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The enigmatic sixth wave of the electrocardiogram: The U wave

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Abstract

The U wave is the last, inconstant, smallest, rounded and upward deflection of the electrocardiogram. Controversial in origin, it is sometimes seen following the T wave with the TU junction along the baseline or fused with it and before P of the following cycle on the TP segment. In this review we will study its temporal location related to monophasic action potential, cardiac cycle and heart sounds, polarity, voltage or amplitude, frequency and shape-contour. We will analyze the clinical significance of negative, alternant, prominent U wave, and the difference between T wave with two peaks (T_1–T_2) and true U wave. Finally we will analyze the four main hypotheses about the source of U wave: repolarization of the intraventricular conducting system or Purkinje fibers system, delayed repolarization of the papillary muscles, afterpotentials caused by mechanoelectrical hypothesis or mechanoelectrical feedback, and the prolonged repolarization in the cells of the mid-myocardium ("M-cells"). (Cardiol J 2008; 15: 408–421)

Key words: U wave, sixth wave of electrocardiogram, source hypothesis

Introduction

The U wave is the last, inconstant, smallest (≤ 1 mm or 11% of voltage of the precedent T wave with a range of 3% to 24%), rounded and upward deflection (except VR, under normal conditions U wave is only negative in VR) of the electrocardiogram (ECG). Controversial in origin, it is sometimes seen following the T wave with the TU junction along the baseline or fused with it and before P of the following cycle on the TP segment. Usually, U wave has the same polarity as the T wave. Patients with negative T waves and positive U waves are called Type I discordance. Patients with positive T waves and negative U waves are named Type II discordance. From 18,750 consecutively recorded ECGs, 53 patients had type I and 26 type II discordance. Types I and II were called group A and B respectively.

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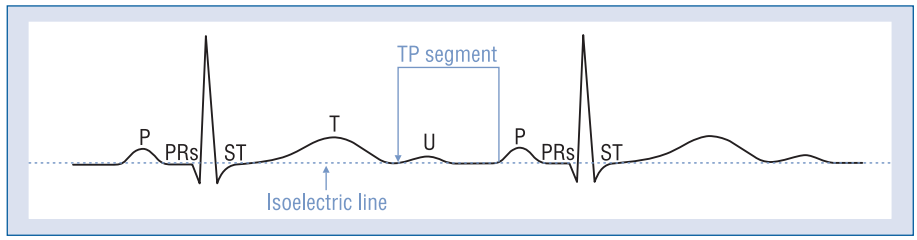

Figure 1. At higher rates the TP segment and U wave disappear when the T wave merges with the following P wave.

Patients with negative T and negative U waves (concordant polarity) were named as group C. Coronary disease was slightly more common in Group A (64%) than in Group B (46%, p = 0.174; NS). Coronary artery disease in Group C was extremely common (88%; p < 0.001). Hypertension in the two discordant groups was similar: Group A (60%) versus Group B (58%; p = NS), Group C was significantly higher (88%, p < 0.001). Left ventricular enlargement (LVE) was 49% in Group A and 58% in Group B (p = NS), but Group C was significantly higher at 70% (p = 0.038). The authors found that the significance of any U wave is not independent of their respective T wave. They propose that the U wave should not be analyzed in isolation, but rather with respect to its T wave [1]. The ratio of the U wave and T wave amplitude is relatively constant in all leads. The U wave is the last integrant of ventricular repolarization together with ST segment, J wave (Osborn) and T wave. In a healthy person at low heart rates the PR, ST and TP segments are at the same level and form the isoelectric line (Fig. 1).

In 1896 Einthoven [2], using an improved electrometer and a correction formula developed independently of Burch, distinguishes only five deflections on ECG which he names P, Q, R, S, and T. The great master identified the U wave only a few years later in 1903, when he used the string galvanometer [3]. He published the first organized presentation of normal and abnormal electrocardiograms recorded with a string galvanometer [4, 5]. In this manuscript, Einthoven described for the first time the U wave among other waves. The U wave was detected only in ECGs made with the string galvanometer. This labeling was used routinely after tracings were made with the galvanometer(adapted from [6]). Willem Einthoven, developed the first electrocardiograph machine. It was a simple string galvanometer — capable of measuring small changes in the electrical potential as the heart contracted and relaxed. Electrodes were attached to the limbs of the patient. As the string deflected, it obstructed a beam of light and the photographic paper recorded the shadow. As the heart contracts and relaxes repeatedly, Einthoven could record the wave's pattern of these impulses. The electrocardiograph machine of today looks very different but works on the same principle.

We will study in the U wave, the temporal location related to monophasic action potential (AP), cardiac cycle and heart sounds, polarity, voltage or amplitude, frequency, normal duration and shape contour.

Location of U wave

U wave needs to be recognized in relationship to the following biological signals.

Monophasic action potential

U wave is coincident with phase 4 of AP. This phase of the AP is associated with diastole of the chamber of the heart (Fig. 2).

Cardiac cycle

In men under normal conditions, the temporal analysis of all phases of cardiac activity shows us that the U wave is registered during the protodiastolic period of the cardiac cycle (diastolic isovolumetric phase and of fast filling) (Fig. 2).

Cardiac sounds

The U wave is concomitant to the second (S_2) or third (S_3) cardiac sounds. The S_2 is produced by closure of the aortic and pulmonary valves (A_2 and P_2), at the end of ventricular systole, and at the beginning of ventricular diastole, S_3 sound occurs after S_2 (Fig. 3).

ECG surface

The distance from the end of T wave until the apex of U wave is between 90 to 110 ms with ranges of heart rates of 50 to 100 beats/min. The distance end of T wave/end of U wave is 160 to 230 ms.

U wave polarity

In the frontal plane, normal U vector is located around + 60°; thus U wave is positive in II, III and

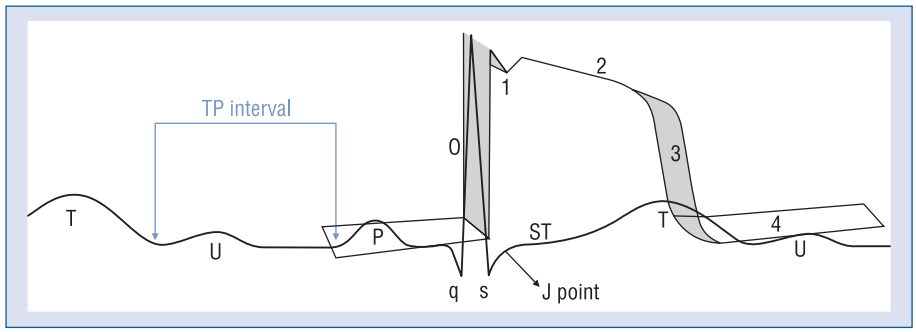

Figure 2. The U wave is coincident with phase 4 of monophasic action potential. The U wave in surface electrocardiogram is located on the TP interval. It extends from the end of the T wave up to the P wave of the following cycle.

