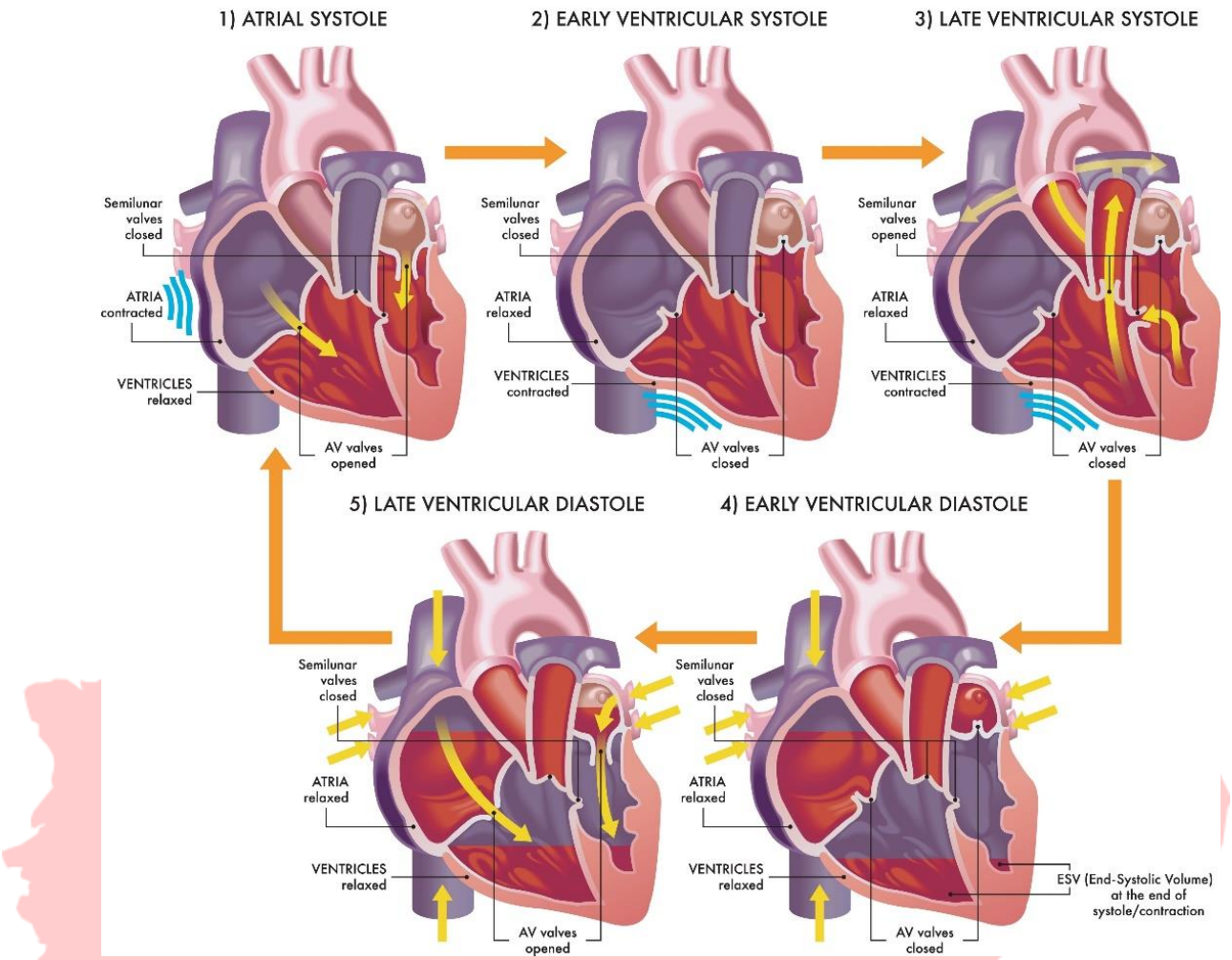
PHYSIOLOGICAL FOUNDATIONS OF THE EFFECTS OF POLYPHENOLS ON THE CARDIOVASCULAR SYSTEM

