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The Prognostic Significance of a Positive or Isoelectric T wave in lead aVR in Patients with Acute Coronary Syndrome and Ischemic ECG Changes in the Presenting ECG - Long-term Follow-up data of the TACOS Study

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Tweet: A positive T wave in lead aVR is associated with increased all-cause and cardiovascular mortality in ACS patients during long-term follow-up.

Abstract

Background. A positive T wave in lead aVR (aVRT+) is an independent prognostic predictor of cardiovascular mortality in the general population as well as in cardiovascular disease.

Subjects and Methods. We evaluated the prognostic impact of aVRT+ in an ECG recorded as close to hospital discharge as possible in acute coronary syndrome patients (n=527). We divided the patients into three categories based on the findings in the admission ECG: ST elevation, global ischemia and other ST/T changes.

Results. In the whole study population, and in all the three ECG subgroups, the 10-year all-cause mortality rate was higher in the aVRT+ group than in the aVRT- group. In Cox regression analysis, the age and gender adjusted hazard ratio (HR) for aVRT+ to predict all-cause mortality in the whole study population was 1.43 (95% confidence interval [CI] 1.12–1.83; p=0.004). To predict cardiovascular mortality, the age and gender adjusted HR for aVRT+ was 1.54 (95% CI 1.14–2.07; p=0.005) in the whole study population and 2.07 (95% CI 1.07–4.03; p=0.032) in the category with other ST/T changes.

Conclusion. In ACS patients with or without ST elevation, but with ischemic ST/T changes in their presenting ECG, a positive or isoelectric T wave in lead aVR in an ECG recorded in the subacute in-hospital stage is associated with all-cause and cardiovascular mortality during long-term follow-up. Clinicians should pay attention to this simple ECG finding at hospital discharge.

Keywords: acute coronary syndrome, lead aVR, ECG, acute myocardial infarction

Introduction

ECG abnormalities in lead aVR are often neglected, and the 12-lead electrocardiogram (ECG) has been referred to as an "11-lead study" based on the false assumption that lead aVR yields only limited information. The T wave in lead aVR is normally negative due to the unique location of this augmented extremity lead. However, previous studies have shown that a positive or isoelectric T wave (aVRT+) in a routine 12-lead ECG is an independent prognostic predictor of cardiovascular mortality in the general population as well as in cardiovascular disease (1-8). Changes in lead aVR are also important in the differential diagnosis of tachyarrhythmias (9).

In acute coronary syndrome (ACS) patients, aVRT+ was associated with severe coronary artery disease, including left main (LM) disease (10), and an independent predictor of 1-year mortality in anterior ST-elevation myocardial infarction (STEMI) (11). aVRT+ was also associated with cardiovascular mortality in patients with prior myocardial infarction (MI) (12, 13). To the best of our knowledge, there is no published data on the long-term prognostic significance of aVRT+ in ACS patients.

The aim of this study was to determine the prognostic value of aVRT+ in an ECG recorded as close to hospital discharge as possible in ACS patients with or without ST elevation in their admission ECG.

Methods

The TACOS (Tampere Acute COronary Syndrome) study included consecutive "real life" ACS patients treated in the Tampere University Hospital, Finland. A detailed description of the original research settings has been described earlier (14, 15). The study inclusion period was from January 1st 2002 to March 31st 2003. During the whole study period, patients with acute MI with elevated troponin values were included. In addition, from September 1st 2002 to March 31st 2003 troponin-negative patients with unstable angina pectoris (UA) were included. The patients were divided into three categories depending on the ACS type: STEMI, non-ST-elevation MI (NSTEMI) and UA. In the TACOS study, there were no specific ECG criteria for inclusion into the NSTEMI and UA categories, except that ST elevation fulfilling the STEMI criteria were not allowed. In this study, only patients with ischemic ST/T changes in their ECG from the acute phase were included.

Mortality data was gathered by linking the personal identity code from the TACOS study to the Causes of Death register, maintained by Statistics Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad. The ethics committee at the Tampere University Hospital accepted the study protocol. All subjects gave their written informed consent for participation.