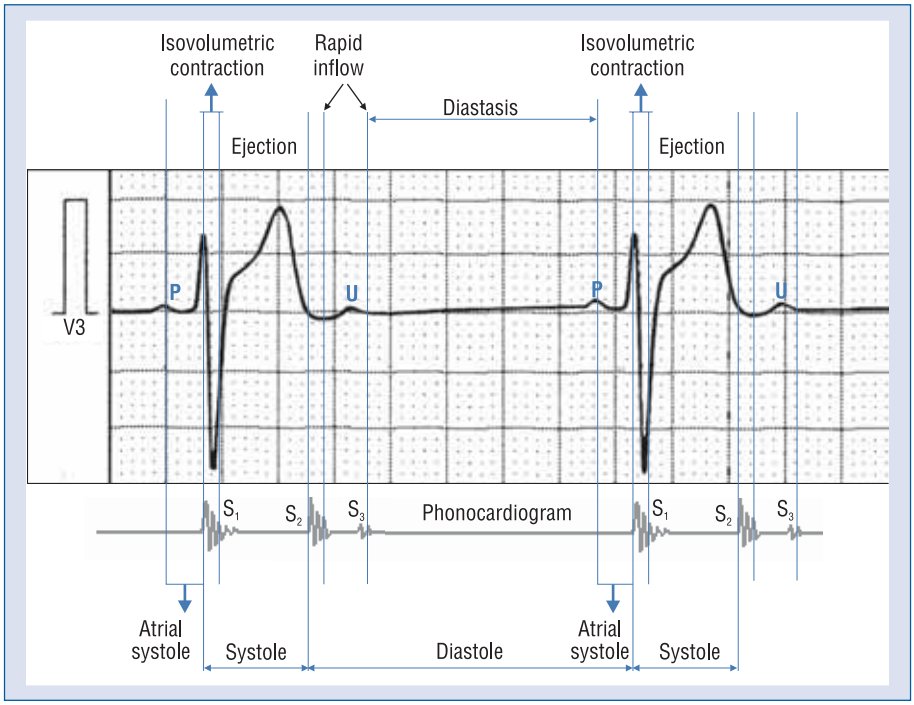

Figure 3. The U wave of electrocardiogram and the contemporary moments of mechanical cycle of the heart and its relationship with the second sound.

VF, and negative in VR and isoelectric in VL. Frequently the U wave has equal polarity to the preceding T, i.e. positive where T also is (Fig. 4).

In precordial leads, U vector points towards the left and the front. Thus, U wave is positive and better observed in V_3 (between V_2 and V_4) (Fig. 5).

Causes of inverted U wave

A negative U wave is highly specific for the presence of heart disease and is associated with other ECG abnormalities in ca 93% of cases. The main causes of negative U wave on ECG are listed below [7]:

— coronary artery disease;
— hypertension (near 40% of cases);
— valvular heart disease;
— congenital heart disease;
— hyperthyroidism;
— primary cardiomyopathy;
— without heart disease (ca 7% of cases).

Additionally, a negative U wave is considered an indirect criterion of LVE.

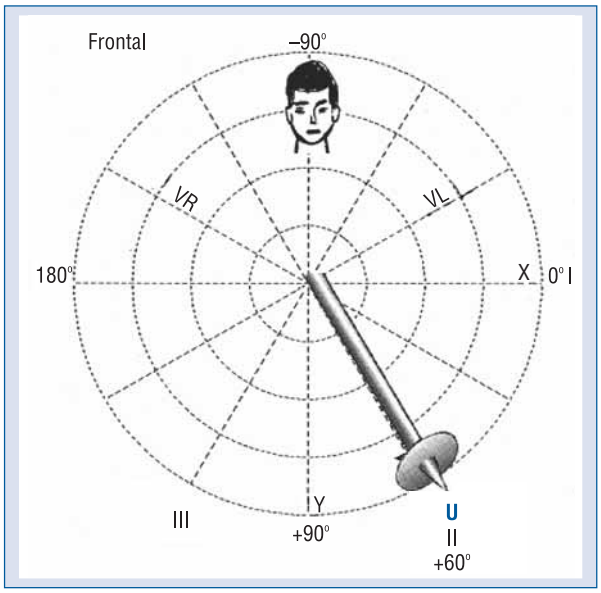

Figure 4. Normal location of U axis in frontal plane.

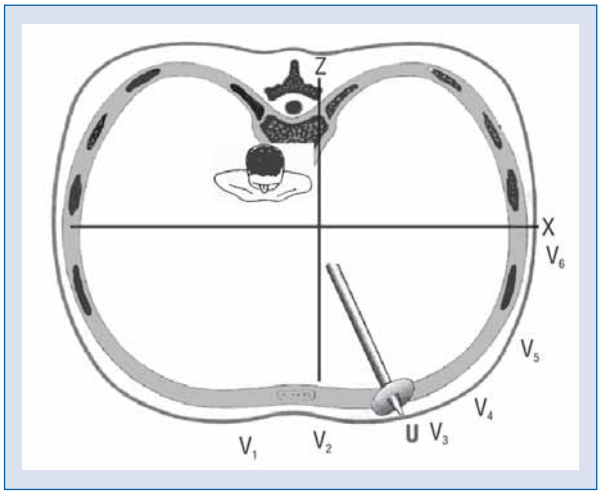

Figure 5. The U wave is better observed in precordial leads (semi direct leads) when compared to frontal plane leads (indirect leads). Usually the tallest are found in leads V_2, V_3 or V_4. U wave is normally positive in all precordial leads.

