# Chapter 1

## Introduction

**Electrocardiography of the normal T wave:**

On a twelve lead electrocardiogram (ECG) a normal T wave is the result of repolarization of ventricular muscle fibers from an active to a resting transmembrane voltage [1]. The voltage changes of the repolarization process traverse the same range as those of the depolarization process, except in the reverse direction, and therefore the T wave may be viewed as the final result of a reversed depolarization process [1]. On the normal human ECG the net areas of the QRS complex and the T wave in any lead are neither characteristically equal, nor opposite in direction [2]. This means that the sequence of ventricular depolarization and repolarization are not in the same direction, but opposite, resulting in an average mean electrical axis of the QRS complex of +60° and for that of the T wave only about 10-12° to the left of this [2].

Three electrocardiographic features of the T wave are noted. The direction (or polarity), the shape (or contour) and the height (or amplitude) [3]. On the normal human ECG the direction (or polarity) of the T wave is as follow [3]: upright in leads I, II and V3-V6; inverted in lead aVR and variable in leads III, aVL, aVF and V1-V2. The shape (or contour) of the normal T wave is normally slightly rounded and asymmetrical [3]. The height (or amplitude) of the normal

T wave does not exceed 5 mm in any standard lead and 10 mm in any precordial lead [3].

The Tp wave, formerly called the Ta wave, represents the repolarization process in the atria and this wave is opposite in direction (polarity) to the P wave [3]. The repolarization process in the atria differs from that in the ventricles. In the ventricles repolarization proceeds in a direction opposite to that of depolarization, yielding a T wave with the same polarity as that of the QRS complex [3]. However, in the atria repolarization proceeds in the same direction as that of depolarization, yielding a Tp wave with a polarity opposite to that of the P wave [3].

T waves can undergo changes in their polarity, amplitude and/or contour [4]. For many years T wave changes were classified according to the Wilson formulation as either primary or secondary in nature and furthermore, it was firmly believed that this classification could explain all possible T wave abnormalities [5]. According to the Wilson formulation secondary T wave changes is the result of changes in the preceding QRS complex, and these QRS complex changes are the result of an altered sequence of ventricular activation [5, 6, 7]. Secondary T wave changes are thus the result of an altered sequence of ventricular activation and are not related to changes/ pathology of ventricular muscle [5, 6, 7]. Primary T wave changes are not associated with changes in the preceding QRS complex and are caused by changes/ pathology of the

ventricular muscle [2] . However, all T wave abnormalities are indicative of a disturbance in ventricular repolarization [8].

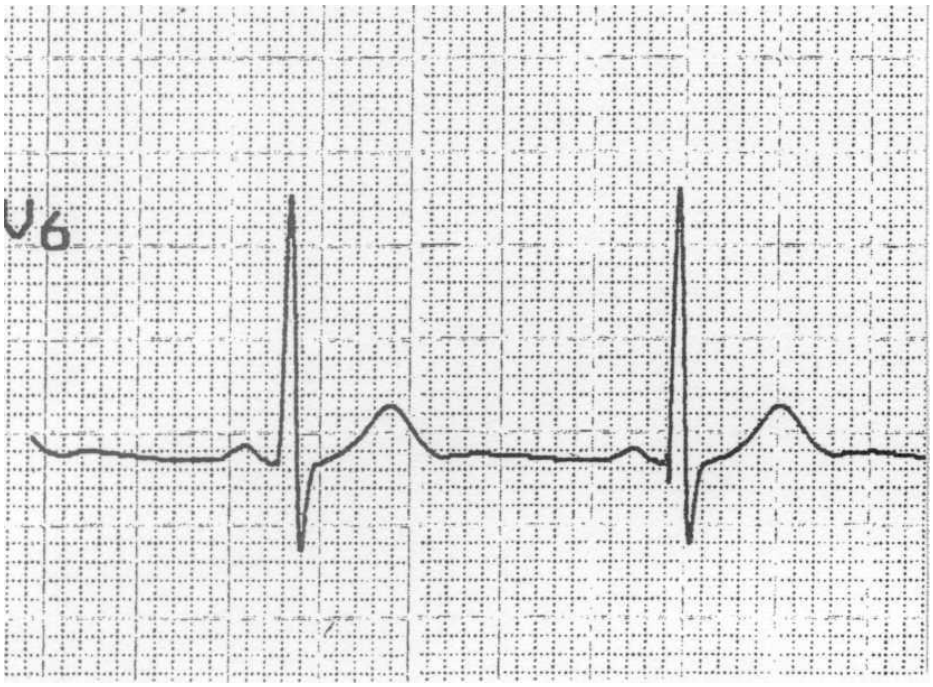


**Figure 1.** This is an example of normal T waves, taken from lead V6 of a 12-leaded electrocardiogram. Note the positive polarity of the T waves with amplitudes of 0.35 mV. Note the morphology of the T waves: the ascending limbs are asymmetric relative to the descending limbs (The ECG tracing is the property of the author).

