Utility of Exercise Electrocardiography in Diagnosis and Management of The Long QT Syndrome

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Diagnosis of LQTS

Exercise stress testing is one of several electrocardiographic modalities that are useful in diagnosing, confirming and managing the Long QT syndrome (1,2,3). First, regarding diagnosis, some patients can be definitively diagnosed with Long QT syndrome based upon a single electrocardiogram. In many more patients, however, more than one electrocardiogram is needed to confirm the diagnosis. Additional ECG tracings can be useful to diagnose the Long QT syndrome because different LQT subtypes appear to demonstrate differences in rate adaptation of the repolarization process (1,2). Moreover, some ECG findings may be intermittent, such as ventricular premature beats, non-sustained ventricular tachycardia, and exercise-induced tachycardia and T-wave alternans. Though these findings are intermittent and uncommon, they are associated with high risk of sudden cardiac death. Exercise stress testing is often helpful in either increasing or decreasing the suspicion of Long QT syndrome in patients with a borderline QT interval or mildly prolonged QT interval (4). It is especially useful in the absence of other factors favoring a diagnosis of Long QT syndrome such as a family history or history of exertional syncope. Grading the likelihood of a diagnosis of LQTS can be done with a scoring system [5].

Usual and unusual exercise related physiology

A number of authors have studied the process of repolarization adaptation to heart rate. Sisakova et al (6) compared various methods of correction of QT intervals during exercise in familial long QT syndrome. The genetically established diagnosis of LQTS correlated best with values obtained with correction by Bazett formula [7]. All the mutation carriers were correctly identified by this method. Other QT adjustment algorithms, such as the Fridericia, Malik and Framingham formulas, were found to be less sensitive for the diagnosis. The strengths of several of the QT correction algorithms are discussed by Zareba and Moss [8]

A number of studies have shown a reduced exercise heart rate and a reduced resting heart rate in LQTS patients. [9]. Lower resting heart rates have also been found in some LQTS patients.

Two groups [10, 11] have reported finding the appearance of notched T waves in the recovery phase of exercise in the majority of LQTS subjects and only rarely among healthy controls. Notching is perhaps only diagnostic if found in 3 or more leads, not for example only in leads V2-V3.

Several authors have evaluated the effects of changes in heart rate during exercise and during the recovery phase after exercise. Inappropriate prolongation of the QT interval during the recovery phase, compared to the same rate during exercise, was reported to be a strong criterion for diagnosis of the Long QT syndrome [12]. Krahn et al (12) have referred to this as repolarization hysteresis. Krahn et al (13) also evaluated patients with long QT syndrome on beta-blocker therapy and found that beta blocker therapy normalized QT hysteresis in LQTS patients. The same hysteresis effect has been reported with pacing, where the QT adapted faster to an increase in rate than to a decrease in rate [14]. Varying effects of exercise and recovery on the QT interval are one aspect of a group of observations related to QT dynamicity. For example, QT intervals appear to be up to about 30 ms longer at night than during the day [15, 16, 17, 18]. Rate independent influences on the QT interval were reviewed by Coumel and Maison-Blanche [19].

Risk stratification of LQTS

When the diagnosis of LQTS has been established by genotyping or is fairly certain because of the degree of QT prolongation, family history and/or syncope, as in the LQTS point scoring system [5], stress testing can still be useful for risk stratification. Although rare, observing nonsustained polymorphic ventricular tachycardia, or even more rarely, sustained polymorphic ventricular tachycardia, may warrant consideration of an ICD, especially if the patient is on treatment with a beta-blocker. Demonstrating a more marked degree of QTc prolongation also increases the patient's risk for a lethal event [20], as does finding macroscopic T-wave alternans [21, 22, 23] although it is rare.

Genotype correlations

Different long QT subtypes appeared to behave differently in adaptation of repolarization to heart rate changes. Long QT syndrome type 1 (LQT1), involving a mutation in the slow component of the delayed rectifier potassium current (IK_s), appears to show the greatest relative prolongation of QT interval with increased heart rate. LQT1 is associated with diminished chronotropic response and exaggerated prolongation of QT interval after exercise (1). The prolongation of the corrected QT interval can be demonstrated with the exercise stress test or by Holter monitoring during different autonomic situations (24). The Long QT syndrome type 2 (LQT2), defined by mutations in rapid component of the delayed rectifying potassium current (IK_r), also demonstrates some abnormality and adaptation to increase heart rate. Most authors feel this is not as marked as in the case of KVLQT1 mutation. Swan et al showed that LQT2 patients differ from LQT1 patients by having marked QT interval shortening and normal heart rate response to exercise (1). Takenaka et al (25) examined T-wave morphology and various

parameters of repolarization in patients with LQT1 and LQT2 before and during exercise stress tests. Both QTc and the interval between peak and end of the T wave (Tpe) were significantly prolonged during exercise in LQT1 with morphological change into a broad based T wave pattern. In contrast, exercise produced a prominent notch on the descending limb of the T wave, with no significant changes in the QTc and Tpe in LQT2. This may partially accounts for the finding that fatal cardiac events in LQT1 are more often associated with exercise [26]. Therefore, LQT1 patients respond most dramatically to beta-blocker therapy. Long QT subtype 3 (LQT3), defined by a mutation in the inward sodium current coded for by the SCN5A gene, show relatively normal adaptation of the QT interval with exercise. Perhaps related to this, LQT3 patients are less likely to have episodes of syncope or cardiac arrest during exercise and are felt by some to be less likely to have a beneficial effect of anti-adrenergic therapy.

Management

Exercise testing is useful in confirming adequacy of treatment with beta-blockers. While the absence of ventricular tachycardia is of limited value because it is only rarely seen, an appropriate limitation of the peak exercise rate can demonstrate therapeutic beta-blockade. Some recent data show that beta-blocker therapy may not need to be pushed to high doses of 3 mg/kg of propranolol per day or its' equivalent. [27, 28] Exercise testing is especially useful in children to assist in dosage adjustment with somatic growth. Stress testing, usually after deactivating detection or therapies, can be used to evaluate maximum sinus rate to facilitate programming a cut-off rate for an implantable defibrillator used in the high risk LQTS patient. However, this can be misleading because many patients achieve peak heart rates that are much higher at other times. Moreover, setting a very high detection rate is usually feasible and safe because of the rapid rate of the VT observed (i.e., > 210 bpm) in these typically young and active ICD patients.

