ELSEVIER
**R**evalidation
FOR ANAESTHETISTS
RCA Revalidation matrix
*Matrix codes: 1A01,*
*2A07, 3G00*
BRITISH JOURNAL OF ANAESTHESIA

# Cardiac muscle physiology

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## Learning objectives

By reading this article, you should be able to:

- Recall the principal ion channels and currents involved in the cardiac action potential.
- Describe the mechanisms underlying excitation-contraction coupling.
- Relate the structure of myofilaments to their function in health and disease.
- Discuss the metabolic pathways that provide energy for cardiac muscle contraction.

## Key points

- Resting membrane potential arises from ionic concentration gradients across the cell membrane coupled with varying membrane permeability to each ion. Potassium concentration has dominant influence because of its high membrane permeability.
- The characteristic shape of the cardiac action potential is a result of distinct sodium, calcium and potassium channels. Genetic variants affecting these channels have been linked to numerous congenital arrhythmia syndromes.
- Type 2 ryanodine receptor plays a central role in calcium-induced calcium release and the activation of excitation-contraction coupling.
- Abnormalities in cellular calcium handling and myofilament structure have been identified as important underlying mechanisms in cardiomyopathies and heart failure.
- An understanding of metabolic remodelling and cellular energetics in heart failure may provide future therapeutic options.

The heart is a biomechanical pump at the centre of our circulatory system. It contracts rhythmically from approximately 6 weeks of gestational age until death.[1] Contractions are initiated by action potentials, arising from pacemaker cells, transmitted to individual cardiomyocytes via specialised conduction pathways, through intercalated discs and gap junctions between cells.[2] The arrival of this electrical signal results in excitation-contraction coupling, sarcomere and cellular shortening and ejection of blood.[3] In this article we describe the cellular processes involved in the activation and mechanics of cardiac muscle contraction and the metabolism fuelling this activity.

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## Electrophysiology

Cardiomyocytes are excitable cells, with a resting membrane potential in non-pacemaker cells of approximately -90mV.[4] This is primarily the result of the electrochemical gradient of ions inside and outside the cell and the variable permeability of the membrane to these ions.[5] The most important are $K^+$, $Na^+$, $Ca^{2+}$ and $Cl^-$. The Nernst equation (Eqn. 1) describes the equilibrium potential for each ion individually given a specific intracellular and extracellular concentration.[4,6] Whereas the Goldman-Hodgkin-Katz constant field equation (Eqn. 2) combines the products of the equilibrium potential and relative permeability ($P'$) of major ions to calculate the membrane potential.[4]

$$E_x = \frac{RT}{zF} ln \frac{[X]_{out}}{[X]_{in}} \qquad (1)$$

Equation 1 $E_X$: equilibrium or Nernst potential for ion X; $[X]_{out}$: extracellular concentration of X; $[X]_{in}$: intracellular concentration of X; R: universal gas constant; T: absolute temperature; z: valency of ion; F: Faraday constant.

$$Em = \frac{P_{Na}}{P_T}E_{Na} + \frac{P_K}{P_T}E_K + \frac{P_{Ca}}{P_T}E_{Ca} + \frac{P_{Cl}}{P_T}E_{Cl}$$

$$Em = P'_{Na}E_{Na} + P'_K E_K + P'_{Ca}E_{Ca} + P'_{Cl}E_{Cl}$$

$$Em = P'_{Na}(+52\,mV) + P'_K(-96\,mV) + P'_{Ca}(+134\,mV)$$
$$+ P'_{Cl}(-90\,mV) \qquad (2)$$

Equation 2 Goldman-Hodgkin-Katz equation. Em: membrane potential; P: ion permeability of the membrane; P': ion permeability relative to total membrane permeability to all ions ($P_T$); $E_X$: equilibrium potential for specific ion "x".

At rest, $P'_{Na}$, $P'_{Ca}$ and $P'_{Cl}$ are very low while $P'_K$ is relatively high, therefore Em is closest to the equilibrium potential of $K^+$.[4] Under these conditions $K^+$ is moving out of the cell while $Na^+$ and $Ca^{2+}$ are diffusing in, down their electrochemical gradients (Table 1). The ionic gradients are maintained by a series of ion-exchange mechanisms. The Na/K-ATPase transports 3 $Na^+$ ions out of the cell and 2 $K^+$ ions in, contributing to the negative resting transmembrane potential as well as the differential ion concentrations.[4] There is also a Na−Ca exchanger (NCX) which exchanges 3 $Na^+$ ions for 1 $Ca^{2+}$ generating a small current and may operate in either direction, depending on the concentration gradients of $Na^+$ and $Ca^{2+}$ and the phase of the action potential (favouring cellular efflux of $Ca^{2+}$ during diastole and $Ca^{2+}$ influx when the membrane potential is more positive than − 20 mV).

The cardiac action potential originates from cells with pacemaker function, which is the ability to generate regular, spontaneous action potentials. Cells in the sinoatrial (SA) node (70−80 beats min$^{-1}$), atrioventricular (AV) node (40−60 beats min$^{-1}$), the bundle of His and Purkinje fibres (15−40 beats min$^{-1}$) are all capable of generating spontaneous electrical activity.[7] However, in the normal myocardium, SA node cells have the highest rate of spontaneous discharge and therefore dictate the beating rate of the heart. In pathological conditions where SA node discharge or action potential conduction fails, other pacemaker cells can take over, but this may result in an abnormally low heart rate, which may require the patient to have a temporary or permanent artificial pacemaker device fitted.

