Electrical stunning and hibernation: suggestion of new terms for short- and long-term cardiac memory

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Abstract
Persistent T wave changes following resumption of sinus rhythm induced by pacing or arrhythmias that cause altering of ventricular activation sequence are named "cardiac memory". After this initial definition there has been a discussion whether such T wave changes are primary, secondary or pseudoprimary. In addition according to the results of pathophysiological studies investigating the mechanism and nature of this repolarization abnormality some authors have preferred to use the term "electrical remodelling" instead of cardiac memory. But these two terms are still not well defined. In this article, the previous terms are discussed and a new term instead of cardiac memory is introduced.

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KEYWORDS
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Introduction

Cardiac memory is one of the T wave abnormalities related to a change in repolarization induced by an altered pathway of ventricular activation [1–3]. This phenomenon, which was first named as cardiac memory in 1982, is characterized by persistent but reversible T wave inversion related to abnormal activation of ventricle [2]. These T wave changes may last for days or weeks, which has been applied to short- or long-term memory, respectively [2,3]. Some different terms (electrical remodelling, electrical gradient) were also used for explanation of the underlying pathophysiological properties of this altered repolarization [3,4]. But still there is no single acceptable term. This review aims to focus on the previous investigations in this field and to discuss what the correct term might be.

Classification of T wave inversion: the position of cardiac memory in this classification

In surface electrocardiography (ECG) the T wave represents ventricular repolarization. A primary T wave abnormality is due to an alteration of the repolarization process that is independent of any abnormality of the QRS complex with normal or
unchanged depolarization. Secondary T wave changes are seen in conduction abnormalities such as those occurring in bundle branch block, Wolff-Parkinson-White (WPW) Syndrome, cardiac pacing and ventricular ectopy. During cardiac memory, the T wave direction is similar to the QRS complex with abnormal depolarization. Following this abnormal depolarization period, despite restoration of depolarization with a normal QRS complex, transient repolarization abnormalities may occur [2–6]. The T wave change, which is called cardiac memory, is neither a typical secondary T wave change nor a primary T wave alteration [2,3].

Suggested similarities between biological and cardiac memory

Memory consists of remembering what has previously been learned and allows adaptation to the environment and response to novel stimuli. To assimilate this information there must be a set of encoded neural connections. Encoding can take place in several parts of the brain. There are many explanatory models for memory and they can be divided into two broad types named explicit (associative) and implicit (non-associative) memory. Non-associative is a memory without awareness. This form is weakly encoded memory which can affect conscious thought and behaviour. Repeated exposure to a single type of stimulus enables the organism to learn about the properties of the stimulus [7]. The non-cognitive memory, which resembles cardiac memory, includes habituation, sensitization and dishabituation (classical conditioning). Habituation is a learned response which is observed after repeated stimulation. Sensitization, involves a more complex learning paradigm and depends on a more complicated cellular regulatory mechanism [7,8]. Like nerve cells in the brain storing patterns of events to form memories, cells in the heart can also form memories of rhythm patterns [2]. With every heartbeat, the myocardial cell is first stimulated, and then it repolarizes and returns to a resting state. The cardiac memory process relates to the T wave and repolarization. According to "remembered T wave" theory when the cell repolarizes during periods of abnormal beating, the cell will remember the abnormal pattern of repolarization for a period of time. The more frequently the abnormal beat occurs, the more the altered repolarization pattern is remembered. Consecutive episodes of ventricular pacing were shown to have a cumulative effect on repolarization and the heart can remember these previous episodes of pacing. The persistent post-pacing changes in T wave morphology increased with the duration of abnormal ventricular activation and the normalization of the T wave occurred slowly, requiring minutes to months or even years, depending on the duration of the stimuli [2–5].

Two different periods for restoration after abnormal depolarization: short- and long-term cardiac memory