For the present study, we divided the patients into three ECG categories based on the findings in the admission ECG: 1) ST elevation (n=329), 2) global ischemia (n=94), and 3) other ST depression and/or T-

wave inversion (other ST/T) (n=108). Global ischemia was defined as ST depression ≥0.5 mm in ≥6 leads, maximally in leads V4-V5 with inverted T waves and ST elevation ≥0.5 mm in lead aVR. Patients with broad QRS (≥120 ms), such as bundle branch block and ventricular pacemaker, were excluded from the study. We also excluded four patients because of poor-quality or missing ECGs, two in the ST elevation category and two in the category of other ST/T changes. The patients, who died during the hospital stay were included, and the last ECG recorded was used for analysis. The final study population consisted of 527 patients.

ECG analysis

The ECGs were analyzed by one investigator (MS). In case of uncertainty, another investigator (KjN) was consulted. T wave amplitudes were measured from all the 12 ECG leads. The ECGs were analyzed manually, if necessary with the help of a magnifying glass. The merging point between the PR interval and the QRS complex was used as the reference for T wave measurement. For T wave amplitudes ~~in lead aVR~~, a cut-off of 1 mm (0.1 mV) was used. In case of beat-to-beat variation, we used an average value. Biphasic T waves were classified by two investigators (MS and KjN). In patients with a biphasic T wave, we used the larger deflection to determine the T-wave polarity: if the negative deflection was larger than the positive, the T wave was classified as negative and vice versa. We used the ECG as close as possible to patient discharge for analysis. During the study period, it was clinical routine to record a 12-lead ECG on the day of hospital discharge. Therefore, in most cases, the study ECG was recorded on the day of hospital discharge.

The patients were divided into two groups: the aVRT+ group had either a positive or isoelectric T wave in lead aVR, while the aVRT- group had a negative T wave in that lead.

Statistical analysis

We used 10-year all-cause and cardiovascular mortality rates. Cox regression analysis was used to test the prognostic significance of the aVRT+ finding in the ECG with the aVRT- group as the reference. In Cox regression analysis, adjustment for age and gender was performed. Cox regression analysis was used to test the prognostic significance of aVRT+ in the whole study population and individually in the ST elevation, global ischemia and other ST/T categories. The deaths were classified as cardiovascular when the ICD-10 code for the immediate or underlying cause of death was I00–I79.

Age and gender adjusted cox regression analysis was also used to test the prognostic significance of a negative T wave in leads I and II. The aim was to assess whether T-wave changes in lead aVR have independent prognostic value, considering the fact that aVR is a calculated lead (aVR = -(1/2)(I + II). Patients with a positive T wave were used as the reference group. In cox regression analysis, we also tested the prognostic significance of the aVRT+ finding in the ECG when adjustment for age, gender and T wave

polarity in lead I or lead II was performed. In the analyses, a negative or isoelectric T wave in leads I and II was classified as a negative T wave.

The Chi-square test and the t test were performed to test the significance of differences between the groups. A p-value < 0.05 was considered as statistically significant. Statistical analyses were performed using SPSS version 25.0.

Results

Of the 527 patients, 293 (55.6%) were classified as aVRT+ and 234 (44.4%) as aVRT-. The relative proportion of the avRT+ sign was highest in the ECG category global ischemia (72.3%), followed by the ST elevation (52.9%) and other ST/T categories (49.1%). Table 1 shows the baseline characteristics of our patients based on the T-wave polarity in lead aVR. The aVRT+ patients were older and more often female. They had lower ejection fraction and higher creatinine values. The aVRT+ patients more often used aspirin, β-blocker, nitrate, calcium blocker or diuretic medication at admission. At hospital discharge, the aVRT+ patients more often used nitrate and diuretic medication. The median delay from hospital admission to study ECG recording was 6 days in both the aVRT+ and aVRT- groups.

“Table 1.”

In the whole study population, the 10-year all-cause mortality rate was higher in the aVRT+ group (63.1%) than in the aVRT- group (44.9%) (Table 2). This was also the case when analyzing the three ECG categories individually. aVRT+ was also associated with higher cardiovascular mortality than aVRT- in the whole study population and individually in the three ECG categories.

“Table 2.”

In Cox regression analysis (Table 3), the age and gender adjusted hazard ratio (HR) for aVRT+ to predict all-cause mortality in the whole study population was 1.43 (95% CI 1.12–1.83; p=0.004).

“Table 3.”

