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ORIGINAL RESEARCH ARTICLE

Research progress and controversy on T wave formation mechanism

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ABSTRACT

Although ECG has been developed for a hundred years, the mechanism of T wave formation is unknown. The proposal of in vitro wedge-shaped model has greatly promoted the understanding of T-wave formation mechanism. By comparing the action potentials of epicardial cells, medial cells and endocardial cells in wedge-shaped ventricular mass with the T wave of body surface ECG, it was found that the T wave was mainly formed by the dispersion of transmural repolarization of ventricular muscle. However, in the subsequent in vivo experiments, electrophysiologists found that the formation of T wave was related to the dispersion of ventricular global repolarization, and the repolarization order of different parts of the three-dimensional global heart determined the polarity of T wave. In the real heart, the mechanism of T wave formation may be more complex, its repolarization gradient may include repolarization in each axis of the heart, and the polarity of T wave may also be the result of multiple factors.

Keywords: cardiology; T wave formation; overview; electrophysiology; mechanism

1. Introduction

Owing t Since Augustus recorded the first ECG in 1887, ECG technology has become one of the most important noninvasive examination methods in clinical cardiology after a century of development. However, although ECG has been used clinically for more than a century, many of its mechanisms, especially the formation of T wave, are still controversial. The author will make a summary of T wave related research.

2. Early study of T wave

In 1856, two German physiologists kollikerandmuller first tried to explore the electrical activity of the heart and found two contraction waveforms. The second “contraction” may be the T wave mentioned by Einthoven in the future[1]. By 1880, Burdon-Sanderson et al.[2] first found that the ventricular activation sequence was from base to apex in frog heart, and recorded positive R-wave and negative T-wave bidirectional waveforms, and believed that T-wave was related to ventricular repolarization. Cohen et al.[3] found that the action potential of the basal part was longer than that of the apical part through electrophysiological detection on the tissue sections of the basal part and the apical part of the sheep ventricle. Moreover, by increasing the temperature of the base, the action potential duration can be shortened, and a deeper, longer and inverted T wave can be formed at the same time. Since then, the apical basal dispersion has been considered as the main

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theoretical basis for the formation of T waves in mammals. It was not until Sicouri and Antzelevitch[4] and Sicouri et al.[5] invented the wedge-shaped model in vitro and proposed the concept of middle layer (m) cells in the early 1990s that this theory was broken.

3. Exploration on the significance of T wave formation

The discovery of M cells has greatly promoted the understanding of T wave formation. Sicouri and Antzelevitch[4], Sicouri et al.[5] and Antzelevitch and Fish[6] found that ventricular muscle is not a homogeneous structure, which can be divided into three types: epicardial cells, M cells and endocardial cells, and each cell has unique electrophysiological characteristics. Subsequently, Yan and Antzelevitch[7] simultaneously recorded the action potentials of three types of cells and the simulated ECG of the myocardium on the isolated left ventricular wedge model. It was found that the potential difference between M cells, epicardial cells and endocardial cells during repolarization formed ascending and descending branches of T wave. The peak of T wave corresponded to the end of repolarization of epicardial cells, while the end of T wave corresponded to the end of repolarization of M cells. Therefore, the action potential duration of M cells is basically equal to the QT interval on the electrocardiogram, the action potential duration of epicardial cells is basically equal to the peak interval, and the distance from the top of T wave to the end of T wave is equal to the ventricular transmural dispersion (**Figure 1**). At the same time, sotalol and other drugs were further used in this study to interfere with the duration and amplitude of action potential of cardiac tissue block, and consistent conclusions were obtained. Subsequently, some studies also provided a theoretical basis for the formation of complex T-waves, such as negative T-waves, bimodal T-waves and even three-phase T-waves[8]. So far, T wave formation depends on ventricular transmural dispersion, which has become the theoretical basis of the new T wave formation mechanism.

