ORIGINAL ARTICLE

Natural History of Early Repolarization in the Inferior Leads

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Aims: Though early repolarization (ER) in the inferior leads has been associated with increased cardiovascular risk, its natural history is uncertain. We aimed to study the serial electrocardiographic behavior of inferior ER and understand factors associated with that behavior.

Methods: We selected electrocardiograms (ECGs) from patients with the greatest amplitude of ER in AVF from ECGs of 29,281 ambulatory patients recorded between 1987 and 1999 at the Palo Alto Veterans Affairs Hospital. Starting from the highest amplitude, we reviewed the ECGs and medical records from the first 85%. From this convenience sample, 36 were excluded for abnormal patterns similar to ER. The remaining 257 patients were searched for another ECG at least 5 months later, of whom, 136 satisfied this criteria. These ECGs were paired for comparison and coded by four interpreters.

Results: The average time between the first and second ECGs was 10 years. Of the 136 subjects, 47% retained ER while 53% no longer fulfilled the amplitude criteria. While no significant differences were found in initial heart rate (HR) or time interval between ECGs, those who lost the ER pattern had a greater difference in HR between the ECGs. There was no significant difference in the incidence of cardiovascular events or deaths.

Conclusions: In conclusion, the ECG pattern of ER was lost over 10 years in over half of the cohort. The loss of ER was partially explained by changes in HR, but not higher incidence of cardiovascular events or death, suggesting the entity is a benign finding.

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electrocardiography; serial ECGs; early repolarization; inferior leads

ST-segment elevation on the resting electrocardiogram (ECG) in the absence of coronary artery disease or pericarditis was first reported in healthy individuals in 1947[1] and titled early repolarization (ER) in 1951.[2] In 1976, Kambara and Phillips[3] reported that ER often included a distinct notch (J wave) or slur on the down slope of the R wave. ER is a prevalent electrocardiographic finding, affecting up to 5% of the population and until recently the condition was considered benign. However, experimental, case-control and cohort studies suggest that this pattern, especially when observed in the inferior leads, is associated with increased risk of cardiovascular death.[4–7]

While ER is more common in the young, suggesting that it recedes with age, there have been limited studies of its prognosis and its natural history is uncertain. Demonstrating that ER can disappear naturally rather than its decreasing prevalence being due to death would supplement

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appropriate studies using survival analysis. Therefore, we present a study of the natural history of inferior ER utilizing serial ECGs in an ambulatory clinical population.

METHODS

A total of 45,829 unique inpatient and outpatient ECGs were recorded for clinical indications from March 1987 to December 1999 at the VA Palo Alto Health Care System. All patients were seen at the main Veteran Affairs (VA) 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. Since 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 one or more of the following were excluded: atrial fibrillation or flutter (n = 1253), ventricular rates > 100 beats per minute (n = 2799), QRS durations > 120 milliseconds (n = 3141), paced rhythms (n = 290), ventricular preexcitation (n = 42), and acute myocardial infarction (n = 29). This left 29,281 patients for consideration. Race was determined by self-report at the time of ECG acquisition.

With the PR interval as the isoelectric line and the amplitude criteria for visual coding of ER as ≥ 1.0 mm (1.0 mm when 10 mm = 1 mV) above isoelectric line in inferior lead AVF, ER was identified when any of the following were seen to fulfill the amplitude criteria: ST elevation at the end of the QRS, J waves as an upward deflection and slurs as a conduction delay on the QRS down stroke. To simulate visual reading of the ECG, ≥0.9 mV was used for computer coding because of the human tendency to round readings to the full millimeter scaling. While our initial reports considered multiple area leads using both a single or contiguous lead criteria, to improve accuracy and reliability of interpretation we considered just single leads for ER classification. Computer-measured amplitude of ER in AVF was sorted from greatest to lowest amplitude to identify a convenience sample with the greatest ER amplitude. Those ECGs underwent visual confirmation, analysis and coding by three independent interpreters with conflicts resolved by the senior author. Due to the labor-intensive nature of reviewing and coding these ECGs, we decided to stop when at least 85% of those available with inferior ER were processed. The ECG database was then queried to determine who had a subsequent ECG. This ECG was printed for coding by three trained individuals and visually compared to the first ECG. When multiple ECGs were available, the ECG at the longest time interval was chosen for comparison. Chart review of the patients with a second ECG was performed to determine if an acute medical condition necessitated this ECG. The paired ECGs were then compared and coded as to whether they maintained or lost ER. Example matched ECGs were chosen by sorting the pairs by the greatest changes in ER amplitude (i.e., lost ER) and the least change (i.e., maintained ER).