In Cox regression analysis, the age and gender adjusted HR for cardiovascular mortality for aVRT+ in the whole study population was 1.54 (95% CI 1.14–2.07; p=0.005). When categories were analyzed individually, the age and gender adjusted HR to predict cardiovascular mortality for aVRT+ was 2.07 (95% CI 1.07–4.03; p=0.032) in the category with other ST/T changes, 1.41 (95% CI 0.95–2.10; p=0.088) in the ST elevation category and 1.44 (95% CI 0.73–2.87; p=0.293) in the global ischemia category.

In cox regression analysis, the age and gender adjusted HR for a negative or isoelectric T wave in lead I and lead II to predict all-cause mortality was 1.42 (95% CI 1.12–1.81; p=0.004) and 1.06 (95% CI 0.84–1.33; p=0.640), respectively.

In cox regression analysis, HR for all-cause mortality for aVRT+ was 1.26 (95% CI 0.93–1.70; p=0.136) after adjustment for age, gender and T wave polarity in lead I. After adjustment for age, gender and T wave polarity in lead II, HR for all-cause mortality for aVRT+ was 1.55 (95% CI 1.18–2.05; p=0.002).

Discussion

“Figure 1.”

“Figure 2.”

“Figure 3.”

The present study showed that a positive or isoelectric T wave in lead aVR in the subacute phase has negative impact on the long-term outcome of ACS patients, who have ST/T changes in their acute phase ECG. For all-cause mortality, this simply identifiable ECG change had negative prognostic impact after age and gender adjustment when all the three studied ECG categories were analyzed together but not when analyzed individually. In the patients, who presented with ST depression and/or T-wave inversion other than global ischemia, the aVR+ sign was associated with cardiovascular mortality during long-term follow-up after age and gender adjustment. Almost three quarters of the patients with global ischemia had aVRT+, while in the two other ECG categories there were almost equal numbers of patients with aVRT+ and aVRT- in an ECG recorded six days (median value) after hospital admission.

Lead aVR is an augmented unipolar limb lead with a unique position compared with the other eleven ECG leads. In the present study, aVRT+ retained its independent prognostic value after including T-wave changes in the neighboring leads I and II in the analyses. Diseases affecting the right upper portion of the heart, the basal portion of the interventricular septum and the subendocardium of the left ventricle (LV) may alter the ST segment and the T wave in lead aVR. In the last 10-15 years, evidence indicating the importance of ECG changes in this lead in the setting of ACS has been accumulating. ST elevation on lead aVR is associated with acute LM coronary artery occlusion and higher mortality rates in NSTEMI patients (16, 17, 18). Transmural ischemia of the basal interventricular septum caused by impaired blood flow to the first major septal branch was proposed as an explanation for this observation (16). In addition, lead aVR ST elevation could represent a “mirror image” of ST depression in the lateral leads, which reflects diffuse LV subendocardial ischemia (19, 20).

aVRT+ has been associated with unfavorable outcome in patients with an implantable cardioverter-defibrillator, heart failure with preserved LV ejection fraction, transcatheter aortic valve implantation, ischemic cardiomyopathy, and hemodialysis therapy (6, 7, 21, 22, 23).

A few population studies have explored the prognostic significance of aVRT+. Tan et al (2) found an association between this ECG sign and cardiovascular mortality during 4-year follow-up of male veterans, whose ECGs were obtained for various clinical reasons. In a population of individuals aged ≥ 30 years, Anttila et al (1) found a 2.2% prevalence of aVRT+, which was an independent predictor of cardiovascular mortality. In a National Health and Nutrition Examination Survey-III substudy, aVRT+ was the strongest multivariate predictor of cardiovascular mortality (24). In the Oregon Sudden Unexpected Death Study, a positive T wave in aVR was associated with sudden cardiac death in the multivariate analysis in some studied subpopulations, including those with normal LV ejection fraction, normal corrected QT interval and no diabetes (25).

There are a few previous studies dealing with the significance of aVRT+ in coronary artery disease, but we are not aware of any previous publications exploring the long-term prognostic value of this ECG sign in the subacute in-hospital phase. To explore the pathophysiologic background for ECG changes, Shinozaki et al (12) performed cardiac catheterization in patients, who had suffered an anterior MI more than six months before study inclusion. They found that patients with a positive T wave (≥1 mm) in lead aVR had higher pulmonary arterial, pulmonary capillary wedge, and LV end-diastolic pressures, and a lower cardiac index and ejection fraction than patients without this ECG sign. Based on these findings, one may speculate that aVRT+ could represent an ECG marker of unfavorable post-MI remodeling. These pathophysiological processes do not necessarily explain the negative impact of aVRT+ in our study, as we explored ECG manifestations in the early ~~post-MI~~ phase of the ACS. However, it is a well-established fact that left ventricular remodeling starts very early after the myocardial injury has occurred (26). Therefore, maladaptive remodeling seems to offer a reasonable explanation for our study findings. However, this study did not aim at exploring pathophysiologic mechanisms acting in the subacute in-hospital phase of the disease.

