The Prognostic Value of T Wave Amplitude in Lead aVR in Males

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Background: Since there is an uncertainty regarding which of the 12 leads provides the most information, we investigated the association between repolarization phenomenon in all of the 12 leads and cardiovascular (CV) mortality.

Methods: Retrospective cohort study was performed at Palo Alto Veterans Affairs Medical Center, Palo Alto, California, which included 24,270 consecutive male veterans with ECGs obtained for clinical reasons from 1987 to 2000. Analysis of computerized 12-lead resting ECGs was performed of all subjects excluding inpatients, patients with atrial fibrillation, WPW, QRS duration > 120 ms, and paced rhythms. Average follow-up was 7.5 years during which time there were 1859 CV deaths.

Results: While ST segment measurements in aVR were univariately predictive of CV death, T wave amplitude superseded them in multivariate survival analysis. In addition, T wave amplitude in aVR outperformed repolarization measurements in all other leads as well as other ECG criteria (Q waves, damage scores, LVH) for predicting CV mortality. As T wave amplitude became less negative in aVR, there was a progressive increase in relative risk (RR). When the T waves in aVR had a positive deflection (i.e., upward pointing) the RR for CV death was 5.0.

Conclusions: T wave amplitude in lead aVR is a powerful prognostic marker for estimating risk of CV death. Upward pointing T waves (a simple visual criterion) was prevalent (7.3% of a clinical population) and was associated with an annual CV mortality of 3.4% and a risk of five times.

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The 12-lead electrocardiogram (ECG) is one of the most commonly utilized diagnostic tools for the investigation of a wide variety of cardiac and noncardiac diseases. Even with today's modern imaging techniques, the interpretation of the 12-lead ECG has a critical role in the diagnosis of acute coronary syndromes and cardiac arrhythmias.[1]

The value of the 12-lead ECG for risk stratification has also been studied.[2] Various ECG scores and criteria have demonstrated associations with cardiovascular (CV) mortality. These include the Minnesota code,[3] cardiac damage scores,[4] and various indices of left ventricular hypertrophy (LVH).[5] Unfortunately, the scores are relatively complicated, limiting their application in the clinical setting.

Despite its diagnostic and prognostic value, the decline in reimbursement and the availability of cardiac imaging techniques has resulted in the ECG being devalued by the cardiologist. While still appreciated for evaluation of acute ischemia and arrhythmias, interpretation of the ECG is often relegated to noncardiologists and less time is given to ECG education because of the breadth of skills and knowledge required to practice modern medicine. Simplification of interpretation would greatly benefit the primary care physician. In that regard, given the universal acceptance of the risk of nonacute repolarization abnormalities, we feel it is important to direct the generalist's attention to the most important leads to assess.

METHODS

Study Design

Since 1987, the Palo Alto Veterans Affairs Health Care System has used a computerized ECG system (GE Marquette) to coordinate collection, storage, and analysis of ECGs. This system has been validated by both the United States Food and Drug Administration and the European Community and is widely used across the world. The current study involved a retrospective analysis of 46,915 ECGs obtained between March 1987 and July 2000. These ECGs were obtained as part of clinical practice and no protocol was followed directing their ordering. ECGs were all performed in the VA Palo Alto Health Care System and included ECGs from the Emergency Department (ED), clinics, and hospital wards. In cases where more than one ECG was available for a patient, only the first ECG was considered.

Exclusion Criteria

At the outset, 1060 patients who died within 1 week of their ECG being recorded were excluded since the ECG could be associated with the death rather than being predictive of death. Women (n = 3992), who have been reported separately, and patients with atrial fibrillation (n = 1254), bundle branch blocks (n = 3142), paced rhythms (n = 290), and Wolff-Parkinson-White syndrome (n = 42) were excluded from the study. A target cohort of 24,270 males remained.