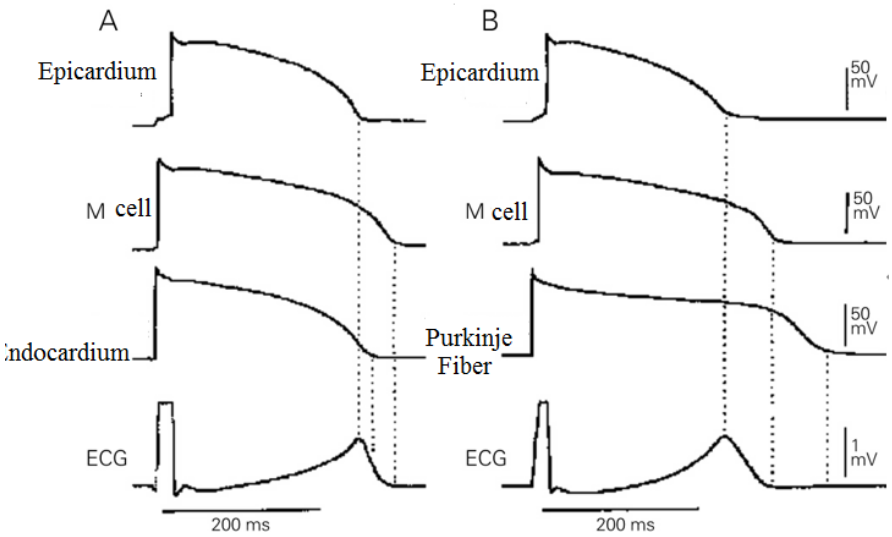

Figure 1. Cellular basis of normal T wave formation.
Transmembrane potentials and transmural electrocardiograms were recorded from two different wedge-shaped canine models in vitro. A: The action potentials of endocardial cells, M cells and epicardial cells were recorded by floating glass microelectrode, and the transmural ECG was recorded at the same time; B: The action potentials of epicardial cells, M cells and Purkinje fibroblasts were recorded in the same way, and the transmural ECG was recorded. In the above two models, the end of epicardial repolarization is consistent with T peak on ECG, the end of M cell repolarization is consistent with tend on ECG, and the duration of endocardial action potential is between the two (a). Although the repolarization of Purkinje fibers ended after M cells, it was not recorded on ECG[7]. Pacing interval: 2000 ms.

4. Progress in the in vivo study of ventricular global repolarization dispersion

Xia et al.[9,10] combined with one-way action potential and three-dimensional electromagnetic mapping system, conducted high-density mapping of pig hearts in vivo at the atrial pacing rate of 120 times/min. The results showed that although unidirectional action potential repolarization was mostly located in the epicardium at the latest, the dispersion of ventricular global repolarization was much greater than the dispersion of transmural repolarization of ventricular tissue blocks under the same conditions. On ECG, the earliest ventricular global repolarization was consistent with T peak, and the latest ventricular global repolarization was consistent with tend, suggesting that tpte may more reflect the dispersion of ventricular global repolarization. At the same time, Janse et al.[11] and Opthof et al.[12] also carried out in vivo research on dogs. While recording the characteristics of ventricular endocardial and epicardial repolarization, they also mapped the potential records in the ventricular wall, and at the same time pacing the ventricle to stimulate ventricular electrical remodeling to observe the changes of T wave. The results were similar to those of Xia et al. And it was found that the repolarization dispersion of the whole ventricle played an important role in the formation of T wave. In addition, although ventricular electrical remodeling increased the dispersion of ventricular transmural repolarization, there was no significant change in peak tend. It is worth mentioning that no middle layer M cells with the longest repolarization duration were found at the central intermuscular electrode throughout the study (**Figure 2**). With the deepening of research, more and more experiments have found that the overall repolarization dispersion of myocardium in different directions, including apical basal and left ventricular right ventricular, plays a leading role in the formation of T wave. This conclusion has also been confirmed in the hearts of different species, including dogs[11–15], pigs[9–10,16] and humans[17–19]. It has also been found that bimodal T wave or notch T wave is caused by the increased dispersion of repolarization in left and right ventricle[20]. In 2014, Meijborg et al.[16] first compared the relationship between repolarization dispersion and T-wave formation in different axes and found that t pte_ Total (defined as the distance from the earliest peak to the latest tend in all leads on ECG) is most relevant to the overall ventricular repolarization dispersion, that is, T wave formation is the result of the combined action of repolarization dispersion in different axes (**Figure 3**). Recently, Opthof et al.[17] injected Langendorff solution and blood into the healthy hearts of three heart donation patients in vitro, and mapped the depolarization, repolarization and activation recovery interval (ARI) of the heart through a total of 92 unipolar electrodes with 24 transmural probes. The results showed that the repolarization modes of the three hearts were different, and repolarization began at multiple sites at the same time, repolarization vector includes all axes of ECG and M cells with significantly prolonged repolarization have not been found (**Figure 4**). Therefore, whether there is cross wall repolarization dispersion, and if so, whether it contributes to the formation of T wave is still under debate. In addition, it is also believed that the formation of T wave is the result of the joint action of ventricular transmural dispersion and global repolarization dispersion[21,22].

