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The value of the electrocardiogram in the diagnosis of acute rejection after orthotopic heart transplantation

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Abstract. The value of a change in summated electrocardiographic voltage as a predictor of cardiac rejection is uncertain in patients treated with low-dose triple immunotherapy (cyclosporin, azathioprine, and corticosteroids) following orthotopic cardiac transplantation. Ten recipients were studied daily and the summated QRS voltages from 600 electrocardiograms were calculated. A single observer graded 147 endomyocardial biopsies. During the study period there were 18 episodes of acute rejection with myocyte necrosis. Only three episodes of rejection were heralded by a significant change in QRS voltage, yielding a positive predictive value of 13% for the technique. Three episodes of severe bacterial infection were preceded by significant decreases in QRS voltage. In one patient with a global pericardial effusion, QRS voltage was related to the depth of effusion measured by echocardiography. These data show that QRS voltage is of extremely limited value in the prediction of cardiac rejection in patients treated with low-dose triple immunotherapy.

Key words: Acute rejection, heart, electrocardiography - Electrocardiography, in acute rejection.

The first human cardiac transplant was carried out 21 years ago [1], yet there is still no simple, reliable, noninvasive test for the diagnosis of cardiac rejection. Changes in the electrocardiogram may indicate that rejection is occurring after orthotopic cardiac transplantation [11, 12, 14]. A 20% decrease in summated QRS voltages has been considered to indicate acute rejection. Dysrhythmias, heart block, ST-segment depression, T-wave inversion, and right axis deviation may also occur [8]. However, collections of fluid in the pericardial or pleural cavities, generalised oedema, pulmonary infection, and systemic infection can all influence QRS voltage [8]. Much of the early work on the value of the electrocardiogram as a predictor of acute rejection was carried out in patients receiving "conventional" immunosuppression (azathioprine, steroids, and antilymphocyte globulin) [5, 6, 12, 14]. Two groups [5, 6], who reported the electrocardiogram as useful in the diagnosis of rejection in patients receiving "conventional" therapy, did not find it of value in patients treated with cyclosporin. This study examined the predictive value of the electrocardiogram in the diagnosis of cardiac rejection in 10 recipients of orthotopic cardiac transplants who were immunosuppressed with cyclosporin, azathioprine, and prednisolone.

Patients and methods

The first 10 recipients of orthotopic cardiac transplants at this institution were studied. There were seven men and three women, aged 21-52 years (mean 38.2 years). Nine patients were alive at 56-478 days (mean 226 days); the tenth died of rejection at 28 days after transplantation. All donor electrocardiograms were normal. Immunosuppression was achieved with cyclosporin, azathioprine, prednisolone, and antithymocyte globulin.

Cyclosporin (Sandoz)

The initial loading dose was tailored to the recipient's preoperative creatinine clearance. Subsequent doses were adjusted to maintain a serum cyclosporin level around 200 ng/ml for the first 6 weeks after transplantation. Thereafter the dose was reduced to achieve a level of 100 ng/ml.

Azathioprine (Wellcome)

A loading dose of 4 mg/kg was given before operation. Subsequent doses were adjusted to achieve a peripheral blood white cell count of $4\text{-}6 \times 10^9$ per liter.

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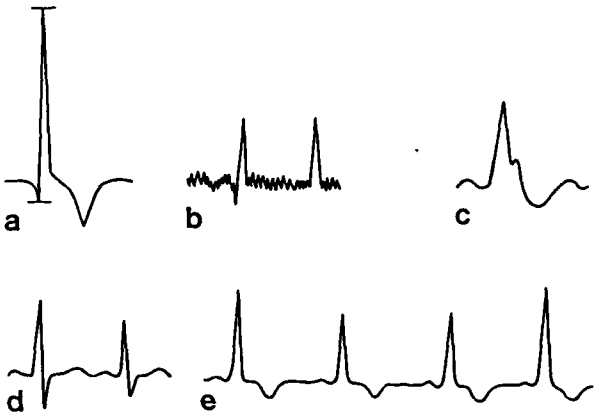

Fig. 1 a–e. Common measurement errors. **a** Inclusion or exclusion of small Q wave; **b** Muscle artefact; **c** Indistinct J point; **d** Electrical alternans; **e** Respiratory variation in V6