Case Studies

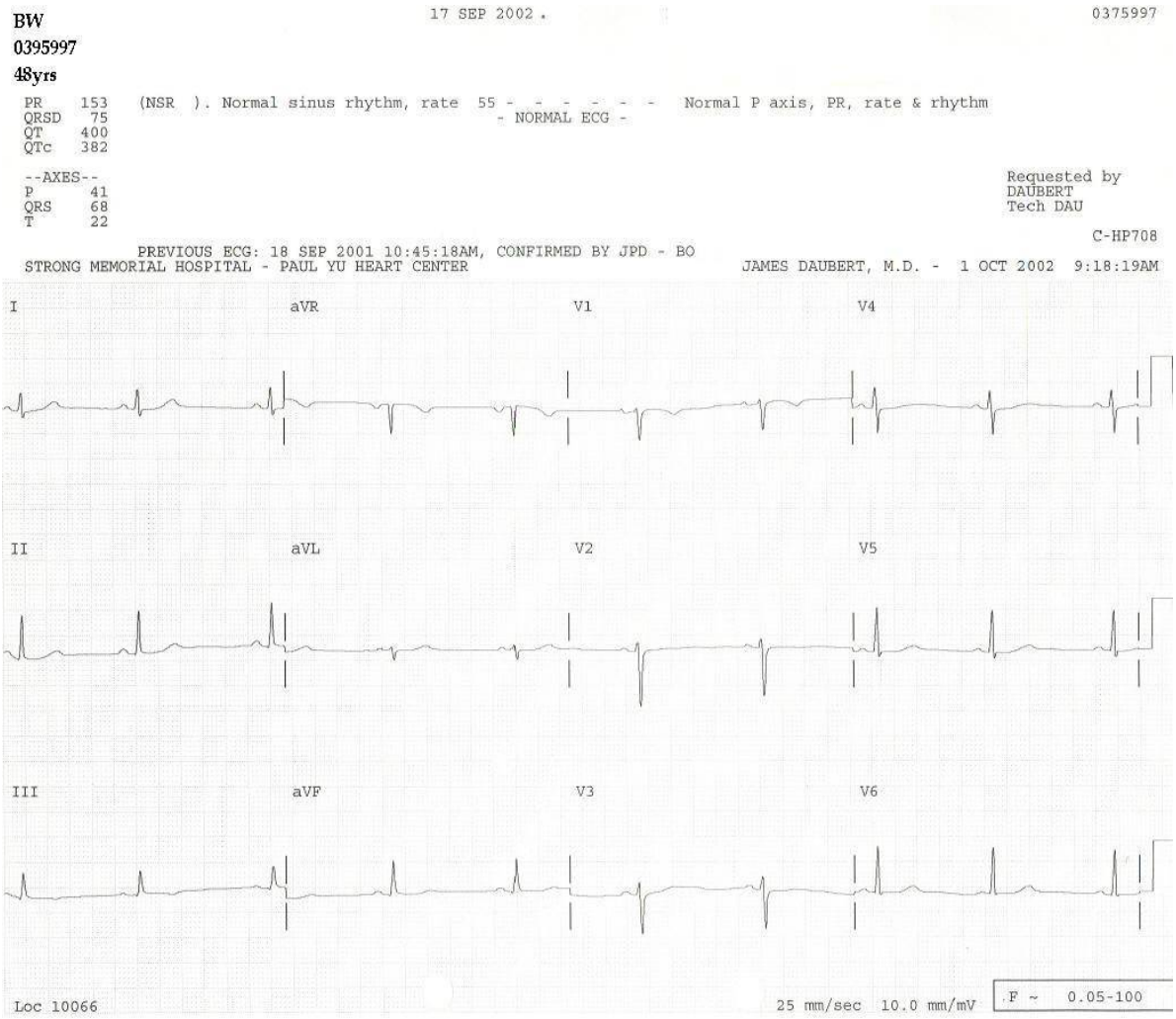

Figure 1: Panel A shows a resting electrocardiogram on patient (BW). The corrected QT interval measures approximately 0.44 seconds. The T-wave morphology is slightly abnormal and it has a low voltage in leads V2-4 leading to difficulty in measuring the termination of the T-wave in these leads. A firm diagnosis of long QT syndrome is difficult to make from this ECG.

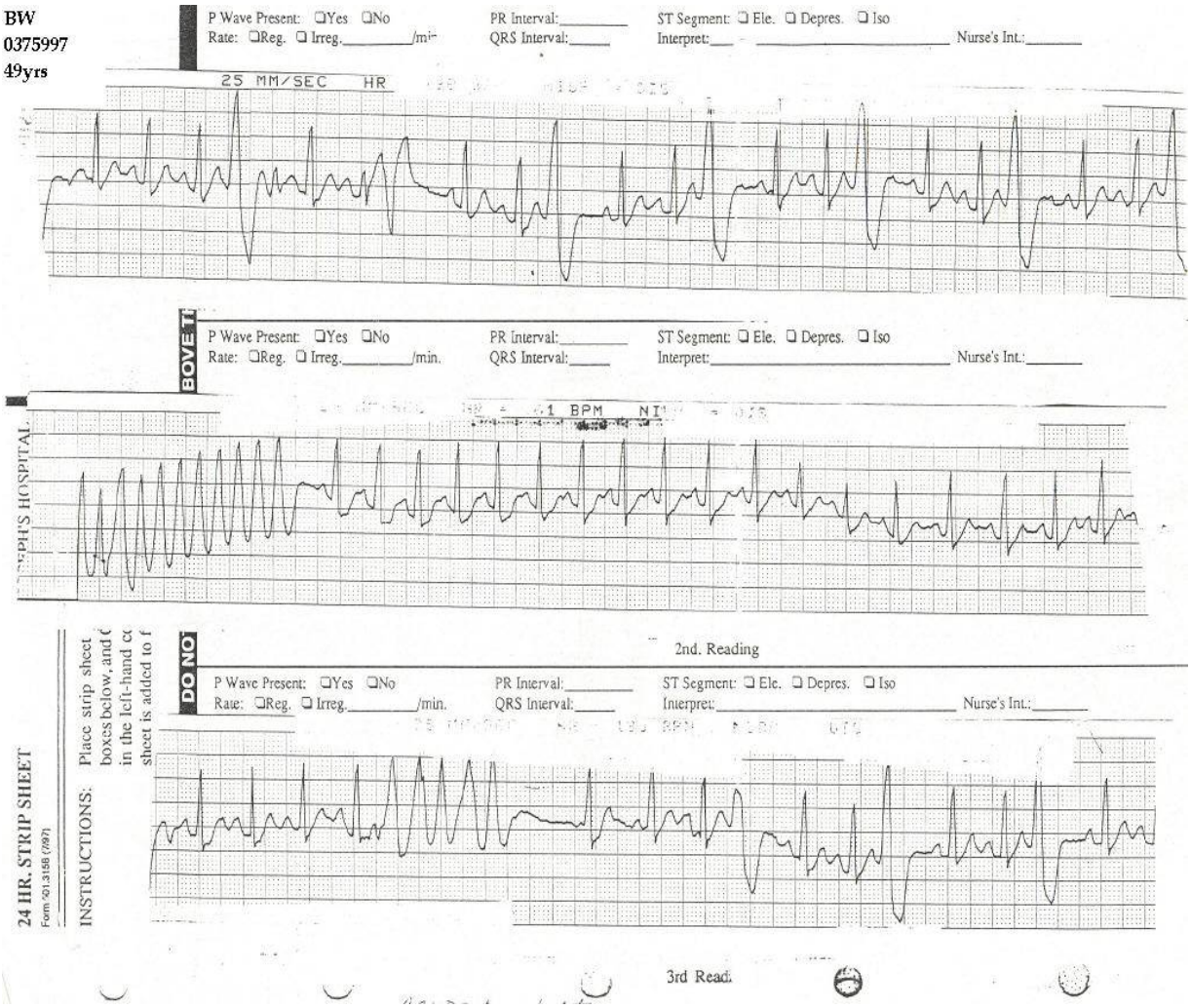

Figure 1 Panel B shows telemetry tracings with runs of nonsustained, rapid, polymorphic ventricular tachycardia. During sinus beats, the corrected QT interval is abnormal, at least 0.47 sec. The end of the T-wave merges with the P-wave and the QTc might be longer than 0.47 sec.