NCSS software 2007 (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

Our target population of 136 patients who had a subsequent ECG for studying the natural history of ER was derived at as follows. Of the total 29,281 ambulatory patients with ECGs in our database, 185 patients were coded as manifesting ER solely in the inferior leads and 163 had ER in both inferior and lateral leads. When this total of 348 patients with inferior lead ER with or without lateral lead ER were sorted by ER amplitude with largest first, we chose to evaluate ECGs with ER amplitude in the top 85% range. This led to a sample of 293 ECGs for visual inspection and coding. When we removed 36 ECGs with pathological findings that could cause a pattern similar to ER (i.e., pericarditis, myocardial injury/infarction), 257 ECGs remained. These 257 patients with otherwise normal ECGs were queried for a repeat ECG more than 5 months later. Of these, 136 (59%) had a subsequent ECGs for comparison and were our target population for studying the natural history of ER. On chart review, 28 patients developed heart disease over the interval but no acute symptoms were present at the time of the second ECG.

Table 1 provides the demographics and annual cardiovascular mortality of the total population and its subgroups according to selection criteria described earlier. Patients with inferior ER were younger compared to the average population. There were significant differences in demographics

Table 1. Demographic Characteristics of the Total Population for Comparison with the Subgroups Showing Greatest Amount of Early Repolarization (including the subgroup with 36 patients with ECGs exhibiting Early Repolarization patterns due to pathological condition)

Characteristic	All Subjects	Early Repolarization			Most Early Repolarization			
		Inferior Leads Only	Both Inferior and Lateral Leads	p value	Inferior Leads Only	Both Inferior and Lateral Leads	p value	Most Early Repolarization Pathological ECGs Removed (Target Population)
N (%)	29,281 (100%)	185 (0.6%)	163 (0.6%)	0.9	137 (0.46%)	156 (0.53%)	0.3	257 (0.9%)
Age (years)	55 ± 15	52 ± 16	42 ± 14	<0.001	55 ± 14	44 ± 14	<0.001	47 ± 14.15
Males (%)	25544 (87.2%)	182 (98.5%)	158 (96.9%)	0.4	125 (91.2%)	152 (97.4%)	0.02	244 (94.9%)
African American (%)	3885 (13.3%)	31 (16.8%)	62 (38.0%)	<0.001	16 (11.7%)	46 (29.5%)	0.001	61(23.7%)
Body mass index (kg/m2)	27.3 ± 5.5	26.0 ± 5.4	24.5 ± 3.4	0.8	26.02 ± 5.3	25.4 ± 5.1	0.4	25.41 ± 5.0
Heart Rate (bpm)	70.6 ± 12.6	69.6 ± 13.1	66.0 ± 12.4	1	71.2 ± 13	69.1 ± 11.3	0.1	69.8 ± 11.69
Inferior Q waves (%)	2079 (7.1%)	25 (13.5%)	4 (2.5%)	<0.001	17 (12.4%)	4 (2.5%)	<0.001	0
Anterior Q waves (%)	593 (2.0)	3 (1.6)	4 (2.5%)	0.6	1 (0.7%)	1 (0.6%)	0.9	0
CV Deaths (%)	1995(6.8)	14 (7.6)	4 (2.5%)	0.03 sd	t17 (12.4%)	5 (3.2%)	0.002	15 (5.8%)

ECGs with early repolarization—inferior leads—irrespective of the presence of pathological ECGs: (137 + 156 = 293).
When 36 ECGs with abnormalities associated with early repolarization removed: (293 − 36 = 257).