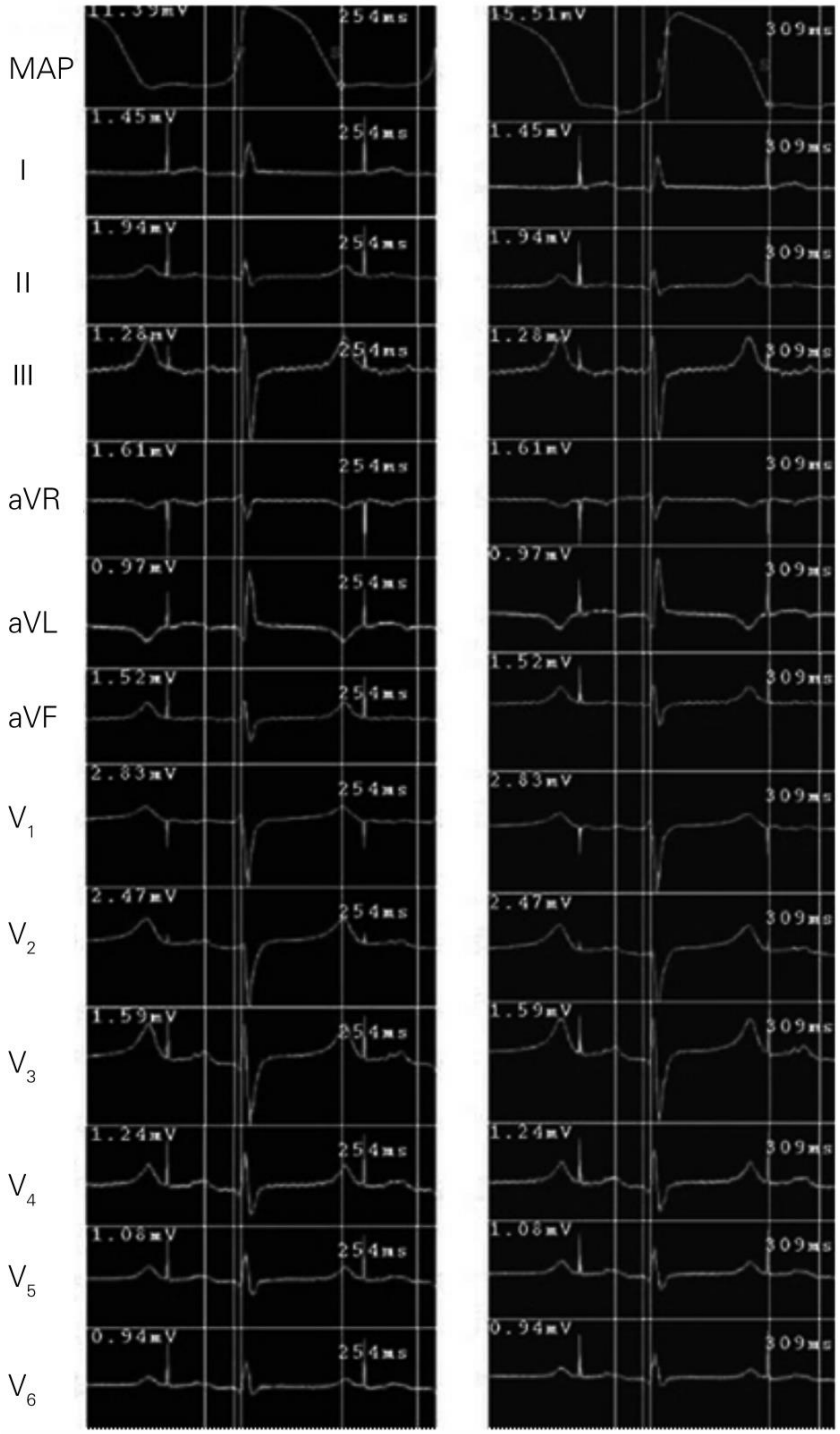

Figure 2. Global repolarization of ventricle using carto three-dimensional mapping system and unidirectional action potential recording technology.

By comparing the changes of 12 Lead ECG, it is found that the earliest recorded local repolarization terminal is consistent with T peak (left), while the latest recorded repolarization terminal is consistent with tend (right). It is suggested that T wave is related to global ventricular repolarization dispersion, not just transmural dispersion[9].