In contrast to contractile cardiomyocytes, pacemaker cells do not have a stable resting membrane potential, instead there is a slow diastolic depolarisation that results in the activation of voltage-gated L-type $Ca^{2+}$ channels resulting in $Ca^{2+}$ influx ($I_{Ca,L}$) and more rapid depolarisation.[5] The origin of this slow, spontaneous depolarisation is thought to be caused by a hyperpolarisation-activated inward current of $Na^+$ and $K^+$, also known as $I_f$ or 'funny current', but more recently other currents and a complex interaction between membrane proteins and sarcoplasmic reticulum (SR) $Ca^{2+}$ cycling, known as the 'calcium clock' have been implicated.[5,8]

Depolarisation spreads from the SA node to the AV node through atrial muscle cells and via some preferential inter-nodal conduction pathways. In health, the AV node is the only avenue of conduction from the atria to the ventricles. It has a complex structure including faster and slower pathways with differential expression of connexin (gap junction membrane channels) isoforms responsible for impulse conduction from cell to cell.[9] From here the signal passes through the bundle of His and down the fast-conducting, non-contractile Purkinje fibres to the ventricular myocardium. Purkinje fibres have very fast depolarisation and impulse conduction (2−3 m s$^{-1}$), because of the high expression of voltage-gated $Na^+$ channels ($Na_v1.5$ isoform) and Cx40 connexins (rather than the slower Cx43 isoform found in myocardial cells) in their gap junctions, respectively.[10]

Contractile myocardial cells have a characteristic action potential (AP) with a flat baseline and a plateau phase, though some differences exist between regions within the heart (Fig. 1): mid-myocardial cells having the longest AP duration, followed by endocardial, then epicardial cells.[5]

Classically, the cardiac AP is considered to have 5 distinct phases, based on a "typical" ventricular myocardial cell AP. Phase 0 is the fast depolarisation of the cell caused by a rapid increase in $Na^+$ conductivity primarily through the opening of $Na_v1$. Voltage-gated $Na^+$ channels in response to an incoming wave of depolarisation from adjacent cells, resulting in the current $I_{Na}$.[4] This $Na_v1.5$ channel is the predominant isoform in the myocardium and is encoded by the SCN5A gene.[5] A loss-of-function variant in SCN5A leads to reduced peak $I_{Na}$ and slowing of AP conduction and is implicated in around 20% of patients with Brugada syndrome, while a gain-of-function variant plays a role in congenital LQT3 syndrome.[5,11] These fast $Na^+$ channels open when a threshold voltage of about -70 to -55 mV is reached, resulting in a large increase in $P'_{Na}$ and the membrane potential rapidly reaching +30mV.[2,4]

Cardioplegia solution given during cardiac surgery has a particularly high $[K^+]$, typically between 16-20 mmol L$^{-1}$. This shifts the membrane potential towards -50 mV, causing deactivation of $Na_v1.5$ and a diastolic arrest providing a motionless target for the surgeons.[12] In Phase 1 fast $Na^+$ channels rapidly inactivate and there is a transient outward $K^+$ current, $I_{to}$, through $K_v4.3$ ion channels resulting in a degree of repolarisation.[13] This $I_{to}$ is downregulated in heart

