Natural History of the Electrocardiographic Pattern of Early Repolarization in Ambulatory Patients

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Although it is known that the electrocardiographic pattern of early repolarization (ER) occurs most commonly in healthy young bradycardic men, its natural history is uncertain. We considered initial electrocardiograms (ECGs) at rest from 29,281 ambulatory patients recorded from 1987 through 1999 at Veterans Affairs Palo Alto Hospital. With PR interval as the isoelectric line and amplitude criterion as >0.1 mV ER was identified when any of the following fulfilled the amplitude criterion: ST-segment elevation at the end of the QRS duration, J waves as an upward deflection, and slurs as delay on the R wave downstroke. The first 250 ECGs with the greatest ER increase were selected and the database was searched for an ECG >5 months later. Of the 250 patients selected with the greatest amplitude of ER 6 were excluded for electrocardiographic abnormalities, leaving 244 subjects, of whom 122 had another ECG ≥5 months later. Their average age was 42 ± 10 years and average time from the first to second ECG was 10 years. Of the 122 patients 47 (38%) retained ER, whereas most (62%) no longer fulfilled the amplitude criterion. There were no significant differences in heart rate or time interval between ECGs. In conclusion, the electrocardiographic pattern of ER was lost over 10 years in more than half of this young clinical cohort and the loss was not caused by higher heart rate, longer time between ECGs, decrease in R-wave amplitude, death, acute disease, or alterations in electrocardiographic diagnostic characteristics. **(Am J Cardiol 2011;xx:xxx)**

ST-segment elevation in the absence of acute infarction was first reported on electrocardiograms (ECGs) of healthy subjects in 1947[1] and was termed "early repolarization" (ER) in 1951.[2] This "normal RS-T segment elevation variant" was characterized as ST-segment elevation with a distinct notch (J wave) or slur on the downslope of the R wave by Wasserburger and Alt[3] in 1961. In 1976 Kambara and Phillips[4] reported that ER was more common in young bradycardic men and in those of African ethnicity and appeared most commonly in the lateral leads. Although ER is more common in the young, suggesting that it must recede with age, there have been limited studies of its prognosis or serial ECGs in subjects with ER. To answer the question of what happens to this electrocardiographic pattern over time, we selected 250 patients exhibiting the greatest amplitude of ER from a large clinical population of ambulatory patients and examined our clinical electrocardiographic database to see who had ECGs ≥5 months later and compared them.

Methods

In total 45,829 unique inpatient and outpatient ECGs were recorded for clinical indications from March 1987 to December 1999 at the Veterans Affairs Palo Alto Health Care System. All patients were seen at the main Veterans Affairs facility or its satellite clinics, and ECGs were ordered by health care providers usually to screen for occult disease and to obtain a baseline when initiating care. Because clinical diagnostic codes were not available, we excluded those with inpatient status (n = 12,319) to eliminate ECGs possibly associated with acute coronary syndromes and other acute processes. Furthermore, ECGs exhibiting atrial fibrillation or flutter (n = 1,253), ventricular rates >100 beats/min (n = 2,799), QRS durations >120 ms (n = 3,141), paced rhythms (n = 290), ventricular preexcitation (n = 42), and acute myocardial infarction (n = 29) were excluded, leaving 29,281 patients for analysis. Race was determined by self-report at time of electrocardiographic acquisition.

With PR interval as the isoelectric line and the amplitude criterion for ER as ≥0.1 mV (100 μV or 1 mm when 10 mm = 1 mV) above the isoelectric line in lateral lead V_5, ER was identified when any of the following were seen to fulfill the amplitude criterion: ST-segment elevation at the end of the QRS duration, J waves as an upward deflection, and slurs as a conduction delay on the QRS downstroke. Computer-measured amplitude of ER was sorted from greatest to lowest amplitude and the first 250 ECGs with the greatest ER amplitude were selected and visually confirmed, analyzed, and coded by 3 independent interpreters with conflicts resolved by the senior author.

