

Cardiac muscle physiology

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The heart muscle is remarkable. At an average heart rate of 70 beats min^{-1} , the heart needs to contract and relax more than 100 000 times a day without stopping or tiring. The rate and strength of these contractions must vary to meet physiological and pathological challenges. This article provides an overview of cardiac muscle physiology. We describe the structure of the cardiac myocyte, the generation and spread of the cardiac action potential, the process of excitation-contraction coupling, and the metabolism and energetics of the heart. Finally, we discuss the mechanics of muscle fibre contraction.

Structure of the cardiac myocyte

Each cardiac myocyte is surrounded by a cell membrane called the sarcolemma and contains one nucleus. The cells are packed with mitochondria to provide the steady supply of ATP required to sustain cardiac contraction. As with skeletal muscle, cardiac myocytes contain the contractile proteins actin (thin filaments) and myosin (thick filaments) together with the regulatory proteins troponin and tropomyosin. Cardiac muscle is striated, although the pattern is not as ordered as in skeletal muscle.

Fig. 1 shows the arrangement of the thick and thin filaments. The myofilaments within the myocyte are surrounded by sleeves of sarcoplasmic reticulum, analogous to endoplasmic reticulum found in other cells. Separate tubular structures, the transverse tubules (T tubules), cross the cell. In the cardiac myocyte, the T tubule crosses at the Z-line, in contrast to the A-I junction in skeletal muscle. The lumen of the T tubule is continuous with the extracellular fluid surrounding the cell and, as in skeletal muscle, the action potential is propagated down the T tubule. Adjacent cardiac myocytes are joined end-to-end at structures known as intercalated disks. These always occur at a Z-line. At these points, the cell membranes form a number of parallel folds and are tightly held together by desmosomes. This results in strong

cell-to-cell cohesion, thus allowing the contraction of one myocyte to be transmitted axially to the next. Gap junctions exist between cardiac muscle cells, providing low resistance pathways for the spread of excitation from one cell to another.

Resting membrane and action potentials

Cardiac myocytes can be divided into work cells and pacemaker cells. The work cells have a large stable resting membrane potential and display a prolonged action potential with a plateau phase. The pacemaker cells have smaller unstable resting potentials and spontaneously depolarize, generating the intrinsic electrical activity of the heart. Pacemaker cells are found in the sinoatrial (SA) and atrioventricular (AV) nodes. The cells of the bundle of His and some Purkinje cells are also capable of spontaneous firing.

The cardiac action potential

The cardiac action potential is very different to that seen in nerves. It has a prolonged plateau phase lasting around 300 ms compared with 1 ms in nerves. The cardiac action potential has five phases as shown in Fig. 2. During phase 0, membrane permeability to potassium decreases and fast sodium channels open, producing rapid depolarization from -90 mV to $+10$ mV. During phase 1, there is partial repolarization, because of a decrease in sodium permeability. Phase 2 is the plateau phase of the cardiac action potential. Membrane permeability to calcium increases during this phase, maintaining depolarization and prolonging the action potential. Membrane permeability to calcium decreases somewhat towards the end of phase 2, and the plateau is partially maintained by an inward sodium current. Sodium flows into the cell through the sodium-calcium exchanger. The exchanger transfers three sodium ions into the cell in exchange for one calcium ion flowing out, and so produces a net inward

Key points

Cardiac muscle is highly organized; it is striated but has a structure distinct from that of skeletal striated or smooth muscle.

The cardiac action potential is reliant upon ionic gradients set up by ion pumps.

Muscle contraction and relaxation are active processes.

Pacemaker cells do not have a stable resting membrane potential.

The force of contraction of cardiac muscle is dependent on the initial tension of the muscle.

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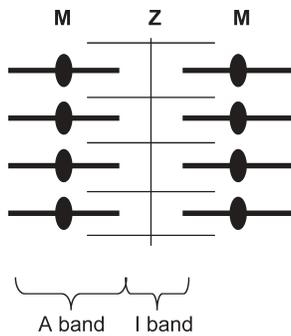


Fig. 1 Schematic representation of a contractile unit in cardiac muscle. The actin filaments are anchored at the Z-line, myosin filaments are connected at the M-line. A sarcomere extends from one Z-line to the next.

positive current. As calcium channels inactivate towards the end of the plateau phase, an inward potassium current produces repolarization in phase 3. The resting membrane potential in phase 4 is approximately -90 mV. This is produced mainly by the selective permeability of the cell membrane to potassium and the concentration gradient for potassium that exists across the cell membrane and is close to the Nernst equilibrium potential for potassium.