Subgroup with Clinical Data

Since the VA clinical data base did not provide accessible clinical data until recently, we did not have complete clinical data on the entire population set. However, we were able to abstract consistently complete clinical data on a subset of 2250 patients after 1998. This included history regarding diabetes, hypertension, COPD, stroke, claudication and the presence of cardiovascular disease (myocardial infarction, coronary bypass surgery, percutaneous coronary intervention), and medication (beta-blocker, calcium antagonist, and nitrate) use. The Cox regression performed on the main cohort of 29,320 patients was also performed in this small subset of 2250 patients for validation purposes with the additional variables considered in the model.

ECG Analysis

The recorded data on each ECG included the timing and voltages at each of the points of the PQRST complex of the basic eight leads with derivation of the remaining four leads. The system was also able to flag rhythm abnormalities and perform waveform analysis to provide the basic electrocardiographic interpretations (GE 12 SL analysis program, www.gesystems.com). Standardized computerized ECG criteria as described by the GE 12-lead electrographic analysis program were used for the diagnosis of Q waves, ST changes and bundle branch blocks. From these, the Cardiac Infarction Injury and Selvester (CIIS) scores as well as the Romhilt-Estes criteria for LVH were calculated.[2,4,5] The deviation of the QRS-ST junction was used as the measurement for the ST segment in all leads. T wave amplitude was taken as the first deflection after the QRS complex and/or the maximum deviation from the PR isoelectric baseline. These measurements were considered for all 12 leads.

Outcome Variables

The primary outcome variable in the study was CV mortality. The California Death Index (from the California Department of Health Services) and the Social Security Death Index were used to ascertain the vital status of each patient as of Dec 31, 2002. Cause of death provided by the California Death Index, could be confirmed by review of the VA computerized database.

Statistical Analysis

The Number Cruncher Statistical System (Kaysville, UT) was used for analysis. Bivariate associations between CV mortality and various ECG criteria were tested via chi-square tests (dichotomous variables) and Student t-tests (continuous variables). All variables were first tested for normal distribution. P-values less than 0.05 were considered statistically significant. Cox proportional hazard testing was conducted to assess the significance and independence of variables for predicting CV mortality, and hazard ratios were calculated. The Cox models were age and heart rate (HR) adjusted. Multivariate models included T wave amplitude in lead aVR, T wave amplitude in all other leads, CIIS and Selvester scores, and the LVH Romhilt–Estes point system. Significant variables were chosen by auto selection

with a Z value of 2 and 20 iterations in a stepwise regression. Kaplan-Meier curves were generated for individual variables to display the impact of T wave amplitude in aVR on survival.

RESULTS

Baseline Demographics

Mean follow-up was 7.5 years. After removing the 1060 deaths, which occurred within 1 week of the ECG recording, there was a total of 6187 deaths; 1859 (31%) of the deaths were due to a CV cause. Table 1 presents baseline characteristics of the total study population comparing patients with positive T waves in aVR ("abnormal") and patients with negative T waves ("normal").

The mean age of the entire study cohort was 56.7 ± 14.7 years with an average HR of 73 ± 16 beats per minute (bpm). The average body mass index (BMI) was 27.3 ± 5.5, which put the population in the overweight category. In the abnormal group (positive T wave in aVR), the patients were older and had a higher average HR and BMI.

ECG abnormalities including Q waves, prolonged QRS duration, ST depression (defined as ST depression in V5), and LVH (defined as Romhilt-Estes >3) were also significantly more prevalent in the abnormal aVR T wave group. For ST depression in particular, 37% of the abnormal group had ST depression while this was observed in only 5% of the normal group. The CIIS score was significantly higher in the abnormal group (23.1 ± 10.4) when compared to the normal group (11.9 ± 9.7) P value ≤0.001. A positive T wave compared to negative T wave in lead aVR was associated with a greater incidence of CV and all-cause mortality.