The electrical repolarization abnormality is referred to as short- and long-term, respectively, after cessation of a period of altered ventricular activation [2,4]. The heterogeneity in repolarization results from heterogeneity of the action potential duration. For example, the action potential is longest in mid-myocardium, then the endocardium, followed by the epicardium [9,10]. Costard-Jäckle et al. [11] performed pacing from the right atrium and right ventricle sequentially in animal models to investigate the relationship between cardiac activation pathway and repolarization time. An inverse relation was shown between activation time and action potential duration (APD) due to a very slow mechanism, which conditioned ventricular repolarization according to the sequence of ventricular activation. Moreover, the others noted that the activation change is associated with an alteration in current flow through gap junctions [4,12]. The changes in the transient outward current of cardiac myocytes occurs when memory is induced. Transient outward potassium current (I\textsubscript{to}) appears to play a role in both short-term and long-term memory [13,14]. However, altered activation is the first step for cardiac memory. New protein synthesis following this activation has also an important role for long-term cardiac memory [10,13]. It is associated with decreases in I\textsubscript{to} density and mRNA for Kv4.3, which encodes the subunit of related channel protein [13,14]. In the study by del Balzo and Rosen [15] intravenous administration of 4-aminopyridine (4-AP), a blocker of the cardiac transient outward current, I\textsubscript{to}, prevented the induction of cardiac memory. These results suggested that the ion channels have an important role in formation of transmural repolarization gradient in short- and long-term memory periods. Plotnikov et al. [16] showed short-term memory is induced by 2 h of ventricular pacing and long-term memory for 21 days. It has been shown that changes in the transient ventricular pacing functions (specific potassium channels) and phosphorylation of related proteins responded to give
short-term memory effects. However, for long-term memory, gene expression of these channels (slow sodium, L-type calcium and several potassium channels) is needed which requires a longer time [10,17]. Therefore, the long-term process is associated with more electrical and structural changes.

Angiotensin II also appears to be involved with short memory changes. The changes in myocardial electrical pattern and its underlying ion channel activity may be induced by angiotensin II. It is postulated that angiotensin II, an important mediator of stretch-induced hypertrophy, increases protein synthesis and induces many genes for cardiac hypertrophy. The change of stress/strain relationships on cardiac cell cultures can increase the release of angiotensin II that is a hypertrophic hormone modulating cardiac electrical activity and structure [18,19]. Ricard et al. [19] also showed that the angiotensin II receptor blockers could prevent short-term cardiac memory. It seems that angiotensin II has a critical role in cardiac structural and functional changes induced by electrical stimulation.

Cardiac memory is not exactly similar to neuronal memory

Biological memory has three basic processes: (1) encoding (putting information into memory); (2) storage (keeping information in memory); and (3) retrieval (getting information out of memory). Memory is the retention of information, personal experiences, procedures and is the ability to recall them. Our brains process all kinds of information at the same time but the response of an organism to these stimuli does not simply depend on the stimulus alone. Learning and storage of the previous experience have impact on the response of the organism. It is also related to previous stimuli to which the organism has been exposed either in cognitive or non-cognitive memory [8,20,21]. The mechanism and synaptic activities are different in these two groups of memory and in the subgroups of non-cognitive memory [20,21].

As noted above in the biological memory process, the short- or long-term memories are also present in the heart. Both short- and long-term memories induced by ventricular pacing have been suggested to be similar to memory in the central venous system [4,10,11]. Short-term cellular changes differ from long-term cellular changes in that short-term changes involve only modification of pre-existing proteins and alterations of pre-existing connections. The short-term process does not involve ongoing macromolecular synthesis. Detailed studies have shown that development of long-term potential requires a stimulus threshold determined by complex interactions between the frequency and the strength of the electrical stimulation to the afferent pathway [21,22]. The brain is selective about which information is stored in long-term memory and only 1% of all information can be stored in there. These examples show that the memory process and suggested mechanisms in the brain are more complex and we do not yet know exactly how memory works. Despite the advances in neurophysiology it is still being debated how the function of memory is accomplished by the brain.

Although there are few similarities between neuronal and cardiac memory, there are many differences: (1) both depolarization and repolarization is altered during cardiac pacing but only the repolarization period is memorized. (2) According to the suggested pathophysiological mechanism in non-associative cardiac memory, if the stimulus is noxious the response of the organism will become sensitized and will increase its response to repeated stimuli. After a painful stimulus the response of the organism may become stronger than previously even to a mild stimulus [8]. But this concept with different responses has not been shown by ventricular pacing induced memory. (3) It is known that an external stimulus is responsible for any form of biological memory. In contrast to pacing induced memory, an external stimulus does not have any role in T wave inversion seen after removal of an accessory electrical pathway in the heart. So the suggested mechanisms for non-cognitive models of memory are not sufficient to explain the nature of T wave inversion, which occurs after ablation therapy.