Much of the calcium influx in the plateau phase occurs through L-type (long opening) calcium channels. Increased activation of L-type channels occurs with catecholamine exposure, whilst they are blocked by calcium channel antagonists such as verapamil.

The cardiac action potential lasts about 300 ms. For the vast majority of this time, the cell is absolutely refractory to further stimulation. In other words, a further action potential will not be generated until repolarization is virtually complete. This prevents tetany from occurring. If a supramaximal stimulus occurs during the relative refractory period, the resultant action potential has a slower rate of depolarization and is of smaller amplitude than normal, producing a much weaker contraction than normal.

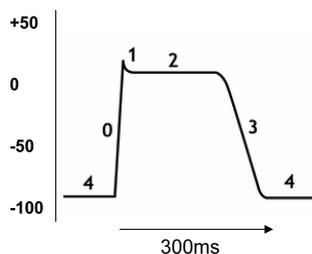


Fig. 2 The cardiac action potential. Phase 0—depolarization because of the opening of fast sodium channels. Potassium flux also decreases. Phase 1—partial repolarization because of a rapid decrease in sodium ion passage as fast sodium channels close. Phase 2—plateau phase in which the movement of calcium ions out of the cell, maintains depolarization. Phase 3—repolarization, sodium, and calcium channels all close and membrane potential returns to baseline. Phase 4—resting membrane potential (-90 mV), resulting from the activity of the Na^+/K^+ ATPase pump which creates a negative intracellular potential because of the exchange of three sodium ions for only two potassium ions.

The pacemaker potential

The pacemaker potential is seen in cells in the SA and AV nodes. As shown in Fig. 3, it differs from the action potential of cardiac myocytes in that phases 1 and 2 are absent. The heart displays auto-rhythmicity: a denervated heart (such as the heart of a cardiac transplant patient) continues to contract spontaneously. Pacemaker cells do not have a stable resting action potential, and it is the spontaneous depolarization of the pacemaker potential that gives the heart its auto-rhythmicity. The pacemaker potential is produced by a decrease in membrane permeability to potassium, a slow inward current because of calcium influx via T-type (transient) calcium channels, and an increased sodium current because of sodium–calcium exchange. Once the threshold potential is reached, L-type calcium channels open, calcium ions enter the cell, and depolarization occurs. In contrast to the cardiac myocyte action potential, there is no inward movement of sodium ions during depolarization. Repolarization (phase 3 of the action potential) occurs because of an increase in potassium permeability. At the SA node, potassium permeability can be further enhanced by vagal stimulation. This has the effect of hyperpolarizing the cell and reducing the rate of firing. Sympathetic stimulation has the opposite effect.

Rate, conduction, and speed

The SA node, other atrial centres, AV node, and bundle of His all have inherent pacemaker activity. The SA node has the highest rate of spontaneous depolarization and therefore suppresses the other pacemakers. In the denervated heart, the SA node discharges at a rate of approximately 100 min^{-1} . Vagal tone leads to a lower heart rate in healthy subjects at rest. From the SA node, impulses spread throughout the atria to the AV node at a rate of 1 m s^{-1} . The AV node is the only means of electrical connection between the atria and the ventricles. Conduction here is slow (approximately 0.05 m s^{-1}). This means that the AV node will only transmit a maximum of $220 \text{ impulses min}^{-1}$, so protecting the ventricles from high rates of atrial depolarization.

Depolarization spreads from the AV node to the bundle of His in the interventricular septum. The bundle splits into right and left bundle branches, supplying the respective ventricles. The left bundle itself divides into anterior and posterior divisions. From the

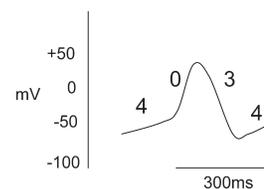


Fig. 3 The pacemaker potential. Phases 1 and 2 do not occur. Phase 4—pacemaker potential. Because of slow inward current of sodium and a voltage gated increase in calcium conductance (via T channels) Phase 0—depolarization. As opposed to the ventricular muscle action potential, this occurs because of voltage gated calcium channels opening. Phase 3—repolarization. This is because of a decrease in potassium.

bundle branches, impulses travel through the ventricular muscle via a network of Purkinje fibres, at a velocity of $1\text{--}4\text{ m s}^{-1}$. The conducting system is arranged so that the apices of the ventricles contract before the bases, propelling blood out of the chambers.

