The T wave: physiology and pathophysiology

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Chapter 1

Introduction and outline

The electrocardiogram (ECG) is commonly used to evaluate the electrical activity of the heart. Due to its non-invasive character and diagnostic power,[1] it has become one of the most essential tests that cardiologists use in their daily practice. The ECG results from the potential difference between the electrodes which is generated by the transmembrane currents running in extracellular space. Implementation of the ECG in the clinical practice dates from the early 20th century when the Dutch physiologist Willem Einthoven modified the string galvanometer as an ECG recorder with a very high sensitivity.[2] Prior to this, he also had contributed significantly to the description of the ECG.[2,3] The 5 typical deflections in the ECG were named P-Q-R-S-T.

Before the first description of the ECG, investigators were already occupied with the electrical activity within the heart. In 1856, Kölliker and Müller developed an inventive method to investigate the cardiac electrical properties.[4] They positioned the cut end of a frog sciatic nerve – still attached to the musculus gastrocnemius – on the surface of the ventricle of the heart. A contraction of the gastrocnemius was observed just before systole of the heart, which is nowadays known as the depolarization phase and manifests as a QRS complex on the ECG.[4] Kölliker and Müller were astonished to observe in some preparations also a second twitch of the frogs leg at the beginning of diastole. Today, we ascribe this second twitch to the repolarization phase of the heart and identify it as the T wave on the ECG.[4,5]

Currently, the physiology and pathophysiology underlying the QRS complex are well understood. Dirk Durrer provided in 1970 the first complete description of the activation in the human heart and related it to the QRS morphology.[6] Since then, many studies were performed to scrutinize abnormal QRS morphologies in conducted and ectopic beats and their relation with the underlying activation.[7,8] Knowledge of the T wave and the corresponding repolarization pattern is however less crystalized. T waves are especially difficult to interpret in ventricular rhythms or rhythms with aberrant ventricular conduction. When the subject has an AV-conducted rhythm, we can merely denote the T wave as having a normal or abnormal morphology and indicate whether it is prolonged or shortened. Nevertheless, T waves hold valuable information on arrhythmogenesis, as T wave abnormalities have indisputably been associated with life-threatening arrhythmias.[1,9,10]

Although major efforts have been made to reveal the exact relation between the typical waveform of the T wave to the underlying repolarization pattern, a thorough description of the T wave is still lacking. A reason for this is that a detailed observation of the T wave – as was done with the QRS complex – is complicated. The QRS complex results from the electrical inhomogeneity during the depolarization phase. Depolarization is a fast process that causes large transmembrane currents and potential differences (about 25 millivolt) over short distances (about 1 millimeter) between excitable and non-excitable cells.[4] The T wave results from the electrical inhomogeneity during the

repolarization phase. In contrast to depolarization, repolarization is a relatively slow process and leads to smaller potential differences over larger distances.[4] In addition, the contribution of cellular coupling in reducing the potential differences is larger during repolarization than during depolarization.[11] The QRS complex is caused by conduction, in which cellular coupling is essential. The T wave is, however, mainly caused by the intrinsic property of individual cardiomyocytes (action potential duration), which is modulated by the amount of cellular coupling, causing more or less 'synchronization' of repolarization.[12] Consequently, repolarization results in a small and widespread dipole, which is more difficult to measure and to interpret. In recent years technology has improved and enabled recordings of multiple channels. This has facilitated more accurate and simultaneous analyses of T waves and repolarization.

Repolarization can be influenced by multiple factors, like temperature,[13] ischemia,[14] potassium level,[14] stretch,[15] sympathetic activation[12] and variants in genes encoding cardiac ion channels.[16,17] These factors may accordingly modulate the vulnerability for arrhythmias. Therefore, the T wave holds valuable information for diagnostics and risk stratification. Yet, knowledge about the genesis and modulation of the T wave is incomplete. This thesis focuses on elucidating the physiological as well as pathophysiological aspects of the T wave and explores the explicit effects that diverse factors (pressure, current, autonomic nervous system) have on the T wave morphology. The thesis also touches on the translation of results from animal studies to the human ECG.