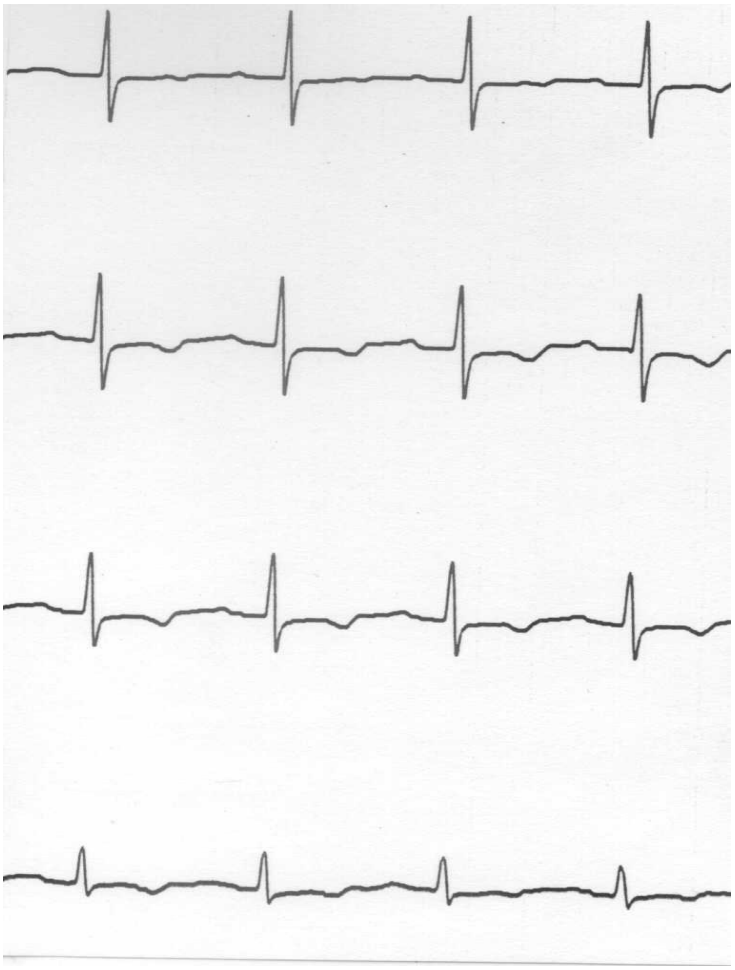

**Figure 2.** This is an example of primary T wave abnormalities. Note the normal preceding QRS complexes, which are followed by inverted T waves (The ECG tracing is the property of the author).

Primary T wave abnormalities can be caused by one of two mechanisms [8]. Firstly, by a uniform and secondly by a nonuniform alteration of the shape and/or duration of ventricular action potentials [8]. Clinically, primary T wave abnormalities are divided into a functional and an organic group [8, 9]. However, this division is based on a clinical evaluation of the subject and not on any electrocardiographic characteristics [8]. Functional T wave

abnormalities can be distinguished from the organic group by the administration of oral potassium salts, which has been shown to correct the former [9].

The first category of primary T wave abnormalities, those due to uniform alteration of the shape and/or duration of ventricular action potentials, can be recognized electrocardiographically by alterations (more specifically depression) of the ST segment[8]. Causes include drugs, such as cardiac glycosides, quinidine, procainamide, disopyramide, amiodarone and phenothiazines, and electrolyte disturbances, such as hyper- and hypokalemia and hypocalcemia [8]. The second category of primary T wave abnormalities, those due to nonuniform alterations of the shape and/or duration of ventricular action potentials, include T wave abnormalities due to post-ischaemic changes, pericarditis, acute cor pulmonale, pulmonary embolism, myocardial tumors, myocarditis and other primary myocardial diseases [8]. Characteristically these abnormalities do not affect the course or duration of the ST segment [8].

Secondary T wave abnormalities can be found during any condition of an altered sequence of ventricular activation (depolarization) [8]. These conditions include ventricular hypertrophy, bundle branch block, ventricular pre-excitation and during periods of ventricular pacing or ventricular ectopy [8]. In patients with primary myocardial diseases T wave abnormalities are usually secondary to alterations in the duration, amplitude or axis of the preceding

QRS complex which are due to ventricular hypertrophy, but sometimes primary T wave abnormalities can precede these QRS complex alterations [8]. Finally, T wave abnormalities can also be the result of various combinations of these primary and secondary mechanisms [8].

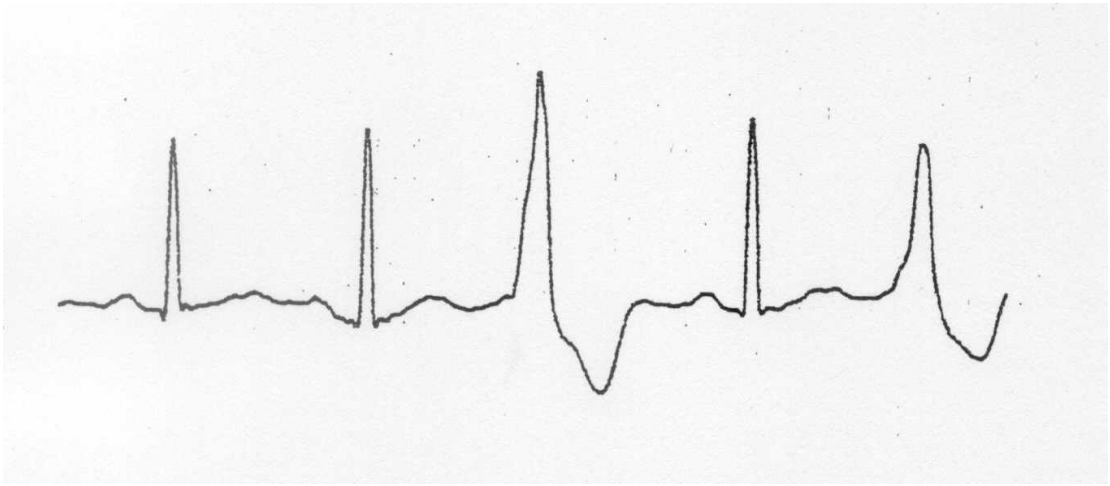

**Figure 3.** This is an example of a secondary T wave change.The third and fifth beats in the tracing are premature ventricular complexes (PVC's). Note the abnormal QRS complexes of the PVC's, which are followed by inverted T waves—classic secondary T wave changes (The ECG tracing is the property of the author).