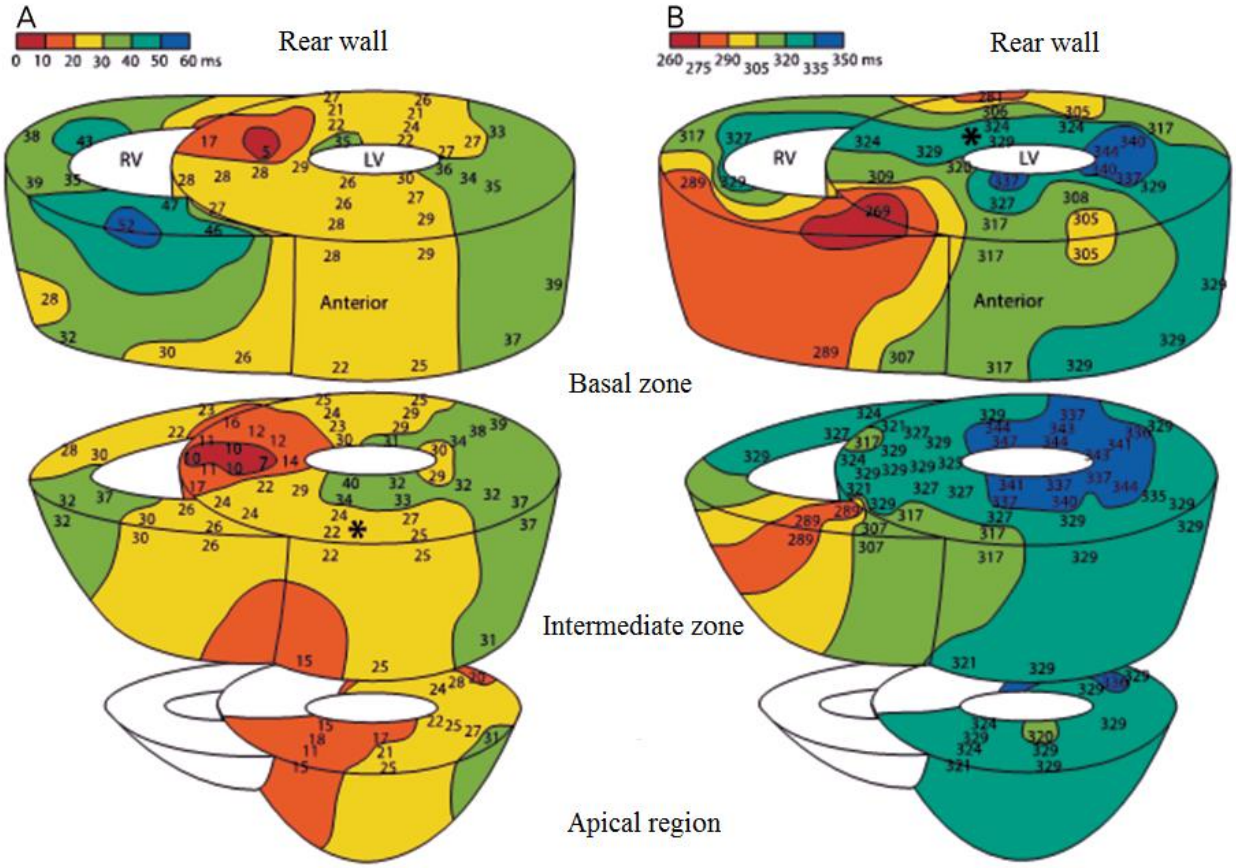

Figure 3. Electrophysiological mapping results of typical depolarization and repolarization at different levels (basal region, intermediate region and apical region).

Red indicates early occurrence and blue indicates late occurrence. A: Depolarization begins at the septum and the intermediate region, and conducts to the posterior and anterior walls of the intermediate region. The final depolarization site is the ventricular free wall (left ventricular depolarization precedes right ventricular depolarization). Endocardium and epicardium began depolarization almost at the same time (the asterisk in the figure is the position with the largest dispersion of endocardium and epicardium, and the maximum dispersion is 18 ms); B: Cardiac repolarization begins at the right ventricle, septum and posterior wall of basal region. The late repolarization was located in the endocardium and intermediate region of the left ventricular basal region. Most of the ventricular transmural repolarization are consistent. Only a part of the ventricles have the maximum transmural dispersion of 48 ms (located at the asterisk of the left ventricular posterior wall in the basal region in the figure, and its endocardial repolarization is later than that of the epicardium)[16].

