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, both in health and in 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 re-fill. 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, namely the 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

What's new?

- Cross-talk between different cell types within the heart (cardiomyocytes, endothelial cells, fibroblasts) is important both for normal physiological function and in the diseased heart
- Calcium regulates numerous intracellular processes within myocytes, including excitation–contraction coupling, excitation–transcription coupling and mitochondrial function. This is achieved through spatial and temporal compartmentation of the calcium signal in cellular microdomains
- Autocrine/paracrine factors and downstream signalling pathways (e.g. those regulated by eNOS and nNOS) are important modulators of cardiac function both in health and disease
- Immune cells reside in the normal myocardium and can also be attracted after cardiac injury. They interact with cardiomyocytes and fibroblasts to initiate an innate immune response that can be detrimental or reparative depending upon the context
- Epigenetic regulation and regulation by microRNAs are important modulators of cardiac structure and function in health and disease

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) 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.

Structure of the myocardium

The heart is composed of cardiomyocytes, fibroblasts, endocardial and endothelial cells, immune cells, coronary vessels, and the extracellular matrix.

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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 the connexins.

The sarcolemmal membrane of cardiomyocytes has invaginations that form an extensive T-tubule network, regions of which lie in close apposition with the sarcoplasmic reticulum (SR). The sarcoplasmic reticulum 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, and 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 generate the energy (in the form of ATP) to fuel contraction.

Fibroblasts are the most numerous cells in the heart. They are responsible for the continual production and turnover of the extracellular matrix of the heart. In response to injury, such as myocardial infarction, fibroblast numbers are increased and undergo a phenotypic change, to so-called myofibroblasts, which play a crucial role in organ repair and healing by fibrosis.[1] 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.[2]

The *extracellular matrix* (ECM) is a complex array of molecules that provides structural support for 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 (MMPs), 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 later).

Immune cells also reside in the healthy myocardium and interact with cardiomyocytes, fibroblasts and the ECM to help maintain normal myocardial structure and function. In the injured myocardium (e.g. after myocardial infarction or in chronic heart failure), a change in immune cell number and subtype makes an important contribution to the overall myocardial remodelling process.[3] Damage-associated molecular patterns (DAMPS), 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.[3]

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). During each heartbeat, the depolarization wave spreads across the sarcolemma and T-tubule system, and initiates calcium influx through voltage-gated L-type calcium channels. This calcium influx or calcium current (I_{Ca}) initiates further calcium release from the SR (calcium-induced calcium release) via the ryanodine receptor. The elementary unit of SR calcium release, the calcium spark, represents calcium released locally from the opening of a few calcium-release channels. According to the local control theory of excitation–contraction coupling, the cell calcium transient induced by an action potential represents the spatial and temporal summation of individual calcium sparks.

The contractile machinery is switched on by binding of calcium to troponin-C on the thin filament, which enables projections (S1 heads) on the myosin molecules to interact with actin filaments, forming cross-bridges. This energy-requiring process involves ATP hydrolysis by myosin ATPase. Repetitive cross-bridge cycles of attachment and detachment continue as long as the cytosolic calcium concentration is high. The power stroke generated by the cross-bridge cycle is responsible for force generation or muscle shortening. Cross-bridge interactions show cooperativity; in other words, force-generating cross-bridges promote further binding of more cross-bridges, which effectively amplifies the calcium signal.

Muscle relaxation is governed by lowering of the cytoplasmic calcium concentration, consequent dissociation of calcium from troponin-C, and switching off of the actin–myosin interaction. This involves active transport of calcium back into the SR (via SR Ca^{2+}-ATPase) and extrusion across the sarcolemma, by both the Na^{+}–Ca^{2+} exchanger and (less importantly) the sarcolemmal Ca^{2+}-ATPase. Mitochondria can also accumulate calcium, particularly when cytosolic concentrations become excessively high (e.g. during severe ischaemia). In addition to the reduction in cytosolic Ca^{2+}, recoil of elastic elements within the myocyte (notably within titin molecules in the sarcomere) may also be involved in the process of relaxation.

The events that comprise excitation–contraction coupling influence the size and kinetics of the calcium transient.[4] An abnormally low calcium transient may lead to depressed contractility. Reduction in SR Ca^{2+}-ATPase activity and abnormalities of SR calcium release (e.g. calcium leak) occur in heart failure and are generally accompanied by diastolic calcium overload; this may contribute to delayed relaxation and diastolic dysfunction, triggering of ventricular arrhythmias, and chronic changes in cell structure (e.g. altered gene expression) as a result of activation of downstream calcium-dependent signalling pathways.[4] Up-regulation of Na^{+}–Ca^{2+} exchanger activity may, to some extent, compensate for reduced SR Ca^{2+}-ATPase activity. Independent of excitation–contraction coupling, changes in myofilament properties (e.g. their responsiveness to calcium) are also implicated in heart failure, ischaemia–reperfusion injury and hypertrophic cardiomyopathy.[5]

Calcium concentrations within the cardiomyocyte also influence other cellular processes. They have been found to be involved in the control of gene transcription (so-called excitation–transcription coupling) and may in part mediate processes such as cardiac hypertrophy. The binding of calcium to calmodulin leads to activation of certain protein kinases (e.g. calmodulin kinase) or phosphatases (e.g. calcineurin), which then modulate signal transduction pathways and/or transcription factors to alter the expression of specific genes.[6]

Calcium is involved in matching mitochondrial energy production (by oxidative phosphorylation) to cardiac work. Various sites within mitochondria, including key dehydrogenases (such as pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase) and also the F1F0 ATPase, are susceptible to changes in activity determined by local calcium concentration. An abnormality in calcium handling therefore affects not only excitation–contraction coupling but also mitochondrial metabolism, leading to a cellular energetic deficit and oxidative stress.[7] The consequent ATP deficit and redox imbalance may further impair excitation–contraction coupling and contractile function.

The multiple described actions of calcium within the cardiomyocyte are feasible because of distinct local calcium concentrations within the cell, in so-called microdomains. For example, excitation–contraction coupling (involving sarcolemmal I_{Ca} and SR ryanodine receptors in close proximity) is likely to involve a local free calcium transient signal that is spatially distinct from that seen in perinuclear pathways identified in excitation–transcription coupling.