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Electrocardiographic Abnormalities in the First Year after Heart Transplantation

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Abstract

Study Aim—Describe ECG abnormalities in the first year following transplant surgery.

Methods—Analysis of 12-lead ECGs from heart transplant subjects enrolled in an ongoing multicenter clinical trial.

Results—585 ECGs from 98 subjects showed few with abnormal cardiac rhythm (99% of ECGs were sinus rhythm/tachycardia). A majority of subjects (69%) had either right intraventricular conduction delay (56%) or right bundle branch block (13%). A second prevalent ECG abnormality was atrial enlargement (64% of subjects) that was more commonly left atrial (55%) than right (30%).

Conclusions—Right intraventricular conduction delay or right bundle branch block is prevalent in heart transplant recipients in the first year following transplant surgery. Whether this abnormality is related to acute allograph rejection or endomyocardial biopsy procedures is the subject of the ongoing clinical trial. Atrial enlargement ECG criteria (especially, left atrial) is also common and is likely due to transplant surgery with subsequent atrial remodeling.

Introduction

The effect of the denervated heart on the electrocardiogram (ECG) of heart transplant recipients is well documented to result in higher resting heart rate and reduced variation of

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heart rate over 24 hours.[1–3] Less is known about other ECG abnormalities in subjects who have undergone a heart transplant within 1 year. This period is especially important to characterize as the heart remains denervated, and the subject is at highest risk for acute cellular rejection; the impact of which is unknown on the ECG. To characterize ECG abnormalities in the first year following transplant surgery, we performed a preliminary analysis of data from heart transplant subjects enrolled in an on-going multicenter clinical trial ending in 2016.[4]

Methods

Sample/Sites

Adult subjects who underwent heart transplantation were recruited from one of three centers: University of California Los Angeles, Cedars Sinai Medical Center in Los Angeles, and Columbia University-New York Presbyterian Medical Center in New York City.

ECG Analysis

All 12-lead ECGs acquired as part of routine clinical care during the first year following transplant were collected from each medical center's ECG digital repository and uploaded via a secure network to the ECG Core Lab at the University of California San Francisco for analysis. Excluded from analysis were ECGs that may have been abnormal due to the initial recovery from transplant surgery (<7 days from surgery). All ECGs were interpreted manually onscreen with the aid of digital magnification using a standardized collection tool by a single reviewer (key ECG measurements in Table 1). The most recently published ECG criteria for myocardial ischemia /infarction were used.[5]

Results

Sample Characteristics

At the time of this report, 98 of the planned 325 subjects had been enrolled in the on-going clinical trial. These 98 subjects had a total of 585 ECGs available for analysis (mean, 6 ±5 per subject). The sample included 71 males (72%) and a mean age of 52 ±12 years (range, 22–75 years). Racial composition was 62% White, 24% Black, 12% Asian, 1% Native American or Pacific Islander. Seventy percent reported their ethnicity as being Non-Hispanic, 24% Hispanic, and 5% unknown.

Cardiac Rhythm

Of the total 585 ECGs, sinus rhythm or sinus tachycardia were present in 580 (99%); atrial fibrillation or flutter was present in 3 (0.5%), and junctional rhythm in 2 (0.3%). Mean heart rate was 94 ±12 bpm. Mean QRS amplitude in lead II was 0.9 ±0.4 mV. Neither heart rate nor QRS amplitude varied over time (r =−.067, p =.11& r =−.106, p =.01 [r^2=0.01], respectively).

Frontal Plane Axis

Distributions for P, QRS, and T wave axis are shown in Table 2. Twenty three per cent of the ECGs had an abnormal QRS axis; right axis deviation was more common (13%) than left axis deviation (8%). Few ECGs had abnormal P wave (1%) or T wave (7%) axis.

ECG Intervals

Mean PR interval was 147 ±20 ms (range=92–218 ms) that had a minor correlation with time (r =.19, p<.05 [r^2=0.035]). Disturbances in atrioventricular conduction were rare with just 4 ECGs (<0.5%) from 2 subjects revealing first degree block. Mean QRS duration was

91 ±18 ms (range=62–168 ms) which had a minor correlation with time (r =.12, p =.005 [r^2=0.01]). However this correlation did not exist after excluding those with intraventricular conduction delays/blocks (r =−.046 p =.49). Mean QT interval was 355 ±27 ms in males and 375 ±38 ms in females; mean corrected QT interval (QTc) was 442 ±24 ms in males and 458 ±34 ms in females. These gender differences in QT and QTc were statistically significant (both p <0.000).