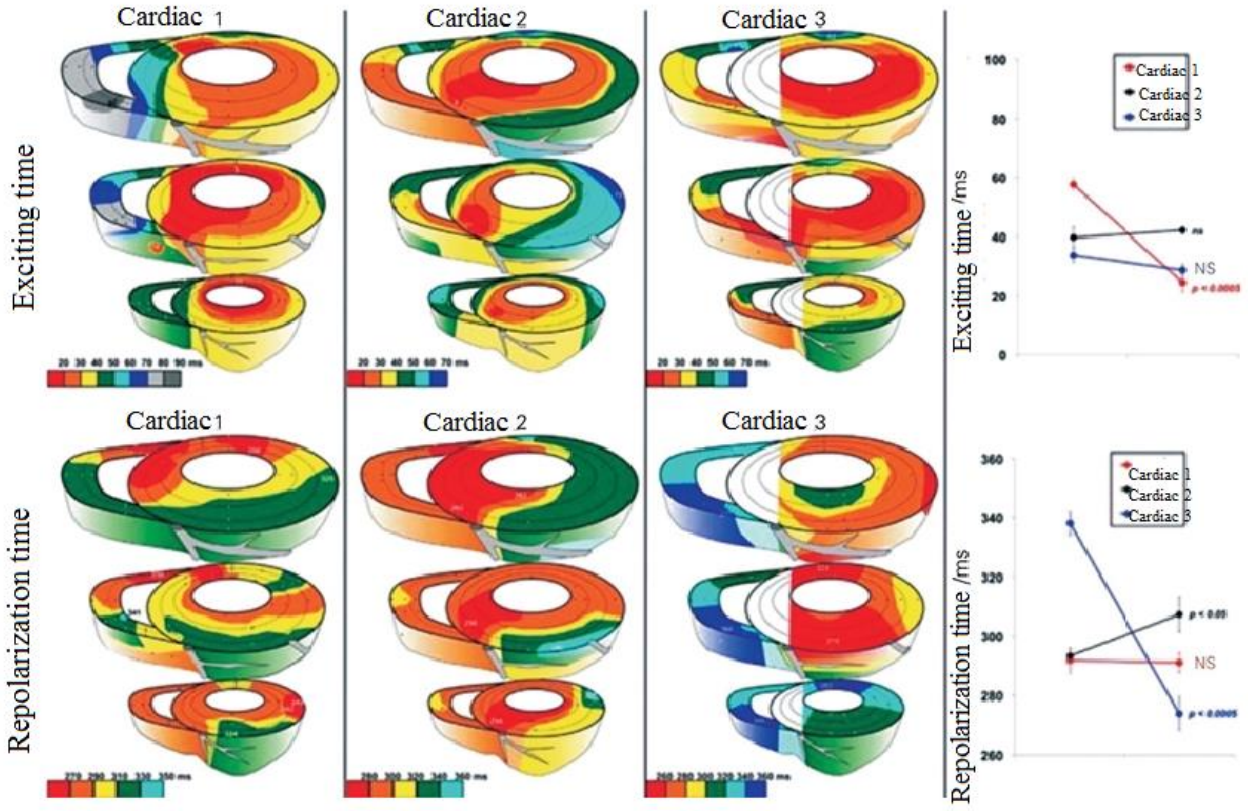

Figure 4. Depolarization (first row) and repolarization patterns of 3 Isolated human hearts (second row). Depolarization starts from the endocardium and is conducted from endocardium to epicardium in the left ventricle, and finally to the basal region. The latest depolarization time of the first heart is 90 ms, that of the second heart is 70 ms, and that of the third heart is 62 ms. The dispersion of repolarization was 99 ms in the first heart, 108 ms in the second heart and 145 ms in the third heart. The right side summarizes the depolarization and repolarization time of the left and right ventricles[17].

