Biochemistry and physiology of cardiac muscle

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Abstract

The heart is composed of muscle cells (cardiomyocytes) that account for most of the heart mass and generate its pumping force. Other cell types (fibroblasts, vascular endothelial cells, vascular smooth muscle cells, immune cells) and the extracellular matrix also play key roles in cardiac function, in both health and disease. Excitation–contraction coupling links the electrical activation of cardiomyocytes to cellular contraction. Calcium is a key second messenger in this process; its entry into the cell triggers further calcium release from the sarcoplasmic reticulum, which then activates the contractile machinery. Subsequent reduction in calcium concentration brings about cardiac relaxation, which is necessary for the heart to refill. Calcium also regulates other critical processes in the heart, including transcription of genes and the matching of energy supply from the mitochondria with cellular demand. In health, the contractile function of the heart is regulated by several factors, including its loading conditions, autonomic influences and many locally produced autocrine/paracrine agents. These factors alter contractile strength through two main mechanisms: modulation of the calcium transient within cardiomyocytes, and/or changes in myofilament sensitivity to calcium.

Keywords Calcium; cardiomyocyte; contractile function; excitation–contraction coupling; fibroblasts; myofilament

Key points

- Intracellular calcium regulation and its interaction with the myofilaments is central to the normal contractile function of the heart
- Physiological contractile regulation involves the Frank–Starling response, heart rate-dependent regulation, autonomic control and the effects of autocrine/paracrine factors such as nitric oxide
- Calcium regulates other important processes within myocytes, including excitation–transcription coupling and mitochondrial function; this is achieved through spatial and temporal compartmentation of the calcium signal in cellular microdomains
- Cross-talk between different cell types within the heart (cardiomyocytes, endothelial cells, fibroblasts, immune cells) is important both for normal physiological function and in the diseased heart
- Overall, cardiac function is also influenced by other cellular processes including the turnover of cell constituents, metabolic function, redox state, epigenetic control and regulation of cardiomyocyte viability

Introduction

The synchronous contraction of cardiomyocytes during ventricular systole generates the power required to pump blood out of the heart. Conversely, active myocyte relaxation and passive mechanical properties of the ventricles (the latter largely dependent on the extracellular matrix (ECM)) determine filling of the heart during diastole. Several interacting regulatory processes operate to ensure that cardiac performance is finely tuned to match changing circulatory requirements. In this article, we provide an overview of the mechanisms that regulate cardiac contractility, dysfunction of which is implicated in disease states such as heart failure.

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Structure of the myocardium

The heart is composed of cardiomyocytes, fibroblasts, endocardial and endothelial cells, immune cells, coronary vessels and ECM.[1]

Cardiomyocytes account for most of the cardiac mass and volume but only approximately 30% of cardiac cell numbers. They are connected to each other via specialized gap junctions, which provide electrical coupling and allow an action potential to spread between adjacent cardiomyocytes by the intercellular movement of ions. This is vital for synchronized contraction of myocytes. Gap junction channels are formed from a family of proteins known as connexins.

The sarcolemmal membrane of cardiomyocytes has invaginations that form an extensive T-tubule network, regions of which lie in close apposition to the sarcoplasmic reticulum (SR). SR is the major intracellular store of calcium and a central regulator of cardiac contractility. The fundamental contractile unit, the sarcomere, is formed from contractile myofibrils, which comprise interdigitating thin filaments (actin and associated regulatory proteins, tropomyosin, troponins C, I and T) and thick filaments (myosin). The sarcomere also contains numerous non-contractile proteins (e.g. titin, myomesin, telethonin) that have important structural and signalling functions. Interspersed between the myofibrils are numerous mitochondria, which

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generate the energy (in the form of adenosine triphosphate (ATP)) to fuel contraction.

Fibroblasts are the most numerous cells in the heart. They are responsible for the continual production and turnover of the ECM of the heart. In response to injury, such as myocardial infarction, fibroblast increase in number and undergo a phenotypic change to so-called myofibroblasts, which play a crucial role in organ repair and healing by fibrosis. In experimental models of cardiac injury, some of these myofibroblasts may be recruited from circulating bone marrow-derived cells or from local endothelial cells that have undergone a phenotypic change known as endothelial–mesenchymal transition.

ECM is a complex array of molecules that provides structural support to the cellular components of the heart. The ECM also allows appropriate transmission of the mechanical forces generated by cardiomyocytes. The major components of the ECM are types I and III collagen. The ECM also contains various protease enzymes, which allow degradation of matrix components. Important among these are the matrix metalloproteinases, of which there are over 20 known subtypes.

The main coronary arteries, which provide the heart with its blood supply, sit on the epicardial surface of the heart. They divide into smaller blood vessels that penetrate the myocardium. At capillary level, there is a close apposition between endothelial cells and cardiomyocytes. These endothelial cells not only provide the lining of blood vessels, but also modulate cardiac function through the release of diffusible factors (described below).