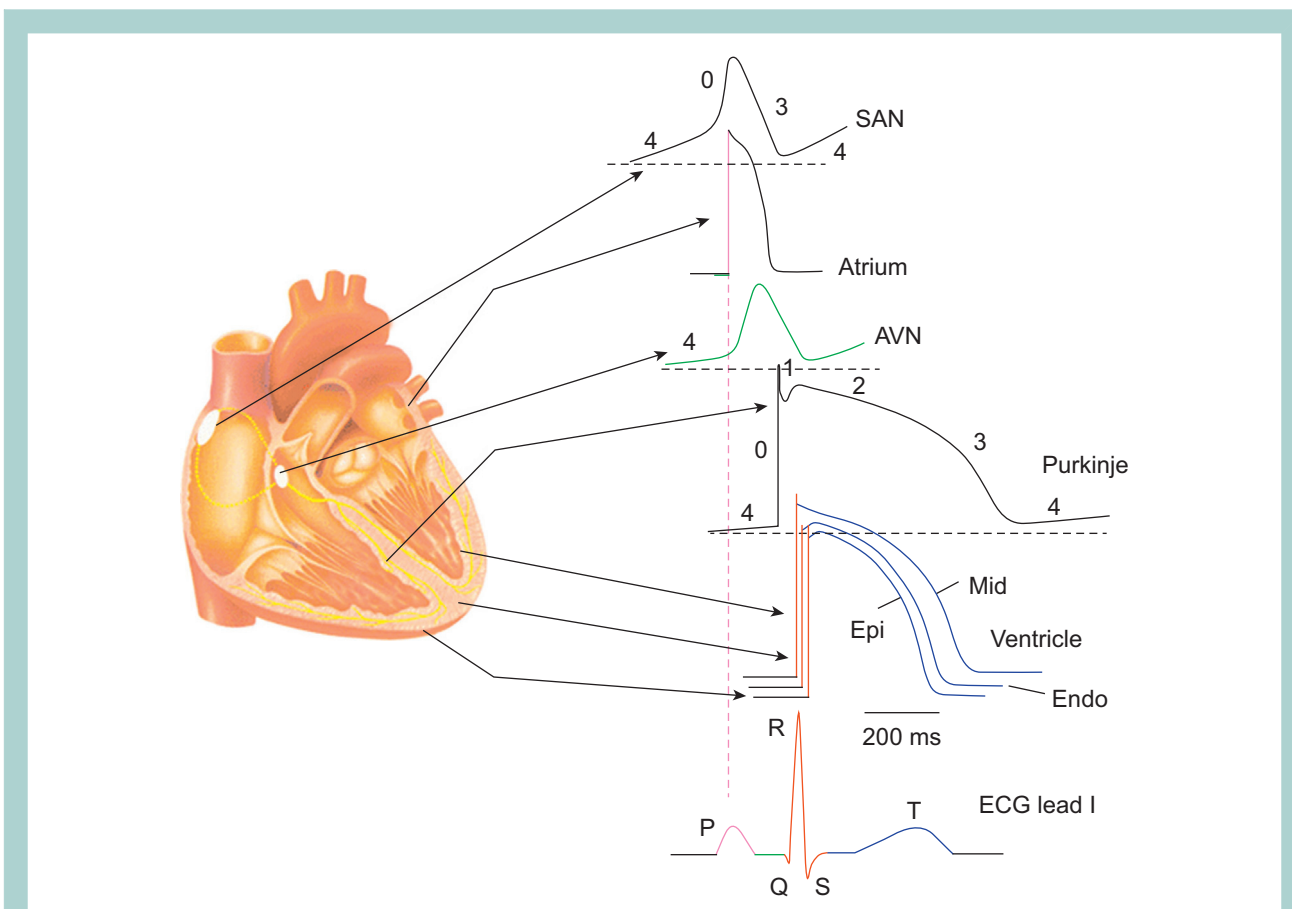| Ion | Intracellular concentration (mmol L$^{-1}$) | Extracellular concentration (mmol L$^{-1}$) |
|---|---|---|
| $K^+$ | 150 | 4 |
| $Na^+$ | 20 | 145 |
| $Ca^{2+}$ | 0.0001 | 2.5 |
| $Cl^-$ | 4 | 120 |

**Fig 1** Regional differences in cardiac action potential configurations. Schematic cross section of the heart depicting the corresponding action potential configuration from different regions of the heart indicated by arrows. Colour-coded sections on the action potentials refer to the corresponding sections on the schematic electrocardiogram (ECG). Note the characteristic action potential of contractile cells with a flat baseline and a plateau phase. Regional differences in action potential duration exist within the myocardium to ensure one-way conduction of depolarisation preventing re-entrant circuits. Pacemaker cells do not have a stable resting membrane potential but are characterised by their slow spontaneous diastolic depolarisation and they also have no plateau phase. AVN, atrioventricular node; Endo, endocardial; Epi, epicardial; Mid, midmyocardial; SAN, sinoatrial node. Reproduced from Varro 2020 *et al.*,[5] licensed under Creative Commons Attribution CC-BY 4.0.

failure, hypertrophic cardiomyopathy and in diabetes, prolonging repolarisation and increasing arrhythmia potential.[5] Phase 2 is a prolonged plateau of around 200 ms where multiple opposing currents are active in maintaining a depolarised membrane potential. The main inward current is $I_{Ca,L}$, an inward $Ca^{2+}$ current through L-type calcium channels ($Ca_v1.2$) activated by membrane depolarisation to above -45mV.[5,13] These $Ca^{2+}$ channels have much slower kinetics than $Na_v1.5$ and remain open for longer contributing not only to the plateau phase but also to excitation-contraction coupling.[5] The reversed NCX is active generating a further inward current.[5] Compensatory outward currents are provided by voltage-gated delayed rectifier $K^+$ channels that can be separated into rapid ($I_{Kr}$) and slow ($I_{Ks}$) components conducted by different ion channels.[13] $I_{Kr}$ is conducted by $K_v11.1$, whose α subunit is encoded by the *KCNH2* gene (formerly known as *HERG* or "human ether-a-go-go related gene"). Loss of function variants in *KCNH2* can cause congenital long QT syndromes, whereas gain of function variants result in short QT syndromes.[5] Multiple drugs inhibit $I_{Kr}$ and therefore assessment of the inhibition of this current is a mandatory part of cardiac safety testing of new drugs.[5] $I_{Ks}$ and other

outward $K^+$ currents also contribute to the maintenance of Phase 2 and with the closure of L-type calcium channels, to the Phase 3 repolarisation. The existence of multiple redundant currents provides a "repolarisation reserve" that is protective against QT prolongation in case of genetic variants or drug effects.[14] Phase 4 represents the resting membrane potential, during which inward rectifying $K^+$ channels open ($I_{K1}$), resulting in a large inward current on hyperpolarisation and small outward current on depolarisation, maintaining a stable baseline potential.[5,13] Figure 2 summarises the principal ionic currents underpinning the atrial, Purkinje fibre (conducting tissue) and ventricular myocyte action potentials, along with physiological modulators of the ionic currents and their pharmacology (therapeutic and experimental).

