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Primun moving and Ultimun dying

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Opinion Article

William Harvey was born in Folkestone, Kent, England, on April 1, 1578, and died on June 3, 1657. He was a British physician who was credited with accurately describing, for the first time, the circulation and properties of blood being distributed throughout the body through the pumping of the heart. This discovery confirmed the ideas of René Descartes, who in his book "Description of the Human Body" had stated that arteries and veins were tubes that carried nutrients around the body. After receiving his medical degree in 1602, Harvey worked at the London hospital of St. Bartholomew and became a member of the Royal College of Physicians in 1604. He presented his circulatory description in the second Lumleian lecture (anatomy course) on April 17, 1616. In this lecture, he publicly presented his revolutionary ideas about the movement of the heart and the circulation of blood in animals. However, his magnificent monograph "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" was not published until 1628. It has been rightfully claimed that his great discovery was the first adequate explanation of an organic process and the starting point of the path that led to the field of experimental physiology. The monograph consisted of 72 pages and included three parts: the dedication, the prologue, and the exposition of the doctrine. It dedicated to the King of England, was Charles I Stuart, to Dr. Argent, the president of the Royal College of Physicians, and to his other colleagues. The prologue is based on his personal experimentation. The exposition of the doctrine covered 17 chapters. In the second of these, the author stated that the heart empties when it contracts, constituting the systole corresponding to cardiac activity, while expansion or diastole corresponded to the filling phase. In the third chapter, he wrote that arterial diastole coincided with cardiac systole and result from the displacement of the liquid vein sent by the heart. In the following chapter, he note that the activity of the atria precedes that of the ventricles and persisted after the latter's cessation. Therefore, the atrium is the "primum movens et ultimum moriens."The "primum movens" (in Greek: "ὃ οὐ κινούμενος κινεῖ," “What moves without being moved ") or the first unmoved mover is a metaphysical concept described by Aristotle as the first cause of all movement in the universe, and therefore, it is not moved by anything. Aristotle speaks of an immaterial being in the eighth book of Physics, which is the physical principle of the world, and in the Metaphysics, he referred to it as God. While our ancient teachers were on the right path, they did not imagine the profound scientific truth that we know today, or at least believe we know.

What do we know today about that first heartbeat?

Scientists generally believe that the first heartbeat occurs when a tubular structure forms in the embryo, which will eventually become the heart. However, it is still unclear how the first heartbeat begins and how it affects the heart's subsequent development. Tyser, Miranda, et al [1]. Demonstrated that the first heartbeat occurs much earlier than previously believed. In experiments, videos of live mouse embryos showed that before the first heartbeat, the flow of Calcium ions already exists among different cardiomyocytes, but it is not synchronized. However, as the heart grows, these calcium flows coordinate, and the first heartbeat occurs, followed by subsequent beats at an initial rate of 35 beats per minute. The beats become faster as the heart grows. Through the use of drugs that block calcium ions, Tyser and others demonstrated that a protein called NCX1 [2]. (Which is an essential membrane protein involved in calcium homeostasis) is responsible for regulating calcium flows before the first heartbeat.

Furthermore, the experiments revealed that these initial heartbeats help drive the growth of cardiomyocytes and shape the developing heart. Overall, the experiments demonstrate that the initial heartbeats are essential for the normal development of the heart. In the future, researchers will need to study what controls the speed of the initial heartbeats and how calcium flows are organized to trigger the first heartbeat. These studies may help scientists better understand congenital heart defects and suggest strategies for reconstructing hearts damaged by heart disease. Once about 100 cells make up the sinoatrial node, given its electrophysiological characteristics, they will command the heart rate throughout an individual's life until a final beat occurs (ultimum moriens), unless unexpected events disrupt the expected progression.

But what makes the sinoatrial node function as the cardiac pacemaker after the primun movens?

Today, we have an-idea of when electrical activity begins to be expressed, but the question of when and why the next beat will occur is a matter for curious minds, which has been addressed both before and after the discovery of the sinoatrial node (SA node) 116 years ago [3]. The debate about the origin of heartbeats in the mid-19th century revolved around two hypotheses: the neurogenic theory, which posited that nerves were responsible for the rhythmic contraction, and the myogenic theory, which argued that a portion of cardiac muscle could beat spontaneously and rhythmically [4]. Both hypotheses were based on studies of bioelectricity and established a causal link between electrical activity and muscle contraction (excitation-contraction coupling) thanks to the invention of the galvanometer. At the end of the century, the "membrane theory of bioelectric potentials" was proposed to explain how cells manipulate their transmembrane voltage (Vm), which was quantitatively demonstrated in 1912 using the Nernst equation [5]. This led Silvio Weidmann to join the effort to solve the enigma of how changes in membrane potential were related to contraction. In 1969, Wood, Heppner, and Weidmann proposed possible mechanisms for the formation of "memory" in cardiac myocytes through experiments involving the manipulation of extracellular calcium ions [6]. They considered the possibility that the storage and release of calcium ions from the sarcoplasmic reticulum (SR) mediated the amplitude of contraction in a given beat, based on patterns of preceding beats [7]. They observed that the process of calcium release from the SR explained how the incoming L-type calcium current triggered the release of sufficient calcium to activate the myofilaments. The discovery of ryanodine receptors (RyR), calcium channels of the SR, and their antagonist, ryanodine, improved the study of intracellular calcium flow in cardiac myocyte contraction [8]. Finally, it was discovered that the SR of ventricular myocytes could generate spontaneous and approximately rhythmic diastolic calcium oscillations [9]. This led to the idea that spontaneous diastolic calcium oscillations might be involved in the normal automaticity of the SA node [10]. Once the first heartbeat occurs, the question is when and why the next ones will follow. In recent experiments, it was demonstrated that isolated SA node cells exhibit local rhythmic releases of calcium ions from the SR (which occur independently of changes in membrane potential). These releases are involved in initiating the action potential by activating the sodium-calcium exchanger (NCX), leading to membrane depolarization, which, in turn, activates a set of ion channels in the cell membrane. Viewed in this way, these rhythmic calcium releases form a calcium clock that is intertwined with a membrane clock composed of surface membrane electrogenic molecules. Together, they form a "coupled clock" that generates spontaneous action potential cycles in SA node cells. The automaticity of these cells is modulated by autonomic receptors influencing both clock molecules. For the proper functioning of these clocks, the functionality of the hyperpolarization-activated inward current (If), identified as the primary ionic current of SA node cells, is critical. Its rectification inward prevents repolarization during the membrane potential toward the theoretical electrochemical equilibrium of potassium channels [11]. Thus, through countless molecular interactions, the sinoatrial node sets the pace of heartbeats for the duration of an individual's life, unless natural aging or pathological processes lead to a final stimulus.