Table 2. Characteristics of the Inferior Lead Early Repolarization Subgroups with ECGs Exhibiting Pathological Conditions Associated with ER Excluded

	Most Early Repolarization Inferior Lead Group	Most Early Repolarization Inferior Group with 2nd ECG	P value*	Maintained Inferior ER	Lost Inferior ER	P value*
Characteristics						
Number N (%)	257	136		64 (47%)	72 (53%)	0.05
Age (years)	47 ± 14.15	46.8 ± 12.68		47.1 ± 12.55	46.45 ± 12.87	0.8
Age at second ECG (years)	–	57.23 ± 12.2		57.3 ± 12.88	57.2 ± 11.7	0.96
Men (%)	244 (95%)	133 (98%)	0.1	62 (97%)	71 (99%)	0.6
African American (%)	61(23.7%)	38 (27.8%)	0.8	22 (34.4%)	16 (30.5%)	0.2
Body-mass index (kg/m2)	25.41 ± 5.0	26 ± 5.0	0.04	25.67 ± 4.4	26.42 ± 5.6	0.4
delta weight (Lbs)	–	4 ± 19.4		5.7 ± 20.3	2.35 ± 18.4	0.4
Cardiovascular Deaths (%)	15 (5.8%)	5 (3.7%)	0.1	1 (1.6%)	4 (5.5%)	0.2
Cardiovascular events (%)		28 (20.5%)		8 (12.5%)	20 (27.7%)	0.04
ECG Measurements						
Computer ST level 1st ECG (μV)	117.84 ± 16.1	120.1 ± 17.9	0.1	121.79 ± 18.7	118.5 ± 17.14	0.3
Computer ST level 2nd ECG (μV)	–	65.97 ± 48.23		91.76 ± 38.45	43 ± 33.55	<0.001
Computer ST level difference (μV)	–	54.08 ± 52.3		30.03 ± 37.97	75.5 ± 41.6	0
Heart Rate						
Heart Rate 1st ECG (bpm)	69.8 ± 11.69	69 ± 11.69	0.1	70.2 ± 12.1	67.9 ± 11.25	0.2
Heart Rate 2nd ECG (bpm)	–	74.7 ± 18.5		70.04 ± 16.7	78.88± 19.3	0.005
Delta Heart rate (bpm)	–	5.7 ± 18.8		(-)0.2 ± 17.4	11 ± 18.6	0.0005
HR > 85 bpm 1st ECG	26 (10.1%)	12 (8.8%)	0.4	6 (9.3%)	6 (8.3%)	0.8
HR > 85 bpm 2nd ECG	–	33 (24.3%)		11 (17.1%)	22 (30.5%)	0.06

(Continued)

Table 2. (Continued)