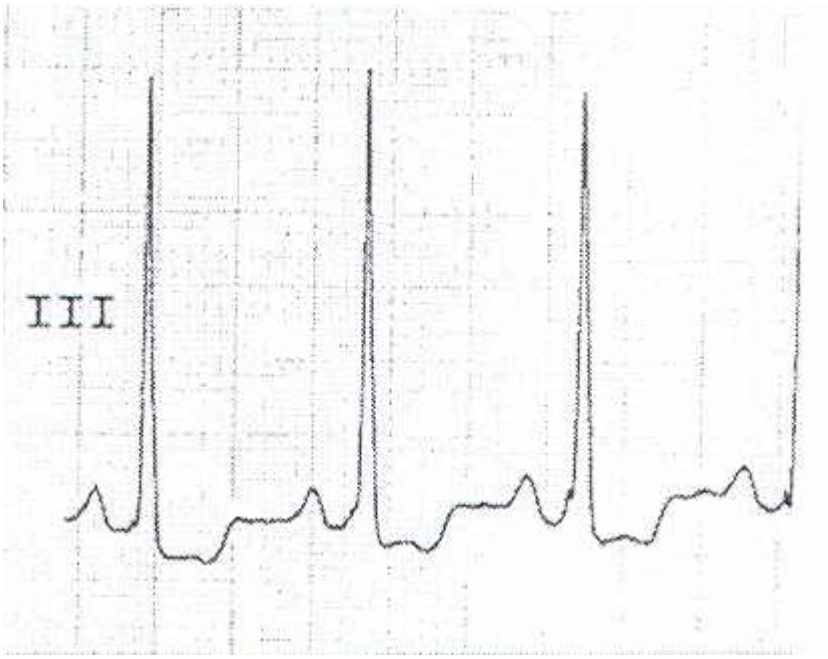


**Figure 4.** This is an example of ventricular preexcitation (Wolff-Parkinson-White syndrome). Note the delta waves in every QRS complex, which is followed by secondary ST depression and secondary T wave changes (The ECG tracing is the property of the author).

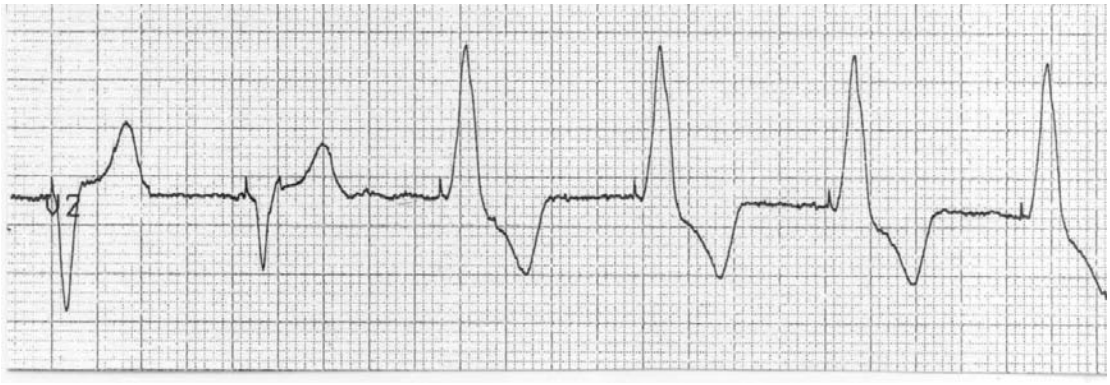


**Figure 5.** An example of ventricular pacing. Note the pacemaker spikes in front of every QRS complex. Ventricular pacing causes abnormal QRS complexes, which are followed by secondary T wave changes (The ECG tracing is the property of the author).

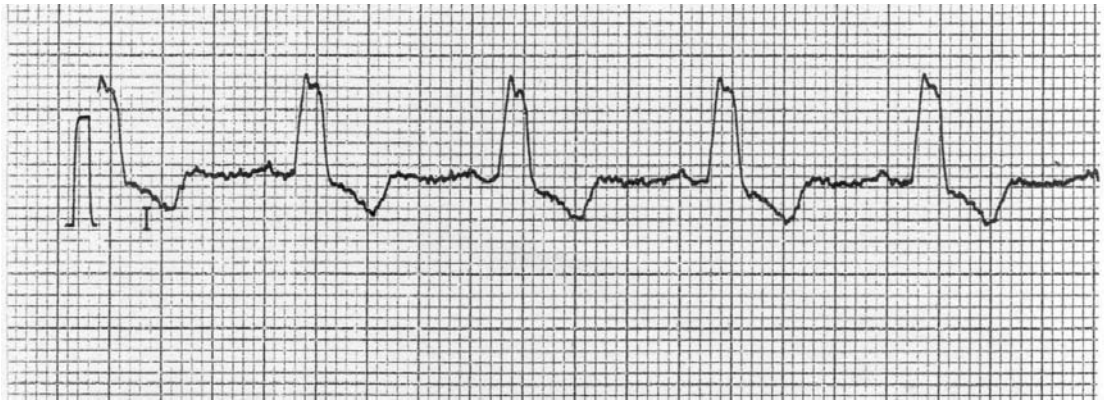

**Figure 6** An example of a left bundle branch block, another cause of secondary T wave changes. Note the abnormal and broad QRS complexes, which are followed by inverted T waves—classic secondary T wave changes (The ECG tracing is the property of the author).