Patients were then queried to determine who had a subsequent ECG. One patient with diagnostic Q waves on the first ECG and 5 patients with abnormalities on the last ECG

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Table 1
Characteristics of total population for comparison between two subgroups of early repolarization (ER)

Characteristics	All Subjects (n = 29,281)	Early Repolarization in Lateral Leads (n = 479, 1.6%)	p Value*	Most Early Repolarization in Lead V_5 (n = 244, 0.8%)	p Value†
Age (years)	55 ± 15	42 ± 13	<0.001	40.7 ± 12.4	0.2
Men	25,544 (87%)	472 (98.5%)	<0.001	241 (99%)	0.5
African-American	3,885 (13%)	210 (44%)	<0.001	102 (42%)	0.2
Body mass index (kg/m^2)	27.3 ± 5.5	26.0 ± 4.1	<0.001	25.6 ± 4.0	<0.1
Heart rate (beats/min)	70.6 ± 12.6	63.2 ± 12.3	<0.001	63 ± 11.9	0.8
Cardiovascular deaths	1,995 (7%)	15 (3%)	<0.001	7 (3%)	0.95

* Between all subjects and those with all early repolarization in lateral leads.
† Between subgroup with early repolarization (n = 479) and most early repolarization in lead V_5 (n = 244).

Table 2
Characteristics of early repolarization (ER) subgroups

Characteristics	Most ER in Lead V_5 (n = 244, 100%)	Most ER in Lead V_5 on Second ECG (n = 122, 50%)	p Value*	Maintained ER (n = 47, 38.5%)	Lost ER (n = 75, 61.5%)	p Value† <0.001
Age (years)	40.7 ± 12.4	42.4 ± 10.3	0.1	39.3 ± 8.3	44.3 ± 10.9	0.008
Age at second electrocardiogram	—	52.3 ± 11.4	—	47.9 ± 10.5	55.1 ± 11.2	<0.001
Men	241 (99%)	122 (100%)	0.2	47 (100%)	75 (100%)	1.0
African-American	102 (42%)	66 (54%)	0.02	29 (62%)	37 (49%)	0.2
Body mass index (kg/m^2)	25.6 ± 4.0	26.3 ± 4.2	0.1	26.3 ± 3.9	26.3 ± 4.4	0.9
Cardiovascular deaths	7 (3%)	5 (4%)	0.5	2 (4.25%)	3 (4%)	0.9
Electrocardiographic measurements						
Computer ST level on first electrocardiogram (μV)	140.1 ± 24.7	138.4 ± 20.4	0.6	144.3 ± 21.8	134.6 ± 18.6	>0.01
Computer ST level one second electrocardiogram (μV)	—	77.8 ± 46.0	—	122.4 ± 25.2	49.8 ± 31.8	<0.001
Computer ST level difference (μV)	—	63.9 ± 40.5	—	30.9 ± 32.4	84.6 ± 29.8	<0.001
Heart rate						
Heart rate on first electrocardiogram (beats/min)	63 ± 11.9	64.7 ± 11.4	0.2	63.4 ± 11.5	65.5 ± 11.3	0.3
Heart rate on second electrocardiogram	—	68.7 ± 14.5	—	65.57 ± 13.5	70.7 ± 14.9	0.1
Change in heart rate (beats/min)	—	4.0 ± 14.2	—	2.2 ± 10.2	5.2 ± 16.1	0.3
Heart rate >85 beats/min on first electrocardiogram	12 (5%)	7 (6%)	0.7	1 (3%)	6 (8%)	0.2
Heart rate >85 beats/min on second electrocardiogram	—	17 (14%)	—	5 (11%)	12 (16%)	0.4
Time factor						
Period between electrocardiograms (years)	—	9.9 ± 5.9	0.1	8.58 ± 5.7	10.79 ± 5.9	0.04
Other early repolarization criteria						
First electrocardiogram						
J wave	114 (47%)	55 (45%)	0.8	24 (51%)	31 (41%)	0.3
Slur	71 (29%)	39 (32%)	0.5	9 (19%)	30 (40%)	<0.01
J wave or slur	185 (76%)	94 (77%)	0.8	33 (70%)	61 (80%)	0.2
J wave or Slur + STE	175 (72%)	81 (66%)	0.6	31 (66%)	50 (67%)	0.8
ST-segment elevation only	59 (24%)	28 (23%)	0.8	14 (30%)	14 (19%)	<0.001
Second electrocardiogram						
J wave	—	17 (14%)	<0.001†	17 (36%)	—	—
Slur	—	10 (8%)	<0.001†	10 (21%)	—	—
J wave or slur	—	27 (22%)	<0.001†	27 (57%)	—	—
ST-segment elevation only	—	17 (14%)	<0.001†	17 (36%)	—	—

