

How the heart relaxes

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Abstract

Normal functioning of the heart is dependent on its ability both to contract and relax. Heart contraction is a complex process that is initiated by an increase in intracellular calcium, which results in myosin binding to actin and myosin movement of the actin filament. Relaxation is reliant on removal of calcium from the contractile filaments, which in turn is dependent on the availability of ATP. If the heart does not relax properly, it cannot fill with blood during diastole, which subsequently compromises its ability to pump sufficient quantities of blood to the body. The inability of the heart to relax properly can cause heart failure. Therefore, reduced ATP levels such as are observed in heart failure may contribute to impairments in heart diastolic function. This paper reviews the mechanism of cardiac muscle contraction and relaxation as well as the role of relaxation in heart disease.

Keywords: Calcium; diastole; sarcomere; sarcoplasmic reticulum

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Introduction

The heart's ability to contract and relax appropriately is essential. Contraction of the heart, termed systole, is responsible for pushing the blood out of the chambers of the heart. Diastole, relaxation of the heart, allows the chambers of the heart to fill with blood. Therefore, both diastole and systole are equally necessary for the heart to function properly.

Contraction and relaxation of cardiac muscle is a complex process. At the subcellular level it involves binding of myosin to actin followed by movement of the myosin head, which moves actin causing the cell to contract (Fig. 1). Initial contraction of the heart muscle is stimulated by a rise in intracellular calcium (Fig. 2) [1]. Alterations in the regulation of calcium release and uptake, or alterations in the response of the contractile proteins to calcium, can lead to arrhythmias and contractile dysfunction [1, 2]. Initiation of calcium uptake by the cardiomyocyte is triggered by action potentials that cause calcium channels on the cell membrane to open. The influx of calcium activates the ryanodine receptor allowing calcium in the sarcoplasmic reticulum (SR) to be released, a process referred to as calcium-induced calcium release [1]. Calcium then binds to troponin causing it to move, which then exposes the myosin binding site on actin. The myosin head can now bind to its site on actin. Upon binding, the myosin head cocks back, pulling the contractile filament inward. Relaxation is reliant on intracellular calcium levels returning to normal [1] and the availability of ATP, which is necessary for myosin to release from actin [3].

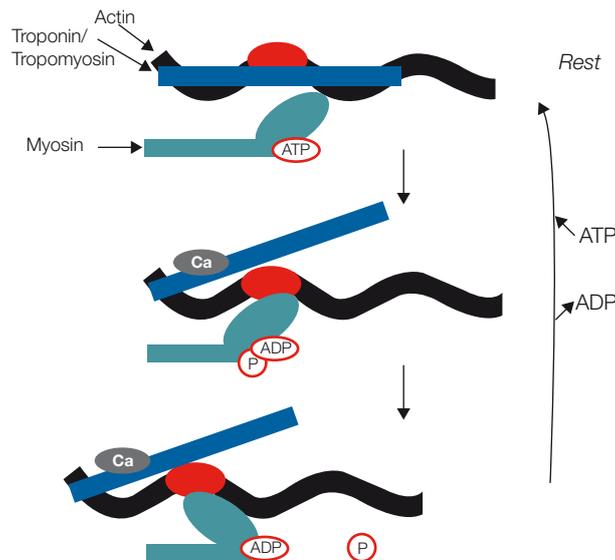


Fig. 1 Myosin and actin involvement in cardiac muscle contraction and relaxation: As a result of the rise in calcium caused by an action potential, calcium binds to troponin C, which in turn moves the troponin/tropomyosin complex from blocking the myosin binding site on actin. Myosin then interacts with actin. Release of the phosphate from hydrolysis of the ATP on myosin produces the energy required for the cocking of the myosin head, which moves actin, a process referred to as contraction. In order for myosin to release from actin, resulting in relaxation, the ADP bound to myosin must be replaced with ATP. When the intracellular calcium levels return to normal the troponin C is no longer bound by calcium and the troponin/tropomyosin complex can once again block the myosin binding site on actin.

