients with acute rejection confirmed by endomyocardial biopsy, we could find changes in the frequency spectrum in two nonoverlapping segments: the total QRS complex and the ST segment. Since changes of the frequency composition of the QRS complex do not necessarily implement changes of the frequency representation of the ST segment (as we have shown elsewhere), the occurrence of shifts of the frequency spectrum in both segments might be considered as independent information. The frequency components of the QRS complex range between 0 and 200 Hz with a maximum at about 15 to 20 Hz (figure 6). Changes of the spectrum during rejection ranged between 60 and 150 Hz. These changes were of very low amplitude within the relative scale of the power spectrum (1% compared with the predominant frequency), hence they are indistinguishable in the time domain even at high amplification without complex filtering (see text signal). The frequency range of the normal ST segment is very low (figure 6); in fact, there is no contribution of frequencies higher than 40 Hz.
The changes during rejection were a loss of frequency content between 10 and 30 Hz, i.e., a shift toward lower frequency could be observed. Since the phase information of a signal is lost after transformation into the frequency domain, the question of where the decrease of frequency content is located within the signal can be answered only by indirect methods: windowing the segment with the Blackman-Harris function emphasizes information in the center of the segment. Analysis of additional segments (i.e., the initial ST segment, not shown here) did not show changes during rejection crises. Therefore the loss of frequency content of the ST segment during rejection is probably due to the repolarization phase (T wave). A broadening and flattening of the T wave could be observed in the time domain in some patients.

The mechanism of the alterations in the frequency spectrum is still unknown. With FFT, changes of the frequency spectrum of the terminal QRS complex and ST segment, but not of the total QRS complex, have been demonstrated in patients with coronary artery disease and ventricular tachycardia.16–18 Late potentials with an amplitude of a few microvolts could be demonstrated in these patients.19 These changes are caused by localized conduction delays in circumspect areas of structurally damaged myocardial tissue. During cardiac rejection after transplantation, however, no circumspect area but the whole organ will be damaged. Because there is no localized conduction delay, we have never observed distinct late potentials at the terminal QRS complex in the time domain during rejection crises. Instead, interstitial edema, necrosis of muscle fibers, and hemorrhage might cause heterogeneous conduction in the muscular tissue leading to changes of the frequency spectrum during the activation phase (QRS complex) and the repolarization phase (T wave). To elucidate this point, animal studies have to be done.

In conclusion, we have shown that FFT of surface ECGs is promising for the noninvasive detection of acute cardiac rejection after cardiac transplantation. The mechanism of the changes as well as the potential use of this method for evaluation of chronic rejection remain to be evaluated.

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