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Surfing the T Wave: A Primer on ECG T Wave Morphologies Encountered in Clinical Trials and Impact on the QT Interval and Patient Safety

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ABSTRACT

Electrocardiogram (ECG) interpretation and measurement is an essential aspect of patient safety and pharmacovigilance in clinical trials. Changes in the T wave segment of an ECG can provide both diagnostic and prognostic information and may be affected by a variety of intrinsic and extrinsic factors related to drug administration. To add, regulators in their guidance encourage sponsors to provide analysis on treatment-emergent T wave morphology changes when submitting clinical study reports. Despite the T wave representing an important element of an ECG and impacting QT interval measurement, there is often a lack of recognition and incomplete understanding of the different T wave configurations that would affect subject management. Moreover, this topic has not been formally incorporated in pharmaceutical research. Therefore, this comprehensive review aims to profile normal and abnormal T wave morphologies that scientists and principal investigators might encounter during study conduct that would influence patient management and safety. This includes commentary on T wave pathophysiology, prognostic information, and short- and long-term management strategies when T wave abnormalities are present.

1 | Introduction

Drug sponsors strive to develop safe and effective therapies. An undesirable property of a new drug in development is the potential to delay ventricular repolarization, which has been associated with life-threatening and lethal ventricular arrhythmias, particularly Torsade de Pointes (TdP). Therefore, regulatory agencies mandate the evaluation of cardiac safety in early drug development in both non-clinical and human clinical settings.

The QT interval on the ECG is an essential element in proarrhythmic risk assessment and is an essential measurement in either dose escalation or thorough QT (TQT) studies. As the T wave is an integral component of the QT interval, changes in T wave morphology may impact the accuracy of measurement of this interval. For example, flat T waves may be difficult to measure if the end of the T wave is not well defined, thereby leading to an erroneous QT value. In addition, T wave configuration can influence several aspects of a clinical trial, including participant enrollment (e.g., inclusion/exclusion criteria), dosing decisions, adverse event reporting, and whether there is a need to refer for cardiac follow-up. To add, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 guidance encourages sponsors to provide analysis on treatment-emergent T wave morphology changes when submitting clinical study reports [1]. While regulators consider T wave abnormalities ancillary in the determination of drug safety, it is imperative to recognize and understand the various T wave presentations

that may be encountered during the conduct of clinical investigations. This primer is therefore designed to provide guidance to those involved in clinical trials concerning the identification of normal and abnormal T wave configurations, their management, and their prognostic significance.

2 | Tutorial Background

The ensuing discussion is based upon evaluation of 12-lead ECGs in normal healthy adults from the general population in which the tracings are acquired at a paper speed of 25 mm/s, with a format that includes multiple P, QRS, and T wave complexes, and with a visible calibration pulse showing a gain setting of 1.0 mv = 10 mm. It also assumes proper patient skin preparation, that the recording electrodes are not expired, all lead cables and equipment are well maintained, filtering is not routinely employed, and the room is devoid of electrical interference. The electrodes should be properly positioned and connected using Goldberger-Einthoven distal placement of limb leads and standard American Heart Association (AHA) precordial lead placement as per the 1938 consensus document [2], see Figure 1. Ideally in women, this involves precordial leads V4–V6 being placed under the breast. It is beyond the scope of this primer to profile the spectrum of T wave manifestations in animal models, the pediatric population, the elderly and those with known and significant clinical disorders, which might affect cardiac repolarization. Discussion of subpopulations dealing with race, ethnicity, and gender identity is also intentionally omitted, and the reader is therefore encouraged to consult other sources for T wave characterization in these subgroups.

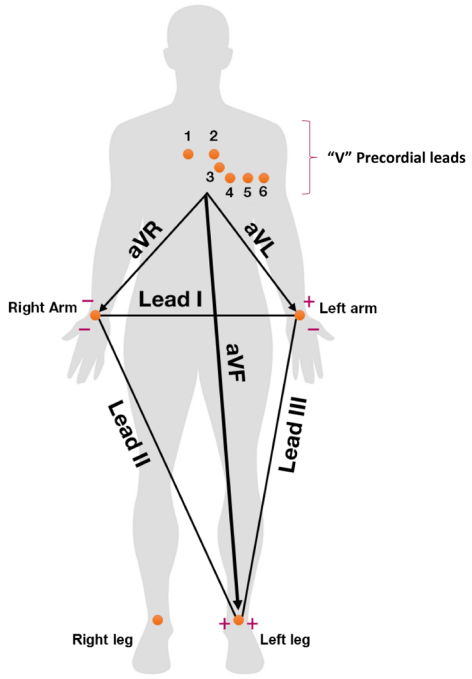

FIGURE 1 | 12-lead ECG electrode placement and T wave polarity. Example of ECG electrode placements and leads. Normally, T waves are positive in leads I, II, and V3-V6 and are concordant with the QRS direction. Leads aVR and V1 are generally inverted or negative. In addition, leads V1-V3 are usually inverted in children under the age of 16. They may remain inverted in leads V1-V3 in young adults up to 25–30 years old ("juvenile T waves"). This finding is more common in females, athletes, and those of African American heritage. V2 and leads III, aVL, and aVF can demonstrate variable direction, in which polarity usually follows the QRS direction when the R wave is 5 mm (0.5 mv) or greater in amplitude.

3 | Clinical Importance of the T Wave

The T wave occupies an important element in electrocardiographic interpretation and QT interval measurement (Figure 2). Changes in its morphology are a frequent byproduct of direct and indirect effects of new chemical entities and contain both diagnostic and prognostic information, which may have a profound influence on patient care, especially for those entrusted with clinical trial oversight. While the Food and Drug Administration (FDA) does not mandate T wave analysis for every new drug evaluation, it does recommend that sponsors provide commentary on T wave morphology changes, as they are an important component of overall cardiac drug risk and comprehensive QT assessment [1].