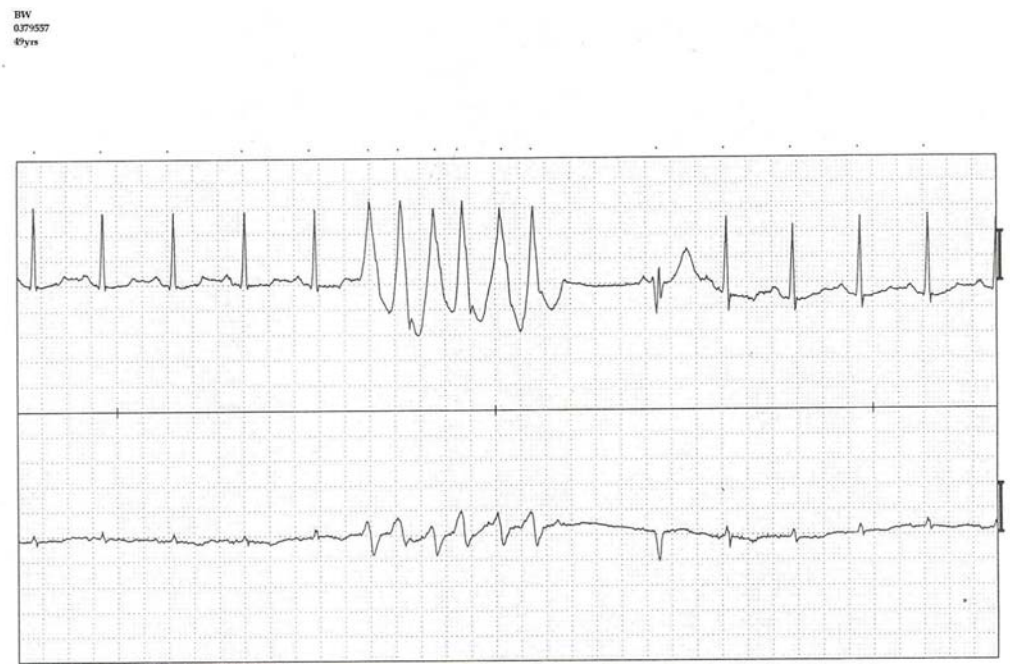

Figure 1 Panel C shows an additional run of polymorphic nonsustained tachycardia during Holter monitoring.

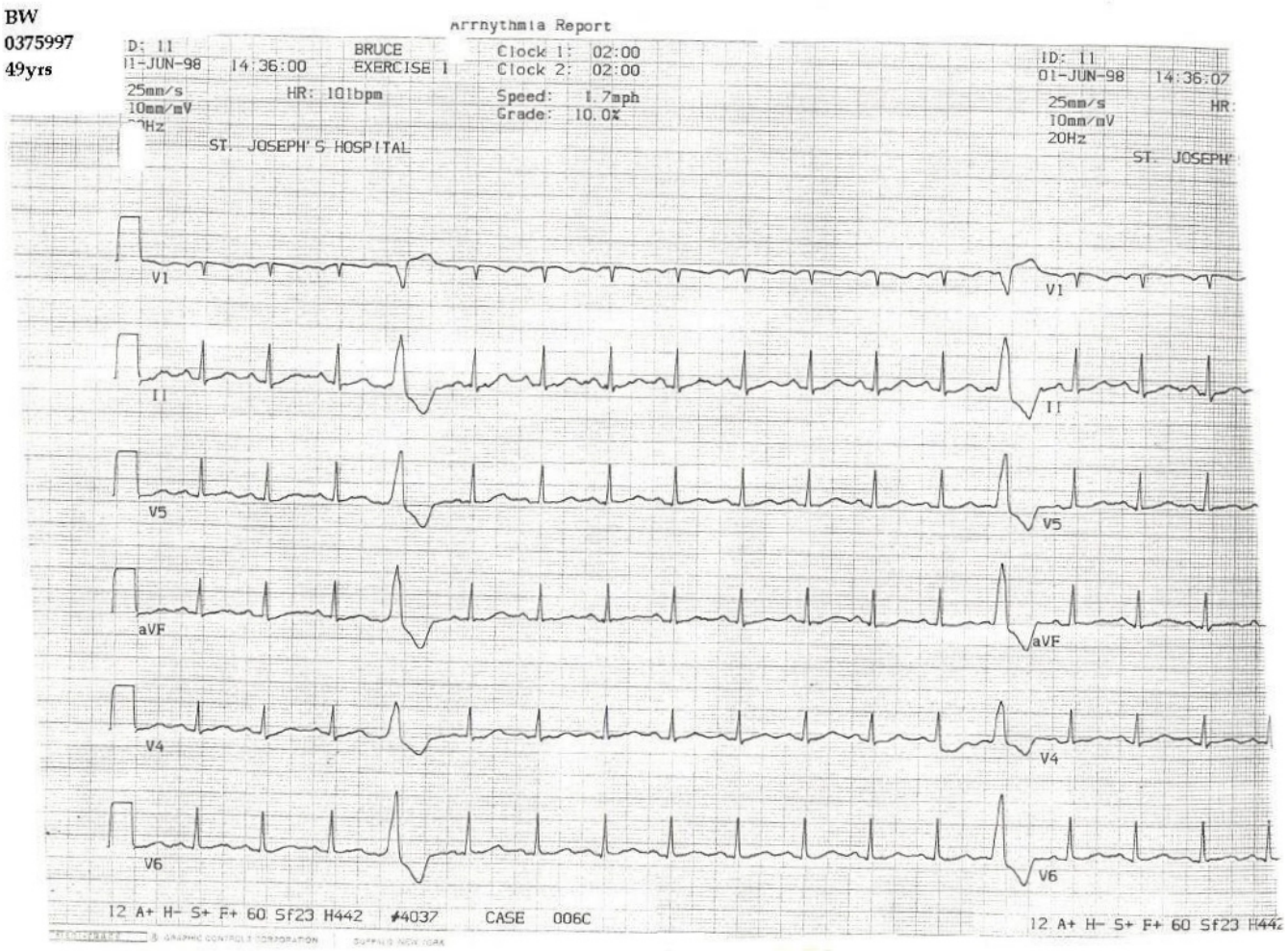

Figure 1 Panel D shows an exercise electrocardiogram on the same patient (BW). This ECG shows the corrected QT interval of approximately 0.47 seconds and a PVC.