Excitation contraction coupling

This is the process linking electrical excitation to contraction. Calcium has an essential role in this process; a raised intracellular calcium concentration is the trigger that activates contraction. An understanding of calcium handling is essential to understanding the function of the heart. The intracellular calcium ion concentration in the cardiac myocyte at rest is $0.0001\text{ mM litre}^{-1}$ and that in the extracellular fluid is 1.2 mM litre^{-1} . During the plateau phase of the action potential, calcium ions flow down this steep concentration gradient and enter the myocyte. Most of this calcium enters through the L-type channels, located primarily at sarcolemmal/sarcoplasmic reticulum junctions. The influx of calcium triggers the release of further calcium from the sarcoplasmic reticulum via ryanodine receptors. This calcium-triggered calcium release is in contrast to skeletal muscle, where the action potential triggers calcium release directly.

Free intracellular calcium interacts with the C subunit of troponin. This leads to a configuration change in the troponin/tropomyosin complex, allowing actin to interact with myosin. Cross bridge cycling occurs, leading to a shortening of the sarcomere and resultant muscular contraction. As intracellular calcium concentrations decrease during repolarization, calcium dissociates from troponin as intracellular calcium concentration decreases, resulting in relaxation. Diastolic relaxation is an active (ATP-dependent) process. Calcium transport out of the cytosol occurs via a sarcoplasmic reticulum Ca^{2+} -ATPase, through sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchange, via a sarcolemmal Ca^{2+} -ATPase, and finally by utilizing a mitochondrial Ca^{2+} uniporter.

The strength of a contraction may be varied by increasing the amount of free intracellular calcium, by altering the sensitivity of the myofilaments to calcium, or both. The latter occurs during stretching of the myofilaments and is responsible for the Frank–Starling mechanism (discussed later). Myofilament calcium sensitivity is reduced by acidosis. High concentrations of phosphate and magnesium also impair cardiac function.

Catecholamines activate beta-adrenergic receptors in the heart to produce a G-protein mediated increase in cAMP and enhanced activity of a cAMP-dependent protein kinase. This leads to the phosphorylation of calcium membrane channels, enhancing calcium entry into the cell. Phosphorylation of myosin also occurs, increasing the rate of cross bridge cycling. Catecholamines also increase the rate of re-uptake of calcium into the sarcoplasmic reticulum, thus aiding relaxation.

Metabolism and energetics

The oxygen consumption of the beating heart is on average $9\text{ ml per }100\text{ g min}^{-1}$ at rest. This increases during exercise. Oxygen extraction from blood in the coronary circulation is high; therefore,

an increase in oxygen demand must be met by an increase in coronary blood flow.

The heart is very versatile in its use of metabolic substrates. Carbohydrate utilization accounts for 35–40% of total oxygen consumption. Glucose and lactate are used in roughly equal proportions. A small amount of energy may be derived from ketones; however, 60% of the basal energy requirement is provided by fat. The proportion of substrates utilized may vary depending on the nutritional state of the person. After a large meal containing glucose, more pyruvate and lactate are used. During periods of starvation, more fat is utilized. Insulin enhances glucose uptake into cardiac myocytes, and in untreated diabetes proportionally more fat is utilized. Normally <1% of the energy used by the myocardium is produced by anaerobic metabolism. This proportion increases during periods of hypoxaemia; however, lactic acidosis impairs myocardial function and can ultimately lead to myocardial cell death.

Contraction of the isolated muscle strip

The mechanics of cardiac myocyte contraction can be studied in the laboratory by examining the behaviour of an isolated muscle strip (Fig. 4). The papillary muscle is convenient for this as its fibres run in roughly the same direction. The muscle is placed under an initial tension or preload. If the muscle strip is anchored at both ends and stimulated it undergoes isometric contraction. The tension generated during isometric contraction increases with increasing initial length (Fig. 4A). Alteration in initial fibre length is analogous to preload. Increasing venous return to the heart results in an increased left ventricular end diastolic volume, thereby increasing fibre length. This produces an increase in the force of contraction and an increased stroke volume resulting in the familiar Starling curve. The conventional explanation for this is that at normal resting length, the overlap of actin and myosin is not optimal. Increasing the initial length improves the degree of overlap and therefore increases the tension developed. It has become clear in recent years that this mechanism is unlikely to account for the shape of the Starling curve under physiological conditions. Several other possible mechanisms have been implicated. Lengthening the muscle increases the sensitivity of troponin to calcium (length-dependent calcium sensitivity) and can also lead to enhanced intracellular free calcium.