Outside of the AHA statement from 2009 [3], there has been a paucity of consensus population data to define and characterize T waves in otherwise healthy adult individuals of both genders and different ethnicities. Moreover, less experienced ECG readers are often not apprised of specific criteria for various T wave abnormalities (TWA), and reliance on computer diagnostic algorithms is frequently misleading. Furthermore, an understanding of T wave pathophysiology and a comprehensive list of potential etiologies are commonly lacking. As such, the purpose of this primer is to bring awareness and foster recognition of primary T wave configurations that may be encountered in clinical practice and serve as a guide to their management. It is also targeted to principal investigators and those involved in reading ECGs for pharmaceutical studies who are tasked with important and timely clinical decisions. These include whether subjects should be included in an investigational drug clinical study, whether there are safety concerns regarding drug dose escalation, whether a treatment-emergent T wave finding should be considered an adverse event, and when the subject should be referred for further cardiac evaluation. Each of these circumstances requires baseline knowledge to aid in distinguishing normal T waves from those that are abnormal, which might convey a higher risk of arrhythmias, cardiomyopathy, and major cardiovascular events (MCE), including sudden cardiac death (SCD).

4 | History of the T Wave

The T wave, representing ventricular repolarization, was discovered in frog hearts in 1883 and later identified as typically being an upright deflection in mammalian dog hearts in 1892. Electrical activity in the human heart was first documented by Augustus Wallen in 1887 using a mercury capillary electrometer attached to the front and back of subjects, although the deflections were poorly defined and distorted and corresponded only to ventricular depolarization and repolarization. Applying mathematical

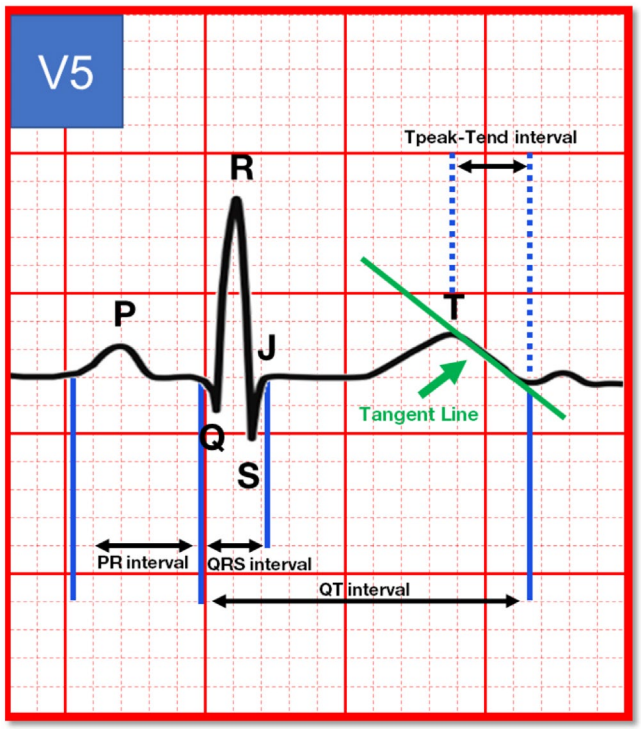

FIGURE 2 | ECG waves and key intervals. Principal waveforms and intervals of an ECG. The T wave amplitude is measured in mv (mm) based on the magnitude of its deflection relative to the baseline (T–P segment). The positions of Tpeak and Tend are indicated by blue dashed lines. The tangent line (green) is drawn to calculate the Tpeak-Tend interval.

calculations to improve upon these primitive waveforms, the Dutch physiologist and physician William Einthoven developed the first practical electrocardiograph using a string galvanometer system that weighed almost 600 pounds and required five assistants to deploy. He further proposed the term "electrocardiogram" while eventually identifying the three principal peak waveforms and naming them P, QRS, and T, which replaced the previous nomenclature of A, B, and C. His discovery and refinement of the first ECG for medical diagnosis earned him the Nobel Prize in physiology or medicine in 1924 (reviewed in Hurst [4]).

5 | T Wave Electrophysiology

The T wave on the ECG represents ventricular repolarization from the epicardium to the endocardium and correlates with phase 3 of the cardiac action potential. During this phase there is restoration of the cell's negative resting membrane potential ushered in by a decline in inward sodium and calcium currents in concert with an outward egress in several voltage-gated potassium currents facilitated by the Na^+/K^+ ATPase pump. Heterogeneity of repolarization currents resulting from gradient differences across areas of the myocardium is thought to manifest on the surface ECG as different T wave morphologies, some of which have been linked to the occurrence of ventricular arrhythmias and MCE [5].

CAVEAT: *Drugs and disease states that directly affect cellular cation channels during phase 3 of the action potential are the primary mediators of changes in T wave morphology as discussed below.*

6 | T Wave Morphology in Animals

Non-clinical studies have been conducted in a myriad of animal models to develop an understanding of both normal cardiac electrophysiology and pathology. This includes investigating arrhythmia mechanisms, ion channelopathies, conduction disturbances, myocardial injury, and drug toxicity, all of which involve a focus on T wave morphology secondary to cardiac repolarization abnormalities. The pivotal role of these studies cannot be overstated, as they have yielded T wave biomarkers for arrhythmogenesis and TdP. Chief amongst these biomarkers are T wave alternans, diffuse T wave flattening, bifid T waves, and prolongation of the terminal portion of the T wave (Tpeak-Tend).