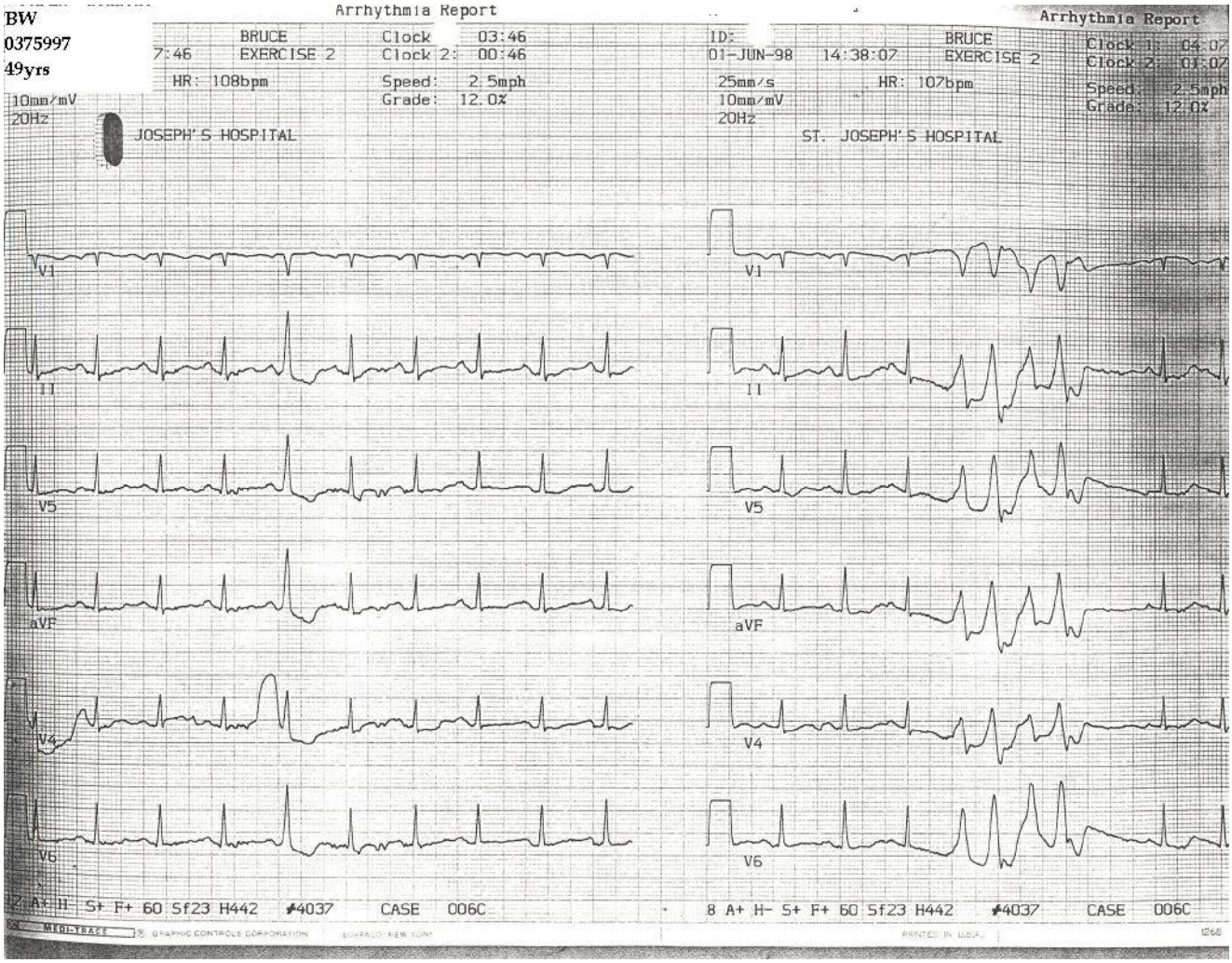

Figure 1 Panel E shows the exercise test with non-sustained ventricular tachycardia. The resting ECG in this patient could not confirm the diagnosis of LQTS but Holter monitoring as well as exercise testing provided additional information that helped confirm the diagnosis of long QT syndrome.

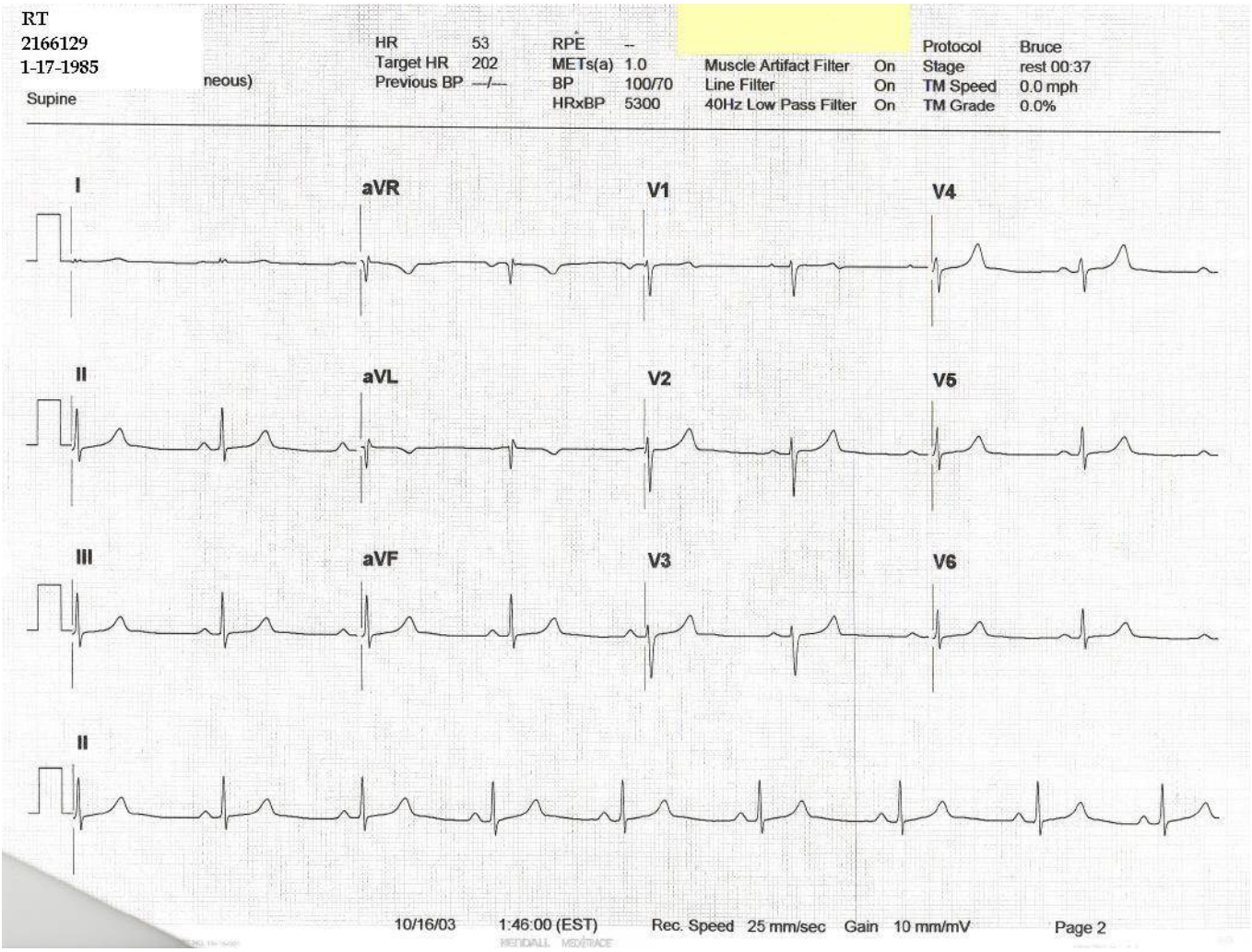

Figure 2: Panel A shows resting electrocardiogram prior to exercise stress testing. The QT interval measures 0.47 seconds with an RR interval of 1.16 second with corrected QT interval of 0.44 seconds. With exercise the QT is 0.34 seconds at a RR interval of 0.52 seconds; the corrected QT interval is 0.47 seconds and T wave morphology is slightly abnormal. In this patient with history of familial long QT syndrome exercise stress testing was very helpful in making a relatively, firm diagnosis of Long QT syndrome.