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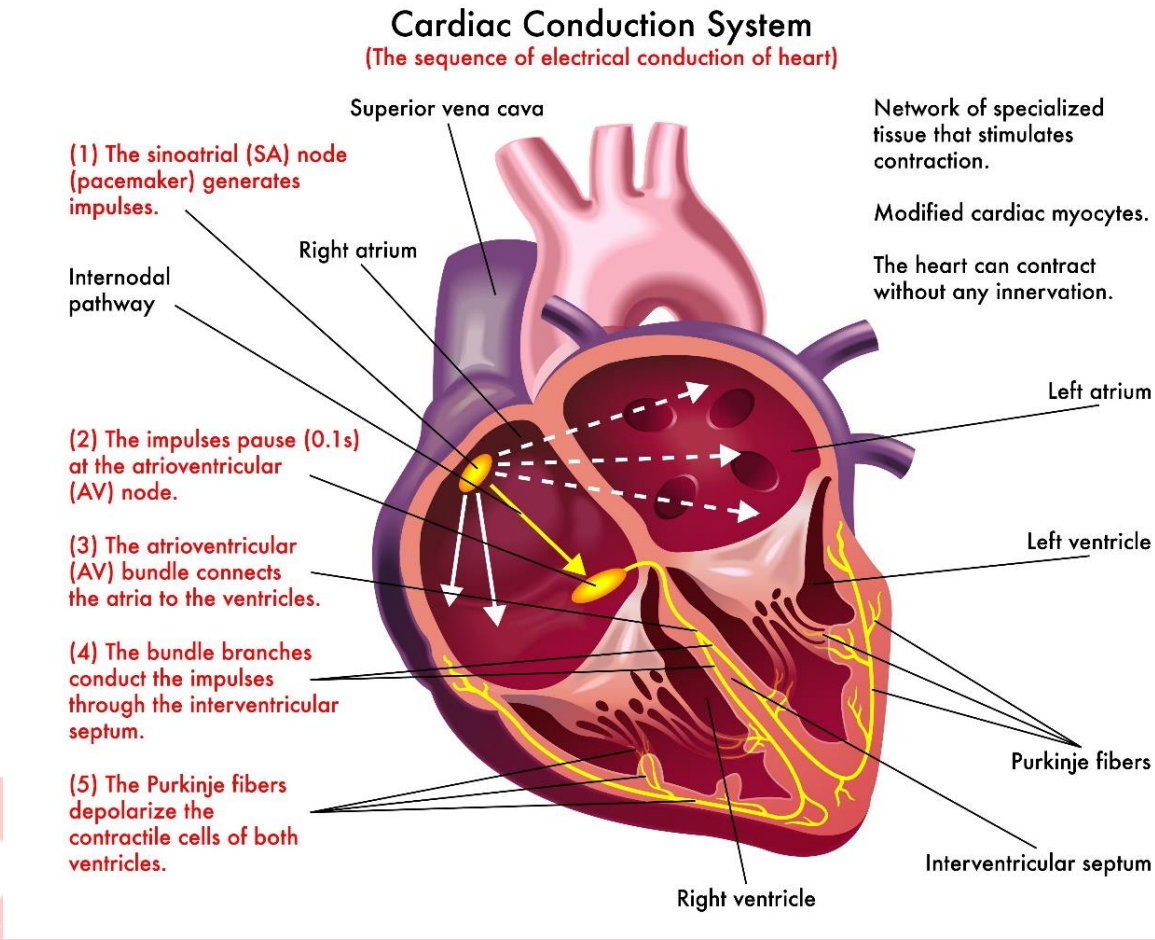
Abstract. *Cardiovascular diseases (CVDs) remain the leading cause of global mortality, necessitating the exploration of bioactive dietary compounds for prevention and therapy. Polyphenols, a diverse class of phytochemicals, exhibit profound cardioprotective effects through multi-target physiological pathways. This thesis investigates the fundamental mechanisms by which polyphenols maintain vascular integrity, regulate blood pressure, and protect myocardial tissue from oxidative and inflammatory stress.*