But why do different conclusions come from different models? Firstly, some studies believe that the difference between the wedge-shaped model in vitro and the complete heart model leads to the difference in conclusions[23]. After mapping the ARI of the intact pig heart, the isolated wedge-shaped model was prepared, and the ARI of the isolated wedge-shaped model was measured by the same method. It was found that the ARI of the isolated wedge-shaped model was significantly longer than that of the intact heart model. It is suggested that the conclusions drawn from the wedge-shaped model in vitro can not be inferred to the complete heart model; secondly, not all the prepared wedge models are the same. The wedge-shaped model obtained by different cutting methods may have a great impact on the results. It has been reported[13] that M cells with significantly prolonged action potential duration can be found in the myocardium by vertically cutting the myocardial block to prepare the wedge-shaped model in vitro. When cutting along the anatomical direction of the cardiac muscle bundle, the action potential duration of the endocardial layer, the middle layer and the epicardial layer are consistent, and no M cells with significantly prolonged action potential duration can be found (**Figure 5**); third, the heart itself is a three-dimensional cavity organ, and the isolated wedge-shaped model can not reflect the influence of the action potential difference of myocardial cells in the anterior wall, posterior wall, apex, bottom and septum of the ventricle on the formation of T wave[22]; fourth, ventricular conduction is temporal, and isolated wedge-shaped myocardium, as a limited size myocardial tissue, cannot reflect the impact of conduction time on ventricular repolarization dispersion[24]; fifthly, the wedge-shaped model in vitro is based on the slower pacing rate (40 times/min), while the dispersion of transmural repolarization will be significantly shortened at the faster pacing rate (100 times/min)[6]; sixth, the wedge-shaped model in vitro lacks

the ability to record the mutual electrical tension and galvanic coupling effects between tissues and cells[25]. In conclusion, the local action potentials of the wedge-shaped model in vitro can not fully reflect the discrete changes of repolarization in vivo, and there are obvious limitations.

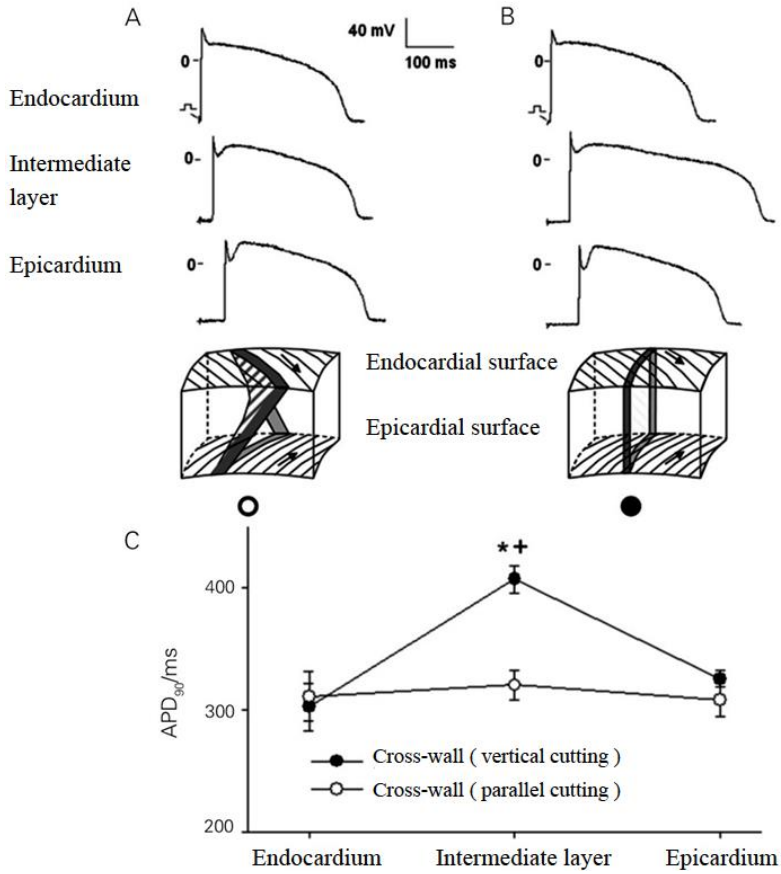

Figure 5. The isolated model was dominated by cutting (a) and direct vertical cutting (b) according to the anatomical structure of cardiac muscle bundle in the dog heart, and the unidirectional transmembrane action potentials of endocardial, intermediate and epicardial cells were recorded respectively.
In model B, intermediate layer cells with significantly prolonged action potential duration were found. C shows the average apd90 values of 8 prepared models (apd90 = action potential duration when repolarization reaches 90%). Pacing interval = 4000 ms[13].