	Most Early Repolarization Inferior Lead Group	Most Early Repolarization Inferior Group with 2nd ECG	P value*	Maintained Inferior ER	Lost Inferior ER	P value*
Time Factor						
Period between ECGs (years)	–	10.46 ± 6.44		10.16 ± 6.95	10.72 ± 6.04	0.6
Other ER criteria						
First ECG						
All (STEL, J, slur) (%)	257 (100%)	136 (100%)		64 (100%)	72 (100%)	
J wave (%)	52 (20.2%)	25 (18.4%)	0.7	14 (21.9%)	11 (15.3%)	0.07
Slur (%)	181 (70.5%)	100 (75.3%)	0.5	47 (73.4)	53 (73.6%)	0.3
J wave or slur (%)	233 (91%)	125 (92%)	0.7	61 (95%)	64 (89%)	0.3
ST elevation only (%)	24 (9.3%)	11 (8.0 %)	0.7	3 (4.6%)	8 (11.1%)	0.17
J wave or slur only (%)	196 (76.3%)	103 (75.7%)	0.9	53 (82.8%)	50 (69.4%)	0.06
J wave or slur+STEL (%)	37 (14.4%)	22 (16.2%)	0.6	8 (12.5%)	14 (19.4%)	0.2
Association with lateral ER (%)	148 (57.6%)	82 (60.2%)	0.6	38 (59.3%)	44 (61.1%)	0.8
Second ECG						
J wave (%)	–	20 (14.7%)		20 (31.3%)	0	0
Slur (%)	–	34 (25%)		34 (53.1%)	0	0
J wave or slur (%)	–	54 (39.7%)		54 (84.4%)	0	0
ST elevation only (%)	–	10 (7.5%)		10 (15.6%)	0	0
J wave or slur only (%)	–	46 (33.8%)		46 (71.8%)	0	0
J wave or slur + STEL (%)	–	8 (5.8%)		8 (12.5%)	0	0
Association with lateral ER (%)	–	29 (21.3%)		29 (45.3%)	15 (20.8%)	0.001

ER = early repolarization; HR = heart rate; ECG = electrocardiogram; STEL = ST elevation.