Keywords: *Endothelial Function, Nitric Oxide, Oxidative Stress, Cardiomyocytes, Polyphenols, Vasodilation.*

The heart's primary function is to rhythmically pump blood received from the veins into the arteries. This function is achieved through the rhythmic contraction and relaxation of the muscle fibers that constitute the walls of the cardiac atria and ventricles. The contraction of the myocardium in these heart chambers is termed systole, while their relaxation is referred to as diastole. Under normal physiological conditions, the systole and diastole of the atria and ventricles are precisely coordinated, forming the cardiac cycle. The atrial systole is considered the onset of each cycle[1]. The contraction originates in the right atrium at the site where the venae cavae enter. Subsequently, the wave of contraction propagates across both atria, which share a common muscular structure. At a heart rate of 75 beats per minute, atrial systole lasts for 0.1 seconds. Following the completion of atrial systole, ventricular systole begins, during which the atria are in a state of diastole lasting 0.7 seconds. Both ventricles contract simultaneously, with their systole lasting approximately 0.3 seconds. Subsequently, ventricular diastole begins, which lasts for 0.5 seconds. Toward the end of ventricular diastole, 0.1 seconds before its completion, a new atrial systole occurs, and the cardiac cycle begins anew.

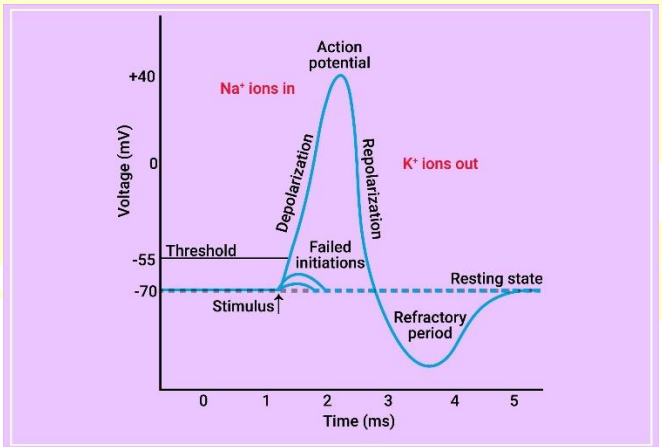


The atrioventricular (AV) node is located in the right atrium, within the region of the interatrial septum, near the fibrous ring that separates the right atrium from the ventricle. The bundle of His, which acts as a muscular bridge conducting excitation from the atria to the ventricles, originates from the AV node. The initial segment of this bundle (also referred to as the common bundle of His) enters the ventricle along the interventricular septum and divides into two branches (the right and left bundle branches), one of which extends to the right ventricle and the other to the left ventricle[2]. The terminal branches of the conduction system consist of a network of Purkine fibers; this network is situated beneath the endocardium and is widely distributed, forming anastomoses with the muscle fibers of the myocardium. The excitation propagates through the branches of the conduction system to the entire heart muscle, triggering its contraction. Thus, the impulse that initiates cardiac contraction originates in the sinoatrial node, spreads through the contractile myocardium of both the right and left atria, and reaches the atrioventricular node. From this node, the impulse travels along the bundle of His to the right and left ventricles, thereby inducing their systole[3].



One of the characteristic properties of the heart is its autorhythmicity (or automaticity). Automaticity is defined as the ability of an organ, tissue, or cell to undergo excitation induced by impulses generated within itself, independent of external stimuli. The underlying cause of automaticity is the intrinsic metabolic changes occurring within the organ or cell. Cardiac automaticity is most easily observed in an isolated frog heart- one that has been excised from the organism. Under appropriate conditions, the heart of a warm-blooded animal can also continue to function rhythmically for several hours in such an isolated state[4].