Intraventricular Conduction

Right intraventricular conduction delay (IVCD) was present in 50% of all ECGs (n=293) from 56% of subjects (Figure 1). Complete right bundle branch block (RBBB) was evident in 10% of ECGs (n=59) from 13% of subjects. Only 2 ECGs had evidence of left IVCD (<1%) and none had left bundle branch block. The onset of right IVCD/RBBB varied. For example, 30 (31%) subjects had right IVCD and 5 (5%) had RBBB from the first ECG analysed (>7 days post-surgery). After an initial normal ECG, 7 (7%) subjects developed right IVCD and 1 (1%) developed RBBB. In addition, 17 (17%) had initial right IVCD that changed to normal conduction and 2 (2%) subjects had initial RBBB that resolved. Criteria for fascicular blocks were uncommon with anterior fascicular block in 5% of subjects; posterior fascicular block in 4%).

Enlargement/Hypertrophy

Subjects were classified as having atrial enlargement or ventricular hypertrophy if the ECG criteria were evident in any one of a subject's serial ECGs. Atrial enlargement criteria were present in 63 of the 98 patients (64%). Left atrial enlargement was more common (54 patients; 55% of subjects) than right atrial enlargement (29 patients; 30% of subjects). Left ventricular hypertrophy criteria were present in 7% of subjects; right ventricular hypertrophy criteria were present in 15% of subjects.

Criteria for myocardial ischemia/infarction

Distributions for ST elevation, ST depression, T wave inversion, and Q waves are shown in Table 3. Of the total 98 subjects, 23 had Q wave criteria for myocardial infarction, 13 had ST elevation, 11 had ST depression, and 21 had T wave inversion

Discussion

Our findings show that sinus rhythm or sinus tachycardia predominate in the first year following heart transplantation. In our sample of 98 patients, supraventricular arrhythmias were rare (<1%) and ventricular arrhythmias or second/third degree AV block were non-existent.

We found that the most prevalent ECG abnormality was right intraventricular conduction delay or block, occurring in 69% of patients. The etiology and clinical significance of right IVCD and RBBB is unclear; it may be a sign of right ventricular strain and remodeling in patients who have had severe heart failure requiring transplantation. However, our cohort did not have irreversible pulmonary hypertension preoperatively because they were all isolated heart transplantation (i.e., we excluded patients with heart ***and*** lung transplants).

Some studies have related right IVCD and RBBB to increased mortality in the post-transplant population,[6,7] whereas others found no such correlation.[8–10] In a sub-analysis of heart transplant subjects with right IVCD, Gao and colleagues[11] demonstrated higher intra-cardiac pressures in those with IVCD than without. However the pressures remained within acceptable ranges and thus, failed to adequately explain this phenomenon. Marcus, et al. conducted one of the larger studies to date with 322 heart transplant recipients followed for

9 ±3 years.[10] They found that right IVCD and RBBB developed over time and therefore argued against a perioperative cause. However, in contrast, Jessen and colleagues[9] found right IVCD and RBBB to be present immediately after surgery, providing the argument that geometric and rotational forces contributed to these conduction abnormalities. Other postulated mechanisms for the early development of right IVCD and RBBB are intra-operative factors such as increased graft ischemia times.[12,13]

Beyond confirming a high prevalence of IVCD, our data do not support one etiological hypothesis over another. In our ongoing clinical trial[4] we will continue to investigate the etiologic and clinical significance of right IVCD/RBBB after heart transplantation, especially in relation to right ventricular biopsy procedures and cellular rejection grading. It might be hypothesized that intraventricular conduction delays/blocks were present in the donor prior to transplantation. However, an argument against our observed high prevalence of IVCD/RBBB originating with the donor is a recent analysis of 980 ECGs from the California Transplant Donor Network that reported 97% of donors had normal intraventricular conduction on their pre-transplant ECG.[14]