As mentioned, regional differences in AP duration exist within the myocardium, for example between endocardium and epicardium (Fig 1), resulting from differential expression of $K^+$ channels, especially $K_v4.3$ responsible for $I_{to}$.[5,13] In health, this ensures one-way conduction of depolarisation preventing re-entrant circuits. In disease, changes in impulse propagation and AP duration and therefore refractory period duration can give rise to formation of an arrhythmia substrate, that
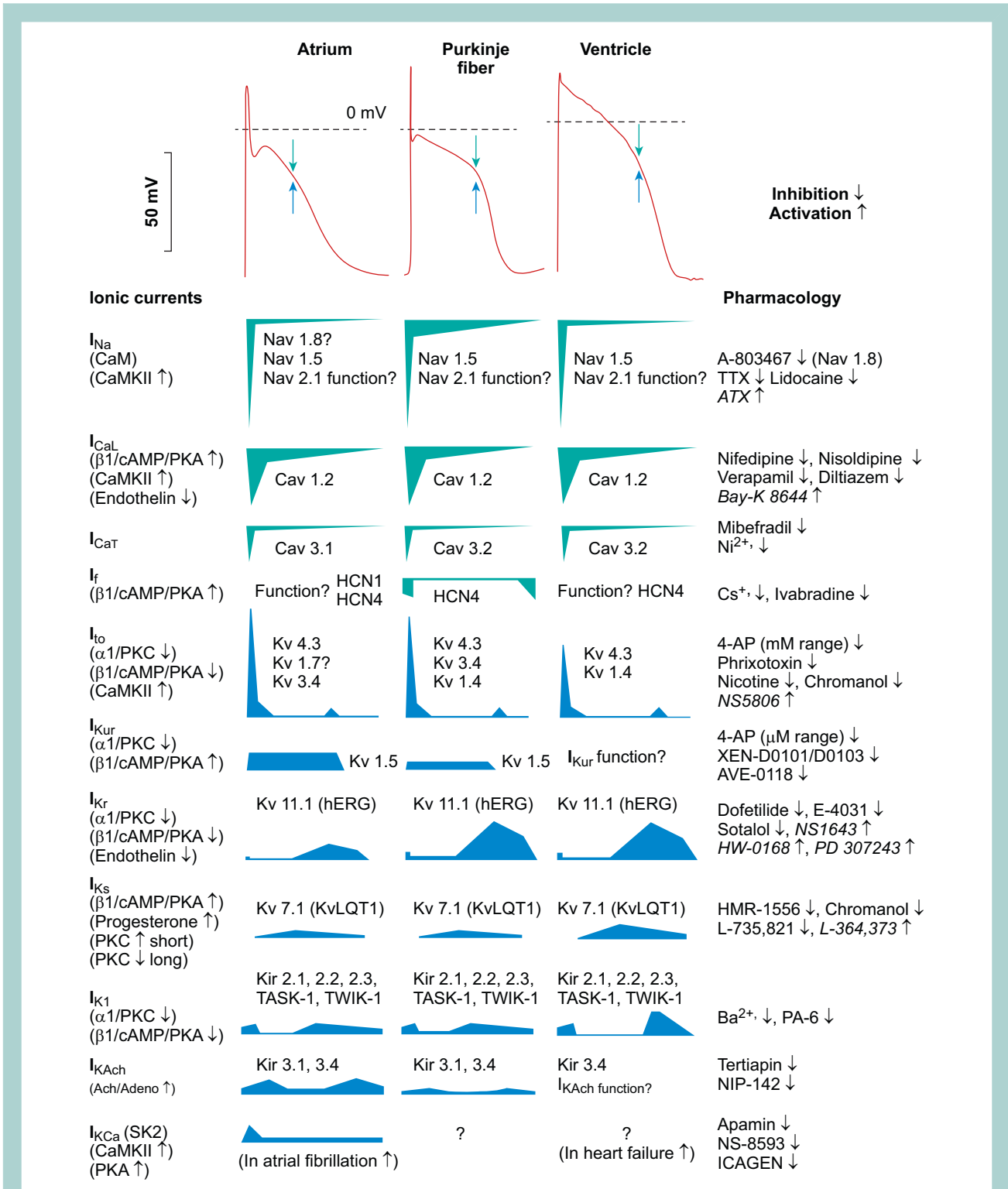
**Fig 2** Tissue-specific (human) cardiac atrial, Purkinje fibre, and ventricular action potentials and the underlying ionic currents in different action potential phases, indicating their pharmacology and modulation. Black arrows indicate inward and yellow arrows indicate outward current. The contributions of different currents to the action potentials are indicated below the action potentials, with a time course adjusted to the action potential. CaM, calmodulin; CaMKII, $Ca^{2+}$-calmodulin kinase II; hERG, human ether-à-go-go-related gene; $I_{K1}$, inward rectifier potassium current; $I_{K,Ach}$, acetylcholine-activated potassium