Mechanism of Cardiac Automaticity and Action Potential Generation in Pacemaker Cells



By employing the technique of perfusion (passing a solution through the blood vessels of an organ), it is possible to revive a stopped heart even several hours after the death of an animal or human. In 1902, A. A. Kulyabko conducted the first successful experiment on reviving a human child's heart. Subsequently, successful experiments were performed in which the hearts of adults were excised from the body and reactivated two days after death. The revived heart continued to beat for more than 13 hours. The sinoatrial (SA) node, which serves as the primary pacemaker of the normal heart rhythm, possesses the highest degree of automaticity. However, the capacity for automaticity also exists in other parts of the heart. For instance, automaticity has been identified in fibers located within the atria adjacent to the SA node, which are structurally similar to its own fibers[5]. The automaticity of these fibers is lower than that of the SA node cells. They are referred to as latent pacemakers (or secondary pacemakers) because, under normal conditions, their automaticity is suppressed; they only assume the role of the primary pacemaker when the function of the sinoatrial node is impaired. The atrioventricular (AV) node also possesses the property of automaticity. Even when the AV node is isolated from the higher components of the conduction system by a ligature, the ventricles continue to contract. In such cases, the Purkinje fibers within the right or left ventricles serve as the pacemakers for the rhythm[6].

The sinoatrial node is referred to as the first-order pacemaker center, while the atrioventricular node is known as the second-order pacemaker center. Under normal conditions, the human heart contracts 70–75 times per minute due to impulses generated by the sinoatrial node. Under an atrioventricular rhythm, the heart rate decreases by approximately half, and when the heart functions under the influence of even lower-order pacemakers, the frequency of ventricular contraction becomes even lower. The duration of the action potential in cardiac muscle cells is significantly longer than that observed in skeletal muscle cells. At a heart rate of 70 beats per minute, the total duration of the action potential in cardiac muscle cells is approximately 0.3 seconds. The duration of the action potential is inversely related to the heart rate: it shortens as the heart rate increases and lengthens as the heart rate decreases. Consequently, the sooner the next wave of excitation begins following the termination of the previous one, the shorter the duration of the action potential; in other words, the faster the action potential progresses. During the period of excitation, the cardiac muscle loses its ability to respond with an additional contraction to either artificial stimuli or impulses arriving from the center of automaticity. This state of non-excitability is called absolute refractoriness. The duration of the absolute refractory period is slightly shorter than the duration of the action potential; at a heart rate of 70 beats per minute, it lasts approximately 0.27 seconds.

The refractory period of the cardiac muscle lasts roughly as long as the systole triggered by a single stimulus. Consequently, the cardiac muscle is unable to respond to rapid, repetitive stimuli with a sustained contraction known as tetanus (tetanic contraction).

In summary, the heart's function is defined by its ability to generate and conduct electrical impulses through a highly specialized system, ensuring rhythmic, coordinated contractions. Key to this process is the heart's automaticity, primarily driven by the sinoatrial node (the first-order pacemaker), with latent centers (AV node and Purkinje fibers) providing a hierarchical safety mechanism.

The cardiac cycle is governed by precise electrochemical coordination:

- Action Potentials**:** The duration of the action potential in cardiac muscle is frequency-dependent, allowing the heart to adapt rapidly to changing physiological demands.
- Refractoriness: A critical protective feature of the heart is its absolute refractory period, which mimics the duration of the systole. This ensures the cardiac muscle cannot undergo tetanus, thereby guaranteeing that the heart always undergoes the necessary diastole (relaxation) to fill with blood and prevent mechanical failure.

These mechanisms collectively ensure the heart functions as an efficient, reliable pump capable of sustaining life under varying physiological conditions.

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