Cardiac Cycle Regulation: Integrative Anatomical, Physiological, Cellular, and Molecular Insights

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Abstract

This review explores cardiac cycle regulation through anatomical, physiological, cellular, and molecular perspectives. It details the heart's structure and conduction system, emphasizing neural, hormonal, and intrinsic regulatory mechanisms that adapt cardiac output to metabolic demands. Key cellular processes include ion channel dynamics and calcium handling critical for pacemaker activity and excitation-contraction coupling. The integration of neurocardiac interactions, hormonal signals, and intrinsic myocardial responses ensures synchronized cardiac function. Dysregulation of these mechanisms contributes to cardiovascular diseases such as arrhythmias and heart failure, highlighting the complexity of cardiac cycle control.

Keywords

Cardiac cycle regulation, Excitation-contraction coupling, Autonomic nervous system

1. Introduction

A cardiac cycle demonstrates an integrated mechanism consisting of electrical, mechanical and regulatory mechanisms that contribute to hemodynamic homeostasis. Rather than being a straightforward cycle of systole and diastole, it is a complex set of multi-level control systems, involving nervous, hormonal and intrinsic myocardial systems, that adapt cardiac output to metabolic needs. Proper regulation of the cardiac cycle plays an important role in maintaining cardiovascular health, as it is necessary to regulate the heart rate and time of contraction in order to provide enough oxygen and nutrients to tissues while preventing mechanical overload of the arterial wall. Recent discoveries demonstrate that regulation of the cardiac cycle involves more complicated mechanisms of neurocardiac interactions, intracellular signalling and mechanoelectrical feedback. Their dysregulation contributes to cardiovascular diseases such as arrhythmias, heart failure and autonomic dysfunction (Hua et al., 2022; Njegic et al., 2020).

In this review, cardiac cycle regulation will be considered from the point of view of its anatomical, physiological, cellular and molecular basis. It will include the mechanisms of its regulation, namely neurogenic, hormonal and intrinsic ones. The objective of the current review is to look into the structure and function of the heart concerning the cardiac cycle and the phases of the cardiac cycle, together with the importance thereof. Additionally, the review looks into the regulations that control cardiac dynamics as well as the cellular and molecular bases of cardiac rhythm and contraction.

2. Anatomy and Physiology of the Heart Relevant to the Cardiac Cycle

There are four major chambers in the heart, which are designed to perform various physiological roles. Deoxygenated blood enters the right atrium of the heart from the body, and oxygenated blood enters the left atrium from the lungs. Ventricles are responsible for performing the pumping action required to move blood through two separate circulatory systems, the pulmonary and systemic circulations. The former is the movement of blood to the lungs for oxygenation, while the latter is the movement of oxygenated blood to all other organs and tissues of the body. The mechanism of heart work is associated with the role of the atrioventricular valves, namely the tricuspid and mitral valves. They perform the function of preventing blood flow to the atria when the ventricles contract forcefully. In addition to this, there are semilunar valves viz. the pulmonary valve and aortic valve which are responsible for blood flow to the pulmonary artery and aorta, respectively. Moreover, there is a special conduction system in the heart, which ensures the synchronization of its mechanical actions. The work starts from the sinoatrial (SA) node situated in the right atrium and works as the heart's pacemaker through the generation of regular impulses. They pass through the atrial myocardium causing atrial contraction, thus

leading to a more efficient transfer of blood to the ventricles. After the delay at the atrioventricular (AV) node, an impulse continues to be transferred to the Bundle of His, where it quickly spreads out to the Purkinje fibers, passing further through the ventricular myocardium and causing ventricular contraction. Thus, a particular timing of the electrical impulse causes a coordinated and synchronized work of all heart valves. Atrial systole leads to ventricular filling, ventricular systole causes an increase in pressure to close the atrioventricular valves and to open the semilunar valves, causing ejection of the blood. Finally, the process of diastole causes the reduction of ventricular pressure and resetting of the valves before the beginning of the next cardiac cycle.