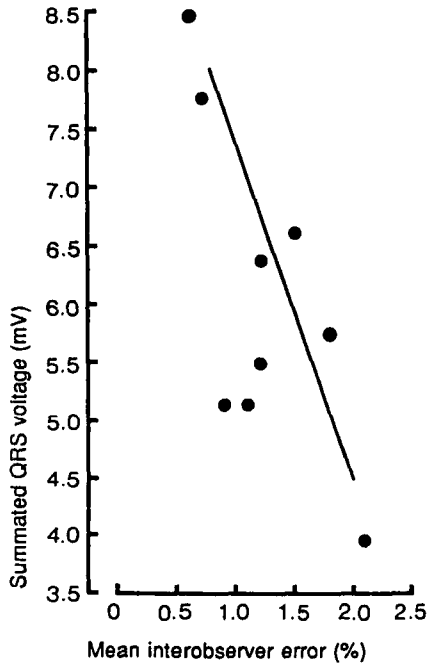

Fig. 2. Plot of mean postoperative summated QRS voltage for individual patients against mean interobserver error for that patient ($n = 9$). There was a moderate negative relationship between magnitude of QRS voltage and error. $r = -0.82$; $P < 0.01$

Steroids

Methylprednisolone (Upjohn; 500 mg) was given at the termination of cardiopulmonary bypass. Three further doses of 125 mg were given at 12-h intervals. Thereafter, oral therapy with prednisolone (0.2 mg/kg or lower) was instituted.

In the first 6 weeks after transplantation, rejection episodes associated with the presence of histologically demonstrated myocyte necrosis were treated with bolus intravenous methylprednisolone. After 6 weeks, rejection was treated with a 3-day course of oral prednisolone (100 mg on the 1st day), tapering to a level double the maintenance dose. Once resolution had been established by two consecutive biopsies, the maintenance dose was reinstituted.

Antithymocyte globulin (ATG)

ATG of equine origin was given immediately before operation and then daily for 10 days. The dosage was adjusted to maintain the rosette-forming T lymphocytes at around 5% of the total lymphocyte count.

Electrocardiography

Standard 12-lead electrocardiograms were recorded daily from marked skin sites using a Siemens Mingograf Minor 3 machine. The QRS voltage of six consecutive complexes from leads I, II, III, V1, and V6 were measured manually. In total, 600 electrocardiograms were examined by technicians from the ECG department. A random sample of 297 of these were examined blind and retrospectively to determine interobserver error.

Echocardiography

Daily examinations were performed using a Hewlett Packard 77020 AC machine. The depth of pericardial effusion was measured from the M-mode trace.

Endomyocardial biopsy

The standard Caves [2] technique was used to perform 147 biopsies. Histologic analysis was carried out by one observer. The grading system was based on the presence or absence of myocyte necrosis and the degree of lymphocytic infiltration. A positive biopsy was one that showed myocyte necrosis requiring treatment with a bolus of steroid.

Statistical methods

The sensitivity, specificity, and predictive values were calculated from the standard formulae.

$$\text{Sensitivity} = \frac{\text{True-Positives}}{\text{True-Positives} + \text{False-Negatives}} \times 100$$

$$\text{Specificity} = \frac{\text{True-Negatives}}{\text{True-Negatives} + \text{False-Positives}} \times 100$$

$$\text{Positive predictive value} = \frac{\text{True-Positives}}{\text{True-Positives} + \text{False-Positives}} \times 100$$

$$\text{Negative predictive value} = \frac{\text{True-Negatives}}{\text{True-Negatives} + \text{False-Negatives}} \times 100$$

$$\text{Percentage} = \frac{\text{True-Positives} + \text{True-Negatives}}{\text{Total Sample}} \times 100$$

Correlation coefficients were calculated using standard formulae.

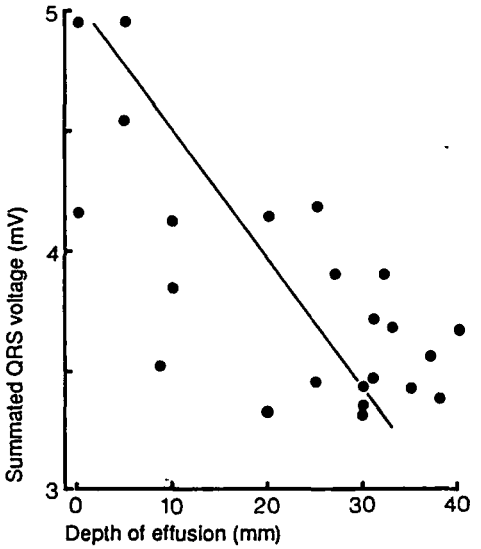

Fig. 3. Plot of summated QRS voltage against depth of effusion for patient 8. There was a moderate negative relationship between depth of effusion and QRS voltage. $r = -0.7$; $P < 0.001$

Results

Rhythm

Eight patients were in sinus rhythm from the 1st postoperative day. Two patients had atrial fibrillation during the 1st week after transplantation which reverted to sinus rhythm with digoxin therapy. There have been no late dysrhythmias.