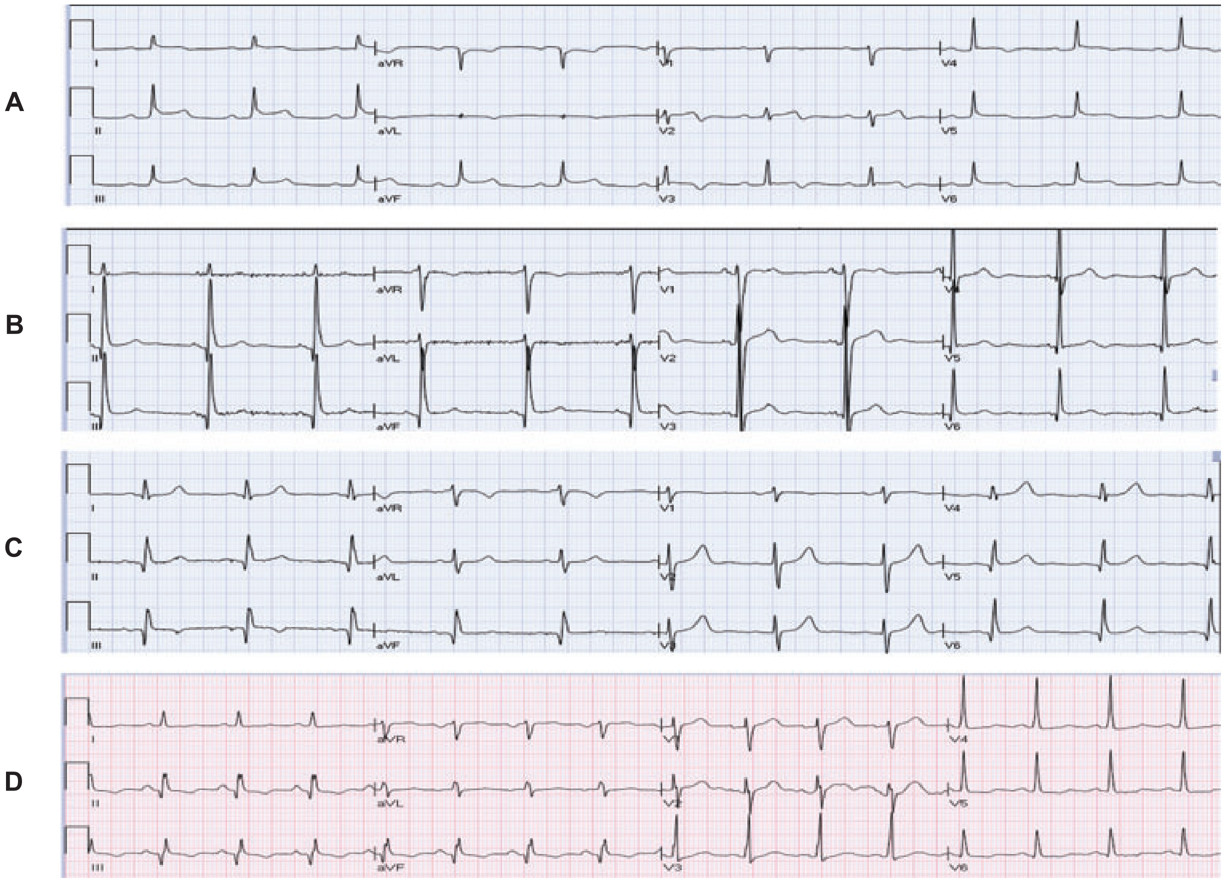

Figure 1. Four examples of excluded patient's ECG's. (A) A 50-year-old Hispanic male; Heart rate of 65 bpm. ECG shows pericarditis. (B) A 69-year-old Caucasian male; Heart rate of 64 bpm. ECG shows hypertrophic cardiomyopathy Q waves. (C) A 69-year-old Caucasian male; Heart rate of 64 bpm. ECG shows inferior myocardial infarction (old). (D) A 75-year-old Caucasian male; Heart rate 94 bpm. ECG shows inferior myocardial infarction (old).

between patients with ER in the inferior leads only versus both inferior and lateral ER. Patients with both inferior and lateral lead ER were younger and had a lower heart rate and a higher proportion of African Americans, a lower prevalence of inferior q waves and a trend towards increased cardiovascular death. The group with ER showed a similar demographic profile as the total population consistent with no selection biases.

Table 2 shows the greatest amplitude "normal" ER group (N = 257) divided into those who had a second ECG at least 5 months later (N = 136). The subgroup with a second ECG had no significant differences from the 257 available for review consistent with an absence of any selection biases. In the greatest amplitude Inferior lead ER and their subgroup with a second ECG, slurs or J waves were present in 75% as the only manifestation of ER, while ST elevation alone was present in less than 10% of the ECGs. Slurs were nearly four times more common than J waves and 15% had both slurs or J waves and ST elevation. Inferior ER was associated with lateral ER in 60% of the cases.

This target group of 136 with inferior lead ER and a subsequent ECG is divided into those who maintained ER and those who lost it for the major comparison in this study. When comparing those who maintained inferior ER to those who lost it, 47% maintained it while 53% lost it; it is important to mention that the average time interval between first and second ECG was 10 years. Those who maintained inferior ER had no difference in heart rate, while those who lost it averaged 10 beats per minute higher on the second ECG. There was no significant difference in male prevalence, body mass index, cardiovascular events, cardiovascular