Shinozaki et al (12) found that patients with aVRT+ ≥1 mm had a higher probability for multi-vessel disease. In our study, the probability of LM and triple vessel disease was higher in the aVRT+ patients than in the aVRT- patients, but the difference was not statistically significant, possibly because of the relatively small number of patients. Additionally, Shinozaki et al found that a positive T wave in lead aVR was related to a long left anterior descending coronary artery wrapping around the ventricular apex as the culprit artery. This scenario may be associated with considerable ischemia and injury of the apical region resulting in ST/T

changes in the lateral precordial leads. It can be assumed that inverted T waves in these leads result in a "mirror image" positive T wave in lead aVR as mentioned previously for ST deviations (19, 20).

Torigoe et al (13) evaluated the significance of a positive T wave (>0 mm) in patients >6 months after an acute MI. aVRT+ was an independent predictor of cardiac death or hospitalization for heart failure during a follow period of 6.5 ± 2.8 years. In a recent study comprising 400 NSTEMI patients, 124 patients (31%) had a positive T wave in lead aVR in the first admission ECG (10). These authors classified patients with an isoelectric T wave as aVRT-, while we classified such patients as aVRT+. As in our study, the patients with aVRT+ were older and more often female. They also had a significantly lower LV ejection fraction. aVRT+ was not an independent predictor of major adverse cardiovascular events in multivariate analysis. However, aVRT+ was an independent predictor of triple vessel or LM disease. In another recent study, Icen et al (27) determined the amplitude of T-wave and ST-segment deviation, and calculated a ratio by dividing the variable with larger absolute value by other variables with a smaller absolute value in lead aVR. They found that this ratio was strongly and independently associated with coronary artery disease severity based on the Syntax score.

We have no definite explanation for the fact that association between aVRT+ and cardiovascular mortality was stronger for the patient category other ST/T changes than for the two other categories. The number of patients in the different categories may have influenced the results, but this does not seem probable, at least for the ST elevation category, which was the largest one. It is probable that different mechanisms are responsible for the T-wave changes in lead aVR in the early subacute stage.

Future studies should explore the association between temporal T-wave changes in lead aVR and left ventricular remodeling. ECG findings should be included in studies dealing with the issue of maladaptive left ventricular remodeling. The ECG could prove to have diagnostic value to predict maladaptive left ventricular remodeling in the follow-up of ACS patients. Considering therapeutic aspects, we have no specific recommendations for patients with aVRT+ in the subacute stage of ACS. Certainly, high-risk markers in ACS patients need to be identified to guarantee that guideline-based recommendations are followed in these patients.

Limitations

The fact that the study was done before the widespread implementation of primary percutaneous coronary intervention in STEMI patients may be considered as a study limitation. However, this is the case for many studies with long-term follow-up of ACS patients. We consider the fact that our study population represents a "real life" cohort of consecutive ACS patients from a tertiary cardiac center as a strength. According to our study inclusion criteria, only patients with ischemic ECG changes were included. Therefore, the results are not applicable to all ACS patients. Coronary angiography was not performed

during the index hospital stay in all patients. Comparison with previous ECGs was not included in the study protocol. Therefore, we can not exclude the possibility that some of the patients had pre-existing aVRT+. Finally, the study included only ACS patients with ischemic ECG changes in their presenting ECG. Therefore, we were not able to assess the prognostic value of aVRT+ in general in ACS patients.

Conclusions

In ACS patients with or without ST elevation, but with ischemic ST/T changes in their presenting ECG, a positive or isoelectric T wave in lead aVR in an ECG recorded in the subacute in-hospital stage is associated with all-cause and cardiovascular mortality during long-term follow-up. Clinicians should pay attention to this simple ECG finding at hospital discharge.