Coronary artery disease

Negative U waves, when present, may be of immense clinical importance. Inverted U wave is a specific electrocardiographic sign of cardiac ischemia [8]. It is not only an early noninvasive marker for acute ischemia, but it also disappeared after successful revascularization [9]. In patients with ischemic heart disease, the U wave vector tends to be directed away from the site of the akinetic or dyskinetic region. Certainly, the clinical usefulness of U waves remains underutilized in the spectrum of coronary artery disease. When U-wave changes are the first and only sign of ischemia, they may contribute to a decision regarding the hospital admission of a patient without typical ischemic symptoms [10].

In patients with acute ischemia, U wave inversion could be explained by [11]:

— abnormal relaxation pattern during the protodiastolic phase; "protodiastolic shortening" or aftercontraction;
— asynchronous segmental early relaxation,which is defined as a localized early segmental outward motion of the left ventricular endocardium during isovolumetric relaxation;
— altered left ventricular relaxation rate.

Effort-induced U-wave inversion in the precordial leads has long been recognized as a marker of stenosis of the left anterior descending coronary artery, but this pattern is seldom taken into account [12]. Lone U wave inversion after exercise or exercise-induced inversion of the U-wave is highly predictive of significant coronary artery disease and, more specifically, of disease of the proximal left anterior descending coronary artery (specificity: 93%; sensitivity 23%) [13].

During attack of Prinzmetal angina

Transient U wave inversion can be caused either by regional myocardial ischemia or by hypertension. The characteristics of U wave inversion during chest pain attacks in 21 patients with variant angina were compared with those observed in 38 patients with hypertension without apparent ischemic heart disease. Differentiation was possible according to the ECG phase in which U wave inversion appeared. U wave inversion was considered to be significant if there was a discrete negative deflection of more than 0.05 mV within the TP segment. U wave inversion proceeded to positive deflection of U wave in patients with hypertension without ischemic heart disease (initial U wave inversion). In contrast, inverted U wave occurred after positive U wave deflection during attacks in patients with variant angina (terminal U wave inversion). When cold pressor test was performed in patients with variant angina during treatment with calcium antagonists, no patient had either anginal attacks or ischemic ST-segment deviation, but 43% had transient initial U wave inversion, which was followed by positive U wave deflection. U wave inversion can be classified as initial U wave inversion and terminal U wave inversion according to the

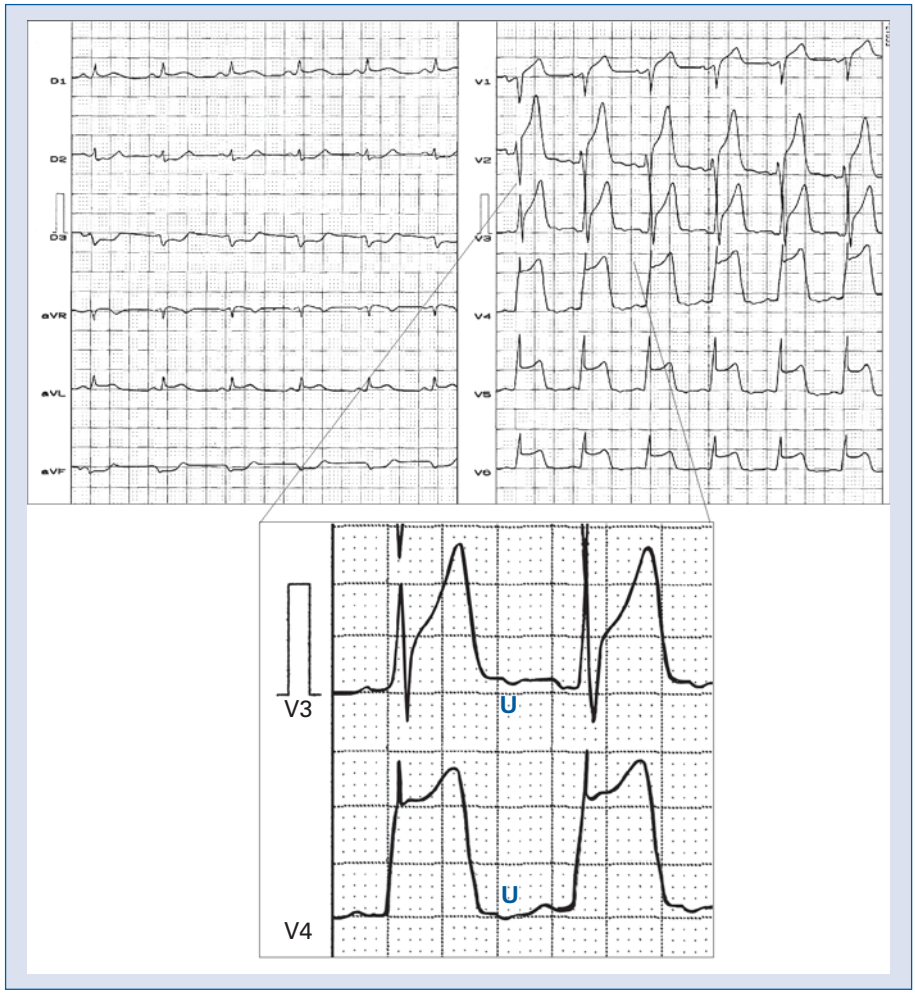

Figure 6. This electrocardiogram belongs to a 66-year-old man, carrier of Prinzmetal's variant angina, recorded during a severe vasospastic crisis. The coronary artery shows a noncritical lesion with < 50% of obstruction. Intermittent negative U wave was observed concomitant with ST-segment elevation.

phasic relationship to positive U wave deflection; the latter is observed in association with regional myocardial ischemia. The former seems to be related to elevated blood pressure rather than to myocardial ischemia [14] (Fig. 6).

Negative U waves in the precordial leads on admission can be seen in about 20% of the cases of acute anterior myocardial infarctions, mainly in those smaller, with less ST segment elevation, better collateral circulation, and larger amount of stunned viable myocardium [15]. In this circumstance, U wave inversion had no predictive value in localizing the diseased artery.

It is suggested that within the appropriate clinical context, an isolated U-wave inversion may precede the typical electrocardiographic changes of an acute myocardial infarction by several hours [16]. The change from a negative to an upright U wave after a coronary arterial bypass graft procedure is associated with a decrease in the QRS amplitude but with no consistent changes in T wave polarity.