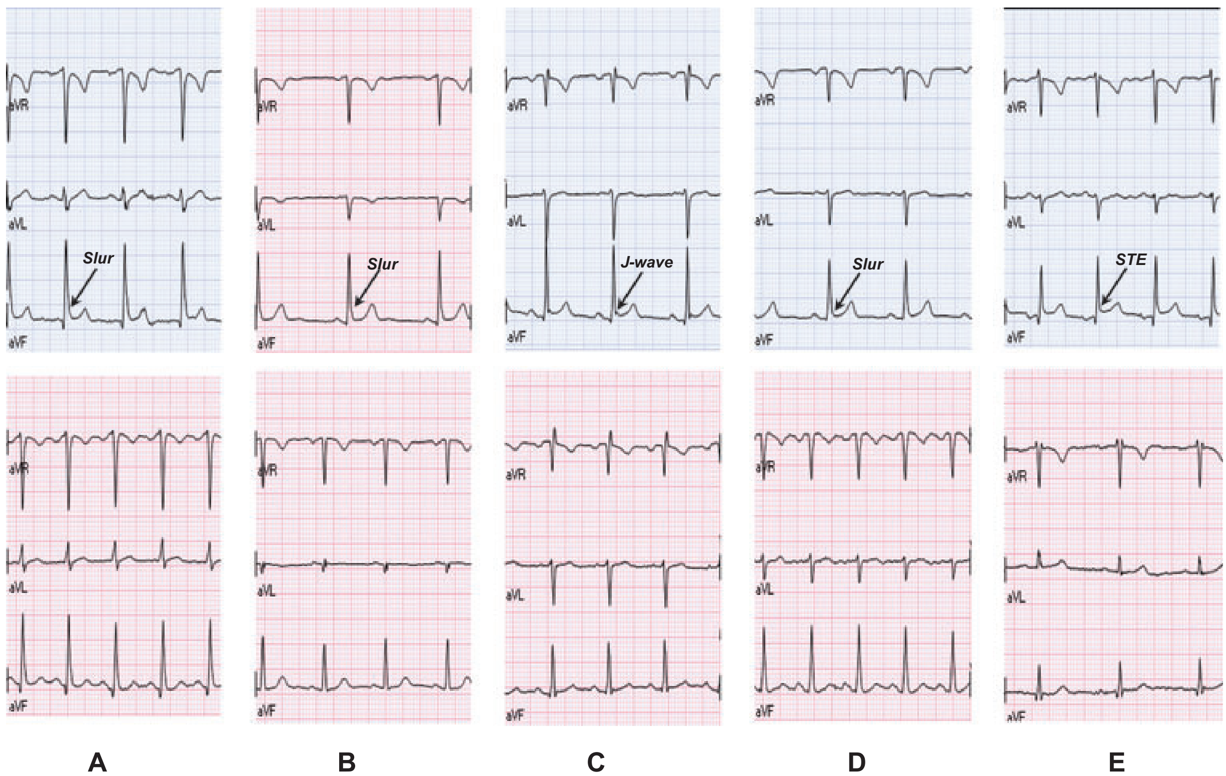

Figure 2. Five examples of paired ECGs with lost early repolarization phenomenon. (A) A 41-year-old African American male; heart rate of 86 bpm. (Top panel). Same male after 3 years; heart rate of 53 bpm. (Bottom panel). (B) A 51-year-old Caucasian male; heart rate of 56 bpm. (Top panel). Same male after 11 years; heart rate of 83 bpm. (Bottom panel). (C) A 20-year-old Caucasian male; heart rate of 75 bpm. (Top panel). Same male after 22 years; heart rate of 92 bpm. (Bottom panel). (D) A 32-year-old Caucasian male; heart rate 71 bpm. (Top panel). Same male after 18 years; heart rate of 110 bpm. (Bottom panel). (E) A 42-year-old Caucasian male; heart rate 85 bpm. (Top panel). Same male after 15 years; heart rate of 82 bpm. (Bottom panel).

deaths, or African Americans in the subgroups. Regarding other ER criteria, the prevalence of J waves or slurs, ST elevation or associated lateral ER was not statistically different between the maintained versus lost inferior ER groups.

Figure 1 are examples of ECGs chosen using the amplitude for inferior ER with pathological findings associated with conditions that could cause ER like patterns and were removed from the study. Figures 2 and 3 are examples of patients who lost inferior ER (greatest change in ER amplitude) and those who maintained inferior ER (least change in ER amplitude), respectively.

DISCUSSION

Our results suggest that in a stable outpatient population, ER in the inferior leads was lost in about half of the population over an average period of 10 years. The conditions that could cause this loss of ER including a higher heart rate, longer time between ECGs, ethnicity, gender, cardiac events between ECGs and death. Within the group that lost the ER pattern, there was a statistically significant increase in heart rate between the first and second ECG. However, there were no significant differences between the groups that lost or retained ER as far as age, body mass index, time interval between ECGs, cardiovascular events, cardiovascular death, gender, and African American ethnicity. The relatively small difference in heart rate (11 bpm) could not explain the loss leading us to conclude that our findings represent the natural history of inferior lead ER.