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Table 1. Baseline characteristics, medication at hospital admission, medication at hospital discharge, in-hospital laboratory test results, angiography findings and proportion of invasive coronary procedures during the index hospital stay in the study patients divided according to the T wave in lead aVR.

	aVRT+ (n=293)		aVRT- (n=234)		
	n / median	% / (Q_1–Q_3)	n / median	% / (Q_1–Q_3)	p-value
Age	74	(65–81)	69	(58–76)	< 0.001
Female gender	148	50.5	81	34.6	< 0.001
Time from admission to ECG	6	(4–10)	6	(3–8)	0.001
Active smoking	56	20.9	48	21.7	0.825
Ex-smoker	77	36.5	79	45.7	0.069
Systolic BP, mean (SD)	146 (31)		148 (30)		0.477
Diastolic BP, mean (SD)	79 (17)		81 (17)		0.218
Diabetes mellitus	84	28.9	51	21.8	0.065
Prior PCI or CABG	27	9.2	22	9.5	0.927
Previous MI	69	23.6	43	18.5	0.158
ACS classification					0.001
ST elevation	173	59.0	154	65.8	
Global ischemia	68	23.2	26	11.1	
Other ST/T changes	52	17.7	54	23.1	
Plasma creatinine (µmol/L)	89	(73–114)	83	(70–95)	0.001
C-reactive protein (mg/L)	18	(5.0–67)	12	(3.3–39)	0.087
cTnI (µg/L)	11	(2.6–42)	12	(1.7–57)	0.803
CCS class					0.159
1–2	81	31.4	66	29.9	
3–4	27	10.5	13	5.9	
Medication at admission					
Aspirin	134	45.7	82	35.0	0.013
Beta-blocker	153	52.2	96	41.0	0.011
Nitrate	142	48.5	72	30.8	< 0.001
Calcium-antagonist	72	24.6	38	16.2	0.019
Diuretic	100	34.1	50	21.4	0.001
Statin	61	20.8	46	19.7	0.742
ACE-inhibitor	54	18.4	35	15.0	0.290
AT2-inhibitor	22	7.5	13	5.6	0.371
Warfarin	27	9.2	15	6.4	0.237
Clopidogrel	4	1.4	1	0.43	0.268
Medication at discharge					
Aspirin	210	80.8	189	85.5	0.167
Beta-blocker	244	93.8	200	90.5	0.170
Nitrate	171	66.0	111	50.5	0.001
Calcium-antagonist	36	13.9	25	11.3	0.396
Diuretic	133	51.4	67	30.3	< 0.001
Statin	173	66.8	157	71.0	0.317
ACE-inhibitor	113	43.5	83	37.6	0.189
AT2-inhibitor	33	12.7	20	9.0	0.198
Warfarin	53	20.5	31	14.1	0.065
Clopidogrel	16	6.2	9	4.1	0.301
Ejection fraction*	50	(40–66)	60	(50–70)	< 0.001
Angiography in hospital	131	44.7	114	48.7	0.359

Number of diseased vessels**					0.055
< 50 % stenosis	12	7.7	14	10.9	
1- vessel disease	40	25.8	48	37.2	
2- vessel disease	44	28.4	35	27.1	
3- vessel disease	59	38.1	32	24.8	
Left main disease[a, **]	14	9.0	8	6.2	0.374
PCI in hospital	54	18.4	49	20.9	0.470
CABG in hospital	32	10.9	22	9.4	0.568
Revascularization in hospital	86	29.4	71	30.3	0.805

Q_1,Q_3= median of the first (Q_1) and third (Q_3) quartile; Time from admission to ECG=delay from hospital admission to study ECG recording (days); BP=blood pressure (at hospital admission); SD=standard deviation; PCI=percutaneous coronary intervention; CABG=coronary artery bypass surgery; MI=myocardial infarction; cTnI=cardiac troponin I; CCS=Canadian Cardiovascular Society; ACE=angiotensin-converting enzyme; AT2=angiotensin II. [a]Includes patients with left main disease either isolated or in combination with 1-, 2- or 3-vessel disease. *n=277. **n=284.

Table 2. All-cause and cardiovascular mortality for aVRT+ and aVRT- in the whole study population and in all the three ECG categories.