Value of intracoronary electrocardiography

Value of intracoronary electrocardiography (IC-ECG) [17] is a sensitive tool in detecting myocardial ischemia. It is a more sensitive method than surface ECG to detect electrical changes during percutaneous transluminal coronary angioplasty (PTCA). It also provides direct monitoring of ST-T segment, QTc intervals, and U-wave genesis during balloon inflation. PTCA of left anterior descending artery (LAD) was performed in 14 patients using the standard balloons and in 11 patients using the perfusion balloons. Patients with perfusion balloon angioplasty had: less ST-T elevation, less ischemia, less QTc-shortening intervals and less positive U waves.

U-wave changes on the IC-ECG during anterior or inferoposterior myocardial ischemia were correlated with the U-wave changes in the precordial leads of the body surface ECG in 28 patients who underwent PTCA of the LAD group (17 patients) or left circumflex (LCx) (LCx group; 11 patients).

The IC-ECG was recorded simultaneously with the body surface multiple precordial leads at the baseline and during PTCA.

The amplitude of the U-wave on the IC-ECG was measured quantitatively, and U-wave changes from baseline to PTCA were assessed qualitatively on the body surface ECG.

Three different patterns of U-wave changes were distinguishable on the IC-ECG from baseline to angioplasty: change to positivity, no change and change to negativity. The incidence of each pattern was similar in the LAD and LCx groups. The IC-ECG was more sensitive for detecting U-wave changes during PTCA than body surface precordial ECG. When compared to the IC-ECG, concordant U-wave changes occurred in the surface precordial ECG in 67% (8/12) of the LAD group with accompanying epicardial U-wave changes, and discordant changes in 33% (3/9) of the LCx group with epicardial U-wave changes [18].

Hypertension

U inversion is observed in nearly 40% of cases of high blood pressure patients. Transient U wave inversion can be caused by an elevation of systemic blood pressure. Negative U wave in left precordial leads is considered and indirect signal of LVE. The deepest negative U wave is usually observed in the area of leads V_5 to V_6 [19].

The ECGs of 297 cases of hypertension were divided into 6 groups on the basis of the relationship between the polarity of the T wave and the U wave. Both waves were positive in all precordial leads in 48.1% of the cases. Negative U waves were found in 21.8% of the cases and these were predominantly in the leads with negative T waves. A negative T wave in V_5 and V_6 was accompanied most frequently by a negative, less frequently by an isoelectric, and least frequently by a positive, U wave. An inverted U wave in the presence of an upright T wave was found in only 2.8% of the cases. A change from a negative to a positive or isoelectric U wave was observed after slowing of the heart rate, a drop in blood pressure, and nitroglycerin administration [20].

Valvular heart disease

An inverted U wave may represent valvular heart disease (mainly aortic and mitral regurgitation) [21].

An inverted U wave may represent left ventricular volume overload [22]. Negative U wave in left leads is considered an indirect criterion of LVE. Both the precordial T-wave imbalance and the U-wave negativity are common findings in early LVE [23].

Right ventricular enlargement: negative U wave in right precordial leads is observed in right ventricular enlargement. The U wave vector is directed opposite to the QRS axis in the horizontal plane in patients with both left and right ventricular enlargement [7].

U wave alternans

The U wave alternans is an electrocardiographic sign of left ventricular failure and increased ventricular irritability [24, 25].

U-wave voltage or U-wave amplitude

It is normally always lower than 50% of the width of the preceding T and generally between 3% and 24% of it. Usually it does not exceed 1 mm, being in average of 0.33 mm. If it reaches 1.5 mm or more, it is considered prominent or high, however, there may be normal U waves of up to 2 mm (0.2 mV) in II and from V_2 to V_4. The tallest positive U wave is usually observed in the area of leads V_2 to V_4. U-wave voltage is inversely proportional to heart rate (RR interval).

Causes of prominent U waves

— **Bradycardia.** U wave voltage is strongly rate dependent (inversely proportional). U wave is observed better during bradycardia. When heart rate (HR) is ≤ 65 bpm, U waves are visible in 90% of cases. When HR is between 80 bpm and 95 bpm U waves are visible in 65% of cases. When HR is > 95 bpm U waves are visible in 25% of cases (Fig. 7, 8). Bimodal T waves with hump-like morphology represent different levels of interruption of the descending slope of the T wave, called T_2 instead of U wave. Bimodal or notched T waves may be distinguished from the T-U interval: the second apex of bimodal T wave (T_2) is at a distance from the first one (T_1) < 150 ms; the T_1-U interval is > 150 ms. The second apex of bimodal T wave (T_2) is at a distance < 150 ms from

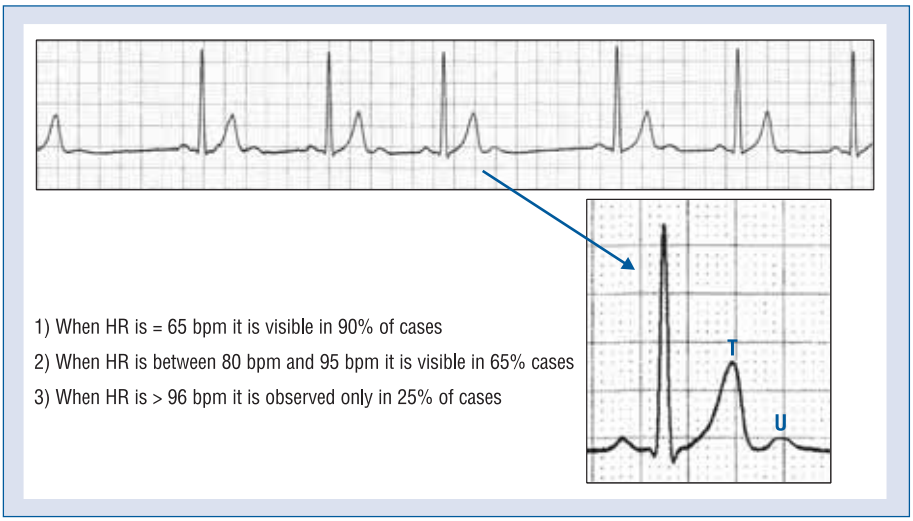

Figure 7. Percentage of U wave visualization related with heart rate (HR).