The animals most often selected for these studies are rats and mice due to the ease in handling and cost, while larger animals such as rabbits, guinea pigs, dogs, goats, pigs, and monkeys have also been employed, though less so due to ethical considerations and expense. Extrapolating the results from non-clinical animal studies to humans is a challenging pursuit, although there is some T wave data from animal models that may be applicable to humans, particularly with respect to proarrhythmic risk. In this regard, Joukar [6] reviewed data derived from multiple rodent and non-rodent animal studies related to cardiac ion channels, action potentials, and their effects on the ECG with respect to normal physiology and disease states. He identified that the best species for assessing cardiac action potential, ion channel physiology, and associated ECG effects was the rabbit model, where repolarization currents were closest to those observed in humans.

There are, however, multiple limitations in evaluating and interpreting T wave findings in animals and extrapolating this data to human subjects. These include:

- Variability in ion channel density, configuration, and function amongst the different animal species may impact T wave morphology.
- The pharmaceutical agent, testing protocol, use of anesthesia, and drug exposures may have a differential impact on the ECG depending upon which species is being employed.
- There is a lack of uniformity and standardization between research laboratories pertaining to the method of ECG acquisition and description of T wave findings.
- There is little information regarding normal T wave magnitude, polarity, and morphology in the spectrum of healthy animals utilized in drug studies beyond the retrospective study of Romito et al. [7] These authors analyzed ECG data from 129 healthy dogs of different somatotypes and generated reference standards in this relatively small cohort. They did not discover any qualitative or quantitative differences in the animals as a function of body weight, breed, age, or gender, implying that their standards may be applicable in other canine drug trials. Although lacking at

present, determining reference standards for other laboratory animal models would be enlightening in differentiating normal versus abnormal T wave morphology.

CAVEAT: *T wave findings in animal studies have yielded proarrhythmic biomarkers that may portend cardiac liability in humans, and efforts to standardize data acquisition and T wave analysis for the various species selected for drug research is recommended. However, caution should be exercised in analyzing T wave data due to species-specific differences in anatomy and ion channel physiology and extrapolating these findings to human subjects.*

7 | Normal T Waves

The T wave orientation and amplitude in the limb leads of the ECG are influenced by the mean frontal plane axes of the T waves and their associated QRS complexes. Since ventricular repolarization proceeds epicardium to endocardium, which is in the opposite direction as depolarization, the T waves typically follow the polarity of the preceding QRS complex. In the precordial leads, T waves are generally upright in all leads except V1, and peak deflections are often seen in leads V2 and V3 (Figure 1). T waves and associated QRS amplitudes tend to be higher in men than in women, presumably due to the larger heart sizes, cardiac mass, and increased expression of repolarizing ion channels in males, though this difference gradually declines with age [8].

The T wave on occasion can be upright in V1, usually in younger individuals, and represents a normal variant when it is an isolated finding. It can also be upright in the setting of various conduction disorders such as with right ventricular pacing and pathologic disorders including ventricular hypertrophy, myocardial ischemia, and left bundle branch block. It should also be noted that T wave morphology can fluctuate, and this variability is a function of which ECG lead(s) are chosen, study protocol design, drug exposures, diurnal variation, environmental factors such as room temperature, anxiety, body habitus, food, and other intrinsic and extrinsic factors (see Table 1) Moreover, T wave variability may be time-dependent, and changes in T waves can occur within minutes, hours, or even days. As such, unless one extracts continuous 12-lead ECGs over an extended period of time and controls for the multiple factors mentioned above, quantifying the time course of T wave variability and the description of any associated changes in morphology would be a challenging undertaking and a topic beyond the scope of this tutorial.

CAVEAT: *T wave polarity is a function of multiple factors, including age, gender, race, QRS amplitude and orientation, assuming correct lead placement and a standard gain calibration pulse.*

8 | Abnormal T Waves

Abnormal T waves may be classified as either primary or secondary and have numerous etiologies. In general terms, primary TWAs are caused by an imbalance in the repolarizing currents within the myocardium needed to restore resting membrane potential, such as when the Na^+/K^+ ATPase pump is altered by ischemia or when there are changes in action potential duration or velocity. Secondary TWAs are predominantly the result of aberrant or slowed conduction through the ventricles as evidenced by changes in the QRS appearance.

- *Primary*: TWA may be due to intrinsic and/or extrinsic factors in the absence of changes in ventricular depolarization. The literature is replete with innumerable entities responsible for isolated changes in T wave morphology, many of which are listed in Table 1. These changes may be evanescent or persistent depending upon the root cause. Attempting to discern which of these factors is the culprit often yields no specific etiology, although a careful history, physical exam, and review of associated laboratory studies, list of current medications, and prior tracings, when available, is always recommended and may be insightful.
- *Secondary*: TWA are those due to alterations in the sequence of ventricular activation and may be inverted, positive, asymmetric, and associated with deviations in the ST segment. Amongst the more common causes of secondary TWA are right and left bundle branch block, right or left ventricular hypertrophy, premature ventricular beats, ventricular pacing, and ventricular pre-excitation.

TABLE 1 | Reported causes of nonspecific T wave abnormalities.

Factors	Example diseases/conditions
Cardiac	Coronary artery disease, myocarditis, pericarditis, cardiomyopathies, post-operative heart surgery, metastases, athletic heart, sinus tachycardia, post-right ventricular pacing, ventricular hypertrophy, genetic channelopathies
Drugs	Investigational products, diuretics, digoxin, antiarrhythmic agents, antidepressants, cocaine, narcotics, cannabinoids, alcohol, caffeine
Endocrine	Hypothyroidism, hypoadrenalism, and pheochromocytoma
Electrolytes	Hypokalemia, hypomagnesemia, hypocalcemia
Gastrointestinal	Pancreatitis, gallbladder disease, gastroenteritis, postprandial ingestion of carbohydrates
Neurogenic	Anxiety, raised intracranial pressure
Pulmonary	Pulmonary emboli, emphysema and chronic lung disease, changes in respiration, pleural effusion, pulmonary edema
Miscellaneous	Hypoglycemia, postural change, cold ambient temperature, anemia, idiopathic, post-electroconvulsive therapy, maxillofacial surgery, normal variant, artifact, amyloidosis

Source: Adapted from Lome [9].