However, during the years following Wilson's formulation it became quite clear that not all T wave abnormalities could be satisfactorily classified as either primary or secondary in nature [5].

## 1. Conditions associated with T-wave changes that cannot be explained by Wilson's formulation:

Since Wilson's formulation in 1943 it has been observed that several conditions can be associated with T wave changes that appear to be primary, but without any manifestations of myocardial pathology [5, 6]. Therefore, there emerged a third category of T wave changes, known as "pseudoprimary" T wave changes [6].

### 1.1 Wolff-Parkinson-White syndrome

Wolff, Parkinson and White were the first to describe an electrocardiographic syndrome of ventricular preexcitation [10]. In these hearts bypass tracts, which are remnants of embryonic conduction tissue, cause activation to pass directly from the atria to the ventricles without an appreciable degree of delay—bypassing the atrioventricular nodal system, hence the term "preexcitation" [10]. These bypass tracts can be present at several sites around the atrioventricular valve rings and can be single or multiple [10]. Ventricular preexcitation may be permanent or episodic, with constant or intermittent conduction through the bypass tract(s) respectively. During preexcitation ventricular activation spreads through the ventricles by myocardial conduction from the preexcited area until it encounters the normal activation wavefront, which results from atrioventricular nodal

conduction and spread via the specialized conduction system [10]. This results in a fusion beat, which can be seen as a delta wave on the electrocardiogram[10]. Two types of Wolff-Parkinson-White (WPW) syndrome are recognized: type A with left ventricular pre-excitation and type B with right ventricular preexcitation[10].

Two categories of T wave abnormalities can be present in WPW syndrome. Firstly, during periods of ventricular preexcitation there is an altered sequence of ventricular activation and classic secondary T wave abnormalities can be seen. However, in most patients ventricular preexcitation is not permanent. Ventricular preexcitation can remit spontaneously [11] or can be cured by radiofrequency catheter ablation of the accessory pathway(s) [12]. The second category of T wave abnormality in WPW syndrome is seen during periods of normal sinus rhythm, when there is no ventricular preexcitation, for variable periods after which they gradually disappear [11]. These T wave abnormalities can also be seen after permanent cure of preexcitation by radiofrequency catheter ablation of the bypass tract(s) [12, 13, 14]. Furthermore, these T wave changes in the ablation group do not correlate with any markers of tissue injury [12] and are thus not primary T wave changes. They are seen during periods with a normal ventricular activation sequence and are thus also not secondary T wave changes. They are regarded as so-called “pseudoprimary” T wave changes [6].

Currently, these T wave changes are regarded to be the consequence of "cardiac memory" [12, 13, 14]. The concept of cardiac memory will be discussed in detail later on (page 21). These pseudoprimary T wave changes, or cardiac memory T waves, can also be seen after right ventricular pacing, periods of intermittent left bundle branch block, paroxysmal tachycardia and premature ventricular complexes [12].

## 1.2 T Wave abnormalities following periods of intermittent left bundle branch block

Left bundle branch block (LBBB) can be the result of conduction delay (or block) of the left bundle branch of the specialized conduction system and can be the result of disease in the main left bundle branch or fibers of the bundle of His (predivisional) or in each of the two fascicles, or in any of several sites in the intraventricular conduction system (postdivisional) [15, 16]. LBBB produces a prolonged QRS duration, marked distortion of the QRS complex and ST-T wave abnormalities [15, 16]. Commonly accepted diagnostic criteria for LBBB are as follow [15]: QRS duration > 120 msec; broad, notched R waves in the lateral precordial leads ($V_5$, $V_6$) and usually also leads I and aVL; small or absent initial r waves in the right precordial leads ($V_1$, $V_2$) followed by deep S waves and absent septal q waves in left-sided leads.

Normally the interventricular septum is activated from left to right and this results in an initial r wave in the right precordial leads ($V_1$, $V_2$) and a q wave in leads I and aVL, as well as the left precordial leads ($V_5$, $V_6$) [16]. During periods of LBBB the septum is activated from right to left and the result is the disappearance of initial r waves in leads $V_1$ and $V_2$ and the disappearance of q waves in leads $V_5$ and $V_6$ [16]. The ventricular activation front then proceeds from the left side of the interventricular septum to the anterior wall of the left ventricle, then to the inferior wall and from there to the postero-lateral free wall [16]. This altered sequence of ventricular activation during LBBB produces two electrocardiographic abnormalities [15, 16]. The first is monophasic QRS complexes: QS in lead $V_1$ and R in leads I, aVL and $V_6$ [16]. The second is secondary repolarization abnormalities [15, 16]. In most cases the ST segment and T wave are discordant with the QRS complex—the ST segment is depressed and the T wave is inverted in leads with positive QRS waves (leads I, aVL, $V_5$ and $V_6$), while there is elevated ST segments and positive T waves in leads with negative QRS complexes ($V_1$ and $V_2$) [15]. According to Wilson's formulation these T wave changes are secondary, as there is an altered sequence of ventricular activation [5, 6, 7].

Rosenbaum *et al* were the first to describe symmetrical T wave inversions during periods of normal conduction in 26 of 35 patients with intermittent left bundle branch block [17]. Denes *et al* confirmed

this finding and documented a high prevalence (83%) of deep, symmetrical, precordial T wave inversions during normal conduction in patients with intermittent left bundle branch block [17]. In that same year (1978), Engel *et al* also described a series of patients with T wave inversion during normal conduction after a period of LBBB [18]. These T wave abnormalities occurred during normal conduction and are thus not secondary T wave changes. Most of these patients had no organic heart disease and therefore, these T wave changes are also not primary. Therefore, these are another example of "pseudoprimary" T wave changes and Denes *et al* became the first authors to refer to the concept that the heart muscle can "remember" periods of abnormal ventricular activation, causing abnormal repolarization to persist beyond the period of abnormal ventricular activation[17].