5. Controversy and exploration on the relationship between repolarization sequence of ventricular myocardium and polarity of T wave

As early as 1913, Mines[26] found that T wave is not only the electrical expression form of myocardial repolarization, but also the polarity of T wave is related to the change of action potential duration. Subsequently, Wilson[27] further improved this conclusion in 1931. He believed that the reason why the polarity of T wave and R wave is consistent is that the depolarization and repolarization of some myocardium must be in the opposite direction, that is, at the cellular level, the depolarized cardiomyocytes must be finally repolarized to make the polarity of T wave and R wave consistent. In other words, the action potential duration of the first excited cardiomyocytes must be longer than that of the last excited cardiomyocytes. Cohen et al.[3] found that there was a significant difference in the time course of action potential between the basal and apical myocardial slices of sheep's ventricles, and believed that this was the main reason for the upright T wave. Higuchi and Nakaya[28] believe that the consistent polarity of T wave and QRS wave is due to the transmural dispersion. They recorded the endocardial and epicardial one-way action potentials of 7 dogs and found that the epicardial T wave was inverted at room temperature (consistent with the ECG of normal dogs). When the epicardial

temperature was gradually heated up, the negative polarity of T wave gradually disappeared. Be careful that the T wave of equipotential line appears when the duration of endocardial action potential is 20–40 ms longer than that of epicardial action potential, and the positive T wave appears when the duration difference of action potential increases to 40~60ms. However, Janse et al.[13] believe that it is not the transmural dispersion that affects the polarity of T wave. Whether the polarity of QRS wave and T wave is consistent depends on the depolarization and repolarization time of epicardium (or endocardium). For normal human, the time of repolarization is short in the area except for very late, and long in the area except for very early. In dogs, on the contrary, the order of repolarization and depolarization is roughly the same the repolarization time in the area with late depolarization is longer. This is why the polarity of QRS wave and T wave is the same in human ECG, but opposite in dog ECG. At the same time, Janse et al. Also compared the linear relationship between repolarization time and activation time in the transmural direction and the apical basal direction, and found that T wave polarity was independent of transmural dispersion (**Figure 6**). Similarly, Cowan et al.[29] and Opthof et al.[30] showed that the repolarization time of the heart with the same polarity of QRS wave and T wave is inversely proportional to the activation time, while the activation time of the heart with the opposite polarity is directly proportional to the repolarization time (**Figure 7**). However, with the development of high-density electrophysiological technology, it is found that not all myocardial depolarization and repolarization follow the above linear relationship in the intact heart. Maffesanti et al.[31] conducted electrophysiological mapping in the left and right ventricles and coronary sinuses of 30 patients with heart failure and left bundle branch block. The results showed that the T wave inversion in patients with heart failure and left bundle branch block was caused by the dispersion of left and right ventricular repolarization, and the polarity of T wave was not only related to the linear relationship between repolarization time and activation time, but may be the result of multiple factors. Therefore, the relationship between depolarization and repolarization sequence and T wave polarity in real heart may be more complex and diverse (**Figure 8**).

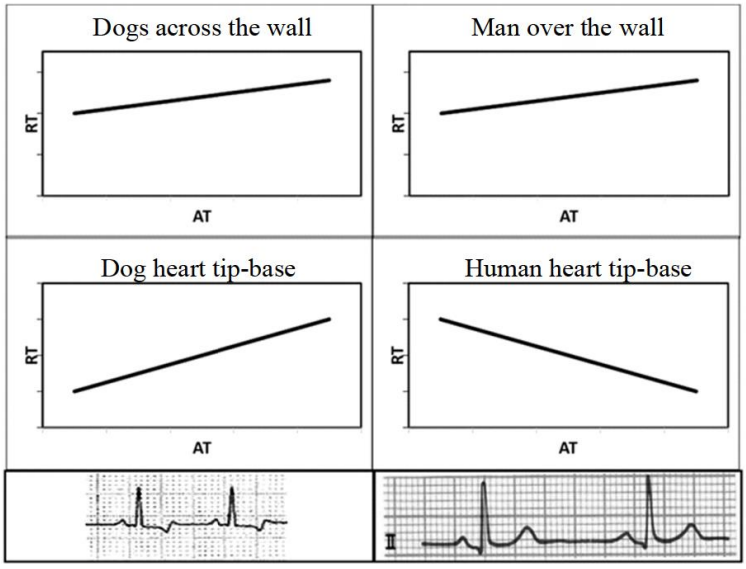

Figure 6. Shows the relationship between repolarization time and activation time in the apical basal direction and ventricular transmural direction in dog and human hearts respectively.
Reasons for the opposite and consistent polarity of QRS and T waves in dogs and humans[13].

In short, after decades of research and development, electrophysiologists have a deeper understanding of the mechanism of T wave formation and the mechanism of cardiac repolarization dispersion. Debate on transmural repolarization dispersion and cardiac global repolarization dispersion with the continuous progress of research, more and more evidence supports the contribution of cardiac global repolarization dispersion to T

wave formation, but this does not mean that it denies the value of isolated wedge model and ventricular transmural repolarization. For electrophysiologists, there are still many unknowns and controversies about the mechanism of T wave formation and cardiac repolarization. For example, whether M cells exist and which lead can better reflect the dispersion of repolarization still need to be further studied and discussed.