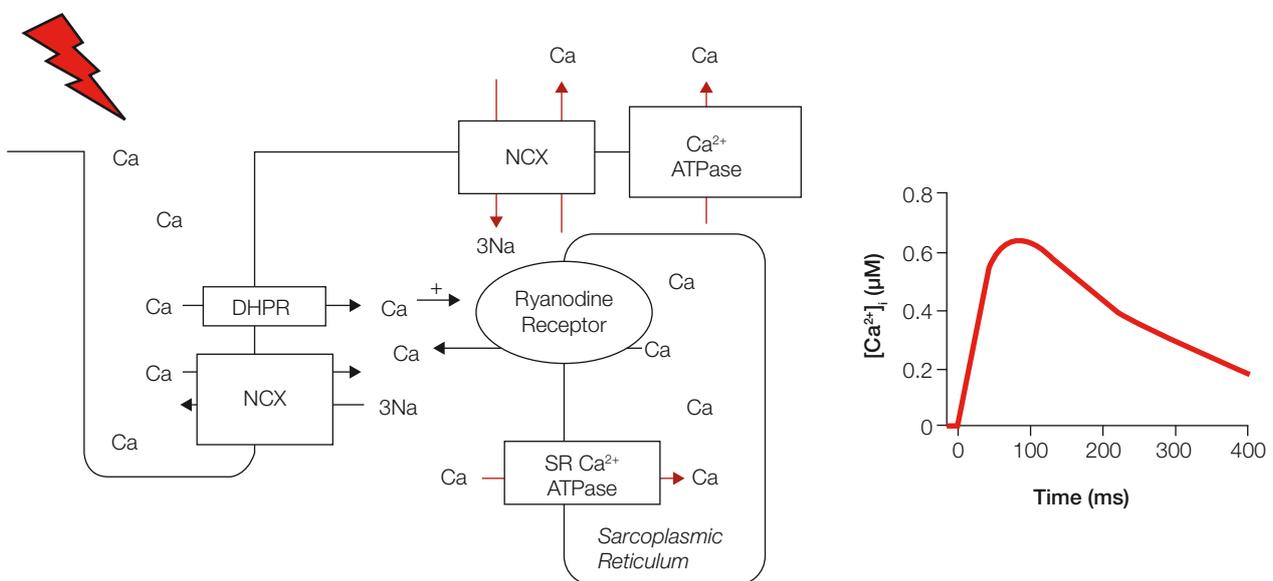


Fig. 2 Calcium handling in cardiac muscle contraction and relaxation. In cardiac muscle, an action potential activates the dihydropyridine receptors (DHPR) and sodium/calcium exchanger (NCX), which causes the initial rise in intracellular calcium. This small increase in calcium stimulates the ryanodine receptor, which transports calcium from the sarcoplasmic reticulum (SR) into the cytosol. Once the calcium reaches a certain level, calcium transporters including SR Ca²⁺-ATPase, sarcoplasmic Ca²⁺-ATPase, and NCX start pumping calcium either back into the SR or out of the cell. Cytoplasmic calcium level must drop in order for the cell to relax and for subsequent action potentials to stimulate cardiomyocyte contraction appropriately. The graph represents the change in intracellular Ca²⁺ ([Ca²⁺]_i) during the process of contraction and relaxation.

Mechanism of cardiac muscle contraction and relaxation

Myosin and actin

The binding of myosin to actin, cocking of the myosin head, and release of the myosin head from its binding site on actin (relaxation) is dependent on both calcium and ATP. The first step involves calcium binding to troponin C causing exposure of the myosin binding site on actin by troponin C moving the troponin I/tropomyosin complex off the myosin binding site (Fig. 1) [3, 4]. The energy necessary for the myosin head to cock comes from the ATP bound to myosin being dephosphorylated to ADP and the phosphate group being released [3]. The cocked myosin head releases from actin once the ADP is replaced by ATP [3]. This process repeats itself once ATP is hydrolyzed again to ADP (assuming the calcium is still bound to troponin C), thereby relieving inhibition by troponin/tropomyosin [3]. If ATP is not available to replace the hydrolyzed ADP on myosin the heart does not relax and would stay in the contracted state despite intracellular calcium levels returning to normal.

In order for the heart to relax cytoplasmic calcium levels must drop down to very low levels. This is achieved by a number of processes, including the SR calcium ATPase (which pumps the calcium back into the SR), the sodium/calcium exchanger (which normally exchanges intracellular calcium for extracellular sodium), and the sarcolemmal calcium ATPase pump (which pumps calcium out of the cell) [1]. The return of cytoplasmic calcium levels back to low levels results in calcium releasing from its troponin binding site, resulting in a conformational change in troponin/tropomyosin, such that it blocks the myosin binding site on actin, resulting in subsequent relaxation of the heart.