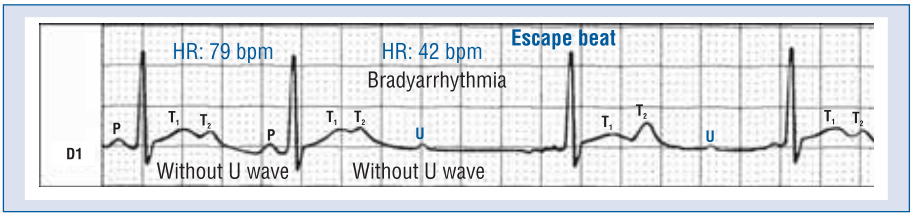

Figure 8. Electrocardiogram differentiation between T_2 (bimodal T-wave) and U wave (HR).

the first module (T_1): The T1-U interval is always > 150 ms [26]. U wave increases its voltage or appears during slow rates or after pauses [27], as in the cases of long QT interval. In this case we observe a bifid T wave and a U wave only with slow HR.

— **Early repolarization variant (ERV).** Because bradycardia U waves are frequent, in ERV they are best observed in the V_3 lead. U waves are frequent when sinus bradycardia is present.

— **Hypokalemia.** Hypokalemia is associated with flattening of the T wave and the appearance of a prominent U wave. A pathological "U" wave as seen with hypokalemia is the consequence of electrical interaction among ventricular myocardial layers at AP phase 3 of which repolarization slows [28]. The main ECG features of hypokalemia are: PR interval prolongation, gradual ST segment depression ≥ 0.5 mm in II or from V_1 to V_3, decrease of T wave amplitude (flat T wave), possible T wave inversion, prominent U wave (U wave > 0.5 mm in II or > 1 mm in V_3) secondary to prolongation of the recovery phase of cardiac AP, characteristic reversal in the relative voltage of the T and U waves, QTc interval prolongation, tendency to torsade de pointes (TdP) atypical tachycardia and digitalis action enhancement. Hypokalemia enhances the tachyarrhythmias produced by digitalis toxicity.

— **Hypomagnesemia.** Prominent and alternant U wave with ventricular irritability was described in patients with low serum magnesium (< 1.8 mmol/L) [25].

— **Hypocalcemia.**

— **Hypothermia.**

— **Class III antiarrhythmic drugs** (amiodarone, dofetilide, sotalol).

— **Class IA** (quinidine, disopyramide, and procainamide). Quinidine effect is characterized by discrete QRS prolongation; only with an extreme quinidine effect, significant QT/QTc interval prolongation, depressed, widened, notched, and inverted T waves, prominent U waves and TdP tendency.

— **Digitalis effect or digitalis action.** The earliest modification of digitalis effect on ECG or "digitalis action" are: PR interval prolongation,

ST segment: shortening and superior convexity ("in spoon") by shortening of phases 2 and 3 of AP, shortening QT and QTc intervals (main cause of acquired short QT interval), flattening with apiculate T wave of terminal portion in 10% of cases, possible symmetrical inversion of T wave (pseudo-ischemic T wave) and prominent U wave.

— **Phenothiazines.** The electrophysiological properties of phenothiazines are comparable to those of the Class Ia antiarrhythmic quinidine. Numerous ECG aberrations may be induced by these agents, including changes in the morphology of the T wave, prolongation of the QT interval, and accentuation of the U wave. Even with standard clinical dosages (100–400 mg/d.), thioridazine causes minimal prolongation of the QT interval, reduction of T wave amplitude, and prominent U waves in nearly 50% of patients.
— **Forced inspiration.**
— **Post-exercise.**
— **Mitral valve prolapse.**
— **Left ventricular enlargement.**
— **Alterations of the central nervous system with endocranial hypertension.** In patients with cerebrovascular event T and U waves are augmented, consequently the T/U ratio is not altered.
— **Cardiomyopathies: i.e.** Hypertrophic cardiomyopathy with solitary hypertrophy of papillary muscle [29].
— **Acquired complete atrioventricualr block.** Torsades de pointes during acquired complete atrioventricular block is rare. The predictors of ventricular arrhythmias during acquired complete atrioventricular block are the presence of prolonged QTc/JTc intervals, pathologic U wave and T-U complex, prolonged Tpeak-Tend interval, and LQT2-like QT morphology [30].
— **Congenital long QT syndrome.** Augmentation and greater degree of merging of the T and U waves and QTc interval prolongation are changes alerting about the possibility of congenital long QT syndrome, specifically genotype 2 or 1 [31]. T or U wave alternans in association with long QTU and TdP is uncommon and its mechanism(s) is unknown. 1) TU alternans may be due to 2:1 propagation of an early after depolarization (EAD) or to alternation of the recovery kinetics of a repolarization current; 2) The constant occurrence of EAD in relation to phase 0 in spite of alternation of plateau duration suggests an ionic mechanism synchronized to depolarization; 3) Tachycardia dependent TdP in clinical and experimental examples of long QTU seems to be characteristically associated with TU alternans. Dispersion of repolarization may underlie the increased ventricular electrical instability in these cases [32]. Andersen-Tawil syndrome (ATS) is a channelopathy affecting inward rectifier potassium I(K1) with QT prolongation, large U waves, and frequent ventricular tachycardia (VT) [33].
— **Left circumflex-related myocardial infarction.** ECG criteria of strictly posterior myocardial infarction with the left circumflex coronary artery as an infarct-related coronary artery apply at less than 6 hours or at 24 hours since the onset of the symptoms. 1) ST depression $\geq$ 0.1 mV in two consecutive chest leads; 2) prominent positive U wave $\geq$ 0.1 mV in leads V_2 or V_3; 3) T/U ratio in leads V_2 or $V_3 \leq 4$. Considering two of the above criteria as positive, the sensitivity was 71.9%, the specificity 97.0%, and the diagnostic accuracy 88.8% (Fig. 9) [34].

U wave duration

It is about 170 ± 30 ms in normal adults.

U wave contour

The normal U wave has an asymmetric shape with rapid ascending limb and more slow descending limb (just the opposite of the normal T wave).

U wave constance

Frequently absent (50% to 75%) [35]; occasionally hard to distinguish from the preceding T wave. Better observed during bradycardia and sometimes related to TdP.

Terms definitions

QT interval. Known as electric "systole". It corresponds to ventricular depolarization and repolarization. Measurement should be conducted in VL so as not to include the U wave. The end of the T wave is the intersection of a tangent to the steepest slope of the last limb of the T wave and the baseline, in lead II or V_5 [36].