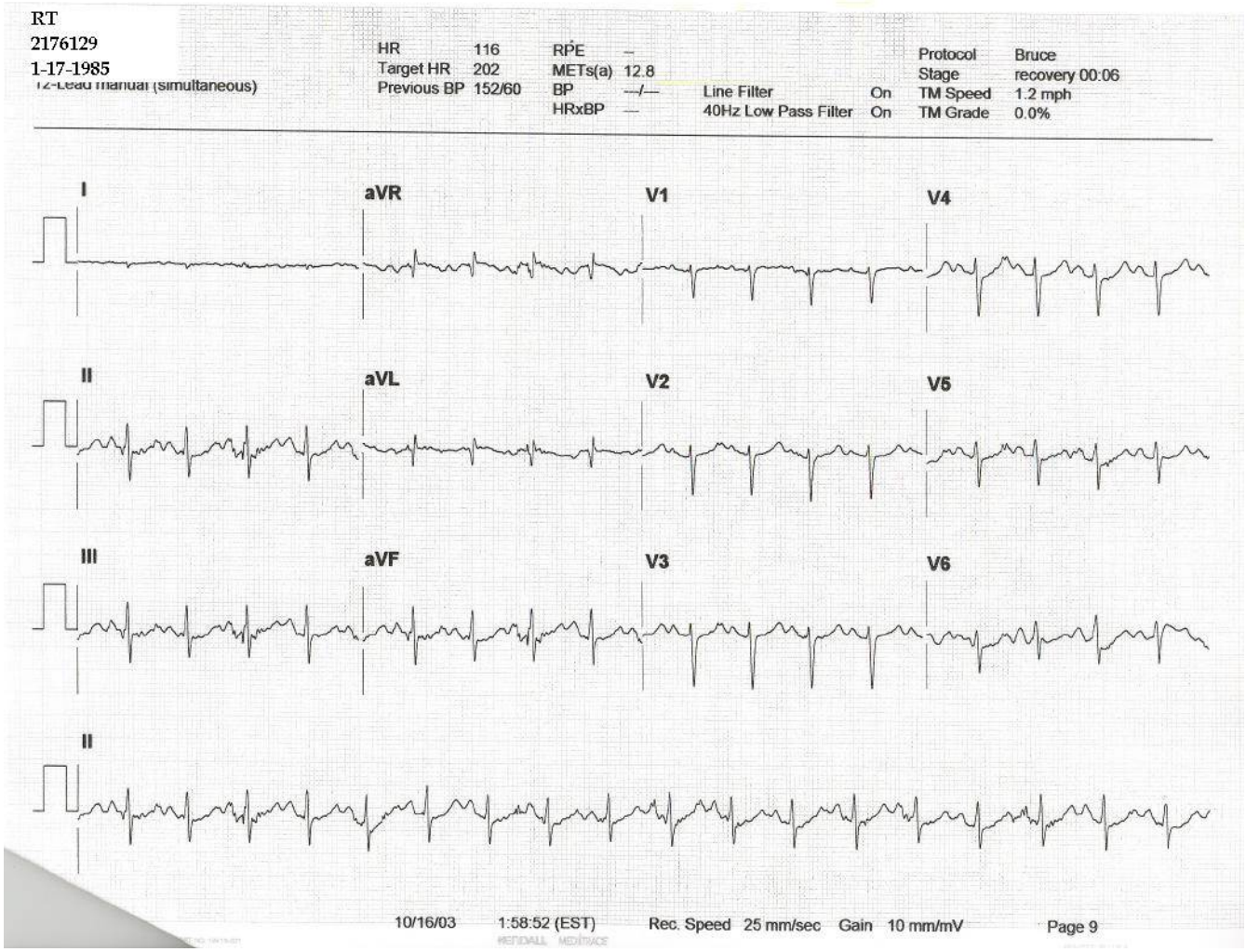

Figure 2: Panel B

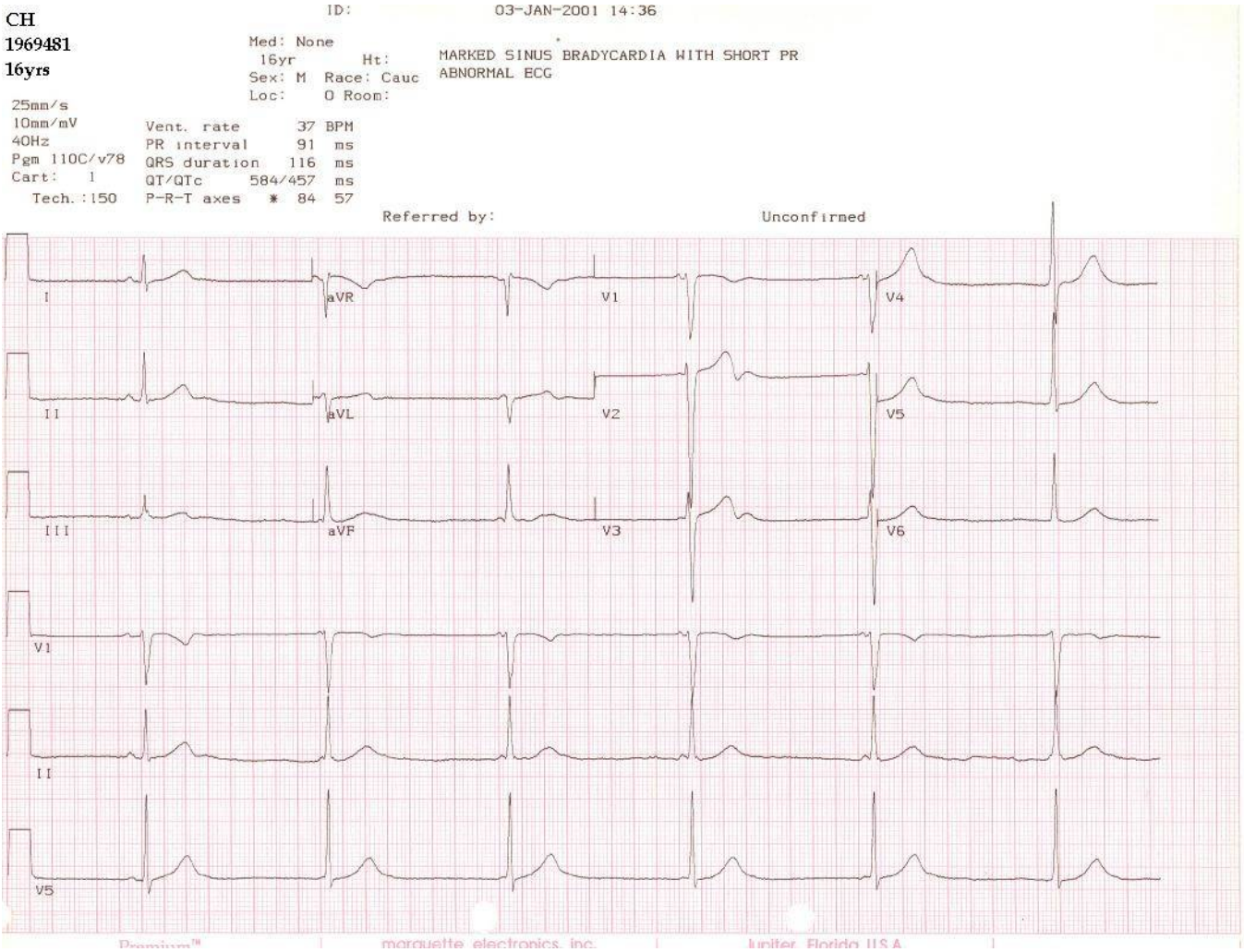

Figure 3: Panel A shows a resting ECG with sinus rate at 37 beats per minute with the QT interval of 0.52 seconds. The RR interval was 1.6 second with corrected QT interval of 0.41 seconds. The T wave morphology is abnormal with a biphasic or triphasic pattern in V2-V3. This can be normal especially in children but if present in more lateral precordial leads it is compatible with abnormal repolarization due to LQTS. In the presence of marked bradycardia the corrected QT interval was within normal limits.