In order to understand the pathophysiology it is essential to first obtain a thorough understanding of the normal physiology. Therefore, this thesis starts with a detailed description of the T wave of a normal pig heart in relation to its underlying ventricular repolarization (**Chapter 2**). This chapter considers the differences in repolarization along the large anatomical axes within the heart (left-right, anterior-posterior, apico-basal and transmural) and gives an explanation for the origin of the T wave peak.

After obtaining insights in the genesis of the normal T wave, this thesis focuses on its modulation by ventricular pressure that induces stretch on the ventricular wall. For decades we are aware of the phenomenon that stretch – by mechano-electric coupling – impacts on the ventricular action potential and arrhythmogenesis.[18,19] The time of application of stretch relative to the phase of an action potential (AP) has differential effects on AP duration, and thus on repolarization.[15] **Chapter 3** will deal with the effect of the normal left ventricular (LV) pressure pulse on the repolarization in early- and late-activated myocardium. It discusses the relevance of physiological LV pressure in the repolarization process within the heart. As stretch is in many diseases also a contributor to arrhythmogenesis,[20] it is relevant to know how the stretch-induced changes in repolarization may be translated to the ECG. Therefore, the thesis continues in **Chapter 4** with the exploration of the effects of LV pressure on the T wave morphology.

In the clinical setting several ECG abnormalities are supposed to be related to abnormal repolarization. In the following chapters of this thesis the analyses of some of these ECG abnormalities will be described. First, in **Chapter 5**, inferolateral J-waves on the ECG will be considered. These inferolateral J-waves are also known as the early repolarization pattern and their presence have been associated with an increased risk for life-threatening arrhythmias.[21] There is, however, an ongoing debate as to its underlying mechanism. It was proposed that J-waves result from an prominent early repolarization phase in the epicardial cardiomyocytes compared to the endocardial cardiomyocytes.[22] An alternative mechanism is based on regional conduction slowing. Chapter 5 presents the results of a study that tested whether repolarization abnormalities or depolarization abnormalities may induce inferolateral J-waves on the ECG.

The long QT syndrome (LQTS) is characterized by a prolonged QT interval and associated with sudden cardiac death.[23] Moreover, patients with LQTS often present with typical T wave morphologies.[24] The congenital LQT syndromes are classified according to their associated genetic basis,[25] resulting nowadays in 15 different types.[26] Type 2 of the LQTS (LQT2) encompasses one of the largest groups of LQTS patients and typically manifests low amplitude bifid T waves.[27,28] From the genetic perspective we learned that in LQT2 a loss-of-function of the fast activating component of the delayed rectifier channels is involved.[16] The mechanism by which the changes in repolarizing currents give rise to the bifid T waves in LQT2 patients is not known. In **Chapter 6** results are shown of a dog model of dofetilide-induced LQT2, in which the relation between the repolarization changes and the bifid T waves is investigated.

In patients with LQTS, T wave abnormalities are not always present on the ECG and in absence of a marked QT prolongation on the resting ECG, the diagnosis of LQTS is less straightforward. It has been shown that LQTS patients have an impaired adaptation of the QT interval – i.e. repolarization duration – in response to a change in heart rate.[29,30] Therefore, in the Academic Medical Center in Amsterdam, ECG tests are currently performed to obtain information about the dynamics in QT adaptation. **Chapter 7** describes the results on the evaluation of the beat-to-beat QT and TQ (i.e. diastole on ECG) responses to sudden standing in LQTS patients compared to healthy controls. These results indicate differences between the groups of individuals. In this chapter a new metric is proposed, which may possibly distinguish LQTS patients from healthy persons.

The last chapter of this thesis provides a comprehensive discussion dealing with all subjects mentioned above, and future perspectives will be presented.