Measurement of the QT interval must be conducted at a double velocity of 50 mm/s and with the 12 leads vertically aligned, with the aim of analyzing one beat simultaneously from the first deflection of the QRS complex until the point of return of the T wave to the baseline or in the lowest point between the T and U waves [37].

Q-aT interval. From the onset of Q up to the apex of T.

Q-aTc interval. Interval from the onset of Q up to the apex of T, divided by the root square of RR.

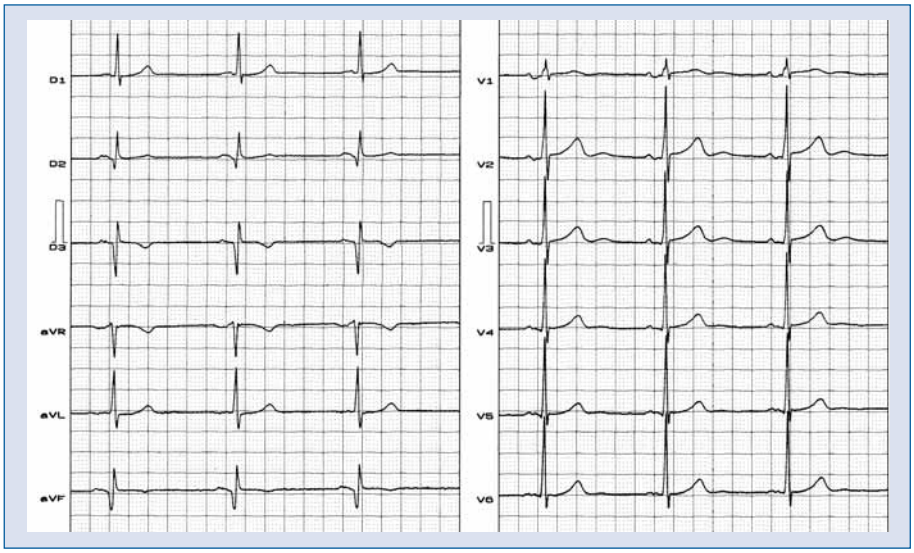

Figure 9. This electrocardiogram was obtained in a 75-year-old asymptomatic female a history of myocardial infarction. This tracing shows sinus bradycardia at 55 beats/min. The abnormal Q waves and nonspecific ST-T changes in leads II, III and VF, and prominent R waves in leads V_1 and V_2 are consistent with prior inferolateral infarction (new topographic myocardial infarction classification). Coronary artery disease should also be coded. Prominent positive U wave ≥ 0.1 mV in leads V_2 and V_3.

Q-oT. Interval from the onset of Q up to the onset of T.

Q-aU. Interval from the onset of Q up to the apex of U. Digitalis frequently cause separation between the end of T wave from the U wave because digitalis shortens the QT interval.

QT + U interval or Q (T + U) interval. This term is employed in cases of marked QT interval lengthening (congenital long QT, severe bradycardia, hypokalemia and hypocalcemia, fad diets, contrast injection into coronary artery, administration of class IA and III antiarrhtymics agents, post-resuscitation, neurogenic, organophosphorus intoxication) when the QT interval is prolonged more than 100 ms (≥ 125%) at heart rates within 50 to 100 beats/min, T occupies the territory of the U wave and masks it [38].

When the T wave has two peaks (T_1–T_2), the distance between the first peak and the second one is always < 0.15 s (150 ms) and the distance between the first T peak and the U peak wave is > 0.15 s (150 ms) [26].

The normal U wave loop vectorcardiogram

Frontal plane. The U loop is directed to +60° near the II lead. Normally, it is always projected into the positive segment of the II lead. U wave may be inscribed in a counterclockwise, in a clockwise, or an 8 configuration.

Horizontal plane. The U loop is directed to front and the left between V_2 and V_4.

The source of U wave

The source of the U wave is uncertain. Several hypotheses for the origin of the U wave in ECGs have been proposed. A satisfactory explanation of its origin is still outstanding. Various explanations have been offered for their origin, but none is universally accepted. The surface potential at any given electrode location is the net result of simultaneously acting and variously directed electrical forces in the myocardium.

Four hypotheses are being entertained about the underlying mechanism:

- tardy repolarization of several endocardial structures:
  - repolarization of the intraventricular conduction system or Purkinje fibers system. This is the Hoffmand and Crannefield hypothesis [39];
  - delayed repolarization of the papillary muscles named by Bufalari and Furbetta "the syndrome of the papillary muscles" [40];
  - afterpotentials caused by mechanical forces in the ventricular wall. Electro-mechanic coupling, mechanoelectrical hypothesis or mechanoelectrical feedback;
  - prolonged repolarization in the cells of the mid-myocardium ("M-cells").

Tardy repolarization of several endocardial structures

Repolarization of the intraventricular conducting system or Purkinje fibers system. This is the Hoffmand and Crannefield hypothesis [39]. It has been suggested that the U wave may reflect repolarization of the ventricular Purkinje system, since the AP duration in these fibers is the longest for any fibers found in the heart. In an experimental canine model, Watanabe conducted a comparison of the AP of Purkinje and ventricular muscle fibers under conditions accentuating the U wave. The author concludes that the U wave represents Purkinje fibers repolarization. The author observed a good temporal correlation between phase 3 repolarization in Purkinje fibers and the electrocardiographic U wave [41].

Against this theory we have the following arguments:

- the small mass of Purkinje fibers, in relation to the very large mass of ventricle, may be insufficient to affect the ECG and generate the U wave [42];
- amphibian hearts have no Purkinje fibers but do show U waves [43];
- the timing of the U wave during ventricular relaxation and the links between U wave and mechanical events favor the mechanoelectrical hypothesis of U wave genesis [44];
- the timing of the U wave apex is dependent on the duration of ventricular repolarization but not on the QRS duration. This observation is better explained by the ventricular relaxation than by the Purkinje fiber repolarization theory of U wave genesis;
- in the presence of complete right bundle branch block, the timing of the U wave correlates better with the presence of right ventricular enlargement than with the dromotropic disturbance [45].

Delayed repolarization of the papillary muscles is the denomination created a long time ago (1956) by Drs. D. Furbetta and A. Bufalari [40]. They identify "the papilary muscle syndrome" and postulate that the U wave represents repolarization of the papillary muscle and neighboring structures. The common factor underlying the varied cardiac pathology is regarded to be ischemia, "strain", or other functional derangement of the papillary muscles in the right or left ventricles. The authors believe that various abnormalities of the papillary muscles, whether anatomic or functional, are detectable by modifications on U waves and T-U segment.