## 1.3 T wave abnormalities following periods of paroxysmal tachycardia

Inversion of T waves on the electrocardiogram may persist for long periods after an episode (or episodes) of paroxysmal tachycardia in the absence of organic heart disease[19]. This phenomenon will occur in about 20% of patients with episodes of paroxysmal tachycardia of both ventricular and supraventricular origin, and is totally unrelated to the

age of the patient or the presence or absence of organic heart disease [8, 19, 20, 21, 22, 23].

Once again, these T wave abnormalities are present during normal conduction and are therefore not secondary. They can occur in the absence of organic heart disease and are thus also not primary. Therefore, the post-tachycardia syndrome, consisting of T wave inversion after an episode (or episodes) of supra- or ventricular tachycardia is another example where the heart muscle "remembers" periods of altered ventricular activation [5].

## 1.4 T wave abnormalities following periods of ventricular pacing

In 1958 artificial cardiac stimulation by way of implantation of a permanent pacing system was introduced as a treatment for patients with complete heart block [24, 25]. Since that time both the indications for cardiac pacing, as well as the complexity of pacing-system design have expanded [25]. In transvenous ventricular pacing systems the lead tip is positioned in the right ventricle and during ventricular stimulation the ECG will demonstrate a left bundle branch block pattern, as ventricular activation is now initiated in the right ventricle [24].

During right ventricular pacing the ECG will demonstrate a left bundle branch block pattern and therefore secondary T wave abnormalities will be observed during the period of pacing [15, 16]. Once again, these T wave changes are secondary, because there is an alteration of the normal sequence of ventricular activation—Wilson's formulation [5, 6, 7]. However, it is well known that T wave inversions can occur in the unpaced ECG subsequent to ventricular pacing and that these T wave abnormalities can persist for variable periods once ventricular pacing is terminated [5, 26, 27]. Therefore, ventricular pacing is another example of a situation where the heart muscle "remembers" periods of altered ventricular activation[5].

## 1.5 T wave abnormalities following premature ventricular complexes

Premature ventricular complexes (PVCs), also known as ventricular extrasystoles, are the result of premature depolarization of the myocardium below the bifurcation of the bundle of His (distal to the atrioventricular junction) [28]. PVCs may have their origin from either of the two ventricles, the interventricular septum or the fascicular system [28, 29]. Electrocardiographically they are recognized by the premature occurrence of a QRS complex that is bizarre in shape with a duration exceeding that of the dominant QRS complex (typically greater than

120 ms) with a large T wave, opposite in direction to that of the major deflection of the QRS complex [30]. However, PVCs may also have narrow QRS complexes if they originate from a point equidistant from each ventricle in the interventricular septum or high in the fascicular system itself [29].

PVCs lead to an alteration in the sequence of ventricular activation and therefore, classic secondary T wave abnormalities are seen in a PVC [31]. However, PVCs also lead to changes in both the amplitude and polarity of the T waves of sinus beats following PVCs [32, 33, 34, 35, 36, 37]. This phenomenon was first described by White in 1915 [32]. These are T wave abnormalities of normal sinus beats after the PVC and are therefore not secondary T wave abnormalities. These post-extrasystolic T wave changes can follow one of two patterns: a subepicardial or a subendocardial pattern [35]. The majority (more than two thirds) of post-extrasystolic T wave changes follow a subepicardial pattern, where there is a decrease in the amplitude or even total inversion of the T wave of sinus beats following the PVC [35]. The remaining third follow a subendocardial pattern, where there is ST-segment depression with less pronounced inversion, or even an increase in amplitude of the T wave of post-extrasystolic sinus beats [35].

These post-extrasystolic T wave changes can persist for variable periods and is another example where the heart muscle "remembers" periods of altered ventricular activation [5, 32, 33, 34, 35, 36, 37].

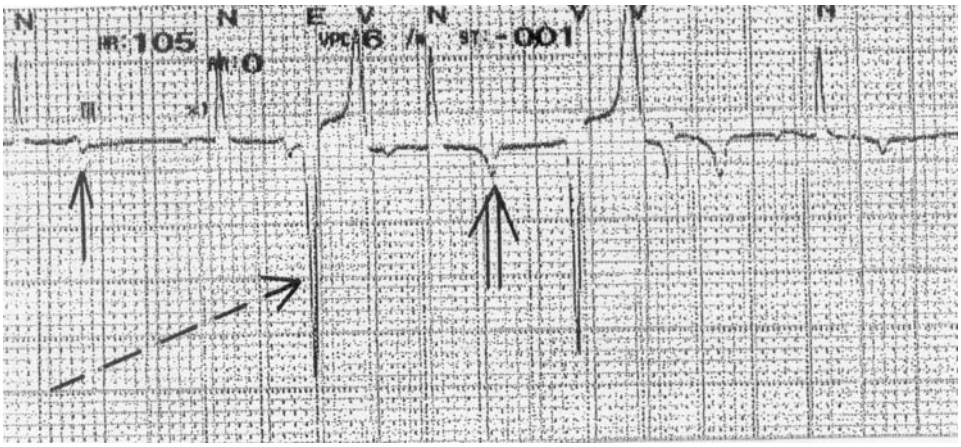


**Figure 7.** An example of cardiac memory. The third and fifth beats are PVC's. Note the bifid T wave (arrow) before the PVC (broken arrow). The T wave of the first normal beat after the PVC (double arrow) is inverted. In this instance the T wave of the first normal beat after the PVC "remembers" the direction of the abnormal QRS complex, therefore the term "cardiac memory" (The ECG tracing is the property of the author).