Cox Survival Analysis

Adjusting for age and HR in the proportional hazards models, the T wave amplitude in the standard 12 ECG leads were individually evaluated. In all leads except lead III and lead V_2, T wave amplitude was significantly associated with CV mortality. ST amplitude in leads aVR, II, V_2, and V_5 were similarly evaluated and all were significantly predictive of CV mortality. When the T wave and ST amplitudes from all leads were considered together in the same Cox model, T wave amplitude in lead aVR was the most powerful predictor of CV mortality. Other ECG measurements such as the CIIS, LVH by Romhilt-Estes criteria, Q waves, QRS duration, ST depression, QT prolongation, and Selvester score were also significantly associated with CV death when considered individually and adjusted for age and heart rate. When these established ECG criteria were entered together in a multivariate analysis with T wave amplitude in aVR, T wave amplitude in aVR superseded them for predicting CV death (See Table 2). Indeed, a positive T wave

Table 1. Baseline Characteristics and Mortality Status

Characteristic	Total Population n = 24,270	Negative T Waves in aVR (Normal) n = 22,500	Positive T Waves in aVR (Abnormal) n = 1770	P Value
Age (yrs)	56.7 ± 14.7	53.9 ± 14.3	63.3 ± 11.7	<0.0001
BMI	27.3 ± 5.5	27.4 ± 5.3	28.0 ± 5.4	<0.0001
Heart rate (bpm)	73.8 ± 16.1	72 ± 14.7	75.8 ± 16.8	<0.0001
QRS duration (msec)	95.7 ± 17.7	93.1 ± 11.0	98.9 ± 14.7	<0.0001
Q waves	2649 (10.4%)	2106 (9.4%)	543 (30.7%)	<0.0001
ST depression*	1830 (7.5%)	1180 (5.2%)	650 (36.7%)	<0.0001
QRS > 110 msec	1747 (7.2%)	1405 (6.2%)	342 (19.3%)	<0.0001
CIIS	13.7 ± 10.6	11.9 ± 9.7	23.1 ± 10.4	<0.0001
T wave amp in lead I (microvolts)	155 ± 13	186 ± 106	−45 ± 100	<0.0001
Left ventricular hypertrophy (LVH)†	1232 (5.1%)	924 (4.1%)	308 (17.4%)	<0.0001
Left-axis deviation (LAD)	1884 (7.8%)	1669 (7.4%)	215 (12.1%)	<0.0001
Right-axis deviation (RAD)	505 (2.1%)	449 (2.0%)	56 (3.2%)	<0.0001
Cardiovascular death	1859 (7.7%)	1434 (6.4%)	425 (24.0%)	<0.0001
All deaths	6187 (25.4%)	5315 (24.0%)	872 (49.2%)	<0.0001

Values are mean ± standard deviation or number of subjects (percentage).
*ST depression defined as more than 0.5 mm drop in ST segment in lead V5 from the isoelectric line.
†Left Ventricular Hypertrophy RomHilt–Estes score >3.

Table 2. Age and Heart Rate (HR) Adjusted Cox Proportional Hazard Analysis

Variable	HR (95%CI)	Chi–Square Increment	Probability
T-wave amplitude in aVR (upright)	2.8 (CI 2.3 – 3.3)	351	<0.001
QT prolongation > 450	1.5 (CI 1.3 – 1.7)	136	<0.001
T-wave amplitude in aVR (−1 to −2 mm)	2.2 (CI 1.9 – 2.5)	107	<0.001
Pathological Q waves	1.5 (CI 1.3 – 1.7)	81	<0.001
QRS duration > 110	1.5 (CI 1.4 – 1.8)	54	<0.001
LVH RomHilt-Estes > 3	1.4 (CI 1.2 – 1.6)	26	<0.001
T-wave amplitude in aVR (0 to −1 mm)	1.4 (CI 1.2 – 1.6)	32	<0.001
T-wave amplitude in lead I	1.3 (CI 1.2 – 1.5)	16	<0.001
CIIS score >30	1.2 (CI 1.0 – 1.4)	6	0.01
ST depression*	NS	NS	0.0859
Selvester score	NS	NS	NS

Data from the Cox Proportional hazards analysis adjusted for age and heart rate. Variables are listed in the order of the model selection. The larger the chi-square increment the more significant the association.
*ST depression defined as more than 0.5 mm drop in ST segment in lead V_5 from the isoelectric line.

demonstrated the highest hazard ratio (2.8, CI 2.3–3.3). The predictive value of T waves in aVR was demonstrated both in the absence of other ECG abnormalities and when they were present. Similar findings were also demonstrated in specific subgroups such as patients with Q waves and ST depression. ST amplitude in lead aVR in contrast, had a very low predictive value, which was not statistically significant in the multivariate model.