They described three different vectorial patterns:

- left papillary muscle syndrome: negative U wave in left leads I, VL, V_5–V_6, because spatial U vector is directed to the front and right. Observed in anterior myocardial infarction, hypertension and aortic valvular disease;
- right papillary muscle syndrome: negative U wave is observed in III, sometimes in VF, and right precordial leads. Observed in right ventricular enlargement and congenital heart disease;
- biventricular papillary muscle syndrome: negative U wave in all precordial leads, II and VL. Biventricular enlargement (strain of both ventricles).

The phenomenon of solitary papillary muscle hypertrophy in hypertrophic cardiomyopathy (HCM) is very rare. Giant negative T and U waves are two common ECG phenomena in HCM and have been attributed to hypertrophy of the posterior papillary muscle. Solitary hypertrophy of the anterior papillary muscle might be a new echo-electrocardiographic syndrome related with the Furbetta hypothesis [29].

Apical hypertrophy, especially of the posterior papillary muscle, may play an important role in the pathogenesis of Giant negative T and negative U waves in HCM [46].

Electro-mechanic coupling, mechanoelectrical hypothesis, mechanoelectrical feedback

Controversies persist regarding whether the U wave is a purely electrical or mechanoelectrical phenomenon. The characteristics of U wave are not compatible with the Purkinje or ventricular muscle repolarization hypotheses. The timing of the U wave during ventricular relaxation and the links between U wave and mechanical events favor the mechanoelectrical hypothesis of U wave genesis [44]. Schimpf et al. [47]. used echocardiographic measurements to discriminate between the hypotheses for the origin of the U wave. Echocardiography and ECG were performed in 5 SQTS patients from 2 unrelated families with a history of sudden cardiac death and 5 age-matched and gender-matched control subjects. In SQTS patients, the end of the T wave preceded aortic valve closure by 111 ± 30 ms *vs*. –12 ± ± 11 ms in control subjects. The interval from aortic valve closure to the beginning of the U wave was 8 ± 4 ms in patients and 15 ± 11 ms in control subjects. Thus, the inscription of the U wave in SQTS patients coincided with aortic valve closure and isovolumic relaxation, supporting the hypothesis that the U wave is related to mechanical stretch. There

is a significant dissociation between the ventricular repolarization and the end of mechanical systole in SQTS patients. Coincidence of the U wave with termination of mechanical systole provides support for the mechanoelectrical hypothesis for the origin of the U wave [48]. There is a reason to believe that the U wave is produced by potentials elicited by the stretching of ventricular muscle during the period of rapid blood inflow into the ventricles [43]. Postpotentials or afterpotentials with triggered activity mechanism are the presumable genesis. Afterpotentials occur in stretched cardiac fibers and the subendocardial tissue is subjected to a greater stretch than the subepicardial muscle. Lepeschkin [49] has stated that the U wave results from potential differences between the ventricular muscle with larger negative afterpotentials and that with smaller afterpotentials, with the latter positive relative to the former. Di Bernardo and Murray [50] proposed a simple method to model repolarization in the left ventricle (LV) and the corresponding T waves on the surface ECG. The authors modeled the cardiac cell APs in the LV with differences in only the duration of the plateau phase. Using published experimental data on the epicardial and endocardial repolarization sequences, for each point on the LV surface the authors set a different AP repolarization starting time, determined by the duration of the plateau phase. The surface source model was used to compute potentials on the surface of the torso, generated by repolarization of the LV. Both the torso and the LV had homogeneous and isotropic conductivity. They simulated T waves on the 12-lead ECG and compared their results with measured T waves from five normal subjects. The orientation and shape in each lead were reproduced. In each lead the authors computed the root mean square error between simulated and measured T waves. The average error across the 12 leads was small, with a mean value of 0.11 mV across all the subjects. The authors concluded that repolarization of the LV can be modeled independently of the depolarization sequence and AP duration gradients. This method is an easy and powerful tool to describe the ECG features of repolarization. The same author using a computer model of LV repolarization demonstrated that a delaying repolarization in different regions of the heart cannot explain the U-wave. The presence of after-potentials on the cardiac AP does explain the U-wave polarity and other characteristic U-wave features. The authors also show that abnormal after-potential timing corresponds with abnormal U-wave inversion [51]. Cancellation in electrocardiology is defined as the degree to which the electrical forces in the heart are opposing each other. This mechanism plays a major role in the formation of the ECG waves. Ritsema van Eck et al. [52] used a digital computer model of the left ventricle to study the effect of source locations on cancellation during the T and U waves. The model represents an anatomically stylized cross-sectional slice of the left ventricle, containing 1961 hexagonal cells in a single layer. The model employs a multi-layered segment of the myocardium. An AP is assigned to each cell. The timing of the APs follows a simulated excitation sequence. The potential differences between the APs of adjacent cells produce time-varying electrical sources, each of which contributes to the potential in an arbitrary point P on the body proportionally to its own, location-dependent, transfer function (lead vector). The ECG at P is the sum of all potential contributions. The potential differences between the APs produce time-varying electrical sources. Each source contributes to the potentials in an arbitrary point P of the body. The strength of this contribution is determined by a specific coefficient, the "lead vector", linking P to the source. The ECG recorded at P is calculated as the sum of all potential contributions. For each time point in the ECG at P, the contribution of each cell is mapped back onto the slice. Adjacent cells with equal contributions form iso-source strings, together forming iso-source maps. The T-U wave as observed in P will be the sum of positive and negative contributions from the iso-source distributions as they change with time. The iso-source maps for an anteriorly located observation point P at 4.2 cm from the epicardial surface show a continuous interplay of positive and negative contributions. During the near-zero ST segment, cancellation varies between 80% and 100%. In the ascending limb of the T wave, positive contributions substantially increase, giving a decrease in cancellation to about 40%. At the end of the T wave (with almost zero amplitude), the positive contributions are only slightly reduced as compared with those at peak T, but greatly increased negative contributions cancel them out. This is contrary to the generally held view that the end of T signifies the end of the repolarization process. The manifest shape of the T and U waves is the result of complex interactions of varying and often largely canceling contributions. The iso-source maps are helpful to understand the genesis of the T and U waves [52]. The repolarization waves constructed in this way reproduce the natural aspects of a T wave followed by a U wave. The creation of a U wave is conditional on small voltage differences