The second most prevalent ECG abnormality observed in our study was atrial enlargement that was present in 64% of subjects. A possible explanation for this finding may be related to the surgical technique in standard orthotopic heart transplantation[15] that involves grafting the donor's ventricles and a portion of the anterior atria to the native posterior and lateral walls of the recipient's atria. This has been shown to result in enlarged atrial cavities of abnormal shape and produce a prominent suture line between the recipient and donor components.[16] An explanation for the high prevalence of positive ECG criteria for atrial enlargement post-transplant may therefore be a combination of the native diseased atrial posterior walls and the surgical scars, rather than disease progression in the post-surgical transplant patient.[17]

In an alternate explanation, Cou and colleagues[18] studied the relationship between cellular allograft rejection post cardiac transplant and changes in P terminal force criteria for left atrial enlargement in Lead V1. They concluded that abnormal left atrial depolarization was multi-faceted; changes in P terminal force were not correlated with either left atrial size or pressure, or systemic hypertension and thus were not indicative of atrial enlargement. These investigators found that only the degree of cellular rejection correlated to P terminal force. The proposed mechanism for this correlation is myocardial cell damage and derangement of myocardial fibres during cellular rejection, resulting in inhomogeneous conduction and P wave abnormalities. Although our preliminary analysis did not include data on acute allograph rejection, it is the subject of our ongoing clinical trial that aims to identify possible ECG markers for acute allograft rejection.

A third ECG abnormality that was present in 23% of patients was Q waves meeting the criteria for myocardial infarction. Delewi and colleagues[19] compared 4 definitions of pathological Q waves that have been published over the years and found that the "classic" criteria of a Q wave ≥40 ms and/or a depth ≥25% of the R wave in the same lead showed the strongest correlation with infarct size as measured by cardiac magnetic resonance. Unfortunately, they did not evaluate the most recent third consensus criteria on universal myocardial infarction published in 2012 that we used in our study. So, it is unclear how our criteria would have compared to the "classic" criteria that Delewi found to correlate best with infarct size. Because the "classic" criteria require a Q wave depth criterion and a wider Q wave (≥40 ms versus ≥30 ms) than the criteria we used, it is likely that some of the 23% of patients in our cohort with Q waves are false positives. In addition, we agree with Goldberger, et al.[20] that: a) not all Q waves are pathological, b) not all pathological Q waves are due to myocardial infarction, and c) there is no firm consensus for diagnosis of

pathological Q waves. Finally, in the present analysis, we did not investigate the timing of Q waves and likely causes such as longer ischemic times; however, we will investigate this possible etiologic mechanism in our final sample of 325.

Limitations to this study are that it is unclear whether any of these ECG abnormalities were present in the heart donor prior to transplantation. In addition, we did not correlate the ECG abnormalities with other diagnostic tests such as echocardiograms for atrial/ventricular enlargement, or serum troponin for evidence of ST-T wave criteria for acute myocardial infarction.

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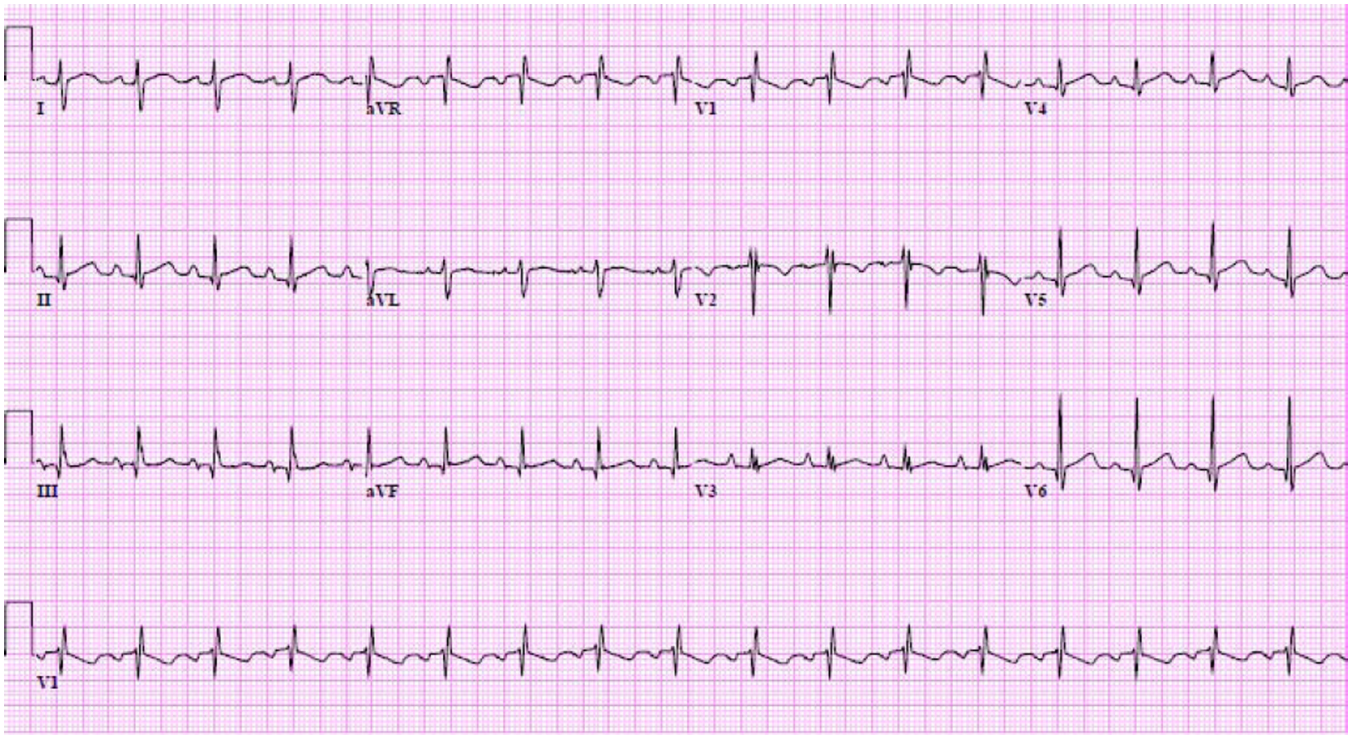