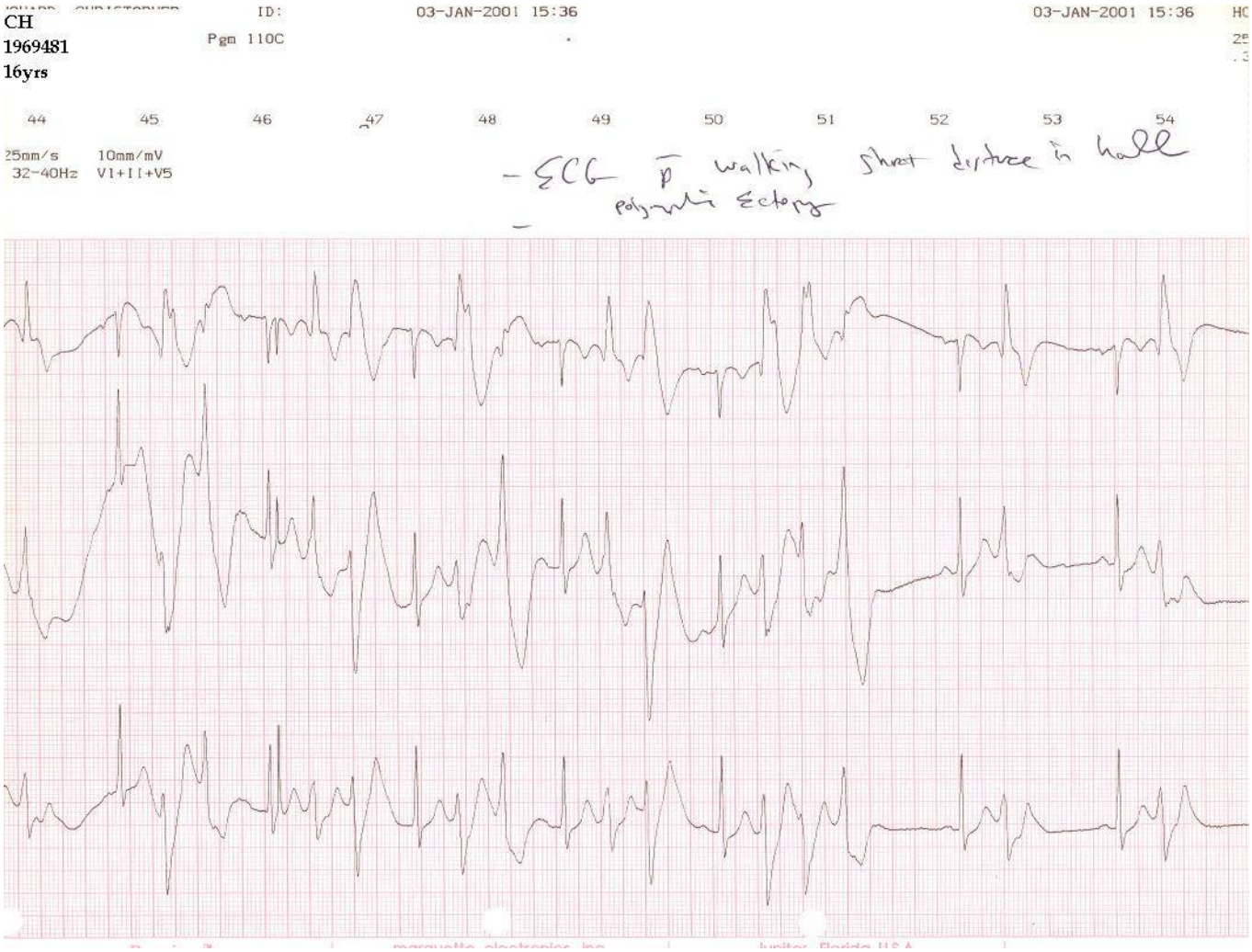

Figure 3 Panel B.The tracing is after walking a short distance in the hall and demonstrates incessant nonsustained polymorphic ventricular tachycardia. The QT interval is 0.36 seconds and given an RR interval of 0.4 seconds the corrected QTc is 0.57 seconds after exercise. The resting ECG's marked bradycardia did not allow one to make a diagnosis of LQTS in this 16 year-old boy with a strong family history of the Long QT syndrome. He had prolongation of the QTc with exercise along with very frequent ventricular tachycardia that helped confirm the diagnosis of LQTS. Given the Family history of sudden death and the patient's ventricular tachycardia during exercise an ICD was implanted. As an aside, the sinus bradycardia may be related to the LQT syndrome in this patient.

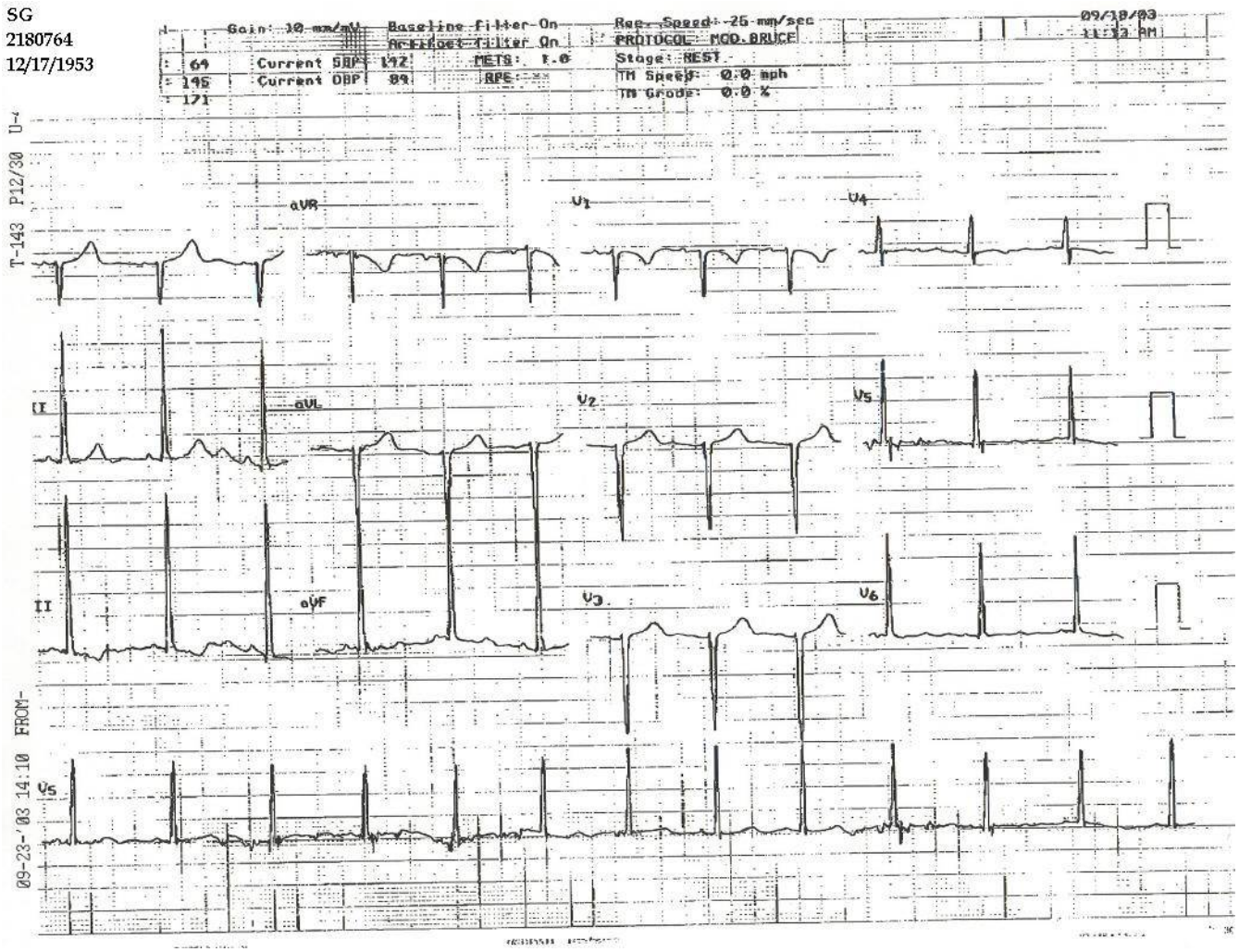

Figure 4: Panel A shows a resting ECG prior to exercise stress testing parentheses (Patient SG) and shows a QT interval of 0.42 seconds with RR interval 0.84 second yielding a corrected QT interval of 0.46 seconds.