3. Regulation of the Cardiac Cycle

3.1 Neural regulation

Regulation of the cardiac cycle by the nervous system is mostly carried out by the autonomic nervous system (ANS) that comprises sympathetic and parasympathetic branches. Both branches precisely regulate heart rate, contraction, and conductivity in order to maintain homeostasis of the cardiovascular system under physiological requirements. The key to this regulation is a neuro-cardio system, comprising various regulatory levels including the intrinsic cardiac nervous system (local control of the heart), intrathoracic extracardiac ganglia (sympathetic ganglia included), the spinal cord (processing sensory information from the heart and triggering sympathetic responses), the brainstem (integrating sensory inputs and controlling autonomic outputs), and high-level brain structures such as the cerebrum (overarching control) (Salavatian et al., 2024).

Sympathetic nervous system stimulates heart rate and contraction through releasing of norepinephrine acting on â-adrenoreceptors of the sinoatrial node cells and myocardium, causing the increase of spontaneous diastolic depolarisation and shortening of cardiac cycle phases, especially systole, which leads to an enhancement of the cardiac output during stress or exercise (Hafez & Chang, 2024; Iellamo, 2023). In turn, the parasympathetic nervous system, through vagus nerves, reduces the heart rate by releasing acetylcholine, which acts on muscarinic receptors slowing down the process of diastolic depolarisation in sinoatrial node cells and decreasing conduction velocity in the atrioventricular node. In the resting condition of the body, when this parasympathetic regulation prevails, it enables heart rate variability and improves the efficiency of the heart (Hafez & Chang, 2024; Rajendran et al., 2018).

3.2 Regulation by hormones

The hormonal control of the cardiac cycle requires the coordination of multiple endocrine hormones that have impacts on the heart function, anatomy and cardiovascular stability. These hormones regulate the heart rate, contractility, fluid balance, and vascular

tone, thus supporting the physiological phases of the cardiac cycle, i.e., systole and diastole. The heart serves as an endocrine organ by producing the natriuretic peptides. They are needed to maintain the regulation of the blood pressure and the fluid balance that play an important role for the proper heart filling and output in the cardiac cycle. Moreover, the hormones are important for myocardial remodelling and its structural integrity (Calcaterra et al., 2025). Hypothalamus-pituitary axis hormones like vasopressin (antidiuretic hormone) impact the blood volume and vascular resistance, thus affecting the preload and afterload in the heart and the duration of cardiac cycle phases (Goth et al., 2001). Sex hormones, for example, estrogen and progesterone, also have great importance. Generally, estrogen stimulates the vasodilation and proper fluid balance affecting the cardiac workload and coronary circulation, while progesterone influences the core body temperature and indirectly affects heart performance. Changes in hormone levels in women during menstrual cycles and different periods of life impact the cardiovascular physiology and regulation of the cardiac cycle phases (Roy et al., 2025; Wenner & Stachenfeld, 2016). Growth hormone and IGF-1 hormones are responsible for regulation of the growth and repair processes of cardiac muscles (Berkovskaya et al., 2024). Nowadays, there is a lot of information about some molecular mechanisms and pathways in the cardiac physiology like the Hippo signalling pathway that integrates hormones and other cell signals to regulate the apoptosis, proliferation and differentiation of cardiomyocytes (Ramaccini et al., 2022). In simple words, the cardiac cycle is controlled by complex interactions of hormones that help to tune the heart function. The signals affect the parameters of heart rate, contractility and fluid balance, etc., to ensure efficient work and adaptation of the heart to changing demands in different life periods (Calcaterra et al., 2025; Goth et al., 2001).

3.3 Intrinsic regulation

Intrinsic regulation of the cardiac cycle is the regulation of the heart's performance due to some internal factors, that do not depend on nerve and hormone systems. One of the most important parts of the intrinsic regulation is the Frank-Starling mechanism as it shows how the changes in preload, myocardial contractility, and afterload impact cardiac output and stroke volume. According to the Frank-Starling mechanism, there is a direct dependence between the length of myocardial fibre (preload) and the force of contraction. Due to the stretching of the ventricular myocardium because of the increased end-diastolic volume, the sarcomere length increases, which leads to better overlapping of actin and myosin filaments in the heart muscle cells. Because of the stretching, the force of contraction is increased during systole, which allows the heart to increase blood ejection. In this way, the mechanism provides the matching of cardiac output and venous return for the efficiency of circulation (Domenech & Parra, 2016; Lookin et al., 2023; Von Lewinski et al., 2009).