But is the sinoatrial node responsible for producing the final cardiac beat?

In 1907, Walter Karl Koch (1880–1962), a German physician who worked in the laboratory of Aschoff, along with Tawara, introduced the eponyms associated with this distinguished group of researchers: the Koch's triangle [12]. Tawara's node [13]. And Aschoff's nodule [14-15]. However, in his work titled "Über das Ultimum moriens des menschlichen Herzens. Ein Beitrag zur Frage des Sinusgebietes" ("On the Ultimum moriens of the Human Heart: A Contribution to the Question of the Sinus Area"), Koch hypothesized that the last part of the heart to lose its rhythmic activity when dying was "its pacemaker." He conducted experiments with deceased human and animal fetuses and located the last part of the heart that ceased to beat as the ostium and the wall of the coronary sinus, concluding that this location should be considered the true pacemaker of the heart. Following the final correction of Koch's work, Erlanger and Blackman published their article titled "A Study of Relative Rhythmicity and Conductivities in Various Regions of the Auricles of the Mammalian Heart" [16]. These experiments were conducted on the perfused rabbit heart, and their conclusions contradicted

Koch's findings. They argued that the region of the right atrium near the junction of the major veins ("sinus junctions") had the greatest ability to maintain activity, and they believed that in many cases, this was where the control of the heart's rhythm was established. After learning of this work, Koch made corrections to his initial work and wrote: "I have learned of the recent publication by J. Erlanger and J.R. Blackman, regarding a study of relative conductivity in various regions of the auricles of the mammalian heart... The difference and conflict between my observations on the dying heart and those on an artificially exsanguinated heart can only find their solution in additional observations, in observations in which the spatial boundaries between the cava funnel and the coronary sinus funnel must be more carefully considered than has been done so far." Perhaps without human intervention, the last part to contract is the right atrium, but starting in the 1950s with the advent of the first implantable pacemakers and their ongoing evolution, the question arises:

Does a natural ultimum moriens exist, or is it an artificial ultimum moriens?

The use of implantable cardioverter-defibrillators postpones and provides a new opportunity for the final beat to occur. The controlled use of electricity is the responsibility of humans who have modified the natural history of cardiac activity. As far back as 2650 BC, there are references to the Egyptians' knowledge of the power of certain fish, which caused painful effects on those who touched them. This phenomenon was so well known that the fish was attributed the ability to be a healer. For this reason, when depicting a man who saved many lives, the Egyptians represented him in hieroglyphics as a torpedo fish (Torpedo is a genus of electric rays in the family Torpedinidae, popularly known as torpedo rays. There are 22 species of torpedo rays, and they can be found in all temperate and tropical seas around the world. Two of them live in the Mediterranean and can generate shocks of up to 220 volts and 1 ampere. The torpedo fish uses these organs for hunting and self- defense). There is a representation that could signify the treatment that an Egyptian performs on another using a Nile catfish (electric catfish, Malapterurus electricus, belongs to the class Actinopterygii, order Siluriformes, which includes catfish, the electricity comes from thousands of disc-shaped electric cells called electrocytes, closely packed and connected in a chain to generate impulses with a voltage that can reach 350-450 volts, depending on the fish's size) by utilizing the electric shocks they provide. While the ancients attributed these observations to the powers of the gods, the first observation of electricity is attributed to the Greek philosopher Thales of Miletus in 600 BC, who observed that dry pieces of amber could attract small bits of dry grass after being rubbed on his robe. By 1600, William Gilbert, the president of the Royal College of Physicians, was familiar with these magnetism experiments and studied the effects of what he called "electricity," derived from the Greek word "elektron" for amber. Human curiosity and experimentation led Alessandro Giuseppe Antonio Anastasio Volta, an Italian chemist and physicist, to develop the first battery in 1799. In a communication to the Royal Society, Volta presented the new device he had invented, which he called an "artificial electric organ" because it imitated the natural electric organ of the torpedo or electric eel. It was constructed by interleaving layers of two metals (zinc and copper discs) placed alternately, stacked, separated by cardboard soaked in salty water, capable of continuously producing an electric current. This fundamental step in energy storage eventually led to the creation of the first implantable pacemaker in the 1950s [17-18]. From this radical new form of treatment, technological advancements now offer us the ability to choose different types of cardiac pacing to mimic the so-called "physiological pacing" when possible. Not only have devices been created to maintain cardiac stimulation, but also for the treatment of severe arrhythmias [19]. And to assist in the treatment of heart failure [20]. With all that science has provided us to date, we cannot be certain where the "ultimum moriens" occurs.

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