## Relative Risks for Cardiovascular Mortality

The relative risks (RR) for lead aVR T wave amplitude thresholds were calculated using the T wave amplitude in aVR < −2 mm (group I) as the reference group since nearly half the population was in this group. As the T wave amplitude in aVR increases, there is a progressive increase in risk. This culminated in a RR of almost 5 when the T wave in aVR was upright.

- group I T waves < −2.0 mm Reference group
- group II T waves −2.0 to −1.0 mm RR 1.5 (CI 1.4 – 1.7)
- group III T waves −1.0 mm to 0 mm RR 2.8 (CI 2.4 – 3.2)
- group IV Upright T waves RR 4.9 (CI 4.0 – 5.2)

The RRs for the four groups T wave amplitudes are illustrated in Figure 1.

Kaplan-Meier Survival Curves

Kaplan-Meier survival curves were plotted for negative and positive T wave amplitude in aVR. A significant and visual separation of the plots was demonstrated (See Fig. 2). The percentage of the population surviving decreased as the T wave amplitude became less negative (P < 0.001). The annual mortality associated was 3.4% in the group with upright T waves, whereas the annual CV mortality associated with negative T wave amplitude < −2 mm was 0.4%. A similar association between T wave amplitude aVR and CV mortality was observed in patients with specific ECG abnormalities. This included those with Q waves, LVH, prolonged QT interval, prolonged QRS duration, and ST depression.
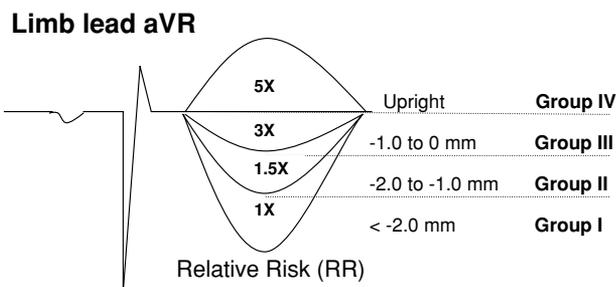
Figure 1. A simple illustration portraying the clinical application of our findings.
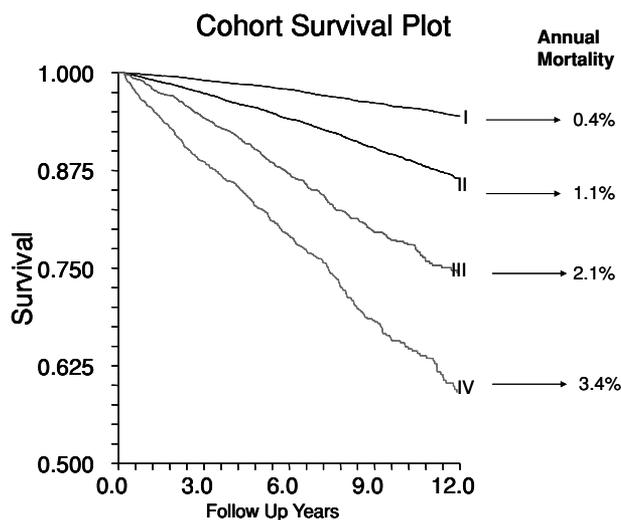
Figure 2. Kaplan-Meier survival curve for all patients defined by the four T wave amplitude in aVR groupings (group I (reference) T waves < −2.0 mm; group II – T waves −2.0 to −1.0 mm; group III – T waves −1.0 mm to 0 mm; group IV – Upright T waves.

Figure 3 shows the Kaplan-Meier survival curves for each specific ECG abnormality according to the polarity of the T wave in aVR.