p <0.01 was accepted as statistically significant.
STE = ST elevation.
* Between 2 consecutive columns.
† Between first and second electrocardiograms in the same column.

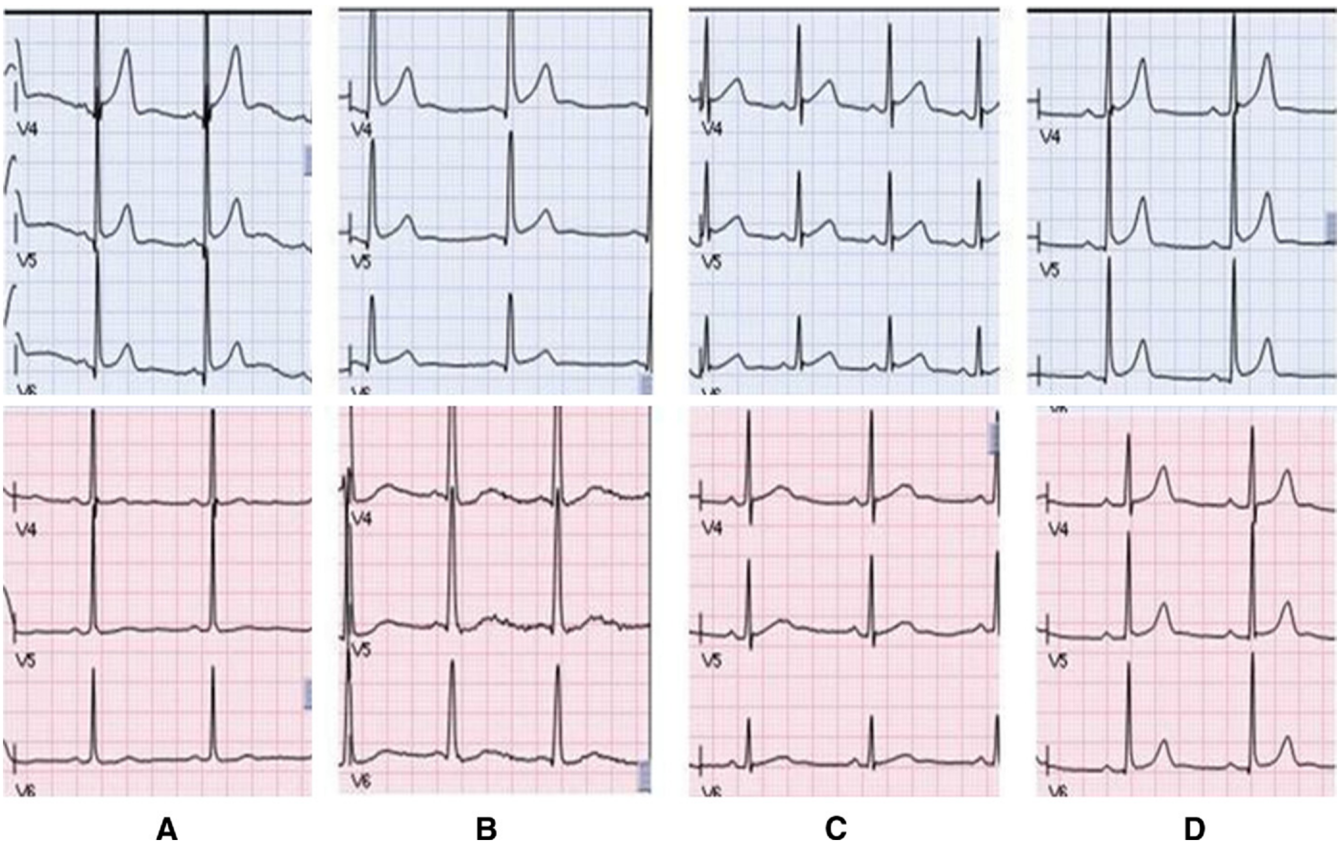

Figure 1. Four examples of paired electrocardiograms with greatest difference of early repolarization measured between them (i.e., loss of early repolarization). *(A)* A 63-year-old Asian-American man with a heart rate of 67 beats/min *(top)* and a heart rate of 63 beats/min after 20 years *(bottom)*. *(B)* A 50-year-old African-American man with a heart rate of 53 beats/min *(top)* and a heart rate of 71 beats/min after 18 years *(bottom)*. *(C)* A 37-year-old Caucasian man with a heart rate of 84 beats/min *(top)* and a heart rate of 60 beats/min after 16 years *(bottom)*. *(D)* A 41-year-old African-American man with a heart rate of 58 beats/min *(top)* and a heart rate of 57 beats/min after 7 years *(bottom)*.

(1 each with a diagnostic Q wave, atrial fibrillation, and sinus tachycardia and 2 with supraventricular tachycardia) were excluded. Thus, 122 patients were identified to have had a second ECG >5 months later. When multiple ECGs were available the ECG at the longest interval was chosen for comparison, paired, and printed for coding by 3 trained subjects. Chart review of patients with a second ECG was performed to determine if an acute medical condition necessitated this ECG. These patients were then compared according to whether they maintained or lost ER. For example, the patients were sorted by the greatest change in ER amplitude (i.e., lost ER) and the least change (i.e., maintained ER).