CAVEAT: *Classification of TWA as primary or secondary is predicated upon the presence or absence of abnormalities in ventricular depolarization and conduction.*

8.1 | Low Amplitude and Flat T Waves

Low amplitude T waves are defined as being < 10% the height of the preceding QRS complex (Figure 3B), while T waves are designated as flat when their excursion is between +1 mm (0.1 mv) and − 1 mm (0.1 mv) [3] (Figure 3C). In both cases, the categorization of these TWAs is contingent upon the QRS amplitude being of sufficient magnitude to enable accurate assessment of T wave height (a QRS amplitude of > 5 mm (0.5 mv) has been suggested along with a QRS R-to-S ratio > 1). Low amplitude and flat T waves should be present in at least two anatomically adjacent leads before these interpretations are tendered.

A mechanism underlying a reduction in T wave amplitude with flattening was explored by Bhuiyan et al. in a study of dogs given the delayed rectifier potassium current (IKr) blocker sertindole designed to precipitate TdP [10]. They found that "triangulation" changes in the endocardial monophasic action potential and lengthening of repolarization produced T wave flattening which immediately preceded the development of TdP. In human subjects, hypokalemia linked to diuretic use is a well-known cause of T wave flattening, and is most likely to occur when the K^+ level is < 2.7 mmol/L. This flattening is attributed to the prolongation of the action potential resulting from alterations in resting membrane potential due to inhibition of the Na^+/K^+ ATPase pump and diminished K^+ channel conductance [11].

Low amplitude and flat T waves are commonly encountered and have been associated with increased mortality in the general population. Prineas et al. [12] evaluated a cohort of over 11,000 middle-aged men followed for 18.5 years and found that minor TWA increased the risk of coronary heart disease-related events. Yamazaki et al. developed a T wave amplitude risk scale derived from a population of 46,950 male veterans and monitored their status for 6 years [13]. During that time, 3926 (8%) men sustained cardiovascular deaths, underscoring the prognostic importance of abnormally low amplitude T waves on overall mortality. However, these studies did not address the question as to whether minor TWA are also linked to SCD and not just total mortality. To explore this issue, a longitudinal study was performed by Holkeri et al. [14] They reported on 6750 Finnish men from the general population over the age of 30 who had their ECGs reviewed and were followed for up to 10 years. In all, 856 (12.7%) participants demonstrated persistent flat T waves, defined as < 1 mm (0.1 mv) tall and < 10% the height of the corresponding QRS in at least 2 leads from within either of the lead groups comprising 1,2 AVL and/or V4–V6. The risk of SCD in this male cohort was increased by almost 2-fold (hazard ratio of 1.81, 95% confidence interval) compared to controls who exhibited no flattening.

Roten et al. [15] reported on the prevalence of factors that would differentiate benign from malignant early repolarization patterns on the ECG and found T wave amplitude to be the most discriminatory. They observed that the prevalence of low T waves in patients (29%, $n = 92$) with a history of idiopathic ventricular fibrillation was higher than in a control group (3%, $n = 247$) of healthy individuals. In another study, albeit in heart failure patients, Okuda et al. [16] evaluated the amplitude of negative T waves in AVR in 331 patients monitored for 33 months. They determined that a reduction in T wave amplitude was an independent predictor of all-cause mortality, adjusting for covariates in this population. There was a progressive increase in mortality as the T wave amplitude decreased, with flat T waves denoting the highest risk. Whether there is prognostic information contained in the T wave in lead AVR from the ECGs of healthy individuals and other subgroups remains an unexplored topic. Finally, low-amplitude T waves have been noted in genetic carriers of long QT syndrome type 2 (LQT2) and may represent a surrogate biomarker for arrhythmic risk [17, 18].

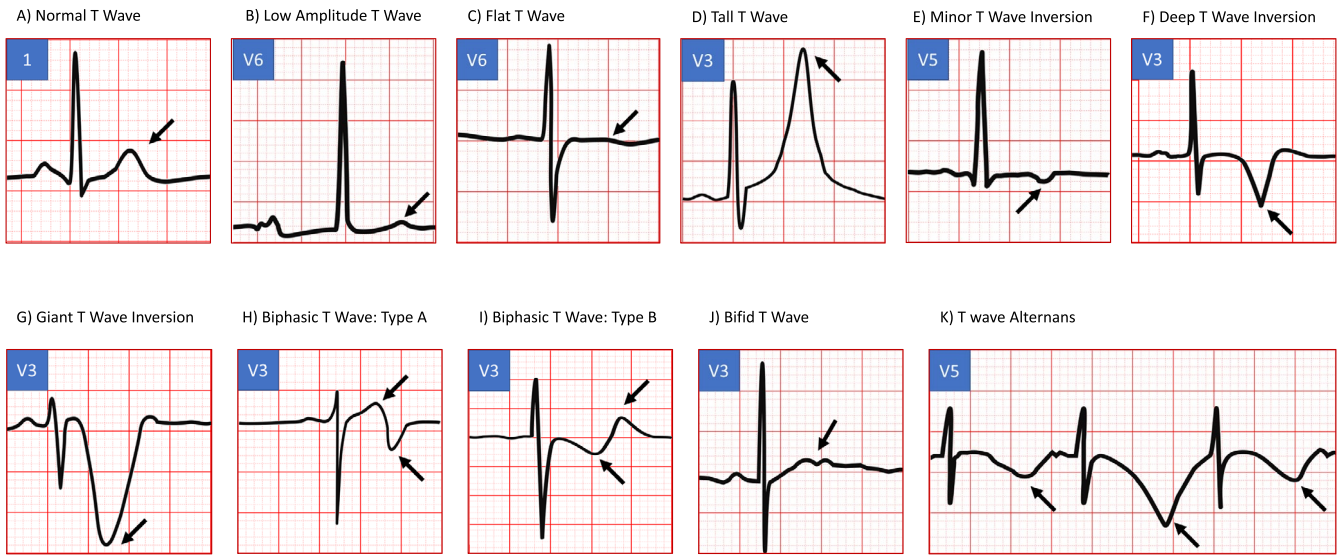

FIGURE 3 | Normal and abnormal T wave morphologies. Examples of normal (A) and abnormal (B–K) T waves. Arrows indicate T wave, and the blue box lists ECG lead. See text for details.