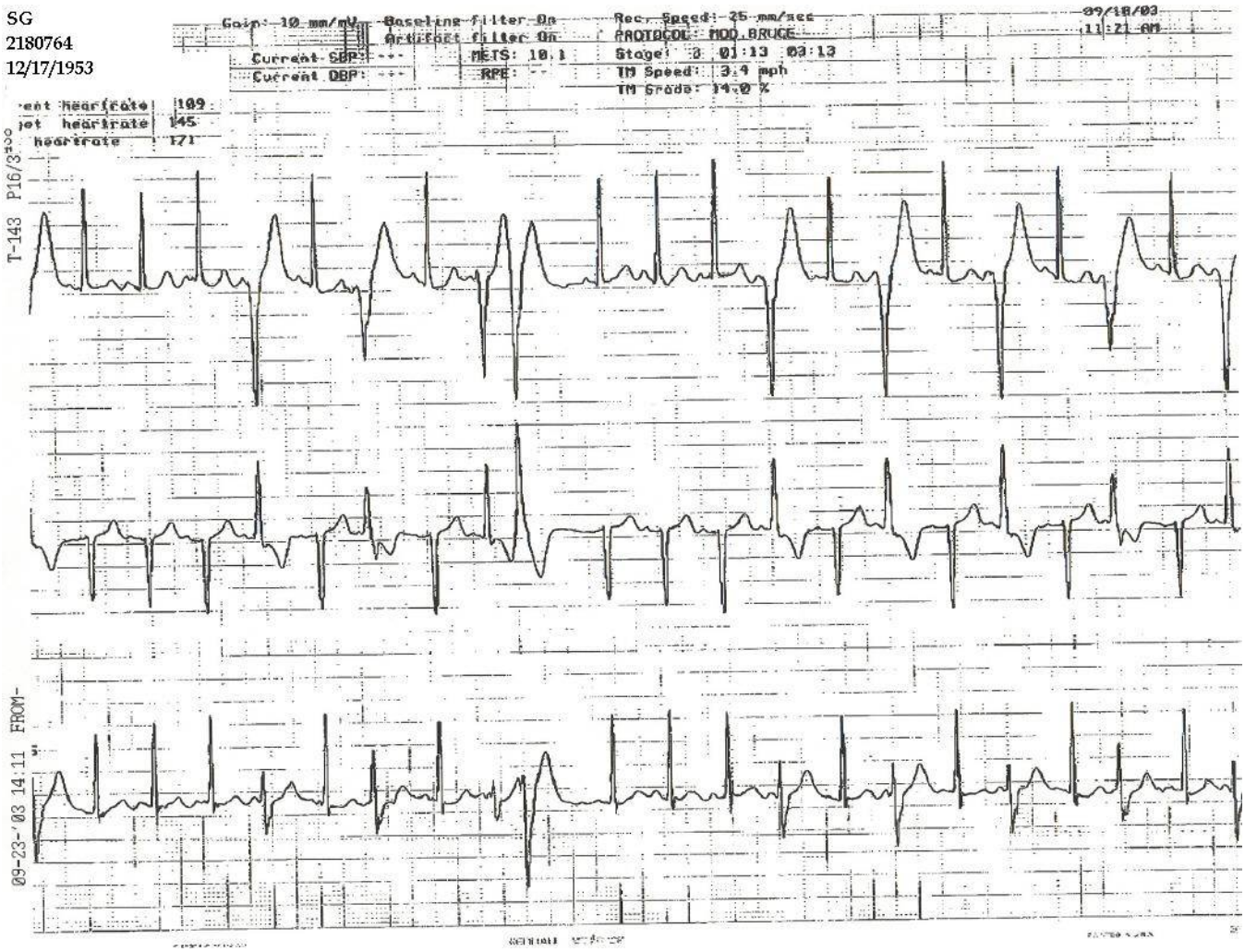

Figure 4: Panel B shows the exercise ECG in the same patients: QT 0.36 sec, RR 0.48 sec and QTc 0.52 sec. The patient also had frequent polymorphic ventricular tachycardia. The QTc is longer with exercise but one must be cautious about over interpreting a borderline or mildly abnormal QTc with exercise especially at faster heart rates. In this case the heart rate is less than 120 beats per minute and probably does represent abnormally prolonged QT interval. The ventricular ectopy may or may not be due to the Long QT syndrome [29]. Previous intracardiac mapping in this patient had shown multiple foci of ventricular tachycardia not amenable to catheter ablation. The exercise test did confirm long QT interval and provided additional information such as the ventricular tachycardia that is useful in understanding the patient's overall risk and pathology.

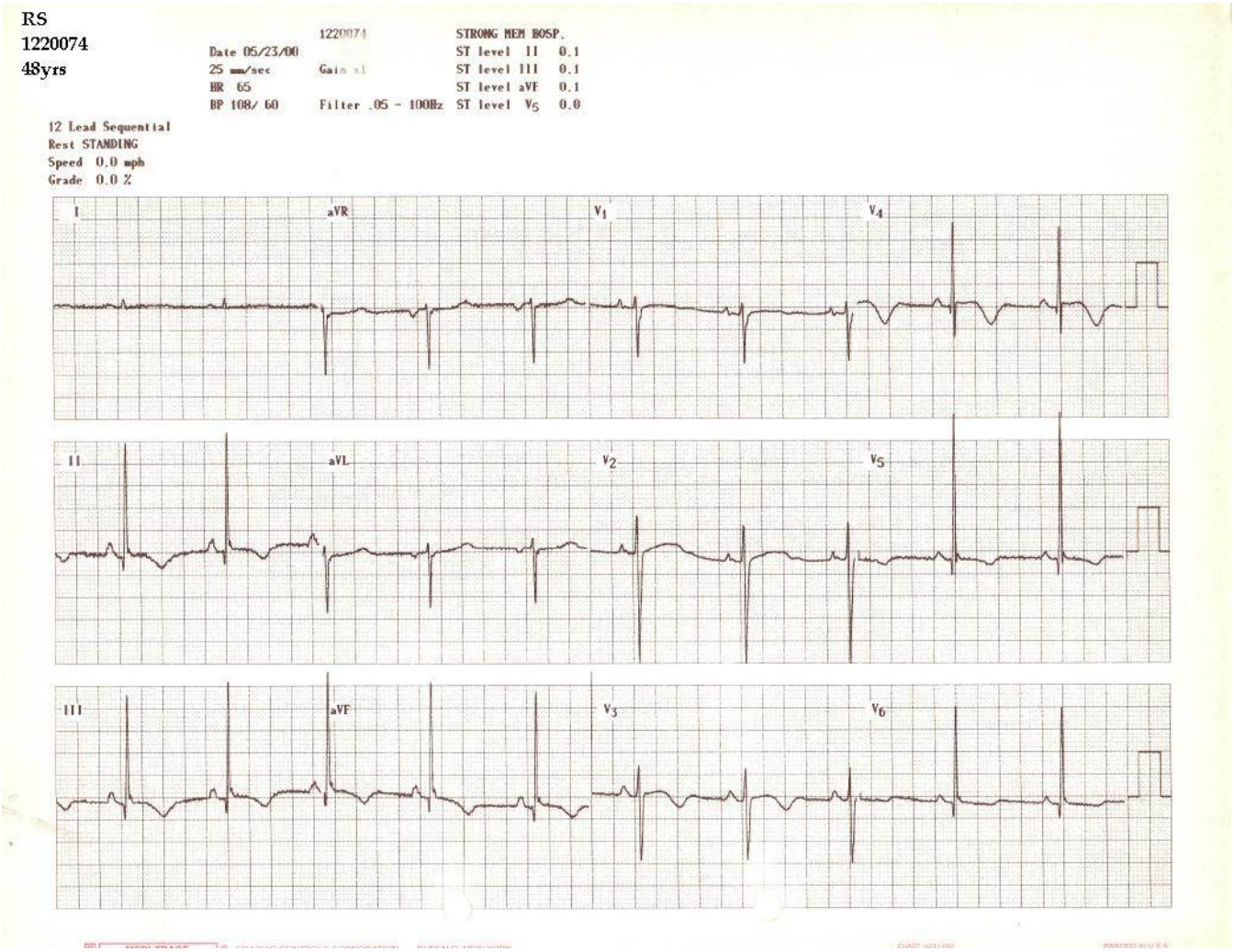

Figure 5: Panel A shows a resting ECG (Patient RS) with abnormal T wave morphology including inverted T waves inferiorly and laterally as well as in V1 through V3. The QT interval is 0.52 seconds yielding a corrected QT interval 0.47 seconds. Although the QTc is only mildly prolonged, given the very abnormal T wave morphology, male sex (0.47 is less likely in non-carriers in males) and the patient's history of exertional syncope, a diagnosis of LQTS was made.