Calcium handling during contraction and relaxation

Alterations in cytoplasmic calcium levels is not only required for cardiac muscle contraction but also for muscle relaxation. Action potentials cause activation of the depolarization activated calcium channels including dihydropyridine receptors (DHPR) on the cardiomyocyte cell membrane, causing an influx of calcium into the cell (Fig. 2) [1]. This increase in calcium activates ryanodine receptors causing a much larger release of calcium from the SR [1]. Once the calcium reaches a high enough intracellular level, calcium binds to troponin C [1]. Calcium binding to troponin C

relieves troponin C inhibition of myosin binding to actin [1]. Half maximal cardiac contraction requires an intracellular calcium concentration of 600 nM [1]. There are a few types of calcium channels involved in the process of cardiomyocyte contraction. These include voltage-dependent calcium channels, which are activated by the action potential and are responsible for the initial influx of calcium, and either transient (T-type) or long acting (L-type) calcium channel, also called DHPR [1]. The rise in calcium due to release of calcium from the SR calcium inactivates DHPR and the ryanodine receptors, contributing to the initiation of cardiomyocyte relaxation [1, 5].

Relaxation of the heart also involves the regulation of intracellular calcium levels. In the rabbit ventricular cardiomyocyte 70% of the calcium is pumped out by the SR Ca^{2+} -ATPase, 28% is pumped out by the sodium/calcium exchanger, 1% by the mitochondrial uniporter, and 1% by the sarcolemmal calcium ATPase [1]. The SR Ca^{2+} -ATPase is negatively regulated by SR phospholamban. Phospholamban inhibition is reduced by phospholamban being phosphorylated by protein kinase A or calmodulin-dependent protein kinase II resulting in decreased time to relaxation [1, 6]. In order for the cell to relax, the calcium levels must drop low enough so that troponin C is no longer bound by calcium. Once the ADP on myosin is replaced by ATP, it allows myosin to dissociate from actin, the troponin/tropomyosin complex can again block the myosin binding site on actin.

Heart failure and energy metabolism

Impairment in the ability of the heart to produce ATP can lead to impaired heart function. ATP content in the failing heart can decrease to 60–70% of levels seen under normal conditions [7–10]. As heart failure progresses, cardiac mitochondrial oxidative capacity tends to decrease along with elevation in glycolysis and glucose uptake [7–11]. Not only is there a shift towards metabolic pathways that produce less ATP, but there is an increase in glycolysis uncoupled from glucose oxidation, which results in the consumption of ATP to maintain sodium and calcium at normal levels (ions that rise as the protons produced as a result of uncoupled glycolysis are transported out of the cell) [11–13]. As mentioned earlier, ATP is required for heart relaxation both for returning calcium levels to normal and for myosin to release from actin. Therefore,

lower ATP levels could impair the ability of contraction to end and contribute to cardiac dysfunction.

Changes in energy metabolism observed in heart failure can be caused by an increase in circulating fatty acids [11]. Fatty acids reduce both the efficiency with which ATP is produced and utilized in the cardiomyocyte. For example, fatty acid oxidation inhibits glucose oxidation (Randle cycle), switching the source of ATP from glucose towards a less efficient source of ATP production (ie, fatty acid oxidation) [11]. For example, the oxidation of palmitate requires 23 O₂ to produce 104 ATP, while 6 O₂ are used in glucose oxidation to generate 31 ATP [4]. In addition, fatty acids cause ATP to be used less efficiently. Many of these mechanisms involve the uncoupling proteins (UCP) 2 and 3 and are related to the finding that UCP2 and UCP3 protein expression is elevated in the failing heart [14]. For example, increased expression of UCP3, which can transport fatty acid anions out of the mitochondrial matrix, would elevate the amount of ATP wasted in transporting fatty acids into the mitochondria [13, 15].

ATP is also necessary for the function of certain ATP-dependent co-transporters and calcium channels necessary for heart relaxation. One such transporter is the Na⁺/K⁺-ATPase, which by pumping three sodium molecules out and two potassium molecules into the cell prevents a rise in intracellular sodium caused by the Na⁺/Ca²⁺ exchanger contributing to relaxation of the cardiomyocyte [11, 16]. In addition, if the activity of the SR Ca²⁺-ATPase is impaired calcium overload occurs, which would impair heart relaxation [11].

Conclusion

The ability of the heart to relax and fill with blood is vital to its ability to function properly as a pump. Alterations in relaxation can lead to an inability to pump enough blood to the body, which can potentially lead to heart failure. Causes of impaired heart relaxation can include insufficient supply of ATP and/or failure to remove calcium appropriately from the cytoplasm following the initiation of contraction. In the future, metabolic modulation may be used to increase ATP levels in diastolic heart failure resulting in an improvement of diastolic function. •

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