CAVEAT: *Minor nonspecific lateral lead TWA are associated with an increase in total mortality and SCD* [12]. *The natural history for these findings in young women and other subgroups from the population at large is uncertain.*

8.2 | Tall T Waves

Tall T waves are defined as displaying an amplitude ≥ 5 mm (0.5 mv) in 2 or more of the limb leads in both genders or ≥ 10 mm (1.0 mv) in 2 or more adjacent precordial leads for males and ≥ 8 mm (0.8 mv) in these same precordial leads for females [3] (Figure 3D). The most noteworthy clinical scenario for an increase in T wave amplitude is usually hyperkalemia due to underlying renal disease, exogenous potassium intake, or various medications, including angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory agents. A potassium level of 5.5–6.5 mmol/L is the threshold where tall and pointed T waves may develop. Tall T waves may also occur in the setting of acute coronary syndromes and are referred to as "*hyperacute*" T waves. They may manifest either by exceeding the height criteria mentioned above or as being taller than the preceding QRS complex in the absence of elevated K^+ levels. Additionally, tall T waves may be an innocent finding as part of an early repolarization pattern, especially in African American individuals, in athletes, or in persons with ventricular hypertrophy. As such, it is incumbent to consider this differential diagnosis when tall T waves are seen to distinguish between them being a benign variant or a marker of serious underlying pathology.

CAVEAT: *Tall T waves may be misinterpreted by computer algorithms as QRS complexes, leading to double counting of the heart rate and erroneous heart-rate-corrected QT (QTc) calculations.*

8.3 | Inverted/Negative T Waves

Negative T waves are defined based upon their amplitude as *minor inverted* when 0–5 mm (0–0.5 mv) in depth (Figure 3E), *deeply negative* when 5–10 mm (0.5–1.0 mv) (Figure 3F), or *giant negative* (> 10 mm or 1.0 mv) [3] (Figure 3G). Representative etiologies for these different categories include the following:

- *Minor inverted T waves, > 1 mm (0.1 mv)*: A common misconception is that inverted T waves are specific for myocardial ischemia. Minor isolated inversions < 1 mm (0.1 mv) can originate from a passel of non-cardiac causes as shown in Table 1, many of which are benign and do not require further workup. However, when inverted T waves occur in multiple anatomically contiguous leads, are symmetrically inverted ("arrowhead T waves") ≥ 2 mm (0.2 mv), are associated with new ST segment deviation, and occur in the setting of suspicious clinical signs or symptoms, the likelihood of ischemia is augmented and cardiac evaluation is warranted.
- *Deeply negative T waves, 5 mm (0.5 mv)-10 mm (1.0 mv)*: May be pathognomonic of Wellens syndrome with findings in V1-V4 due to acute proximal left anterior descending coronary artery occlusion. Moreover, any of the entities listed below in the giant category may also be responsible for deep inversions.
- *Giant negative T waves, > 10 mm (1.0 mv)*: May appear with severe intracranial hemorrhage, ischemia or trauma, hypertrophic cardiomyopathies, acute myocardial infarction, post pacing, or during tachydysrhythmias, with cocaine use or severe right ventricular hypertrophy as seen in acute pulmonary embolism [19].

Primary T wave inversions (TWIs) are usually discordant in polarity from the QRS in the same lead. The specificity for inverted T waves to be categorized as abnormal is increased when they reach > 1 mm (0.1 mv) in two anatomically contiguous lead pairs: most often II and AVF, 1 and AVL, and V5 and V6. An isolated TWI of this magnitude in either V5 or V6 is also considered abnormal. Any new persistent TWI especially > 1 mm (0.1 mv) in two anatomically adjacent lateral leads is always abnormal and merits further cardiac investigation. TWIs in those of African or Caribbean descent, or athletes, are not rare in leads V1–V3 and are likely normal unless they exceed > 2 mm (0.2 mv), which may indicate a cardiomyopathy or some other pathologic disorder [20]. For example, TWI in leads V1–V3 in young adults in their 20's are usually innocent unless there are other features suggestive of cardiomyopathy and arrhythmogenic right ventricular dysplasia, such as an epsilon wave (major criterion) and prolonged terminal portion of the QRS > 55 ms (minor criterion). In other populations, TWI in leads V2-4 that exceed 2 mm (0.2 mv) after 30 years of age have been associated with an increased risk of MCE and require further investigation. Finally, TWIs > 3 mm (0.3 mv) isolated to lead III without corresponding ST depression or those that exceed the R wave amplitude when the QRS polarity is negative (RML, unpublished observation), despite being rarely seen, have been considered as abnormal, although the basis for this finding and prospective outcomes data is not available.

The natural history of TWI was explored in the Seven Countries Study [21]. This was the world's first observational epidemiological project designed to evaluate diet, activity, and other risk factors that would affect coronary heart disease (CHD) mortality in a population of 11,579 males ages 40–59 years without obvious heart disease. They were followed for up to 40 years. The overall prevalence of isolated TWIs was 1.6% and was found to be an independent predictor of short- and long-term CHD mortality. After 5 years, those with TWIs had a hazard ratio of CHD mortality of 3.68 compared to those with normal ECGs after adjusting for baseline factors including age, body mass index, cholesterol, smoking, and systolic blood pressure [22]. Although the hazard ratio gradually declined with time, at 40 years of follow-up there was still a 50% excess risk of CHD with a hazard ratio of CHD mortality of 1.51 [22].

