Ectopic Sinoatrial Node Pacemaker Cells: A Postprint Study

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Abstract

Arrhythmia is a common myocardial electrical phenomenon in clinical practice; any individual experiences or has experienced different types of arrhythmias during various time periods. Despite rapid developments in modern medicine and an increasingly comprehensive understanding of myocardial electrophysiology, the mechanisms underlying certain arrhythmias still lack satisfactory explanations to date. The constituent cells of any organ are not completely and absolutely differentiated; the expression of their biological effects is established on the basis of combining internal and external factors, with the former representing the essence and the latter constituting the condition. The existence or induction of specific or similar cardiac pacemaker cells within working cells may provide a more reasonable explanation for arrhythmias with enhanced automaticity under specific conditions, which this paper will explore.

Full Text

Investigation into Ectopic Automatic Cells of the Sinoatrial Node

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Abstract

Arrhythmias are common clinical manifestations of myocardial electrical activity, with every individual experiencing or encountering various types of arrhythmias at different times. Although modern medicine has developed rapidly and our understanding of myocardial electrophysiology has become increasingly comprehensive, the mechanisms underlying some arrhythmias remain without satisfactory explanation. The component cells of any organ are not completely or

absolutely differentiated, and the expression of their biological effects is based on the combination of internal and external factors, where the former represents essence and the latter represents condition. The existence or induction of specific or similar cardiac automatic cells within working cells may provide a more reasonable explanation for arrhythmias with increased automaticity under specific conditions, which this article will explore.

Keywords: sinoatrial node; automaticity; ectopic cell; arrhythmia

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Active ectopic rhythm refers to a cardiac rhythm dominated by an ectopic automatic focus with a frequency exceeding that of the sinoatrial node. Twenty-four-hour Holter monitoring reveals that approximately 60% of healthy adults experience atrial premature contractions, with ventricular premature contractions being even more common than atrial ones, particularly in patients with organic heart disease [1]. The underlying causes of increased automatic focus frequency remain incompletely understood. While external induction constitutes an important condition, the intrinsic presence of sinoatrial node-like automatic cells may represent the key to active ectopic arrhythmias. Previous animal studies have identified cells resembling sinoatrial node cells in the pulmonary vein myocardial sleeves of pigs [2] and pacemaker-like cells in the left and right atrial tissues of rats and mice [3]. The existence of these inherently ectopic or induced pacemaker-like cells, which can become the dominant cardiac rhythm under specific conditions, provides a more straightforward explanation for active ectopic arrhythmias and offers a theoretical basis for radiofrequency ablation therapy for such arrhythmias under particular circumstances.

1. Possibility of Ectopic Existence of Sinoatrial Node Automatic Cells

It is generally accepted that abnormal myocardial electrical conduction and increased myocardial automaticity constitute the most common causes of arrhythmias. The former encompasses specific cardiac anatomical structures, abnormal pathways, and myocardial injury, while the latter includes ischemia, hypoxia, neuroendocrine imbalance, and electrolyte disturbances. Although the former is readily comprehensible, the latter exhibits considerable randomness and uncertainty. Without inherent differences among myocardial cells, injury mechanisms would unlikely produce increased automaticity in specific cells. Even though injured myocardial cells exhibit reduced excitation thresholds, appropriate stimulus intensity remains necessary for depolarization. Late sodium currents and calcium homeostasis imbalance are considered primary mechanisms of arrhythmias caused by injury [4]; however, their fundamental effect is to reduce the excitation threshold of injured myocardial cells, making them more susceptible to excitation. The unstable presence of injury currents increases the risk of myocardial electrical disorder but does not possess the current characteristics of sinoatrial node automatic cells. Genetic and acquired ventricular arrhythmias

in structurally normal adult hearts are primarily associated with ion channels [5]. Triggered activity, essentially a phase 3 arrhythmia representing supernormal period excitation with increased excitability, does not constitute true increased automaticity [6]. Reentry is considered the most common mechanism of premature contractions, yet such arrhythmias may not occur frequently from myocardial electricity itself and also do not represent increased automaticity [7]. Although conduction system cells possess automaticity, they have strict protective mechanisms, and how their excitation thresholds and pacemaker currents could change in the short term to become the dominant cardiac rhythm remains merely speculative based on superficial observations.

Clinically, arrhythmias with increased automaticity are too common to attribute their etiology simplistically without medical rigor. However, if ectopic sinoatrial node automatic cells or functionally similar cells inherently exist within myocardial cells, their expression of biological effects under specific conditions becomes readily understandable.