NCSS 2007 (NCSS, Kayesville, Utah) was used for all statistical analyses. Unpaired *t* tests were used for comparisons of continuous variables and chi-square tests were used to compare dichotomous variables between groups. A significance level of 0.01 was used.

Results

Of the total database of 29,281 patients, 479 patients (1.6%) were coded as manifesting ER in the lateral leads. When sorted by ER amplitude, of the 250 ECGs exhibiting the greatest amplitude 244 had otherwise normal ECGs and were queried for a repeat ECG >5 months later. Of these 122 (50%) had a subsequent ECG for comparison. On chart review 5 patients developed heart disease over the interval but no acute symptoms were present at the time of the second ECG.

Table 1 presents demographics and annual cardiovascular mortality of the total population and its subgroups according to selection criteria. Although there were significant differences between the total population and the ER subgroups, none were found between the 2 subgroups. There were 1,995 cardiovascular deaths (7%) over a mean follow-up of 7.6 ± 3.8 years in the total population with a significantly lower mortality ($p < 0.001$) in the ER subgroups (3.0% and 3.0%). Patients with ER were significantly younger (42 ± 13 vs 55 ± 15 years, $p < 0.001$) and had a lower heart rate (63 ± 12 vs 71 ± 13 beats/min, $p < 0.001$). There was a higher prevalence of men (99% vs 87%, $p < 0.001$) and African-Americans (44% vs 13%, $p < 0.001$) in the ER subgroups compared to the total population.

Table 2 presents the greatest amplitude ER group (n = 244) divided into those who had a second ECG ≥5 months later and a comparison between those who maintained ER to those who lost it. The total ER group had an average ER amplitude of 140 ± 25 μV (1.4 ± 0.25 mm) with 12 patients (5%) exhibiting a heart rate >85 beats/min. J waves