The prognostic significance of TWIs based upon lead groups was also studied by Istolahti et al. [23] They examined ECGs in a heterogeneous cohort of 6354 Finnish adults from the general population who were greater than 30 years of age. The tracings were compared to individuals who had no TWIs, and subjects were followed for up to 15 years. Leads II and AVF were classified as inferior, V2–V4 as anterior, and 1, AVL, and V5, V6 as

lateral. At follow-up, the presence of TWI in the anterior leads was most closely associated with CHD but not total mortality. Findings in the lateral leads were correlated with an increased risk of cardiovascular morbidity and mortality and conferred a greater hazard ratio of SCD (3.27, 95% confidence interval) compared to those without TWI. Minor TWIs in the inferior leads were deemed to be benign [23].

Kim et al. explored the diagnostic significance of TWI that persisted after 1 year in asymptomatic Korean Air Force recruits that were evaluated with a battery of tests, including cardiac magnetic resonance imaging, computed tomography, and echocardiograms [24]. In the 3929 recruits with baseline ECGs, only 0.6% (23 subjects) had TWI defined as ≥1 mm (0.1 mv) in any lead group other than leads V1–V2. They identified papillary muscle displacement and hypertrophic cardiomyopathy in the majority of those with lateral lead inversions ≥2 mm (0.2 mv), but no significant pathology was discovered when inversions were of lesser magnitude or present in only the inferior leads. Long-term observation of those with minor inversion was not performed.

Finally, Ho and colleagues examined the ECGs of 69,714 males of which 562 (0.8%) demonstrated negative T waves ≥1 mm (0.1 mv) in any two anatomically contiguous inferior, anterior, or lateral leads [25]. Cardiac ultrasound was performed in all participants who met this negative T wave criterion. A total of only 12 (2.1%) individuals who underwent echocardiographic examination had evidence of a cardiomyopathy, and all of these had changes confined to the lateral leads. The likelihood of diagnosing a cardiomyopathy was enhanced in cases where greater T wave depth was present. TWI in either the inferior or anterior leads, or both at the same time, was not associated with cardiomyopathy. As this was a select population consisting of only young males, it is unclear if the same results would be obtained in young women or other specific populations.

CAVEAT: *The depth of TWIs may provide a clue to a specific etiology, and the greater the depth beyond 2 mm (0.2 mv), the higher the likelihood of underlying pathology, particularly when TWIs are new.*

8.4 | Biphasic T Waves

This categorization refers to T waves that demonstrate both a positive and a negative component, with traditional nomenclature describing the biphasic wave as positive or negative based upon the terminal element. An alternative classification has been advanced describing the biphasic waves as being either a type A (Figure 3H) or type B pattern (Figure 3I). Type A waves may evolve into type B waves and are denoted by a positive deflection followed by a negative component and account for approximately 25% of biphasic waves. Type B waves demonstrate a negative deflection followed by a positive component and represent 75% of cases. Biphasic T waves are most commonly seen in the setting of myocardial ischemia and injury, with hypokalemia or hypercalcemia, and may be apparent in genotype/phenotype LQT2 and rarely LQT3 individuals [18]. They have also been reported in women with breast implants, as have concurrent TWIs in leads V1-V4 in this subgroup, thereby confounding interpretation as to whether these are innocent findings or signs of underlying structural heart disease [26].

CAVEAT: *The presence of biphasic T waves may serve as a marker for various cardiac disorders and should not be viewed as an independent predictor of risk.*

8.5 | Bifid T Waves

Bifid or notched T waves are those that typically have 2 positive deflections, the so-called "camel hump" appearance, and are most often manifested in a limited number of precordial leads (Figure 3J). They can be present in multiple scenarios as listed in Table 2. The second positive component needs to be distinguished from either superimposed U or P waves. A superimposed U wave is probable if the distance between peaks is >150 ms when the heart rate is between 50 and 100 beats per minute [3]. Fusion of the U wave with the T wave may occur when there is increased sympathetic tone or in the setting of a markedly lengthened QT interval. A superimposed P wave may be present in cases of profound 1st degree heart block, 2nd degree block, or during periods of sinus tachycardia. Bifid T waves may be a biomarker for proarrhythmic risk, particularly when the second peak is noted to be greater in amplitude than the first peak, as in LQT2 patients who display an extremely prolonged QTc interval.

CAVEAT: *It is imperative to differentiate a bifid T wave from a superimposed U wave or a superimposed P wave on the terminal portion of the T wave. These scenarios of superimposed U and P waves are most commonly observed when there is a very rapid heart rate or when profound 1st degree AV block is present. Either of these presentations may result in the end of the T wave being misidentified and mismeasured, leading to an erroneous QT interval value.*

TABLE 2 | Common etiologies associated with bifid T waves.