current; $I_{Na}$, sodium current; $I_{CaL}$, L-type calcium current; $I_{CaT}$, T-type calcium current; $I_f$, funny/pacemaker current; $I_{to}$, transient outward current; $I_{KCa}$, calcium-activated potassium current; $I_{Kr}$, $I_{Ks}$, and $I_{Kur}$, rapid, slow, and ultrarapid components of delayed rectifier potassium current; $K_{ir}$, inward rectifier potassium channel; $K_V$, voltage-gated potassium channel; $Na_V$, voltage-gated sodium channel; TASK, tandem of pore domains in a weak inward rectifying potassium channel (TWIK)-related acid-sensitive potassium channel; TTX, tetrodotoxin. Reproduced from Varro 2020 *et al.*,[5] licensed under Creative Commons Attribution CC-BY 4.0.
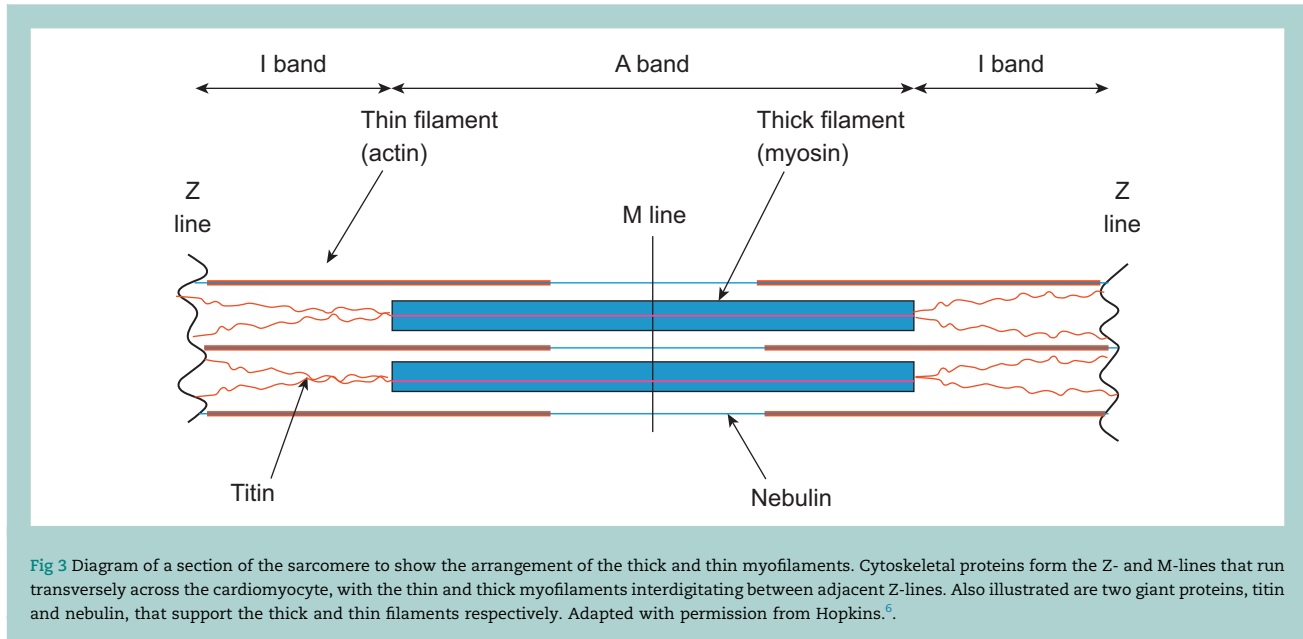
**Fig 3** Diagram of a section of the sarcomere to show the arrangement of the thick and thin myofilaments. Cytoskeletal proteins form the Z- and M-lines that run transversely across the cardiomyocyte, with the thin and thick myofilaments interdigitating between adjacent Z-lines. Also illustrated are two giant proteins, titin and nebulin, that support the thick and thin filaments respectively. Adapted with permission from Hopkins.[6]