## 2. Cardiac Memory:

Memory is a property of several biological systems, such as the brain, the gastrointestinal tract and the immune system [6, 38]. It is now quite clear that the heart also remembers and this memory is seen electrocardiographically in the T wave [6]. As stated previously, for many years it has been assumed that Wilson's formulation, classifying all T wave changes as either primary or secondary in nature, covers all

possible T wave abnormalities occurring on the human electrocardiogram [5]. Secondary T wave abnormalities are the result of an altered sequence of ventricular activation and are thus dependent on the preceding QRS complex [6]. As discussed previously these are the T wave changes seen during periods of ventricular pacing, left bundle branch block, ventricular pre-excitation and the T wave abnormalities of premature ventricular complexes. Primary T wave abnormalities are independent of the QRS complex and are the result of alterations in ventricular ion channels and/or myocardial pathology [5, 6].

In the years after Wilson published his formulation on T wave changes a third category of T wave change became evident. These are T wave changes seen after periods of altered ventricular activation when normal sinus rhythm has returned. Rosenbaum *et al* coined the term pseudoprimary for these T wave changes [5]. However, these "pseudoprimary" T wave changes actually has characteristics of both secondary (they are dependent on a previous period of altered ventricular activation) and primary T wave changes (they are the result of changes in the ion-channel determinants of repolarisation, as will be discussed shortly) [6]. As already discussed, these T wave changes are seen during normal sinus rhythm after preceding periods of ventricular pacing, ventricular preexcitation, left bundle branch block, paroxysmal tachycardia and premature ventricular complexes.

Rosenbaum *et al* were the first to coin the term “cardiac memory” to refer to the phenomenon where T waves during normally conducted beats seem to “remember” the QRS complex of the previous abnormally conducted beats [5]. Cardiac memory can be characterised in the following way: after a period (or periods) of abnormal ventricular activation, the T wave during subsequent normal sinus rhythm retains the vector of the previously abnormal QRS complex (es) [5, 6, 39, 40, 41, 42]. Furthermore, with recurrent periods of altered ventricular activation these T wave changes may increase in magnitude—referred to as accumulation [5, 6]. When cardiac memory is noted on the ECG, the direction of the T wave(s) is similar to the direction of the QRS complex(es) noted during the period(s) of abnormal ventricular activation and these cardiac memory T waves may be observed after either short or long periods of abnormal ventricular activation and are thus referred to as short- and long term cardiac memory respectively [40]. However, the time period required to separate short- from long term cardiac memory has not been defined at present [40].

The T wave reflects transmural and apico-basal gradients for ventricular repolarisation and certain changes in ventricular ion currents has been described in cardiac memory [43]. T waves are the result of a balance between inward and outward ion currents in individual ventricular myocytes [6]. During the action potential inward current is carried by sodium ions during phase 0, the action potential

upstroke and during the phase 2 plateau [6]. Calcium ions also contribute towards the inward current during the plateau [6]. Outward, repolarising currents are carried by potassium [6]. An initial- and three types of delayed rectifier potassium currents contribute to ventricular repolarisation [6]. The initial, transient, outward ($I_{to}$) potassium current contributes to the notch during phase 0 of the action potential [6]. Three types of delayed rectifier potassium currents contribute to phases 2 and 3 of the action potential: $I_{ks}$ (slow), $I_{kr}$ (rapid) and $I_{kur}$ (ultra-rapid) [6]. There is also an inward rectifying potassium current ($I_{ki}$) that contributes to phase 3 [6].

Regional differences in these ionic currents, the resulting action potentials and the temporal sequence of ventricular activation are all factors that affect expression of the T wave, as they create voltage gradients apico-basally, as well as transmurally in the ventricular myocardium [6]. For example, the action potential duration is longer midmyocardial than that in the endocardium or epicardium [6].

Cardiac memory is associated with decreases in $I_{to}$ density and mRNA for Kv4.3 (this encodes the $\alpha$-subunit of the $I_{to}$ channel protein) [43]. Furthermore, $I_{to}$ kinetics are also altered, such that recovery from inactivation prolongs 20-fold and as a result there is an altered transmural repolarisation gradient [43]. Further evidence for the role of $I_{to}$ in inducing cardiac memory is that it's absence prevents memory

from occurring [43]. This was shown by administering the $I_{to}$ blocking agent, 4-aminopyridine to intact dogs and isolated tissue, after which cardiac memory could no longer be induced [43]. Cardiac memory is also associated with ultrastructural changes in the myocardium: there is a reduction in the density of the gap junctional protein connexin 43 (Cx43) and there is also changes in the distribution of Cx43—from being concentrated at the longitudinal poles of myocytes to a more uniform distribution across the lateral cell margins [43, 44]. These changes are not uniform as they are greater epicardially than endocardially [44]. Together, these molecular and ultrastructural changes contribute to an altered transmural repolarisation gradient with resultant memory T waves.

Periods of altered ventricular activation alters the stress/strain relationship in the myocardium and it is well known that an altered stress/strain relationship increases the release of angiotensin II [43]. Angiotensin II is a known mitogenic molecule and is closely linked to myocardial remodeling, hypertrophy and fibrosis in a variety of cardiac disorders [45, 46, 47, 48]. Therefore, a very important, but as of yet an unanswered question is: might cardiac memory be an initial, electrocardiographic sign of structural myocardial disease to come?

There is no data available on cardiac memory T waves as an electrocardiographic warning for myocardial disease to come. However, current available data suggest that there is a very definite

risk for structural myocardial disease in patients exposed to prolonged and/or repetitive episodes of altered ventricular activation. As these episodes are a cause of cardiac memory T waves, it is a possibility that these memory T waves may serve as a warning to the practising clinician.