Clinical Data

In the subset of 2250 patients with clinical data, the T wave amplitude in aVR was independently and strongly associated with cardiovascular mortality after adjusting for these potential confounding variables. The hazard ratios were similar to those demonstrated in the entire population.

DISCUSSION

The findings from this study demonstrate that simply considering T wave polarity in aVR identifies patients at risk of CV death regardless of other abnormalities on the ECG. When T waves are positive in aVR, the patient is at increased risk and should be considered for additional diagnostic evaluation and therapy. The converse is true as well, with negative T waves in aVR decreasing the risk of CV death.

T Waves as a Prognostic Tool

There are numerous studies that have found T waves to be significant predictors of mortality in leads other than aVR. For instance, the Framing-ham study reported that isolated T wave flattening or inversion carried a significant risk of CV mortality.[6] The Multiple Risk Factor Intervention Trial demonstrated the prognostic significance of isolated minor T wave abnormalities.[7] Danish researchers found that T wave changes were predictive of mortality in patients who had ongoing ischemia.[8] In a previous study from our group, we found that T wave amplitude in lead I was highly predictive of mortality, but aVR was excluded from the analysis.[9] A subanalysis of the WOSCOPS study also showed that frontal axis T waves and T amplitude wave in lead I were predictive of CV events.[10] While computerized measurements have been complicated by the presence of biphasic T waves particularly in the anterolateral leads, the T wave in aVR is almost never biphasic adding to its clinical utility.

Clinical Utility of aVR

In spite of the following studies, Pahlm et al. demonstrated that most electrocardiographers at an ECG conference who were given a series of ECGs, some with reversed polarity of lead aVR, did not report it.[11] In a study considering lead aVR in patients with a first non-ST elevation MI, ST elevation in aVR was a short-term predictor of CV mortality.[12] Other researchers have reported that in patients with acute MI, such ST elevation is associated with left main disease and increased mortality.[13,14] ST elevation in aVR during an acute ischemic event also appears to be associated with left main disease or other serious CAD.[15–18] In other than ischemic disease patients, in those with psychotropic drug overdose, the R wave/S wave ratio in aVR was a better predictor of risk for cardiac arrhythmia than QRS duration.[19] Prominent R waves and ST segment elevation in lead aVR are possible ECG signs of pulmonary embolism.[20,21]