combined with a trigger can result in dangerous re-entry tachycardia.[5] Such triggers may be ectopic beats resulting from early or delayed after-depolarisations, most commonly caused by reactivation of L-type calcium channels during prolonged AP duration, or spontaneous diastolic SR $Ca^{2+}$ release leading to a depolarising NCX current respectively.[5]

## Excitation − contraction coupling

When an action potential reaches a cardiomyocyte, a rapid increase in intracellular $[Ca^{2+}]$ is triggered, which results in activation of the contractile proteins, actin and myosin (Fig. 3), resulting in sarcomeric and thus cellular shortening. The force of cardiac muscle contraction, or inotropy, for a given muscle mass depends on the increase in intracellular $[Ca^{2+}]$ and the sensitivity of the myofilaments to $Ca^{2+}$.[3] Thus mechanisms that control inotropy either regulate calcium handling or affect actin-myosin interaction.[3]

### Calcium release

Numerous T-tubule invaginations of the sarcolemma ensure complete and synchronous action potential propagation into the core of the cell and their loss in heart failure contributes to contractile dysfunction.[15] L-type calcium channels within the t-tubules are in close apposition to multiple type 2 ryanodine receptors (RyR2s) located within the junctional SR membrane.[3] These units are called 'couplons', with a RyR2 to L-type calcium channel ratio of approximately 4:1 resulting in signal amplification.[16] $Ca^{2+}$ entry via $I_{Ca}$ triggers opening of RyR2s resulting in further $Ca^{2+}$ release from the SR, a process called calcium-induced calcium release (CICR).[3] L-type calcium channels are inactivated by the rising intracellular $[Ca^{2+}]$, while RyR2s are closed by intrinsic inactivation and a decrease in SR $[Ca^{2+}]$, which decreases by 50−75% during contraction.[3,15] In fact SR $[Ca^{2+}]$ is a major determinant of the amplitude of $Ca^{2+}$ release and abnormalities in this flux have been identified in multiple pathologies.[15] Increased $Ca^{2+}$ leak from the SR caused by protein kinase A (PKA)-mediated RyR2 hyperphosphorylation in heart failure may contribute to the

reported decrease in SR $[Ca^{2+}]$ and the amplitude of calcium release during contraction.[3,15] In general, increased diastolic $Ca^{2+}$ leak via RyR2 promotes spontaneous SR $Ca^{2+}$ waves, which induce a transient inward current associated with $Ca^{2+}$ extrusion via electrogenic NCX. If the resulting delayed after-depolarisations reach threshold, this may trigger ventricular arrhythmias, as seen in catecholaminergic polymorphic ventricular tachycardia and heart failure.[15,17] In health, when SR $[Ca^{2+}]$ decreases, there is reduced inactivation of $I_{Ca}$ leading to increased calcium entry to the cell and replenishment of SR stores.[3] During diastole, cytosolic $Ca^{2+}$ must decrease to allow relaxation. In humans, the majority (approx. 70%) of $Ca^{2+}$ is removed by the SERCA (sarco-endoplasmic $Ca^{2+}$ ATPase), while the rest is mainly extracted by NCX.[3] In heart failure there is reduced expression of SERCA and the contribution of NCX is increased, also contributing to $Ca^{2+}$ depletion.[3] In neonates the immature SR contributes less to systolic calcium flux and there is an increased reliance on extracellular calcium entry, mainly through L-type calcium channels and NCX, to maintain contractility.[18]

Sympathetic stimulation results in enhanced inotropy and lusitropy via increased cAMP production and PKA activation. There is phosphorylation of phospholamban, L-type Ca channels, RyR2, cardiac troponin I (cTnI) and myosin binding protein C. Phosphorylation of phospholamban is the most important for lusitropic effect.[3] This protein normally inhibits SERCA but when phosphorylated, inhibition is removed and SERCA activity is increased leading to an increase in SR $Ca^{2+}$ content, systolic $Ca^{2+}$ release and contractility. Phospholamban genetic knockout results in a hyperdynamic heart in rats.[3]

### Actin-myosin interaction

Striated muscle contraction is the result of interaction between thick and thin filaments within the sarcomere (Fig. 3). When intracellular $[Ca^{2+}]$ rises, $Ca^{2+}$ binds troponin C of the troponin complex; this leads to displacement of tropomyosin from myosin-binding sites on actin.[6] Myosin heads complexed with ADP and inorganic phosphate (Pi) in the high

energy position bind to actin (Fig. 4), which induces a conformational change resulting in dissociation of ADP and Pi, pivoting of the myosin head and sliding of the filaments.[6] Following this, ATP binds the myosin head, resulting in detachment from actin, ATP hydrolysis and a return to its high energy position.[6] Each cycle generates a force of approximately $3.5 \times 10^{-12}$ N, and 11 nm of displacement.[19]

Myosin is a hexameric protein molecule, consisting of two heavy chains, and four light chains.[20] Heavy chains are the molecular motors of contraction with a long tail segment, a lever arm region and the cross-bridge forming head.[21] Two heavy chains are intertwined at their tail ends with an essential and a regulatory light chain binding each lever arm.[20] There are two main isoforms of myosin heavy chains in mammalian hearts, α and β, the former possessing nearly three times higher ATPase activity.[19] This leads to increased velocity of contraction but at the expense of higher ATP consumption. Relative expression of α and β heavy chains in health and disease is an active area of research.[21] B-myosin heavy chain is the predominant isoform in human hearts and variants in its encoding gene (MYH7) together with variants in the cardiac myosin binding protein-C gene (MYBPC3) account for almost 70% of inherited hypertrophic cardiomyopathies.[22,23]

Cardiac myosin binding protein-C (cMyBP-C) regulates cross-bridge formation between myosin head and actin, serving as a brake in its dephosphorylated state.[24] When phosphorylated by PKA, it facilitates the binding of the myosin head with actin, thereby modulating cardiac contractility.[24]

At rest some myosin heads are available for actin binding, protruding from the thick filament in their "on" configuration, while some lie parallel to the their tail segment in the "off" configuration.[21] Regulatory myosin light chains (RLCs) bind the lever arm region of the heavy chains, and through their phosphorylation status, influence the configuration of the head.[20,21] (Fig. 5) When RLC is phosphorylated by myosin light-chain kinase (MLCK), it stabilises the myosin head in the "on" configuration, making it available for actin binding, enhancing contractility. In health, approximately 40% of RLCs are phosphorylated within the sarcomere, suggesting significant contractile reserve through this tuning mechanism and it has been shown that RLC phosphorylation is reduced in human heart failure.[21]