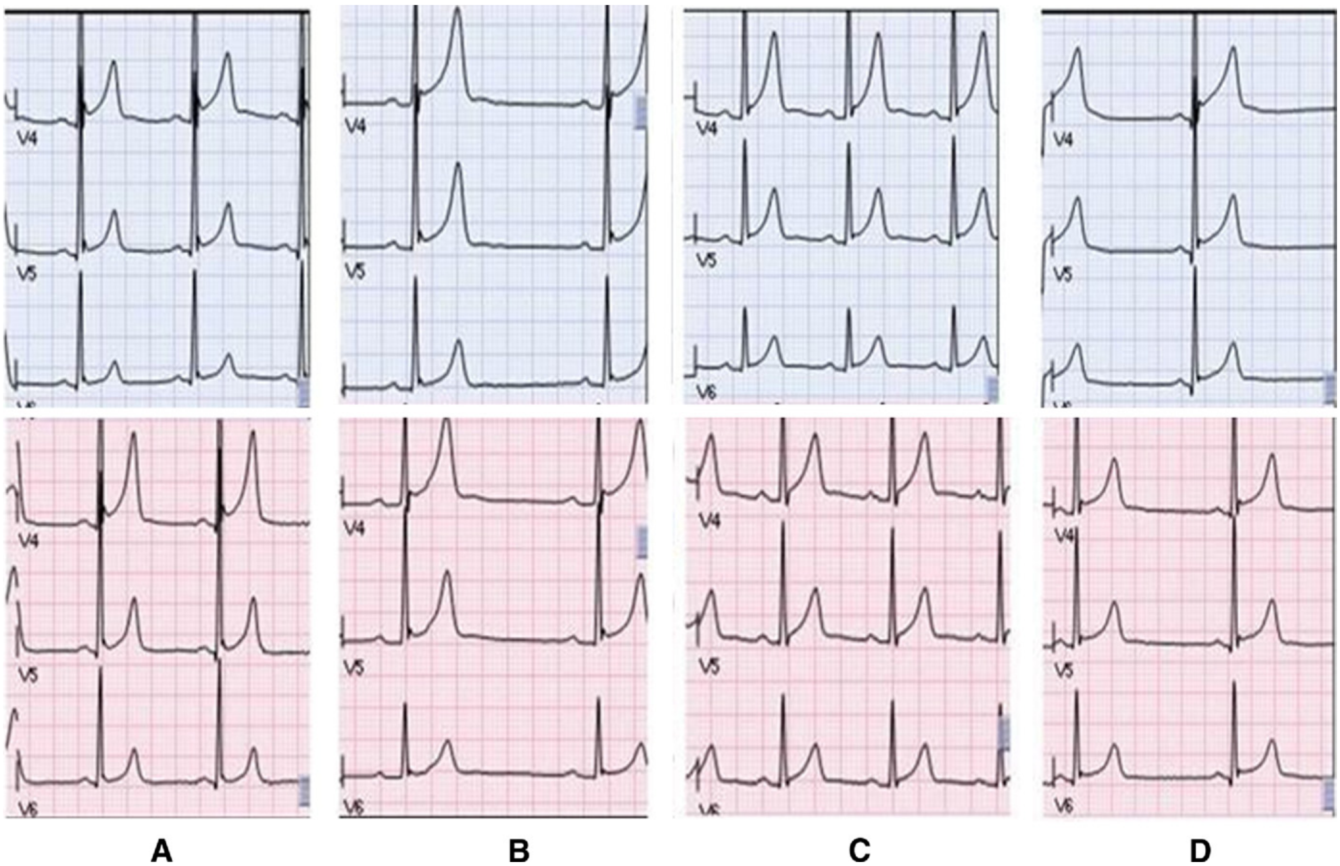

Figure 2. Four examples of paired electrocardiograms with least difference of early repolarization measured between them (i.e., maintenance of early repolarization). *(A)* A 42-year-old African-American man with a heart rate of 62 beats/min *(top)* and a heart rate of 64 beats/min after 2 years *(bottom)*. *(B)* A 46-year-old Caucasian man with a heart rate of 36 beats/min *(top)* and a heart rate of 40 beats/min after 10 years *(bottom)*. *(C)* A 46-year-old Pacific Islander man with a heart rate of 74 beats/min *(top)* and a heart rate of 74 beats/min after 13 years *(bottom)*. *(D)* A 43-year-old African-American man with a heart rate of 44 beats/min *(top)* and a heart rate of 43 beats/min after 9 years *(bottom)*.

or slurs occurred in 76% with J waves being 1 1/2 times more common than the slurs, whereas only 24% of subjects (59 of 244) had only ST-segment elevation. Most ECGs with J waves and slurs also exhibited ST elevation measured at the mid point of the ST segment. On the second ECG (n = 122) average ER amplitude was 78 ± 46 μV with an average of 9.9 ± 5.9 years between the 2 ECGs. A significantly higher percentage of the second ECGs showed a heart rate >85 beats/min (14% vs 6%, p <0.001) and a lower prevalence of J waves and slurs (22% vs 77%, p <0.001) than the first ECG.