Electrical remodelling

Some investigators described the term electrical remodelling and showed many basic differences between biological and cardiac memory. The results of pathophysiological studies in this field also vary [2,3]. Electrical remodelling is characterized by delayed repolarization, prolonged action potential duration, increased dispersion of refractoriness and electrophysiological heterogeneity within the myocardium. In the presence of heart failure or chronic atrial fibrillation the electrical remodelling is secondary to structural myocardial changes. It is well established that alterations in heart rate or activation sequence induce electrical remodelling.
in the atria. However, ventricular electrical remodelling is poorly understood. Also, the electrophysiological abnormalities, which cause the remodelling processes, are different in atrium and ventricle. Despite atrial remodelling being characterized by a shortened atrial refractory period, the main electrophysiological properties of ventricular remodelling are related to prolongation of action potential duration or to the reversal of ADP gradient orientation with rapid rate [2,23–25]. However, the electrical remodelling implied in cardiac memory is not associated with secondary myocardial disarrangements. Some investigators prefer to use the primary remodelling term for this phenomenon [2,3,26]. In addition, there is not enough research and only a single concept of the clinical effect of ventricular electrical remodelling, and its role in ventricular arrhythmias.

The relationship between myocardial mechanical and electrical events

Alteration of the pathway of normal ventricular activation by pacing or arrhythmias may affect stress/strain patterns in the heart. The altered activation pathway of part or all of the ventricle can be assumed to change the mechanical pathway of contraction, direction of stretch and relaxation of myocytes. Mechanical stretching leads to the accumulation of cAMP, which is one of the secondary messengers that leads to long-term memory, stimulates phosphoinositide hydrolysis and causes transient increase in inositol phosphate [27,28]. These changes could lead to acute changes in the electrophysiological properties of the heart. In the study by Prinzen et al. [29], it is suggested that ventricular pacing could change the myofibre function of the left ventricular wall. Alessandri et al. [30] reported a relationship between electrical and mechanical changes following long-term ventricular pacing and cardiac memory. They were able to demonstrate that cardiac memory is a phenomenon that applies also to diastolic function.

Discussion

The T wave is a reflection of cardiac repolarization and there are many clinical features causing T wave inversion. Cardiac memory is one of them related to a change in the direction of depolarization of the heart on ECG. As noted before, the classification of all T wave changes grouped as primary and secondary, is insufficient to define this phenomenon [2–4,31]. Therefore, these repolarization abnormalities might be included in another category or the subject of different terminology [29].

After the first description of this phenomenon, Chaterjee et al. [5] showed that with ventricular pacing the same T wave inversion might persist for many days despite return of a normal depolarization vector and without simultaneous QRS changes during non-paced beats. They noticed the three important points: (1) the duration of pacing influenced the duration of T wave inversion; (2) the greater the energy used for pacing, the more T wave changes; and (3) this T wave inversion is most prominent in the leads corresponding to where the electrode is touching the endocardium. Although cardiac T wave memory can occur after ventricular pacing, it is unclear whether all patients with pacemakers show this phenomenon during intermittent pacing [32]. The long-term cardiac memory of repolarization dispersion has also been reported after catheter ablation in patients with WPW syndrome. It is interesting that this phenomenon was not seen with concealed accessory pathways and appears related to location of the accessory pathway [33]. The effects of pacing site in the ventricle and the location of the pathway also show differences between brain and cardiac memory. The normalization time of the repolarization period is also not the same in these patients after successful ablation therapy. It seems the location and the extent of pre-excitation of the ventricle may have an important role in the recovery time.

Either this T wave change is due to pacing or not, the word memory might be discussed for this phenomenon. Surawicz [35] by asking "memory of what?", suggested that the terms T wave memory and pseudoprimary repolarization had low specificity and were unnecessary. The simplest form of memory is externally induced, in which the external stimulus activates the cerebral cortex and causes recollection of old memories. But in this response, the roles of individuals’ characteristics are important and not only depend on the novel stimulus [34]. This raises another matter for description of memory. Is this mental reaction remembering or thinking? In the discrimination between non-associative memory and cardiac memory, it must also be noted that the term cardiac memory may not be correct for this electrical activation.