Factors	Example diseases/conditions
Genetic	• Long QT syndromes • Congenital heart disorders such as ventricular septal defect producing right ventricular predominance and delayed repolarization of the right ventricle
Electrolyte abnormalities	• Hypokalemia • Hypocalcemia or hypercalcemia • Hypomagnesemia
Organ Injury	• Myocardial ischemia and infarction • Brain injury
Drugs	• Medications such as amiodarone or adriamycin
Environmental	• Hypothermia

8.6 | T Wave Alternans

This rare and rate-dependent phenomenon represents instability in spatial or temporal cardiac repolarization caused by beat-to-beat changes in action potential duration (Figure 3K), which may predispose to MCE and SCD. It is not typically seen at rest in normal hearts but is usually confined to persons with underlying cardiac pathology [27]. The precise mechanism for T wave alternans is unknown, although it may reflect the inability of cardiac cells to cycle intracellular calcium, alterations in membrane proteins (connexins), or the inability to produce adenosine triphosphate. This phenomenon has been observed with intracardiac electrical recordings ("microvolt T wave alternans") and on surface ECG recordings ("macrovolt T wave alternans"). It is more pronounced on the surface ECG during periods of bradycardia and may present as a change in T wave amplitude, morphology, or polarity. It is most often transient and noted in the precordial leads and may produce changes in the QT and J-T peak measurements in every other complex corresponding to changes in the intracardiac action potential. It may be a prelude to the onset of TdP and other ventricular tachydysrhythmias, although the specificity and positive predictive value of T wave alternans for serious dysrhythmias and MCE are presumably very low in the drug-naïve general population.

CAVEAT: *This rare biomarker is a unique electrophysiologic entity and is distinct from the more common electrical alternans predominantly observed in the QRS complexes.*

8.7 | Prolonged Tpeak-Tend

In 1998, Anzelevitch et al. [28] proposed that prolongation of the Tpeak-Tend interval reflects an increase in the temporal dispersion of repolarization (TDR) and is an independent predictor of arrhythmic risk, particularly in individuals with underlying cardiac diseases. The authors used a ventricular wedge preparation model to establish that the electrophysiologic substrate for Tpeak-Tend lengthening and arrhythmogenesis is a result of increased TDR in concert with the development of a steep repolarization gradient. They have further shown that arrhythmic potential increases as the TDR gradient becomes steeper and the distance it travels shortens. The magnitude of increase in TDR was found to be less important than the steepness of the repolarization gradient, and this steepness is greatest within the ventricular wall rather than between the ventricles.

Typically, the Tpeak is measured on a single beat in lead V5 while a tangent function is employed on the descending limb of the T wave on the same beat to determine the Tend (see Figure 2). Prolonged Tpeak-Tend is viewed as highly specific but not very sensitive for predicting MCE, although correcting the value for heart rate may improve its predictive strength. An early clinical, community-based study of Tpeak-Tend's predictive value was carried out by Panikkath et al. [29]. ECG and ventricular function data, along with demographics, were acquired antemortem in a cohort of 353 patients who experienced SCD and compared to a control group of 342 living individuals with known CHD. After adjusting for the covariates of age, sex, QTc, and ejection fraction, they still found that Tpeak-Tend remained as a separate predictor of SCD in this select population [29].

The most comprehensive evaluation of Tpeak-Tend's proarrhythmic risk was a meta-analysis of 33 observational studies comprising 155,856 individuals by Tse et al. [30] They suggested that a value > 103 ms increased the likelihood of an adverse cardiovascular event. The highest risk was noted in those with Brugada syndrome, a genetic channelopathy, while all-cause mortality in the entire population incorporating this metric was found to be approximately 4.56 times greater than those with values below 103 ms. Increased risk of ventricular arrhythmias, cardiovascular death, and SCD based upon this cutoff was further identified in this analysis in those with long QT syndromes, hypertension, heart failure, ischemic heart disease, and hypertrophic cardiomyopathy.

The notion that prolonged Tpeak-Tend is a biomarker of risk for ventricular arrhythmias and sudden death has been challenged most recently in a review by Porthan et al. [31] They measured this interval in lead V5 in a large longitudinal study of 5618 individuals from the general population over 30 years of age followed for 8 years. There was no association of a prolonged Tpeak-Tend interval with SCD after adjusting for other baseline factors. Rather, the highest risk of SCD was linked to two parameters: T wave morphology dispersion, representing quantitative measures of T wave variability observed in different ECG leads, and total cosine R to T as an estimate of spatial deviation between depolarization and repolarization [31].

Tpeak-Tend remains a potential and intriguing prognostic biomarker with the greatest applicability in those with channelopathies and structural heart disease. Nonetheless, the lack of standardized procedures and measurement algorithms across studies and consensus agreement of what constitutes an abnormal value impedes it being routinely adopted as a risk predictor in the adult population. Consequently, regulators and stakeholders have declined to embrace this measurement, and it is not currently required when submitting QT liability datasets and clinical study reports of new chemical entities.

CAVEAT: *Tpeak-Tend measurements > 103 ms demonstrate the greatest risk of MCE in those with channelopathies and underlying structural heart disease, whereas the value of this metric in screening ECGs obtained in healthy people has not been established.*

8.8 | Nonspecific TWA

T waves can fluctuate over time, and their shape can change from a normal pattern to an abnormal appearance without any obvious precipitating factors. Their configuration may also be determined by patient, environmental, and technical factors, including tab integrity and lead placement as well as changes in ECG acquisition equipment. Whenever there are minor nondiagnostic primary TWAs involving low amplitude or negative waves, it is challenging to identify a specific etiology, and it is imperative that interpretations avoid ambiguous language or inappropriate diagnoses. In these circumstances, the generic term "non-specific or indeterminate or slight T wave abnormality" [3]

has been promulgated, which does not mean that the finding is unimportant or should be dismissed as clinically insignificant. Knowledge of the common causes of primary T wave changes, along with a review of prior ECG tracings and patient clinical and laboratory information, may discern the basis for these findings and provide a guide to further management. Lastly, since T waves can be labile, it is suggested to repeat the ECG at a later time to determine if the TWA is persistent or may have morphed in a manner that suggests a specific cause.

CAVEAT: *Any new significant inversion in leads where the T wave had previously been upright is always abnormal if it persists and warrants further cardiac evaluation.*

9 | Prevalence of TWA in Young Athletes

The presence of TWI is uncommon, although not rare, in those engaged in sports. In this regard, the prevalence of TWI in athletes was evaluated by Pelliccia et al. [32] who interrogated their database containing 12,550 athletes, of whom 881 (7%) had ≥2 mm (0.2 mv) TWIs in at least 3 leads, and an underlying cardiomyopathy was discovered in 51 (6%) of these individuals. These same authors also stated that elite-trained individuals had a similar prevalence of TWI as did a large cohort of young amateur athletes, thereby underscoring that this finding is not predicated upon the level of training or fitness.