When comparing those who maintained ER to those who lost it, 38% maintained ER compared to 62% who lost it (p <0.001); those who maintained ER had 1-year less difference between their first and second ECGs but this was not statistically significant (8.9 ± 5.7 vs 10.8 ± 5.9 years, p = 0.04). Those who maintained ER were significantly younger than those who lost ER (39 ± 8 vs 44 ± 11 years, p = 0.008). There was no difference in prevalence of men, body mass index, or percent cardiovascular deaths (4%) between subgroups. Although African-Americans were more likely to have ER, they were not more likely to maintain it (62% vs 49%, p = 0.2). No significant difference was found in heart rates of the 2 groups on the first or second ECG or the percentage with heart rates >85 beats/min. Regarding other ER criteria, prevalence of J waves or slurs on the first ECG was not statistically different (70% vs 80%, p = 0.15) between the maintained versus lost ER groups.

Figures 1 and 2 show examples of patients who lost ER (greatest change in ER) and those who maintained ER (least change in ER), respectively.

Discussion

This is the largest serial electrocardiographic comparison study in a clinical population of the natural history of ER. Our cohort was selected from a group (n = 29,281) with computerized measurements. The target group for this serial electrocardiographic study (122 of 250 subjects) with the greatest amplitude of ER in lead V_5 had a repeat ECG for clinical reasons other than cardiovascular problems. In these apparently healthy subjects, we demonstrated that most lost ER (62%) and that the loss could not be explained by differences in changes in heart rate or interval between ECGs or by alterations in baseline electrocardiographic pattern. These findings imply that ER must be lost with age. Because our target group had the greatest amplitude for ER, it is likely that the entire group with ER was even more likely to have lost this phenomenon.

In an apparently asymptomatic healthy population ER has been considered a benign finding. However, ST-segment elevation patterns with or without J waves can also be found in hypothermia, ischemia, and Brugada syndrome. The J waves of hypothermia, also called "Osborn waves," are usually more marked than those seen routinely in ER.[5] The ST-segment elevation seen in Brugada syndrome is isolated to the right precordial leads.[6] Elegant cellular physiology studies have associated electrocardiographic patterns with channelopathies, which has led to concerns that their presence even in apparently healthy subjects could be markers of cardiac events.[7–9] Several recent clinical studies have supported this hypothesis.[10–12] Results of our study challenge this hypothesis, supporting the long held clinical belief that ER is primarily a benign phenomenon.

There are limitations to our study including a population of predominantly men, focus on 1 lateral lead (lead V_5), and use of computerized electrocardiographic technology. Furthermore, our target population is a convenience sample because ECGs were ordered for clinical indications and not by protocol. Those selected for repeat ECGs at a later time could have had a new clinical indication for doing so. However, repeat ECG did not show diagnostic changes that could be associated with pathologic conditions causing the loss of ER and chart review did not reveal any acute clinical condition. Focus on lead V_5 permitted a more consistent less fragmented classification of ER, avoiding confusion with pattern changes between other leads or meeting ER criteria in adjacent leads. Our application of computerized measurements and display with visual confirmation are more consistent with current clinical practice. Development of algorithms to identify and quantitate R-wave slurring and J waves should be a priority for future studies.

The electrocardiographic pattern of ER was lost over time (average interval 10 years) in more than half of this young clinical cohort (average age 42 years) and the loss was not caused by a higher heart rate, a longer time between ECGs, death, acute cardiac conditions, decreased R-wave amplitude, or alterations in electrocardiographic diagnostic characteristics.

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