Nine of the ten donor hearts developed incomplete right bundle branch block after transplantation. Patient 4 developed complete heart block on day 24 after transplantation. An endomyocardial biopsy showed acute rejection with myocyte necrosis. Treatment with intravenous methylprednisolone produced spontaneous reversion to sinus rhythm.

QRS voltages

Interobserver error was calculated from the difference between the initial measurement made by an ECG technician and the second blind measurement made by a single observer, expressed as a percentage of the second measurement. For the random sample of 297 electrocardiograms, the range of error was 0%–9.9% (mean 1.5%). Common sources of error were the inaccuracy of manual measurement, the inclusion or exclusion of small Q waves, muscle artefacts, ink smudging, indistinct endpoints of complexes, and variation of voltage during respiration (Fig. 1). A comparison of the mean QRS voltage for the total postoperative period for each patient with the mean interobserver error for that patient is shown in Fig. 2. Interobserver errors were larger in patients with lower summated QRS voltages.

Of the 600 electrocardiograms, 23 showed decreases of 20% or more in summated QRS voltage when compared to the previous recording. Only 3 of these decreases heralded an episode of rejection (true-positive). The remaining 20 (false-positives) included 3 decreases in QRS voltage that preceded episodes of pulmonary ($n = 1$) and systemic ($n = 2$) infection. As 18 biopsies showed rejection and 3 were heralded by electrocardiographic changes, the number of false-negative electrocardiograms was 15. Using the given formulae, the predictive value of a 20% decrease in summated QRS voltage in the diagnosis of rejection can be calculated (Table 1). Patient 8 developed a global pericardial effusion on day 13. The effusion was maximal (40 mm) on day 28 and took 70 days to resolve. There was a moderate negative correlation between QRS voltage and depth of effusion: $r = -0.7$, $P < 0.001$ (Fig. 3).

Discussion

In the assessment of these results, the causes of error must be considered. The manual measurement of QRS voltage is inherently inaccurate, and the electrocardiogram may contain any combination of the recording errors described above. However, the maximum interobserver error was 9.9%; it is unlikely that a significant decrease in QRS voltage could be explained by technical errors in measurement.

In this series of 600 electrocardiograms from ten recipients of orthotopic cardiac transplants receiving low-dose triple immunotherapy, we have shown that the positive predictive value of a 20% decrease in summated QRS voltage is only 13%. The data confirm other studies [5, 6] that stated that the elec-

Table 1. Predictive value of 20% decreases in QRS voltage in cardiac rejection and infection

	Rejection	Infection
Sensitivity %	16.7	42.9
Specificity %	96.5	96.6
Positive predictive value %	13.0	13.0
Negative predictive value %	97.4	99.3
Percentage correct	94.2	96.0

trocardiogram is unreliable in the diagnosis of cardiac rejection in patients treated with cyclosporin. Both these groups reaffirmed Lower's [12] contention that electrocardiography is a useful predictor of rejection in patients receiving "conventional" immunosuppression. A possible explanation of this difference is that myocardial oedema due to rejection is not as marked in patients taking cyclosporin as in "conventionally" immunosuppressed recipients [4]. However, there is doubt about the reliability of the electrocardiographic diagnosis of cardiac rejection in "conventionally" immunosuppressed recipients of heterotopic heart transplants [3].

If a 20% decrease in QRS voltage is not due to rejection, infection, or error, then what is the cause? Possible explanations are the normal diurnal variation in QRS voltage [10, 13], alterations in fluid balance, or pericardial and pleural fluid [8]. We have demonstrated the relationship between QRS voltage and depth of effusion in one patient.

This study has shown the standard 12-lead electrocardiogram to be of extremely limited value in the diagnosis of cardiac rejection. More sophisticated surface measurements of cardiac activity may be of use. The measurement of total high frequency voltage amplitude of the QRS complex, integrated time-product of the QRS, and voltage amplitude of the middle third of the QRS by signal-averaged electrocardiography may be a useful adjunct to endomyocardial biopsy after the 1st postoperative month in patients treated with cyclosporine [9]. In the first 4 weeks after transplantation, frequency analysis of the surface electrocardiogram during rejection episodes can show progressive changes in spectral morphology of the QRS complex and the ST segment [7].

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