	All				ST-elevation				Global ischemia				Other ST/T changes			
	aVRT+		aVRT-		aVRT+		aVRT-		aVRT+		aVRT-		aVRT+		aVRT-	
	n=293	(55.6)	n=234	(44.4)	n=173	(52.9)	n=154	(47.1)	n=68	(72.3)	26	(27.7)	n=52	(49.1)	n=54	(50.9)
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Death	185	63.1	105	44.9	94	54.3	64	41.6	56	82.4	16	61.5	35	67.3	25	46.3
CV death	134	45.7	68	29.1	67	38.7	43	27.9	41	60.3	11	42.3	26	50.0	14	25.9

Table 3. Age and gender adjusted Cox regression analysis for the whole study population and for all the three ECG categories to predict all-cause mortality in the aVRT+ group.

	n	Hazard ratio	95% CI	p-value
All	527	1.43	1.12–1.83	0.004
ST elevation	327	1.36	0.98–1.89	0.065
Global ischemia	94	1.41	0.80–2.50	0.238
Other ST/T changes	106	1.56	0.93–2.64	0.094

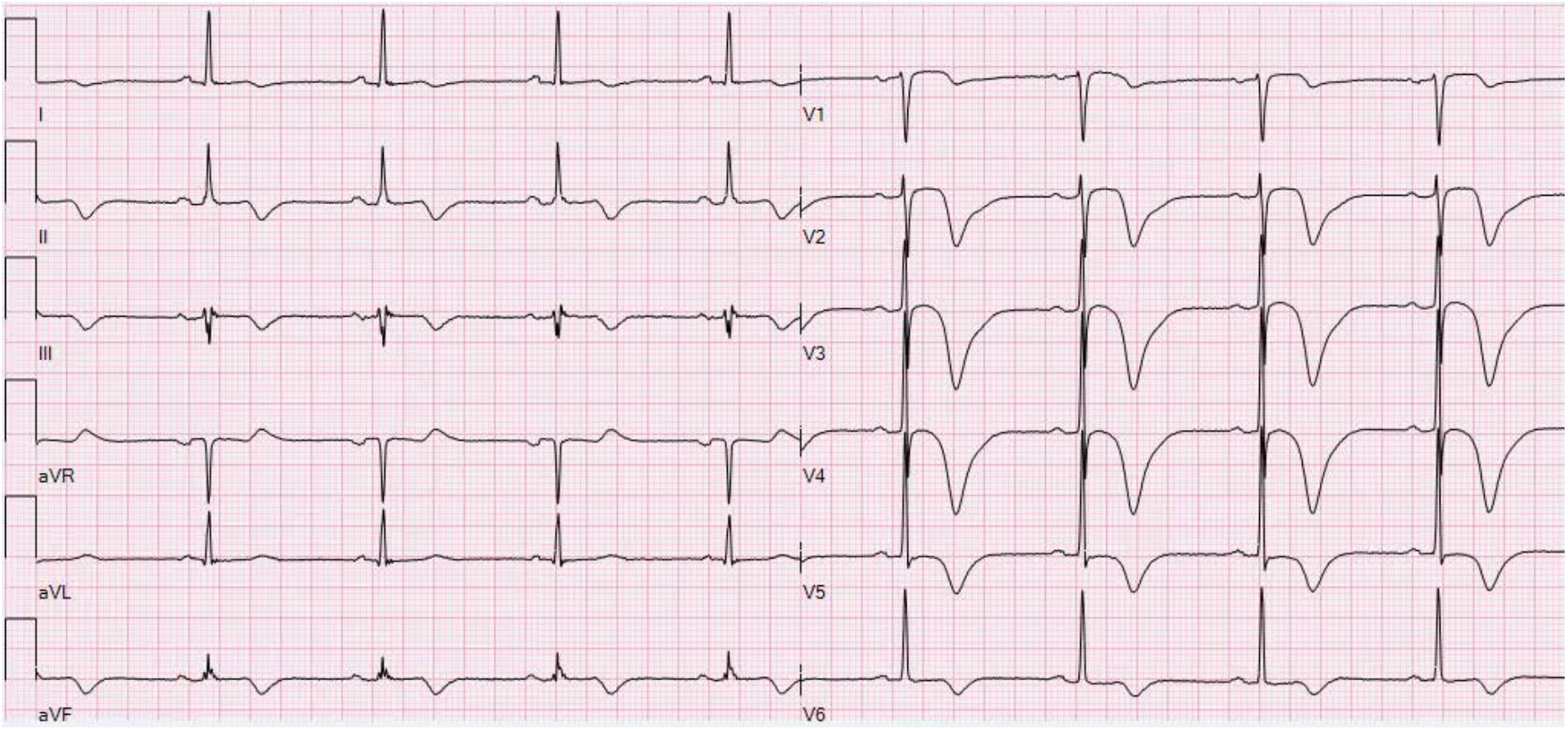