T waves in athletes may be altered due to electrical or structural remodeling of the heart, and distinguishing benign changes from those that indicate underlying cardiac disease can be problematic without further investigation. As an example, Noyes and Shulman reported a case in which a 26-year-old African American male football player was referred for deep TWIs in the anterolateral leads [33]. He was eventually cleared to play sports after cardiac magnetic resonance and echocardiographic imaging were found to be normal. This example highlights that asymptomatic athletes may manifest remarkably abnormal screening ECGs. In these cases, further workup including cardiac imaging, is essential to exclude occult pathology that places the individual at higher risk of SCD during competition.

In 2017, the international consensus criteria for interpreting TWA in athletes was published [34]. The primary focus was on abnormal TWIs, which were defined when ≥1 mm (0.1 mv) was noted in the following lead groups in Table 3. Subsequently, using these definitions, Torabi et al. [35] evaluated how often general cardiologist initial interpretations were ultimately changed by experienced sports cardiologist ECG readers. Using ECG tracings from 1643 athletes from the National Football League, they found a 67% overall reduction in the number of athletes initially deemed to have important TWA that were reinterpreted as either being normal or insignificant. This adjudication was most impactful in the anterior chest leads, followed by the inferior and lateral precordial leads. These findings underscore the importance of having trained specialists that rely upon standardized criteria to ascertain whether TWA are present in competitive athletes and assess their clinical significance.

TABLE 3 | Defining TWA in athletes.

Leads	Comment
Anterior	Leads V2-V4, excluding Black athletes with an early repolarization pattern that includes TWI, those under 16 years of age, or individuals with biphasic T waves in only lead V3
Lateral	Leads 1 and AVL or leads V5 and/or V6 (only one of these leads would be sufficient)
Inferior	Leads II and AVF with lead III excluded from analysis

Note: Reviewed in Drezner et al. [34].

CAVEAT: *Athletes in competitive sports should ideally have screening ECGs interpreted by sports cardiologists. Significant TWI in the lateral precordial leads is most predictive of underlying structural heart disease and the risk of MCE.*

10 | QT Interval and T Wave Measurement

Measurement of the QT interval and assessment of QTc liability are critical elements in new drug development, and determining the end of the T wave can be problematic. This topic has been reviewed in detail by Lester et al. [36], and several key points should be emphasized. It is essential to not rely upon computer algorithms for this determination, which can be inaccurate if there is variability in the heart rate, concurrent dysrhythmias, or changing T wave morphology, when superimposed U or P waves may be present on the end of the T wave, and in the setting of baseline artifact. In addition, when the descending portion of the T wave has a shallow slope and approaches the baseline in an asymptotic prolonged manner, measuring the end of the T wave, where it returns to the baseline, would lead to an erroneous long QT value. In these situations, a tangent function should be employed in which a line is drawn down the steepest slope of the descending limb of the T wave to where it intersects the isoelectric line, and that would define the T wave end Figure 2. It is also suggested that a median single lead complex or a superimposed 12-lead representative beat complex be utilized, as there can be considerable change in beat-to-beat T wave shape in a single lead, producing variable QT intervals depending upon which beats in that lead are analyzed.

CAVEAT: *Reliance on and acceptance of computer-generated values of the QT interval may provide erroneous results and is discouraged when accurate interval measurements are required.*

11 | Conclusion

Foundational knowledge about T wave qualitative and quantitative biomarkers of proarrhythmic risk in humans has been derived in non-clinical animal studies employing a variety of different species. The movement to standardize animal trial design and execution will undoubtedly uncover additional insights that would hopefully enhance assessment of cardiac liability. Moreover, applying artificial intelligence algorithms

and predictive models may further facilitate the development of more timely, cost-efficient, innovative, and informative animal studies. This information could then be translated into the clinical arena to accelerate drug development and identify new and potentially significant safety signals and biomarkers of risk.

The T wave contains a wealth of diagnostic and prognostic information when it is properly scrutinized, acknowledging that many of the observational natural history studies have been restricted to men. Understanding the spectrum of T wave expression on the surface ECG and associated pathophysiology is critical in constructing a framework for clinical decision-making and assuring accurate QT assessment vis-à-vis investigational drug trials. Equally significant is the application of standardized and evidence-based criteria to distinguish between normal and abnormal findings in both adult males, females, and ethnic populations, which are pivotal in guiding patient care. For example, TWIs ≥ 1 mm (0.1 mv), particularly in the lateral leads in adult men, may be a sign of unrecognized cardiac pathology, including cardiomyopathy, which may portend adverse clinical outcomes. These TWAs can surface in the screening of both healthy sedentary individuals as well as accomplished amateur and elite athletes and should prompt the need for further cardiac investigation. Similarly, the prognostic significance of transient versus persistent TWAs in these groups, and particularly in subjects enrolled in pharmaceutical trials, epitomizes an important clinical management conundrum that merits further exploration. Additional biomarkers that have been associated with cardiovascular risk include diffuse flat T waves, bifid T waves, T wave alternans, and prolongation of the Tpeak-Tend interval, although these findings are rarely evident in screening ECGs from the general population, and their prognostic value is primarily driven by the disease state underlying their appearance. Most importantly, early recognition of TWA by principal investigators, their surrogates, and researchers involved in ECG interpretation should facilitate more timely and appropriate study oversight, including, triage for additional cardiac evaluation when indicated resulting in improved participant safety.

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Conflicts of Interest

The authors declare no conflicts of interest.

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