Another mechanism of fine tuning cardiac muscle contraction is through phosphorylation of cTnI at serines 23/24 (cTnI-Ser23/24) by PKA, which reduces $Ca^{2+}$ sensitivity, leading to increased relaxation or lusitropy.[25] Loss of β-adrenergic sensitivity leads to reduced PKA activity and reduced cTnI phosphorylation which has been demonstrated in a wide variety of heart failure aetiologies, including patients with diastolic dysfunction.[25] Phosphorylation of cTnI-Ser23/24 may also play a role in Frank-Starling's law of length-dependent activation of myofilaments.[25]

Genetic studies have highlighted the importance of the structural proteins that maintain the normal alignment and spatial orientation of the thin and thick filaments within the cardiomyocyte sarcomeres. Of particular note is titin, a giant protein that extends between the Z- and M-lines to support the thick filaments. Variants in TTN, the gene encoding titin, are associated with dilated cardiomyopathy, hypertrophic cardiomyopathy type 9, early onset atrial fibrillation and heart failure.[26]

## Metabolism

The heart requires vast amounts of energy to power its contractile and basic cellular functions. It has the highest oxygen extraction of any tissue and the average adult heart turns over approximately 6 kg ATP in a day.[27] Mitochondria occupy a third of the cellular volume, as >95% of ATP is generated by oxidative phosphorylation, glycolysis making up a meagre, but important 5%.[27,28] Energy in the heart is stored as ATP and creatine phosphate, their conversion being catalysed by creatine kinase (CK). However ATP and creatine phosphate stores are limited and ischaemia rapidly results in overt ATP depletion and contractile dysfunction. Some energy is stored as glycogen but myocardial stores are much lower than in skeletal muscle.[27] The heart is 'omnivorous', but under usual conditions, 70–90% of ATP is generated from fatty acid oxidation, the rest from glucose, lactate and ketone bodies.[28] Fatty acid and glucose pathways are closely interlinked and reciprocally inhibit each other's metabolism via the Randle cycle.[28] Lactate and ketone bodies can become an important fuel source during exercise and fasting respectively.[27]

Cellular fatty acid uptake is facilitated by fatty acid translocase (CD36), whereas glucose enters via glucose transporters GLUT1 and GLUT4.[28] GLUT1 is constitutively active and is the main transporter in the fetal heart, whereas GLUT4 is insulin regulated and is predominant in the adult heart.[28] Fatty acids require specialised transport to enter the mitochondria, through the carnitine shuttle, where they undergo β-oxidation, to yield NADH, FADH and acetyl CoA.[28] Carnitine palmitoyltransferase I (CPT1) is inhibited by high glucose levels, whereas excess cytosolic fatty acids reduce the activity of
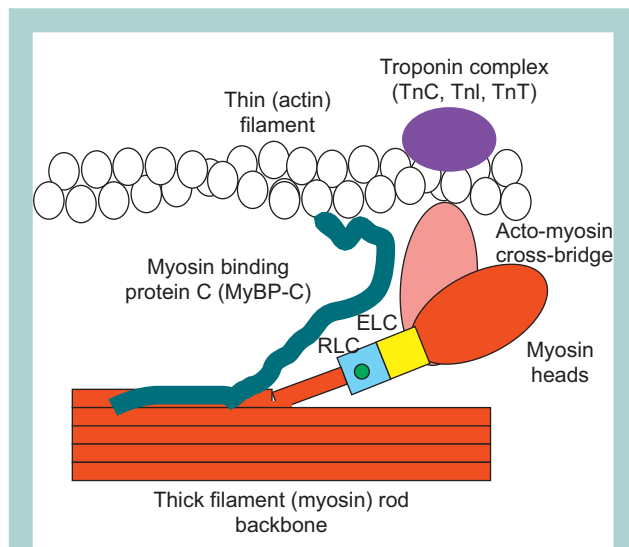