Our findings are consistent with the concept that ER has a higher prevalence in younger populations and that the pattern is often lost over time. How much of the loss is due to basal heart rate increases,

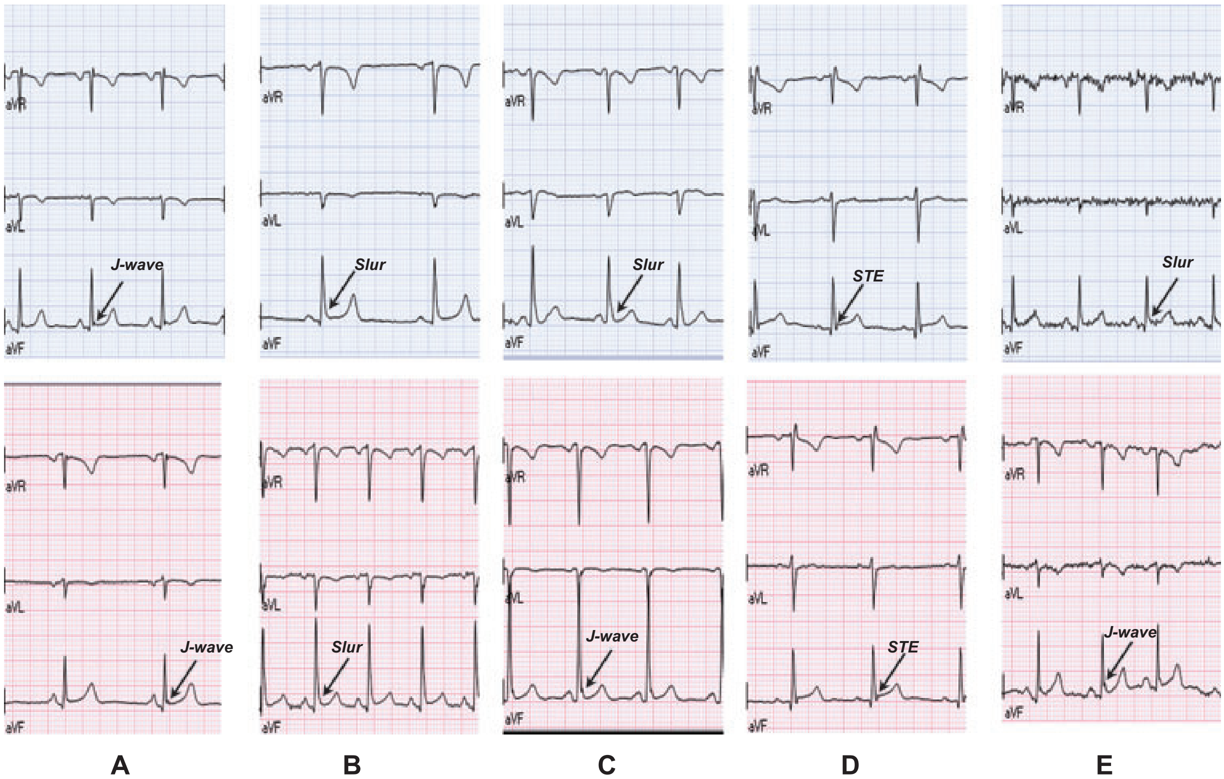

Figure 3. Five examples of paired electrocardiograms with maintained early repolarization phenomenon. (A) A 46-year-old Caucasian male; heart rate of 73 bpm. (Top panel). Same male after 18 years; heart rate of 52 bpm. (Bottom panel). (B) A 37-year-old African American male; heart rate of 47 bpm. (Top panel). Same male after 22 years; heart rate of 98 bpm. (Bottom panel). (C) A 41-year-old African American male; heart rate of 74 bpm. (Top panel). Same male after 18 years; heart rate of 74 bpm. (Bottom panel). (D) A 23-year-old Caucasian male; heart rate 63 bpm. (Top panel). Same male after 3 years; heart rate of 61 bpm. (Bottom panel).(E) A 61-year-old African American male; heart rate 80 bpm. (Top panel). Same male after 17 years; heart rate of 82 bpm. (Bottom panel).