Sinoatrial node automatic cells or sinoatrial node-like cells that are ectopic or misplaced outside the sinoatrial node have their inherent biological effects restricted when removed from specific environmental conditions. The ectopic location, functional integrity, and changes in the internal environment of these cells determine the expression of their biological effects. Consequently, ectopic sinoatrial node automatic cells generally cannot express their corresponding physiological functions. Furthermore, the realization of biological effects requires integrated cellular coordination. The limited number of sinoatrial node cells wandering outside the sinoatrial node makes it difficult for them to achieve sustained expression of their biological effects, even if they occasionally generate intrinsic rhythmic excitation under specific conditions. They become submerged and even assimilated among the vast number of working myocardial cells. However, under particular conditions such as myocardial ischemia, hypoxia, or delayed signal stimulation, the excitation threshold of ectopic sinoatrial node automatic cells decreases while their excitability increases, providing the possibility for these cells to become occasional or periodic excitation sources. This represents specific cells realizing their specific biological effects in specific environments [8]. A small number of ectopic or induced automatic cells are not completely suppressed by working myocardial cells under normal conditions, making it possible for ectopic pacemakers to become active rhythms.

2. Formation Mechanisms of Ectopic Sinoatrial Node Automatic Cells

Currently, no academic discussion has addressed the relationship between ectopic sinoatrial node automatic cells and arrhythmias, nor has the concept of ectopic sinoatrial node automatic cells been established. However, evidence of Cx45-positive staining in extracardiac myocardium suggests potential pacemaker characteristics [9]. Regarding the formation mechanisms of ectopic sinoatrial node automatic cells, we propose that, in addition to transitional hetero-

geneous cells, ectopic sinoatrial node automatic cells may be categorized as primary or secondary. The former refers to the presence of small quantities of misplaced or wandering, mature or immature, sinoatrial node or sinoatrial node-like functional automatic cells mixed in during myocardial differentiation, with a pathogenesis similar to endometriosis. The latter involves the induction and transformation of original working cells into automatic cells under specific environmental conditions, with a mechanism analogous to atypical hyperplastic cells or metaplastic tumor cells. Animal experiments have demonstrated that canonical Wnt5b signaling can induce free Nkx2.5+ mesoderm to become pacemaker cells [10]; transcription factor TBX18 can reprogram vascular smooth muscle cells of the ascending aorta into pacemaker-like cells [11]; and blocking the classical Wnt pathway can promote the differentiation of brown adipose-derived stem cells into pacemaker-like cells [12]. These findings indicate that normal cells can be induced to become pacemaker cells under specific conditions. Due to environmental constraints, ectopic sinoatrial node automatic cells rarely realize their biological effects under normal conditions. However, conditions such as increased myocardial heterogeneity, impaired normal myocardial excitation, and altered internal environment provide opportunities for these cells to express their biological effects. Idiopathic arrhythmias originate from several anatomical sites in both ventricles and tend to favor outflow tract structures [13], suggesting that increased cardiac heterogeneity facilitates arrhythmia occurrence.

The emergence of any phenomenon necessarily involves causality, representing the combined result of internal and external factors. Currently, discussions of arrhythmias with increased automaticity emphasize only external influences, without addressing the potential internal factors of the corresponding cells. Despite current medical development levels preventing anatomical and morphological support for some electrophysiological phenomena, the microscopic world forever holds secrets unknown to humanity, and some seemingly reasonable explanations may merely be superficial rather than fundamental [14]. Understanding the corresponding biological effects of arrhythmias with increased automaticity requires reasonable speculation based on established electrophysiological knowledge, with experimental therapy serving as an important means and method to ascertain truth. Medicine has no absolutes or certainties; unknown mechanisms and lack of rigorous logical thinking require gradual exploration and improvement. The essence of triggered activity is phase 3 arrhythmia [15]; the nature of the “R on T” phenomenon is actually “T to R” [16]. Multi-directional thinking enables us to approach the truth more comprehensively. Ectopic sinoatrial node automatic cells not only reasonably explain arrhythmias with increased automaticity from an internal factor perspective but also provide a theoretical basis for treating such arrhythmias.

3. Ectopic Sinoatrial Node Automatic Cells and Clinical Practice

Ectopic sinoatrial node automatic cells provide a robust explanation for the mechanisms of arrhythmias with increased automaticity, offering a valuable supplement and a novel understanding of arrhythmia pathogenesis. In other words, cells with increased automaticity are likely ectopic sinoatrial node automatic cells or sinoatrial node-like cells. When the dominant function of sinoatrial node automatic cells weakens or under specific conditions, opportunities arise for these ectopic cells to realize their physiological functions. Whether ectopic sinoatrial node cells can exert their biological effects depends critically on an appropriate internal environment and the influence of native sinoatrial node cells. Although ectopic sinoatrial node automatic cells possess advantages in self and neighboring cell excitation, their limited quantity, altered internal environment, and lack of coordinated action present obvious drawbacks.