The available data on the risk for structural myocardial disease in patients exposed to prolonged and/or repetitive episodes of altered ventricular activation will now be reviewed.

## 3. Conditions associated with cardiac memory T waves that may cause myocardial disease:

As there is no data available on the possibility that cardiac memory T waves may be an electrocardiographic warning of pending myocardial disease, the available data on the five conditions associated with cardiac memory T waves and all the possible myocardial diseases associated with these five conditions: ventricular preexcitation (Wolff-Parkinson-White syndrome), left bundle branch block, paroxysmal tachycardia, ventricular pacing and frequent premature ventricular contractions will be reviewed.

## 3.1 Myocardial diseases associated with ventricular preexcitation

Wolff-Parkinson-White syndrome has been associated with various cardiac disorders, such as hypertrophic cardiomyopathy [49, 50], dilated cardiomyopathy [51, 52, 53], histiocytoid cardiomyopathy [54] and peripartum cardiomyopathy [55]. Interestingly, even myocarditis—both atrial and myocardial—has been associated with Wolff-Parkinson-White syndrome [56, 57]. In 1995 Lopez *et al* [56]described a case report of a patient with lymphocytic myocarditis who also has Wolff-Parkinson-White syndrome and in 2001 Basso *et al* [57] in a post-mortem study, demonstrated the presence of focal, active, atrial myocarditis in 50% of a series of Wolff-Parkinson-White patients who died suddenly.

All of the above interesting observations raise the question: “can ventricular pre-excitation lead to myocardial disease?”. If this proves to be the case, can cardiac memory T waves serve as a warning to the clinician performing electrocardiography? To date this question has not been answered.

## 3.2 Myocardial disorders associated with left bundle branch block

Among patients with established heart disease, especially acute myocardial infarction, the presence of complete bundle branch block (both left and right) is associated with an increase in mortality [58]. What about new and permanent versus old or transient bundle branch block in acute myocardial infarction? Two studies in the thrombolytic era have shown that the development of new and permanent bundle branch block (both left and right) during acute myocardial infarction is an independent predictor of an increase in mortality, whereas an old or transient bundle branch block is associated with only a slight increase in mortality [58, 59, 60].

But what is the situation in the general population? Fahy *et al* [58] found a prevalence for bundle branch block of 0.3% which increased to 1.6% in persons older than 64 years. The Reykjavic study [58] found a prevalence for left bundle branch block of 0.4% in middle aged men, while the Tecumseh study [58] reported a prevalence of bundle branch block of 2.4% in men older than 50 years. In all of these studies an increase in mortality was only observed in patients with established coronary artery disease [58].

In 1998 Eriksson *et al* [58, 61] reported that the prevalence of complete bundle branch block (both left and right) increases from 1% to 17% in

men between 50 and 80 years of age and that there is no relation to coronary artery disease or mortality. However, those who subsequently developed bundle branch block were more likely to develop congestive heart failure than men without bundle branch block [58, 61].

In 2001 Hesse *et al* [62] published a paper, in effect linking data from population studies with those in acute myocardial infarction. They evaluated 7073 patients with either known or suspected coronary artery disease who were referred for nuclear exercise testing. After a mean follow-up of 6 years both left and right bundle branch block were associated with an increase in mortality, even after adjusting for demographic, clinical, exercise and nuclear scintigraphic parameters [58, 62].

However, based on these epidemiological studies it is unclear if left bundle branch block can cause heart disease in healthy individuals. Therefore, let's look at the functional effects of left bundle branch block. Left bundle branch block has profound hemodynamic effects [63]: it leads to asynchronous myocardial activation which may trigger ventricular remodeling, it impairs both systolic and diastolic function and it causes mitral regurgitation which can also trigger ventricular remodeling [63].

In patients with dilated cardiomyopathy and left bundle branch block it is not always clear whether left bundle branch block is the cause or the

consequence of left ventricular dilatation: a classic chicken-egg dilemma [63].

Therefore, there is another gap in the literature: it is unclear whether left bundle branch block can be a cause of myocardial disease and if so, whether cardiac memory T waves can serve as an electrocardiographic warning in that subgroup of patients with intermittent left bundle branch block.

## 3.3 Myocardial disorders associated with repeated episodes of paroxysmal tachycardia

Exposure of the mammalian heart to repeated episodes of paroxysmal tachycardia can lead to cardiomyopathy, a condition termed tachycardia-induced cardiomyopathy, also known as arrhythmia-induced cardiomyopathy [64, 65, 66, 67, 68, 69]. Tachycardia-induced cardiomyopathy is a partially or totally reversible left ventricular dysfunction after normalisation of the tachycardia [65]. There are two forms [65]: a pure form that occur in apparently normal hearts and the more common form in which there is underlying cardiac disease associated with the tachycardia.

Episodes of paroxysmal tachycardia are a known cause of cardiac memory T waves [8, 19, 20, 21, 22, 23]. Disappointingly, there is no literature examining whether cardiac memory T waves can serve as a warning for impending tachycardia-induced cardiomyopathy.