Figure 1.
Typical ECG findings in the first year following heart transplantation in a 30 year old female showing sinus tachycardia, rightward QRS axis, right intraventricular conduction delay, and left atrial enlargement.

Table 1

Definitions for selected ECG measurements

ECG Measurement	Operational Definition
PR, QRS, QT, QTc intervals	Automated values after manual verification
Frontal plane axis (P, QRS, T)	Automated values after manual verification
Atrial or ventricular premature beats	Present/not present
Right intraventricular conduction delay	RSR' pattern in V1 with QRS 100–119 ms
Right bundle branch block (RBBB)	RSR’ pattern in V1 with a QRS duration ≥120 ms
Left intraventricular conduction delay	QS or rS pattern in V1 with a QRS duration 100–120 ms
Left bundle branch block (LBBB)	QS or rS pattern in V1 with a QRS duration >120 ms.
Anterior fascicular block	Left axis deviation with qR in aVL and onset to peak R ≥45 ms.
Posterior fascicular block	Right axis deviation with rS in I, aVL, and qR in III, aVF
Left atrial enlargement	Biphasic P wave in V1 with a large terminal negative component whose area ≥40 ms by −0.1 mV; or, notched P wave in II with inter-peak interval >40 ms
Right atrial enlargement	P wave amplitude in V1 or V2 ≥0.15 mV
Left ventricular hypertrophy	Sum of S wave in V1 + R in V5 or V6 ≥3.5 mV or R in aVL ≥0.9 mV for women or ≥1.1 mV for men
Right ventricular hypertrophy	Right axis deviation and R/S ratio in V1 ≥1
ST elevation (2 contiguous leads)	J-point ST elevation with cutoff points in V2, V3 of ≥0.2 mV in men ≥40 years; ≥0.25 mV in men <40 years; ≥0.15 mV in women.
ST depression, T inversion (2 contiguous leads)	Horizontal or down-sloping ST depression of ≥0.05 mV and/or T wave inversion of ≥0.1 mV

ms = millisecond; mV = millivolt

Table 2

Frontal plane axis in 585 ECGs from heart transplant patients

Axis	P	QRS	T
Normal	577 (99)	452 (77)	539 (92)
Right	3 (>1)	74 (13)	24 (4)
Left	0 (0)	46 (8)	5 (>1)
Superior	1 (>1)	9 (2)	13 (2)

Table 3

ECG criteria for myocardial ischemia/infarction in 98 heart transplant recipients

ECG Criteria	Inferior*	Anterior*	Lateral*	Any Location
Q wave	17	8	8	23
ST elevation	2	13	3	13
ST depression	4	25	10	11
T wave inversion	5	12	19	21

* Inferior: II, III, aVF; Anterior: V1-V4; Lateral: I, aVL, V5, V6