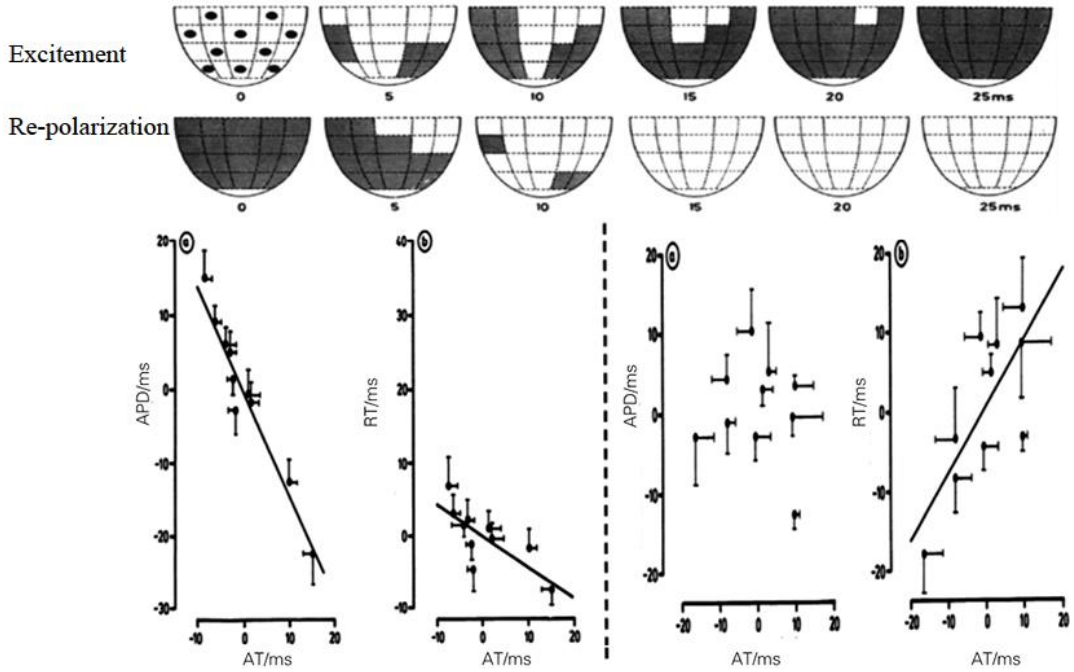

Figure 7. Relationship between at, RT and APD in patients with consistent or inconsistent polarity of T wave and QRS wave. Upper row: depolarization and repolarization time of 10 Parts. Lower row: left side of dotted line: Patients with normal T wave shape but opposite polarity to QRS wave; right side of the dotted line: Patients with normal T wave shape and the same polarity as QRS wave[29,30].

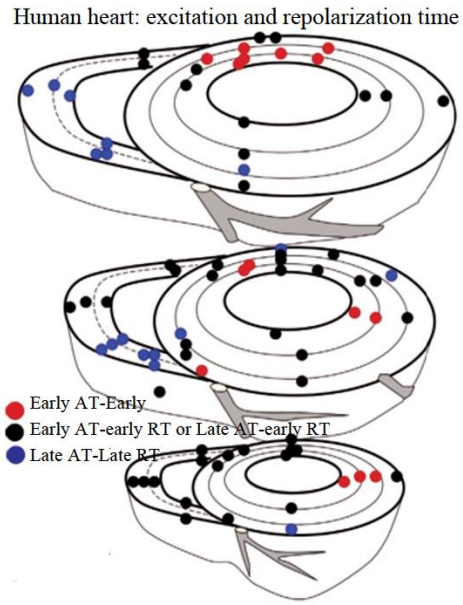

Figure 8. Sequence of depolarization and repolarization in different parts of normal human intact heart. The heart was perfused by Langendorff in vitro with a pacing interval of 700 ms. Black represents the sites whose depolarization time is earlier than the median time of depolarization and whose repolarization time is later than the median time of repolarization, or the sites whose depolarization time is later but whose repolarization time is earlier. Red represents sites with early depolarization and early repolarization. Blue represents sites with late depolarization time and late repolarization time[30].

Conflict of interest

The authors declare no conflict of interest.

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