REFERENCES

1. Zipes DP, Camm a J, Borggrefe M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Com. Circulation. 2006, pp. e385–e484.
2. AlGhatrif M, Lindsay J. A brief review: history to understand fundamentals of electrocardiography. J. Community Hosp. Intern. Med. Perspect. 2012,.
3. Einthoven W. Nieuwe methoden voor clinisch onderzoek [New methods for clinical investigation]. Ned Tijdschr Geneeskd 1893; 37:263–286.
4. Noble D, Cohen I. The interpretation of the T wave of the electrocardiogram. Cardiovasc Res 1978; 12:13–27.
5. Burdon-Sanderson J, Page FJM. On the Electrical Phenomena of the Excitatory Process in the Heart of the Frog and of the Tortoise, as investigated Photographically. J Physiol 1884; 4:327–338.
6. Durrer D, van Dam RT, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. Circulation 1970; 41:899–912.
7. SippensGroenewegen a, Spekhorst H, van Hemel NM, Kingma JH, Hauer RN, Janse MJ, Dunning a J. Body surface mapping of ectopic left and right ventricular activation. QRS spectrum in patients without structural heart disease. Circulation 1990; 82:879–896.
8. Van Dessel PF, van Hemel NM, de Bakker JM, Linnenbank T a, Potse M, Jessurun ER, Sippens-Groenewegen a, Wever EF. Relation between body surface mapping and endocardial spread of ventricular activation in postinfarction heart. J Cardiovasc Electrophysiol 2001; 12:1232–1241.
9. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol 2011; 4:441–447.
10. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 1994; 330:235–241.
11. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. Circulation 1987; 75:379–386.
12. Conrath CE, Opthof T. Ventricular repolarization: an overview of (patho)physiology, sympathetic effects and genetic aspects. Prog Biophys Mol Biol 2006; 92:269–307.
13. Coronel R, de Bakker JMT, Wilms-Schopman FJG, Opthof T, Linnenbank AC, Belterman CN, Janse MJ. Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: experimental evidence to resolve some controversies. Heart Rhythm 2006; 3:1043–1050.
14. Moréna H, Janse MJ, Fiolet JW, Krieger WJ, Crijns H, Durrer D. Comparison of the effects of regional ischemia, hypoxia, hyperkalemia, and acidosis on intracellular and extracellular potentials and metabolism in the isolated porcine heart. Circ Res 1980; 46:634–646.
15. Zabel M, Koller BS, Sachs F, Franz MR. Stretch-induced voltage changes in the isolated beating heart: importance of the timing of stretch and implications for stretch-activated ion channels. Cardiovasc Res 1996; 32:120–130.

16. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995; 80:795–803.

17. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet 1996; 12:17–23.

18. Lab MJ. Contraction-excitation feedback in myocardium. Physiological basis and clinical relevance. Circ Res 1982; 50:757–766.

19. Franz MR. Mechano-electrical feedback in ventricular myocardium. Cardiovasc Res 1996; 32:15–24.

20. Taggart P, Sutton PM. Cardiac mechano-electric feedback in man: clinical relevance. Prog Biophys Mol Biol 1999; 71:139–154.

21. Wu SH, Lin XX, Cheng YJ, Qiang CC, Zhang J. Early repolarization pattern and risk for arrhythmia death: a meta-analysis. J Am Coll Cardiol 2013; 61:645–650.

22. Yan GX, Antzelevitch C. Cellular Basis for the Electrocardiographic J Wave. Circulation 1996; 93: 372–379.

23. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. N Engl J Med 2003; 348:1866–1874.

24. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA, Vincent GM, Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995; 92:2929–2934.

25. Goldenberg I, Moss AJ. Long QT syndrome. J Am Coll Cardiol 2008; 51:2291–2300.

26. Mizusawa Y, Horie M, Wilde AA. Genetic and Clinical Advances in Congenital Long QT Syndrome. Circ J 2014; 78:2827–2833.

27. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-Wave Patterns and Repolarization Parameters in Congenital Long-QT Syndrome: ECG Findings Identify Genotypes. Circulation 2000; 102:2849–2855.

28. Kanters JK, Fanoe S, Larsen LA, Bloch Thomsen PE, Toft E, Christiansen M. T wave morphology analysis distinguishes between KvLQT1 and HERG mutations in long QT syndrome. Heart Rhythm 2004; 1:285–292.

29. Viskin S, Postema PG, Bhuiyan ZA, et al. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. J Am Coll Cardiol 2010; 55:1955–1961.

30. Adler A, van der Werf C, Postema PG, et al. The phenomenon of "QT stunning": the abnormal QT prolongation provoked by standing persists even as the heart rate returns to normal in patients with long QT syndrome. Heart Rhythm 2012; 9:901–908.