Immune cells also reside in the healthy myocardium and interact with cardiomyocytes, fibroblasts and ECM to help maintain normal myocardial structure and function. In the injured myocardium (e.g. after myocardial infarction, in chronic heart failure), a change in immune cell number and subtype makes an important contribution to the overall myocardial remodelling process. Damage-associated molecular patterns, comprising components of injured cells and tissues, are involved in stimulating immune responses. The effect of immune activation ranges from damaging inflammatory responses to tissue reparative processes whose overall balance dictates the acute and chronic response to cardiac injury.

Excitation–contraction coupling and contractile function

Electrical excitation of the cardiomyocyte initiates a dramatic transient rise in intracellular calcium concentration (the so-called calcium transient). The events that couple sarcolemmal depolarization to elevation of calcium concentration and initiation of contraction are known as excitation–contraction coupling (Figure 1).[2]

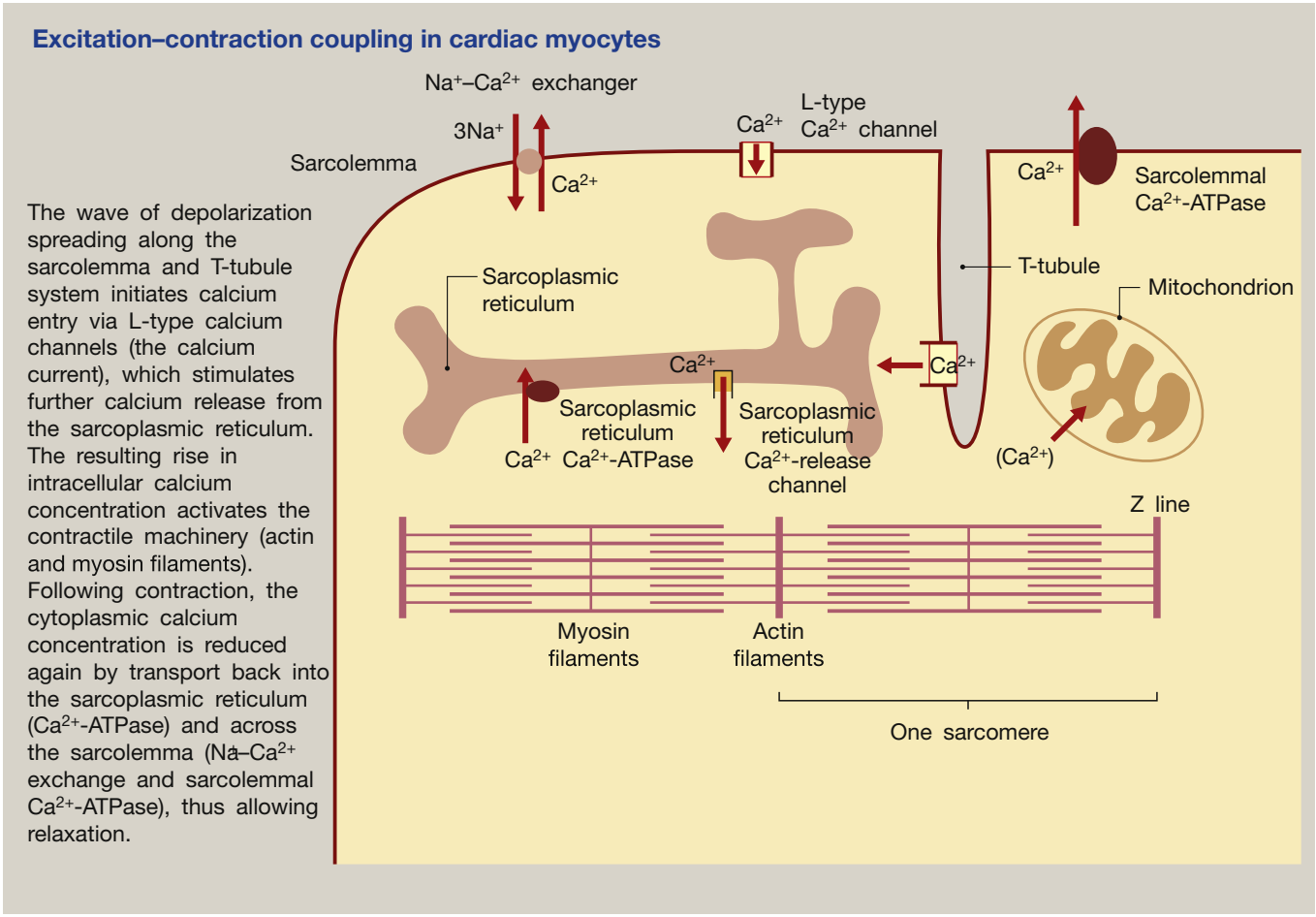

Figure 1

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