CLINICAL IMPLICATIONS

This study validates the prognostic utility of T-wave amplitude in lead aVR for predicting CV mortality in a general medical population. The findings support the use of the T wave in lead aVR as a tool for risk stratification and clinical decision making. Naturally, the clinical presentation supersedes the ECG in this process but when the clinical risk and ECG results are available, they can help the clinician in deciding what other tests are indicated.
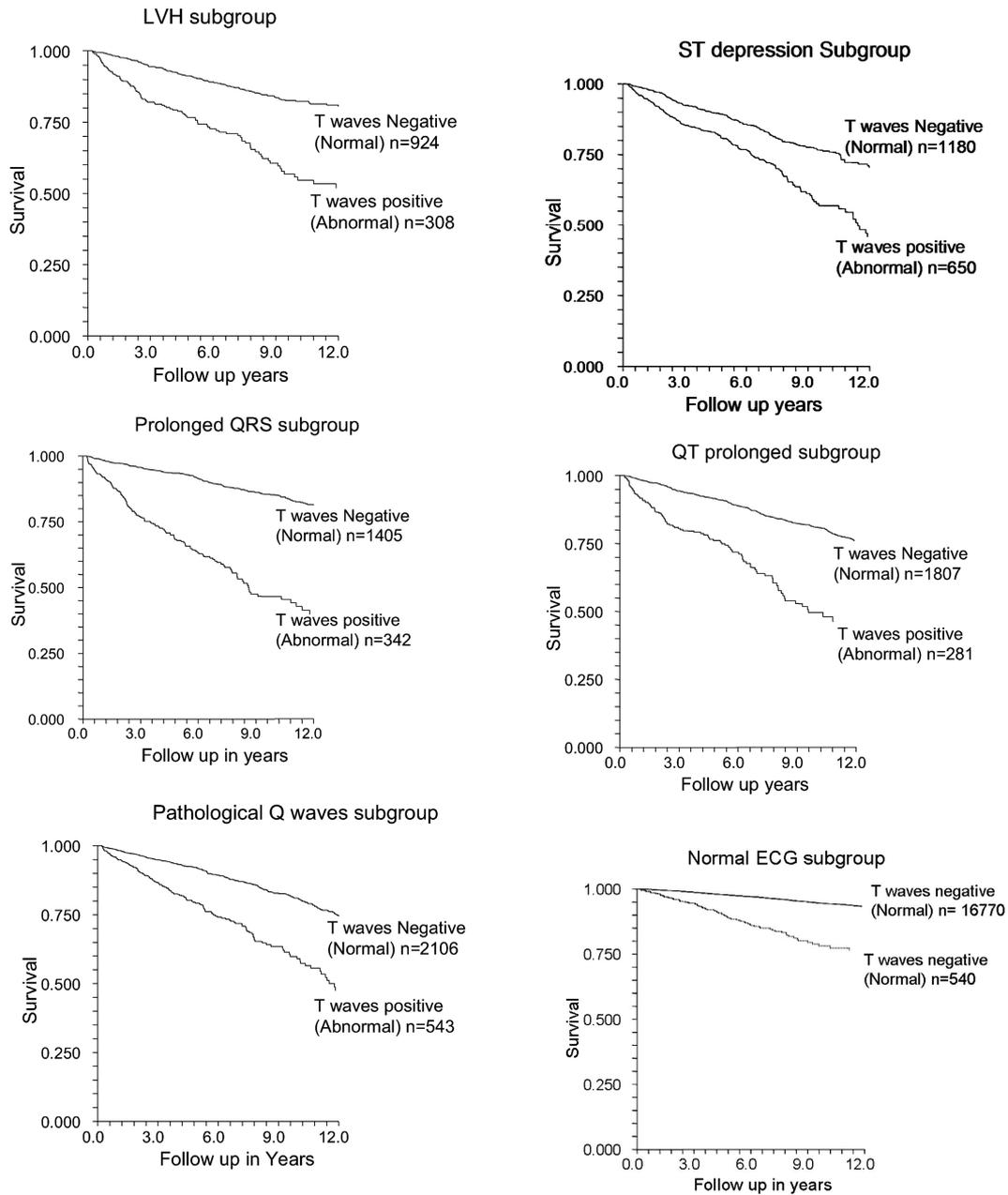
Figure 3. Kaplan-Meier survival curves for patient subgroups with patients classified according to having right T waves in aVR or having the normally inverted T waves.

To the best of our knowledge, this is the only study to consider the association between T wave amplitude in lead aVR and CV mortality. Our data suggest that lead aVR is the most powerful ECG predictor of CV mortality. It supersedes myocardial damage and LVH scores, all with demonstrated ability to predict CV mortality, and in fact stratifies risk in patients with these abnormalities. It simpli-

fies ECG interpretation in that T waves pointing upward in aVR should signal additional work-up and referral to a specialist. The presence of a positive T wave in aVR can thus raise the clinical index of suspicion for CV disease. We can only speculate why the T wave in aVR has such prognostic power. If you electrically reverse aVR (–aVR), it is a regular augmented lead at +30°C in the frontal plane,

that is, between lead I and II. Thus, –aVR provides information about the so-called apical region of the heart and is similar to the other frontal leads.

CONCLUSION

The present findings help simplify interpretation of the ECG; irrespective of other ECG abnormalities, risk for CV death can be estimated by lead aVR. If T waves in aVR are upright, CV risk is elevated and further evaluation is indicated in patients referred for an ECG for clinical reasons. These findings should stimulate interest in aVR leading to prospective outcome studies in specific clinical cohorts accompanied by imaging studies to explain the pathophysiology.

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