Clinically, arrhythmias with increased automaticity are not uncommon, particularly non-reentrant arrhythmias in patients without organic heart disease [17]. Due to variations in the number, location, and internal environment of ectopic sinoatrial node automatic cells under different conditions, various forms of arrhythmias with increased automaticity become possible, including monomorphic and polymorphic, occasional and frequent, sustained or chaotic patterns [18]. In patients without structural heart disease, increased automaticity often presents without clear clinical symptoms, with premature ventricular contractions being the most common manifestation [19]. Idiopathic premature ventricular contractions frequently occur in young patients, typically manifesting as premature ventricular contractions without structural heart disease. These arrhythmias generally originate from specific anatomical structures, predominantly the endocardium and less commonly the epicardium, and exhibit characteristic electrocardiographic patterns based on their anatomical background [20]. For these patients, ectopic sinoatrial node automatic cells provide an excellent explanation for the arrhythmia mechanism. Ventricular parasystole involves ectopic automatic pacemaker foci with inherent frequencies, and the presence of such automatic cells provides an excitation source for sustained, repetitive extra ventricular excitation, making these ectopic automatic cells therapeutic targets [21]. Frequent premature ventricular contractions are not rare in patients without organic heart disease. These patients generally lack obvious clinical symptoms, occasionally experiencing palpitations or anxiety. Except for a minority with specific causes, most cannot be explained by existing mechanisms [21]. Ectopic sinoatrial node automatic cells not only provide a satisfactory explanation but also offer a reasonable theoretical basis for treating such arrhythmias. Occasional premature ventricular contractions are observed in most populations. Although their increased excitability has some randomness, specific cellular excitation does not exclude the presence of potentially automaticity-increased myocardial cells [23].

Ectopic sinoatrial node automatic cells are generally constrained by the inter-

nal environment and interactions with neighboring cells, which inhibit their physiological functional effects and typically prevent arrhythmias. However, in patients with increased cardiac heterogeneity and organic heart disease, structural cardiac changes ultimately affect myocardial electrophysiology, and compromised cardiac function deteriorates intrinsic circulatory metabolism [24]. Myocardial ischemia, hypoxia, and electrolyte disturbances further increase cardiac heterogeneity, elevate the excitation threshold of ectopic automatic cells, weaken intercellular coordination, and increase the risk of desynchronized depolarization-repolarization. These factors enhance the probability that originally ectopic sinoatrial node automatic cells will realize their physiological functions, and myocardial electrical disorder provides the possibility for various arrhythmias to occur [25]. Malignant arrhythmias are common in organic heart disease, where increased myocardial cell automaticity and phase 3 arrhythmias provide the basis for sustained electrical disorder.

Arrhythmias disrupt cardiac rhythm, compromising myocardial blood supply and stability of cardiac function, with frequent premature ventricular contractions potentially causing myocardial disease [26]. Currently, the application of radiofrequency ablation therapy for arrhythmias continues to expand and is widely recommended clinically [27]. Radiofrequency ablation represents an injurious treatment for myocardial cells. If pathogenic mechanisms consider only external factors such as ischemia and hypoxia, such injurious treatment would itself aggravate disease progression and lack reasonable theoretical basis for treating arrhythmias with increased automaticity. However, in reality, it is difficult to explain automatic arrhythmias in young patients using ischemia or other stress mechanisms, yet radiofrequency ablation demonstrates remarkable efficacy [28], suggesting the possible existence of ectopic sinoatrial node automatic cells or sinoatrial node-like cells. Isolation or destruction of such cells can achieve curative outcomes. Therefore, the presence of a certain number of sinoatrial node or sinoatrial node-like functional automatic cells in myocardial tissue readily explains how ectopic origin cells with increased excitability cause arrhythmias. Studies have found that even false tendons may contain cells with increased automaticity [29], thus providing a rational therapeutic basis for radiofrequency ablation.

4. Summary

The occurrence of any phenomenon results from the combined action of internal and external factors, and arrhythmias are no exception. The internal factor is the existence of myocardial heterogeneity differences, while external factors such as neuroendocrine imbalance and internal environment disorder further amplify these differential biological effects [30]. Ectopic sinoatrial node automatic cells undoubtedly increase myocardial heterogeneity, providing the possibility for arrhythmias with increased automaticity to occur. Although myocardial compensatory reserve function is sufficiently robust and the probability of arrhythmia occurrence in the microenvironment is small, a sufficient microen-

vironmental base under specific conditions enables arrhythmias to manifest [31]. Currently, the reentry concept is widely accepted, and radiofrequency ablation demonstrates remarkable efficacy. However, accessory pathway cells cannot be distinguished based on tissue anatomy and morphology—that is, such cells may be indistinguishable from normal working myocardial cells morphologically but differ physiologically [32]. Therefore, even when the existence of corresponding cells cannot be observed, reasonable predictions have important practical significance for advancing related fields. Although ectopic sinoatrial node automatic cells represent only a hypothesis proposed by the author, it better explains the intrinsic mechanisms of arrhythmias with increased automaticity and warrants further clinical investigation.

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