Figure 1. A 68-year old man without traditional cardiovascular risk factors and no regular medication was treated with PCI of the LAD within three hours from symptom onset. There was a sub-total mid-LAD occlusion, and the artery was big, wrapping around the apex. The first ECG showed ST elevation in leads III, aVF and V1-V4 and ST depression in V5 and V6. This ECG (25 mm/sec) was recorded at hospital discharge on the third day of hospital stay. There are deep T-wave inversions in many leads and a positive T wave in lead aVR ("aVRT+").

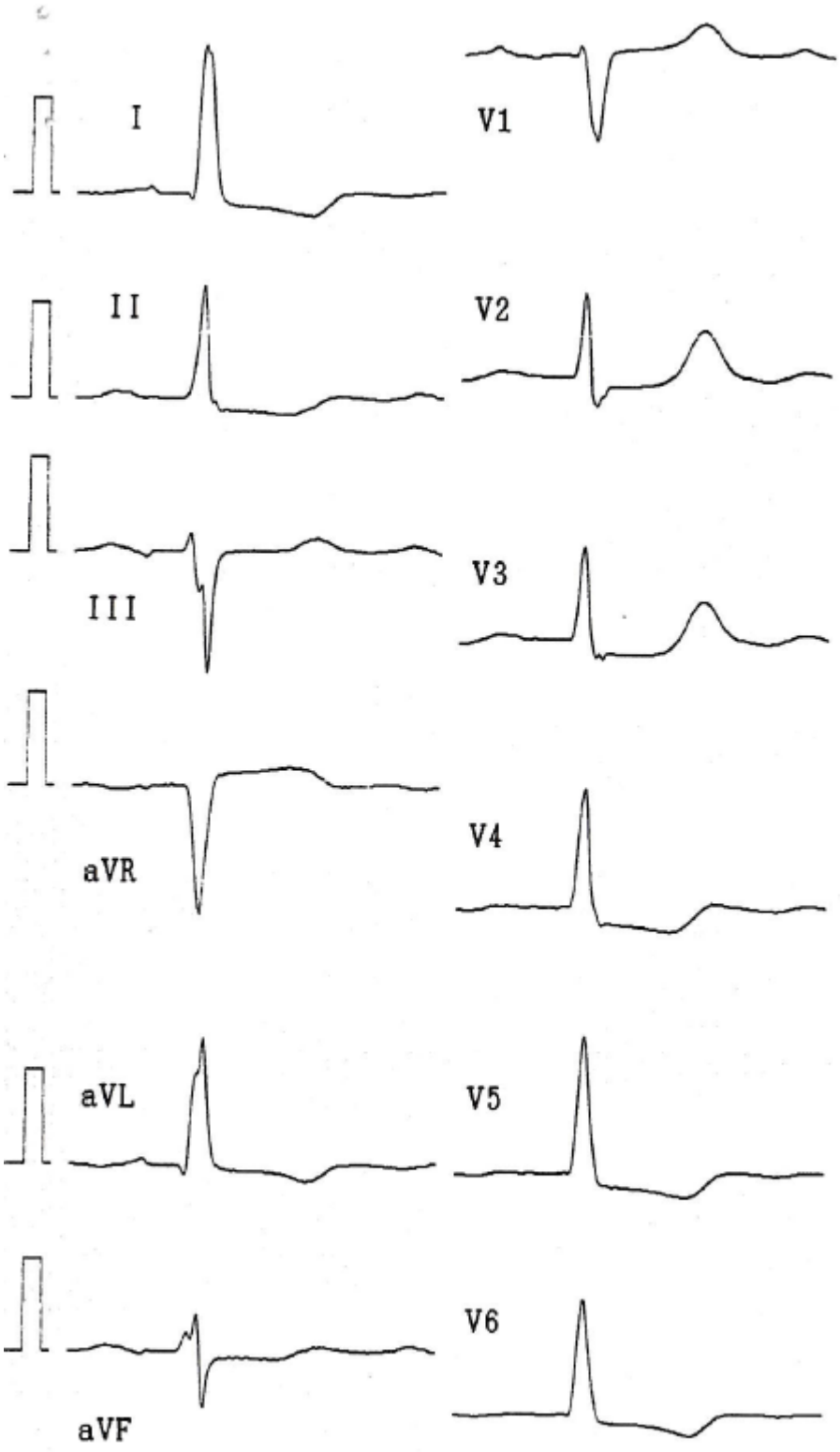

Figure 2. The ECG (50 mm/sec) from a 77-year old woman with acute non-ST-elevation myocardial infarction. There is ST depression in nine leads. The maximal ischemic changes (ST depression and T-wave inversion) are in leads V4-V5. The T wave in lead aVR is clearly positive (aVRT+).