age related myopathic changes and/or death was poorly defined. Our prior data evaluating the natural history of ER in lateral leads did not identify that loss to be associated with changes in heart rate, cardiovascular events, or deaths.[8] Similarly, in our current study we find that the age related attrition of inferior ER is not related to increased cardiovascular death. This argues against the hypothesis the ECG finding becomes less prevalent as carriers of the inferior ER suffer arrhythmic deaths.

ER was long believed to be a benign clinical entity until a case cohort study by Haissaguerre et al. identified a higher prevalence of ER in patients with idiopathic ventricular fibrillation.[5] This finding was subsequently evaluated on a population level by multiple groups suggesting a small, but statistically significant, increased risk of arrhythmic or cardiovascular mortality associated with ER.[6,7,9–11] We attempted to evaluate the risk in our own ambulatory population and failed to identify an increased cardiovascular hazard when controlling for demographics and concomitant ischemic findings on ECG.[12] We did find a higher prevalence of other ECG abnormalities with inferior ER compared to lateral ER. This was again evident in this study with the high number of ECGs that had to be excluded due to concomitant ECG findings of ischemia compared to our experience with lateral ER.[8] This association might explain the increased cardiovascular risk some groups identified with inferior ER.

Study by Tikkanen et al. reported that over 80% of the population with inferior ER retained the phenomenon.[6] This is divergent from the 53% retention rate we report here and from the 38% retention rate in the lateral leads previously reported.[8]

The variation in results might be related to several factors. The demographics of our populations are different with our population being predominantly male, more ethnically diverse and older. Furthermore, we used a definition of ER that relied mainly on ST elevation, not limited to J waves or slurs. In addition, the average duration of follow up ECG was longer in our study (10 years vs. 5 years). The study did not stratify risk based on retention or loss of the repolarization pattern.

We acknowledge that prospective population studies are the best method to determine prognostic significance, but the natural history of a finding can provide some insight into the behavior of a phenomenon. Our study found that approximately half of the patients lost ER over time confirming the long held classic description that ER decreases in prevalence with age. If inferior ER carries an increased risk of cardiovascular deaths then one would expect to see that the decreasing prevalence of the phenomenon to be associated at least partially with cardiovascular mortality. In other words, assuming a sustained risk model, the group that retains the ECG phenomenon should have a higher cardiovascular event rate over time. Our study did not identify this difference, and if anything saw a trend towards decreased cardiovascular events in the group that retained inferior ER. This does not provide a prognostic conclusion regarding the phenomenon, which was previously reported by our group and others; instead this demonstrates that the loss of ER over time was not due to cardiovascular deaths.

Main limitations to our study are that it is a retrospective convenience sample and not a prospective natural history study, but our data provides a hypothesis to be tested in prospective fashion. In addition, our target population is a selected sample, given that the 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, the repeat ECG did not show diagnostic changes that could be associated with pathological conditions causing the loss of ER nor did chart review reveal any acute clinical condition. Also, we chose to define one lead each for assessing inferior and lateral ER. This improves accuracy of identifying ER and avoids potential discordance between partial lead changes across different ECGs. This increases the specificity of identifying ER and decreases the probability of committing a type 1 error. Lastly, our population was predominantly male, thus restricting the interpretation of our data to males.

To our knowledge this is the first report describing the natural history of ER in the inferior leads. Our findings suggest that inferior lead ER was lost in over half of the population due to heart rate changes and other aging related phenomenon, but not cardiovascular death. This suggests that the age related attrition part of the natural history of inferior ER is not related to an increased cardiovascular risk eliminating carriers of the phenomenon.

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