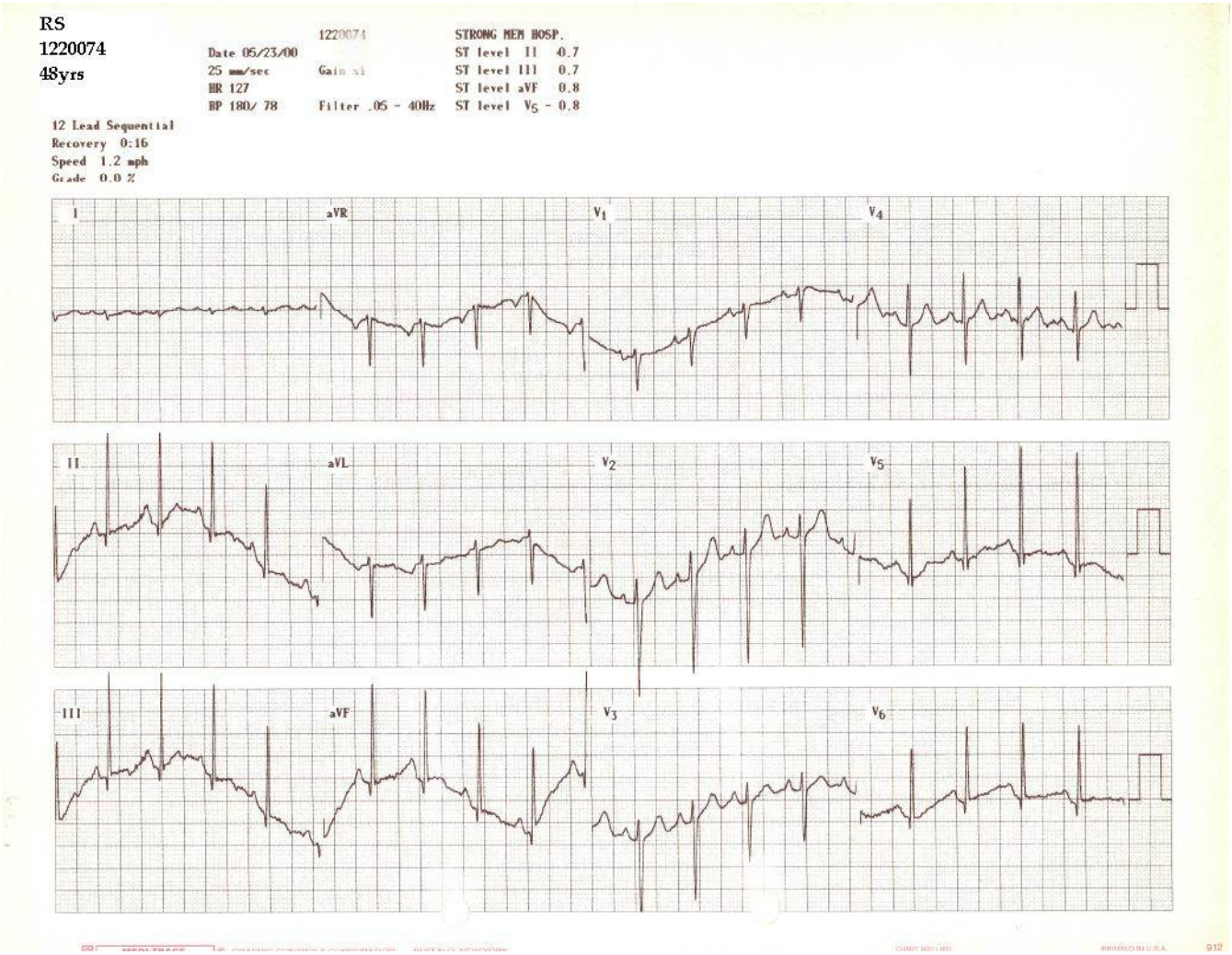

Figure 5: Panel B shows the exercise ECG in the same patient during the early recovery phase. The QT interval is difficult to measure due to the polyphasic T-wave. The QT is at least 0.32 seconds with an RR interval of 0.74 seconds resulting in a corrected QT 0.37 seconds. However, it is likely that the QT interval is underestimated given the low amplitude T-waves in some leads and the polyphasic T wave and wondering baseline during the exercise test.

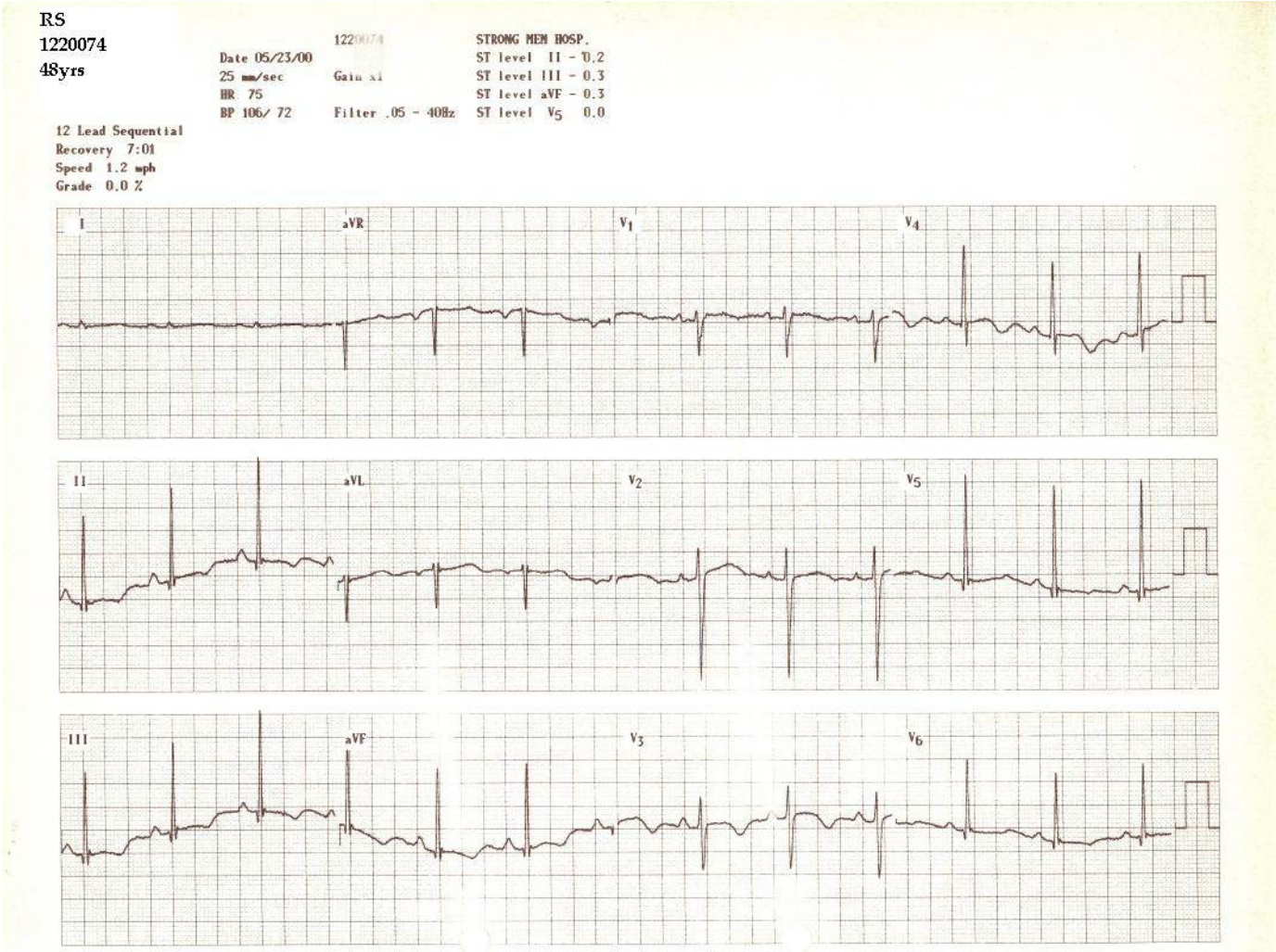

Figure 5: Panel C shows the ECG in RS later in the recovery phase, and again demonstrates a clearly abnormal QTc and abnormal T-wave morphology. The possibly “normal” QTc with exercise in this patient obviously should not dissuade one from diagnosing LQTS. The complex T-wave morphology and possible shortening of the QTc with exercise fit with LQT2.

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