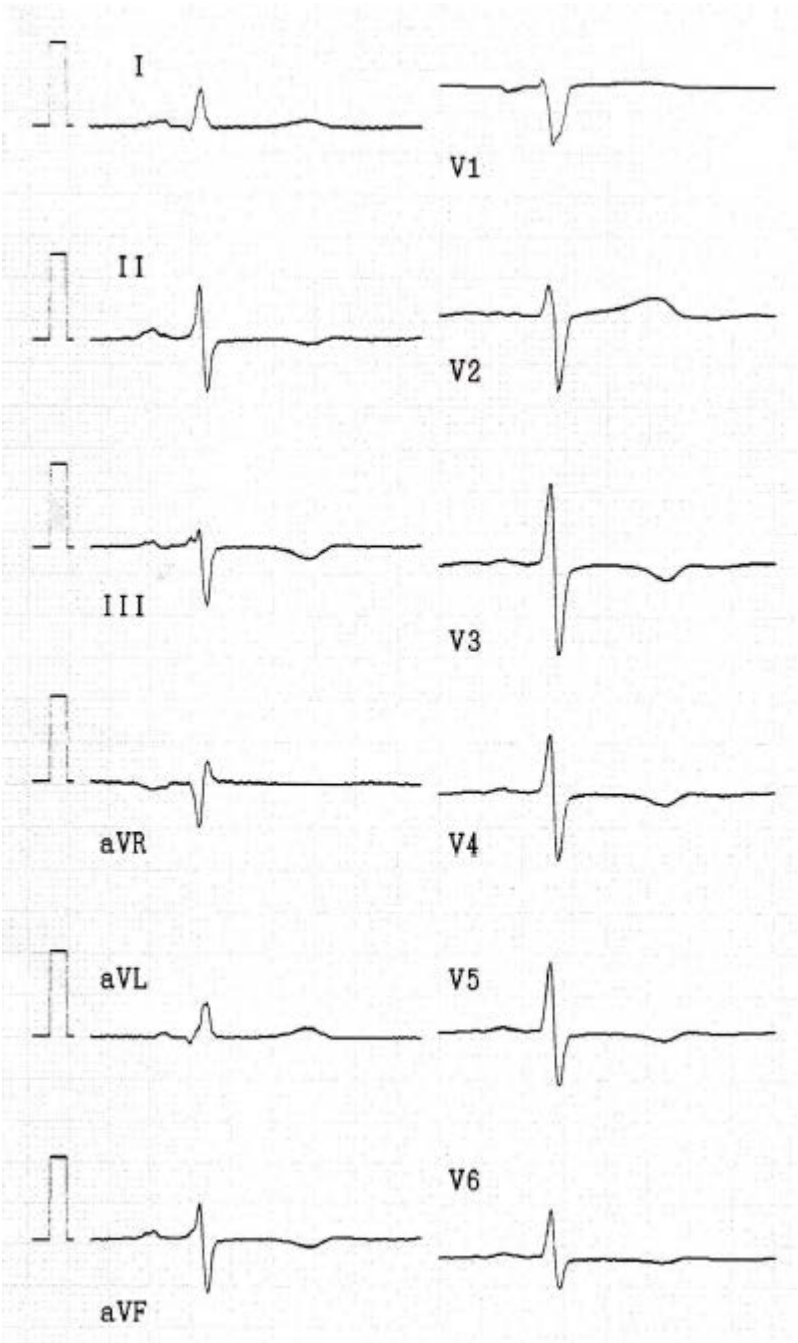

Figure 3. The ECG from a 42-year old woman with non-ST-elevation myocardial infarction. There is mild ST depression and T-wave inversion in many leads with maximal ST depression in the inferior leads. In lead aVR, the T wave is isoelectric, fulfilling the criteria for aVRT+.