## 3.4 Myocardial disorders associated with ventricular pacing

In 1990 Karpawich *et al* [70]examined the hemodynamic, electrophysiologic and histologic complications of right ventricular apical pacing in 12 beagle puppies. They found significant elevations of right atrial and pulmonary artery pressures, as well as alterations in sinus node function and prolongation of ventricular refractory periods in the paced group. Furthermore, they found significant histological alterations in the paced hearts which consisted of myofibrillar disarray, dystrophic calcifications, prominent subendocardial Purkinje cells and various mitochondrial alterations [70]. They concluded that chronic right ventricular apical pacing leads to various adverse cellular changes, which are associated with hemodynamic and electrophysiological deterioration. Right ventricular pacing has also been demonstrated to be associated with hemodynamic deterioration in human adults [70]. In 1999 Karpawich *et al* [71] also performed myocardial biopsies in young, human patients (median age 16 years) who were being paced due to congenital atrioventricular block. They identified the same histological

alterations: myofiber size variation, fibrosis, fat deposition, sclerosis and mitochondrial changes [71].

It has been known for a long time that right ventricular apical pacing alters the sequence of ventricular activation profoundly and results in major interventricular dyssynchrony, delaying left ventricular activation from 30 to 60 msec in normal hearts and up to 180 msec in diseased hearts [72]. In 2001 Tantengco *et al* [73] published a paper, proving that chronic right ventricular apical pacing in young patients is a cause of left ventricular systolic and diastolic dysfunction.

Thus, it is clear that altering the normal sequence of ventricular activation by right ventricular apical pacing is a cause of left ventricular dysfunction and structural alterations. However, once again there is no data on the possibility that cardiac memory T waves, seen during interspersed periods of normal sinus rhythm may be a warning for these structural sequelae.

## 3.5 Myocardial disorders associated with premature ventricular complexes

According to current knowledge all textbooks on cardiovascular diseases have consensus that in the absence of underlying heart disease, premature ventricular complexes have little significance and treatment is not indicated [28, 29, 30, 31]. However, it is also known that the

presence of premature ventricular complexes (PVC's) in apparently healthy, middle-aged men is associated with an increased incidence of coronary heart disease and a greater risk of subsequent death [30, 74, 75, 76, 77, 78].

The discrepancy is clear: "PVC's occur in many healthy individuals and in the absence of heart disease, there is little or no increased risk [31]. But, in apparently healthy middle-aged men PVC's are associated with an increased incidence of coronary heart disease. Where does this leave the practising clinician ?

Chronic PVC's increase both the total and sudden death rate in patients with chronic heart disease, such as ischemic heart disease, hypertensive heart disease and all of the cardiomyopathies, especially in patients with a reduced ejection fraction [31].

Once again we are faced with a chicken-egg dilemma. PVC's are a very common occurrence in both normal and cardiomyopathic hearts [28, 29, 30, 31]. But can they be a cause of heart disease? Only one publication in the literature addresses this question [81]: Redfearn *et al* [81] presented a case where persistent PVC's from the right ventricular outflow tract resulted in left ventricular dilatation and systolic dysfunction. After successful ablation of the ectopic focus the cardiomyopathy resolved [81]. This case raises the possibility that frequent PVC's may be a cause of

left ventricular dysfunction. Once again, there is no data available on the possibility that cardiac memory T waves may serve as a warning for cardiomyopathy that may be caused by PVC's.

In summary, the available data on the five conditions able to induce cardiac memory T waves (ventricular preexcitation, left bundle branch block, paroxysmal tachycardia, ventricular pacing and premature ventricular contractions) and the evidence linking them to structural myocardial disease was presented. Of the five conditions PVC's are the most common and furthermore, the evidence linking PVC's as a possible cause of cardiomyopathy is the weakest.

PVC's originating from the right ventricle initiate depolarisation from the right ventricle, inducing ventricular asynchrony. They share this feature with right ventricular outflow tract tachycardia and right ventricular pacing. The major difference between ventricular tachycardia, ventricular pacing and PVC's are basically only the frequency of depolarisations. Ventricular tachycardia is defined as more than 3 PVC's with a rate more than 100/min [82] and ventricular pacing is usually set at a physiologic rate of about 70/min.

As discussed before, both ventricular tachycardia and ventricular pacing are known causes of left ventricular structural changes. Therefore, it is very plausible that PVC's, originating from the right

ventricle, can be a cause of left ventricular structural changes. And indeed, a case report was found in the literature where the authors believed that persistent PVC's from the right ventricular outflow tract caused left ventricular dilatation and systolic dysfunction [81]. Once again, there is no data that cardiac memory T waves can serve as an electrocardiographic indicator of myocardial dysfunction arising in such a scenario.

**Hypothesis**

Cardiac memory T waves can serve as an electrocardiographic surrogate for structural myocardial alteration in the hearts of Dorper sheep.

**Null Hypothesis**

Cardiac memory T waves can not serve as an electrocardiographic surrogate for structural myocardial alteration in the hearts of Dorper sheep.

**Research needed in order to prove this hypothesis**

Dorper wethers, aged between 10 and 12 months, were chosen for this project. When asked why Dorper wethers I refer the reader to the statement made by Albert Szentgyörgyi: "Life is a similar process in cabbages and kings; I choose to work on cabbages because they are cheaper and easier to come by." [43] But on a serious note, sheep are a well known animal model for the study of cardiac dysrhythmias and the ovine anatomy makes access to the heart via the internal jugular vein with a catheter, using the Seldinger technique, relatively easy.

In this proposed ovine model, the following will need to be achieved:

- Establish a method to produce consistent and reliable 12-lead, surface electrocardiograms.
- Establish a method to induce PVC's, originating from the right ventricle.
- Document whether these PVC's are in fact able to induce cardiac memory T waves, as cardiac memory has never before been described in the ovine heart.
- Document the normal histological appearance of the ovine myocardium.

- Afterwards, it will be determined whether any structural changes can be seen in the ovine hearts subjected to persistent right ventricular PVC's and if so, if any correlation can be found with cardiac memory T waves.

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