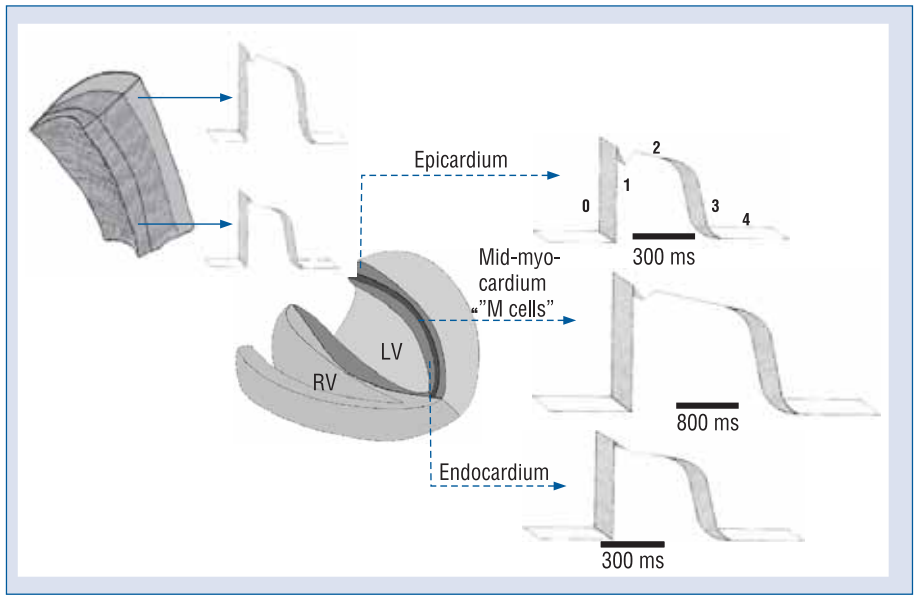

Figure 10. The thickness of the ventricular wall is formed by three functional layers, with different action potential. In the depth of the middle layer we find M cells, which have a subpopulation of cells with a great conduction velocity and electrophysiological properties of their own, which are very relevant in the pathophysiology of long and short QT syndromes.

between the tail ends of the APs. No fundamental demarcation exists between U wave and the preceding T wave. The morphology of the T-U wave is dependent on the geometrical position of P with respect to the myocardium. T and U form a continuum. Together they are the result of one and the same process of repolarization of the ventricular myocardium. This has implications for the measurement of QT duration and for safety testing of drug-induced QT prolongation [53]. Depolli et al. [54] used a spatial model of a left ventricle constructed from 12 layers composed of cubic cells. Each cell is assigned its own time-dependent AP with its own contribution to the electrical potential at arbitrary points where ECGs are measured. Simulated ECGs show that U waves can be generated using various combinations of APs across the different layers of the ventricular wall. The authors conclude that the U wave can be generated in the presence of strong intercellular coupling. Myocardial layers with prolonged action potentials, like M cells, are not necessarily needed for U-wave genesis.

Theory of origin in M-cells observed in acquired or congenital long QT syndrome

Besides the three basic types of cells in the ventricular myocardium: epicardial, mesocardial and endocardial, there is a cellular subpopulation called "M-cells", located in the midmyocardium with very differentiated electrophysiological and pharmacological features. The authors from the Masonic Medical Research Laboratory suggest that M-cells, more abundant in mass and having a prolonged repolarization time comparable to Purkinje cells, may be responsible for the pathophysiologic recording of the U wave in the presence of acquired or congenital long QT interval. The discovery of M-cells and their electrophysiology has established the cellular basis for repolarization and has contributed to our knowledge of U-wave genesis [55].

A second component of an interrupted T wave is more likely to be, and argue for use of the term T2 in place of U to describe this event [56].

Postextrasystolic U wave augmentation (a marked increment in U wave amplitude after premature ventricular contractions is an adverse prognostic sign in "pause-dependent long QT syndrome").

Postextrasystolic T wave changes are common and lack predictive value.

Postextrasystolic U wave changes may be a specific marker of a tendency to the development of spontaneous ventricular arrhythmias (Fig. 10, 11) [57].

Final considerations

Although the sixth wave of the ECG remains a mystery regarding its genesis, new investigations

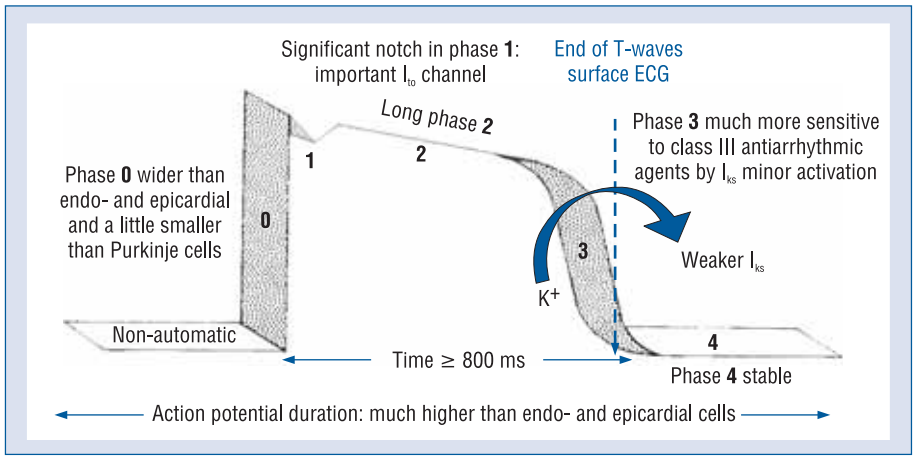

Figure 11. Characteristics of action potential of M cells. It is a fast and non-automatic fiber; therefore, we could say that it is a mixture between Purkinje cells and contractile ventricular myocardium. It is very sensitive to bradycardia and class III antiarrhythmic drugs, such as amiodarone and sotalol.

indicate the electro-mechanical theory is true, except in the cases of long QT interval, where the M cell would have a decisive role. As we can see, the clinical observation of this "neglected" small wave has a great clinical significance in very different pathologies. We believe it is necessary to carry out more experimental and clinical research to provide a basis for the last "enigma" of the ECG.

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