If the muscle is able to shorten, but has to lift a weight, this is known as isotonic contraction. The weight moved by the muscle strip represents afterload. As afterload increases, both the amount and velocity of shortening decreases (Fig. 4B and C). Conversely, reducing the afterload enhances shortening, a fact of considerable importance in the management of the failing heart. If the preload is increased by stretching the muscle and the experiment repeated, both velocity and shortening are enhanced. (Fig. 4B and C).

In vivo, the initial phase of cardiac contraction, from the closure of the mitral and tricuspid valves to the opening of the aortic and pulmonary valves, is isotonic. Tension is developed, but

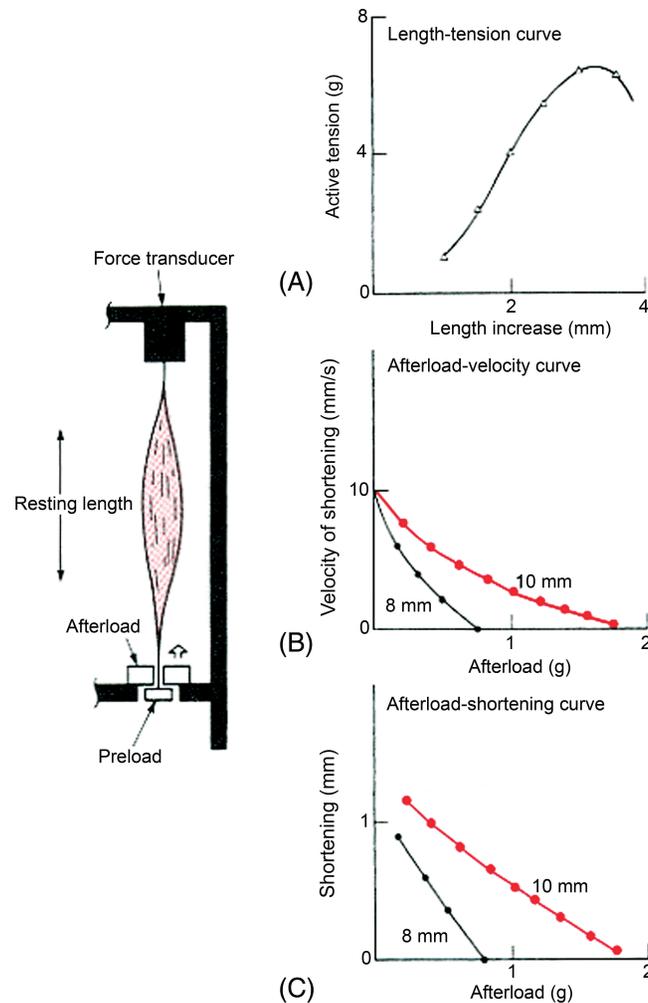


Fig. 4 Contractile properties of myocardial muscle. Left: Simplified arrangement to study contraction of isolated cat papillary muscle. In isotonic contractions the weight labelled ‘afterload’ is picked up as soon as shortening begins. The weight labelled preload sets the resting length. If the preload is clamped in place contraction becomes isometric. Right: Three fundamental relations: (A) isometric contraction at increasing lengths, (B and C) isotonic contractions beginning from two different resting lengths (8 and 10 mm). Contractile force, velocity, and shortening are all increased by stretching the relaxed muscle.³

the ventricle does not eject blood, as there is no muscle fibre shortening. After the opening of the aortic and pulmonary valves, contraction becomes isotonic, tension is maintained, but blood is ejected and tonic shortening occurs.

In vitro, perfusing papillary muscles with norepinephrine increases the strength and rapidity of the isometric contraction. This increased contractility (i.e. an increased force of contraction for a given fibre length) occurs *in vivo* after sympathetic stimulation and release of catecholamines. As mentioned earlier, catecholamines may augment both contraction and relaxation of cardiac muscle. However, as catecholamines increase the intracellular calcium load, more energy is required to fuel the pumps that sequester the calcium in diastole. In a failing myocardium, energy demand may outstrip supply (e.g. because of fixed coronary stenoses) and the addition of catecholamines may result in

impaired diastolic relaxation. Levosimendan is a new drug that increases the sensitivity of troponin to calcium such that the heart performs better with lower intracellular calcium concentrations. Less energy is then required in diastole to reduce intracellular calcium concentrations.

References

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Please see multiple choice questions 13–17