It is suggested that altered ventricular action potential duration (prolonged APD) or reversal of APD gradient (pacing-induced) lead to T wave changes. These T waves return to normal after resumption of sinus rhythm. Some authors preferred to use the term electrical remodelling (remodelling of
ventricular repolarization) instead of cardiac memory [2–4]. But there are some problems with the electrical remodelling concept. Despite the presence of abnormal ventricular repolarization and remodelling of an accessory pathway, the term remodelling is insufficient to explain this phenomenon. (1) Mechanical or structural heart diseases can cause alteration of ventricular conduction; the cardiac memory concept cannot be included in such secondary remodelling forms. (2) T wave inversion returned to normal after resumption of sinus rhythm spontaneously or without any medication. This dramatic recovery has not been shown with any other secondary structural remodelling conditions. (3) In contrast to the atrial model, the electrically triggered remodelling in the ventricle as a primary form is also questionable and may not be a satisfactory term. Furthermore, there are still questions that must be answered about the remodelling concept and its relation to ventricular action potential duration [3]. Although the term “electrical remodelling” has been used initially to explain the electrophysiological changes in persistent atrial fibrillation, the widespread use of the word “remodelling” may lead to confusion even in this case [36].

On the other hand, in the absence of any mechanical wall stress initially, such persistent T wave change has potential association with altered ventricular function parallel to an altered electrical pathway [29]. Waligora et al. [37] noted that long-term ventricular pacing leads to persistent left ventricular diastolic dysfunction even after cessation of ventricular pacing. The study by Ono et al. [38] using both thallium and coloured microspheres showed a significant regional myocardial perfusion defect during short-term ventricular pacing. Altered regional workload of the myocardium affecting ventricular function and the timing of this electrical activation is important for distribution of ventricular fibre strain and its blood flow [29].

These pathophysiological studies showed that changes in electrophysiological properties of the normal heart conduction system cause regional abnormality in contractile function of the myocardium, inhomogeneous hypertrophy and altered structural or mechanical changes in the ventricle. Also the levels of this process were described by Katz [27]: (1) altered structure (activation pathway); (2) altered metabolism (myocyte) and ion channels; (3) gene expression and altered ventricular mechanical function. When the first two steps are reversed rapidly, the long-term alteration in electrical activation may take days or weeks.

Myocardial stunning and hibernation

After coronary occlusion, myocardial wall motion abnormality of the left ventricle can be observed in the region supplied by the occluded artery. In myocardial stunning, despite early reperfusion of coronary blood flow and relief of ischaemia, there is a persistent wall motion abnormality. The recovery of ventricular function may take hours to days. The presence of impaired resting left ventricular function related to reduced coronary flow, which can be restored by revascularization, is named hibernating myocardium [39]. The mechanism of hibernation is a debate. Camici et al. [40] suggested that “repetitive” ischaemia in patients with coronary artery disease can be cumulative, and lead to more severe and prolonged stunning. This suggestion lends further support to the hypothesis that stunning and hibernation are “two facets of the same coin”. The underlying mechanism of these two clinical features is the occlusion of the normal coronary pathway. With the re-establishment of the normal flow pathway, the abnormal myocardial function recovers.

We need new terminology

These data suggest the necessity for new terminology: (1) The suggested mechanisms and classification of T wave inversion that are seen in cardiac memory remains controversial [4,32]. Whether these repolarization changes are primary or secondary is questionable. (2) The cardiac memory concept is not similar to either cognitive or non-cognitive brain memory. (3) Ventricular electrical remodelling is also not the correct term. In our opinion, electrical stunning and hibernation can be substituted for short- and long-term cardiac memory. The ion channel and myocardial structural changes seen in persistent T wave inversion (cardiac memory) are similar to those in myocardial stunning and hibernation. However, there is no standard concept for deterioration of contractile performance or other myocardial structural abnormalities in cardiac memory. The electrical stunning and electrical hibernation can be more explanatory for short- and long-term or primary and secondary electrical remodelling concepts (Fig. 1). Like myocardial stunning, acute change in normal conduction of sinus rhythm causes alteration of ventricular activation and persistent repolarization changes. The normalization time of altered repolarization is not the same in all subjects. If the electrical phenomenon which we prefer to name stunning is repeated or continued for longer, this
will lead to further change in ventricular structure and action potential. We suggest that electrical hibernation can be used to describe this condition. These electrical changes may be "two facets of the same coin" [40]. The "electrical" term also omits a pathological process, which is anticipated for myocardial stunning or hibernation. The heart cannot remember, but can restore its myocardial or electrical changes. The time of electrical recovery may depend on the nature and extent of electro-mechanical abnormalities.

In conclusion, we introduce electrical stunning and hibernation as new terminology for cardiac memory or electrical remodelling.

References