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4. Cellular and Molecular Mechanisms Underlying Cardiac Cycle Regulation

4.1 Ion channel dynamics in pacemaker and myocardial cells

The ion channel dynamics in pacemaker cells and myocardial cells provide the cellular and molecular mechanisms for the regulation of the cardiac cycle through generation and conduction of electrical impulses to induce contraction of the heart muscle tissue. In pacemaker cells, mostly SA nodal cells, action potentials are generated spontaneously owing to distinct dynamics of the ion channels. The cells possess specific ion channel dynamics to allow gradual depolarization in diastole termed the pacemaker potential to develop automaticity. Important channels responsible for these dynamics include the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels also referred to as "funny" channels as they are permeable to Na^+ and K^+ ions, and open during hyperpolarization to produce an inward depolarizing current initiating gradual depolarization. The T-type Ca^{2+} channels participate in the late stage of depolarization and opening of the L-type Ca^{2+} channels allows generation of the upstroke of the action potential to excite the heart (Bello et al., 2023; Despa & Vigmond, 2016).

On the other hand, myocardial cells have different types of ion channels for a prolonged phase of the action potential, ensuring continuous contraction. The rapid phase of depolarisation is conducted by fast voltage-dependent sodium channels, causing rapid inward flow of sodium ions. The plateau is maintained by L-type calcium channels, permitting calcium ions to enter the cell, which induces excitation-contraction (EC) coupling by releasing the stored calcium from the sarcoplasmic reticulum (SR) via ryanodine receptors. This is followed by repolarisation, which is mainly governed by diverse potassium channels including voltage-dependent and inward rectifying potassium channels, thereby returning the resting membrane potential and preparing for the next cycle (Eggett, 2015; N et al., 2024). These channels do not act independently because their functions are regulated by cellular metabolism and redox status and signalling molecules. In addition, reactive oxygen species (ROS) regulate the cardiac ion channels by changing the gating properties of ion channels and Ca^{2+} handling, which affects the action potential and contractility. Any disorder in ion channels can cause arrhythmias due to excitability or conduction abnormalities (Orfali et al., 2025). Coordination of the activity of these ion channels in pacemaker and myocardial cells provides coordinated generation of the cardiac action potential. Such coordination of ion channels in pacemaker and myocardial cells plays an important role in automaticity in pacemaker cells and EC coupling in myocardium, being the basic cellular and molecular mechanism of the cardiac cycle (Despa & Vigmond, 2016; Eggett, 2015; N et al., 2024).

4.2 Calcium handling and EC coupling

Calcium regulation is important for the EC coupling process which is an important cellular event involved in regulating the rhythmicity of the heart. In cardiomyocytes, cardiac muscle cells, there is contraction due to an electrical signal that causes a transient increase in intracellular Ca^{2+}, resulting in contraction and relaxation of the muscle due to the fall in the concentration of Ca^{2+} (Sutanto & Heijman, 2022). EC coupling in the heart occurs through the generation of an action potential that causes the opening of L-type calcium channels in the cell membrane allowing for the entry of a small amount of Ca^{2+} into the cytoplasm followed by further release of Ca^{2+} from the SR through RyR2 in a process known as calcium-induced calcium release (CICR) (Bers, 2000; Marks, 2000). An increase in cytoplasmic Ca^{2+} concentration binds to troponin C at the thin filaments in myofilaments, thus allowing cross-bridge cycling involving actin and myosin, resulting in contraction (Bers, 2000). An increase in intracellular concentration of Ca^{2+} during systole allows the generation of contractile force, while removal of Ca^{2+} during diastole occurs actively through transport into the SR using the SERCA2a pump as well as expelling Ca^{2+} out of the cytosol through the NCX (Kistamás et al., 2020; Sutanto & Heijman, 2022). Proper regulation of these processes allows synchronized and coordinated contraction of the cardiac muscle that is important in ensuring effective pumping function. Failure to regulate these calcium movements can lead to disruption of the electrical and mechanical coupling, resulting in cardiac arrhythmias and heart failure (Kistamás et al., 2020; Pfeiffer et al., 2014). This is evidenced by mutations in the RyR2 complexes and SERCA2a leading to decreased efficiency in calcium cycling and contractility (Keefe et al., 2022; Zarain Herzberg et al., 2011).

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