Fig 4 A simplified pictorial representation of the actin-myosin structure with (RLCs). The diagram shows the thick (myosin containing, *red*) filament backbone and thin (actin containing, *white circles* represent actin monomers) filament with an actin-myosin cross-bridge. The essential myosin light chain (ELC, *yellow box*) and phosphorylated regulatory myosin light chains (RLC, *blue box*) are in the neck region of the myosin heavy-chain monomer. The myosin head interacts weakly or strongly with the thin filament forming a cross-bridge structure. The troponin complex (*purple oval*) on the thin filament comprised of troponin C, troponin I, and troponin T activate muscle contraction via calcium binding. Myosin binding protein C (MyBP-C) (*cyan*) is associated with the thick filament backbone and also interacts with the thin filament (not drawn to scale). Reproduced from Yu *et al.*, 2016,[19] licensed under Creative Commons Attribution CC-BY 4.0.
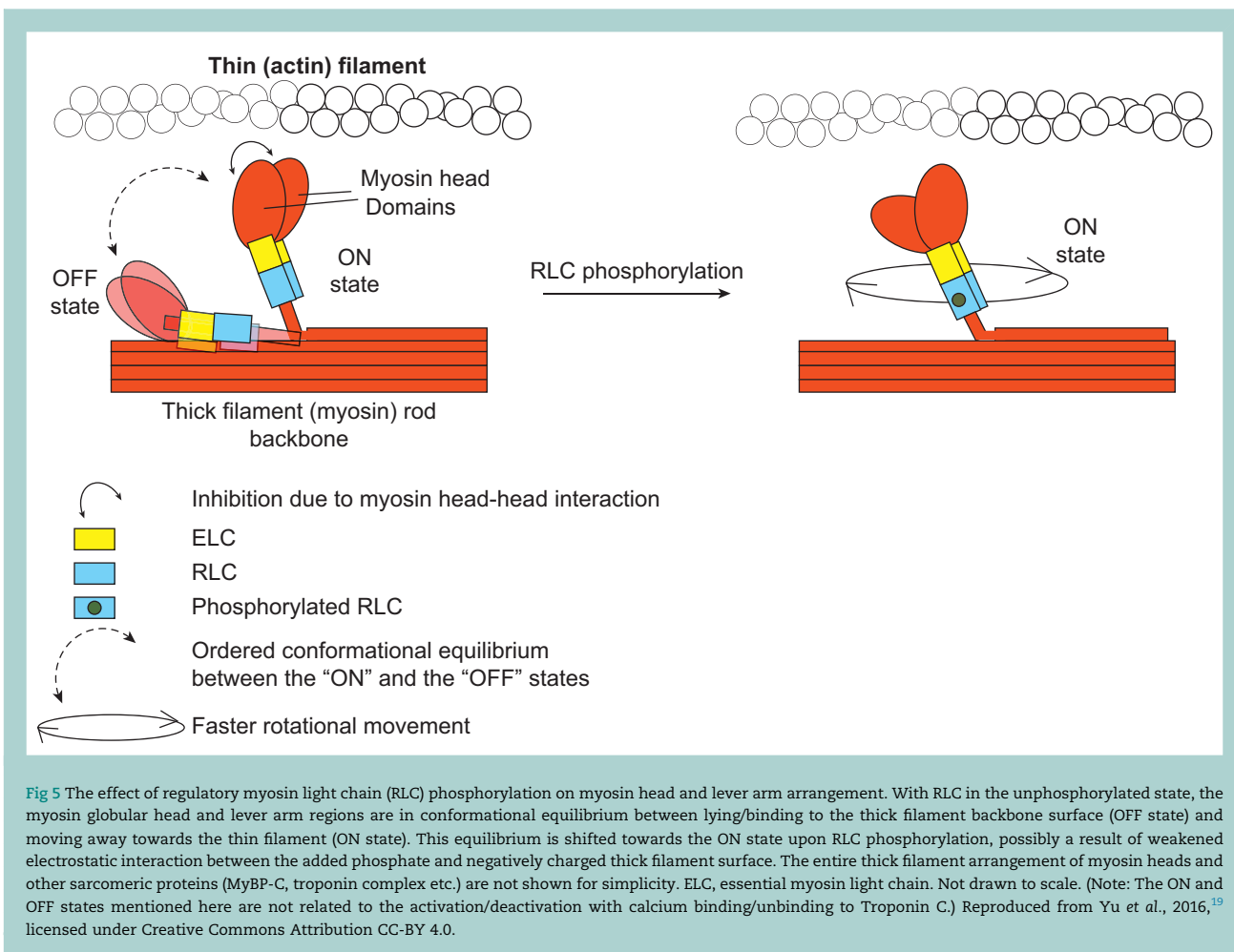
**Fig 5** The effect of regulatory myosin light chain (RLC) phosphorylation on myosin head and lever arm arrangement. With RLC in the unphosphorylated state, the myosin globular head and lever arm regions are in conformational equilibrium between lying/binding to the thick filament backbone surface (OFF state) and moving away towards the thin filament (ON state). This equilibrium is shifted towards the ON state upon RLC phosphorylation, possibly a result of weakened electrostatic interaction between the added phosphate and negatively charged thick filament surface. The entire thick filament arrangement of myosin heads and other sarcomeric proteins (MyBP-C, troponin complex etc.) are not shown for simplicity. ELC, essential myosin light chain. Not drawn to scale. (Note: The ON and OFF states mentioned here are not related to the activation/deactivation with calcium binding/unbinding to Troponin C.) Reproduced from Yu *et al.*, 2016,[19] licensed under Creative Commons Attribution CC-BY 4.0.

pyruvate dehydrogenase (PDH) a crucial regulator of glucose metabolic flux.[29] Oxidation of fatty acids yields more ATP per mol of substance than glucose but at the expense of higher $O_2$ consumption.[29] Many metabolic intermediates have signal transducing roles, that extend to the control of metabolism, mitochondrial biogenesis and beyond, therefore modulating metabolic pathways can have far-reaching and complex effects.[28] Under ischaemic conditions there is an accumulation of excess lipids and metabolites which uncouple oxidative phosphorylation, reducing ATP synthesis and stimulating cytochrome c release and apoptosis as well as interacting with sarcolemmal ion channels to increase arrhythmia potential.[29]

In hypertrophy and heart failure there is a switch from fatty acids to glucose as the primary fuel, similar to the fetal heart, resulting in improved efficiency but eventually reduced overall ATP generation.[27] Whether this is adaptive or maladaptive is still a matter of debate but with disease progression there is worsening mitochondrial dysfunction, inefficient transduction of energy from ATP to myofilaments and contractile dysfunction.[27,28]

Manipulation of this metabolic balance has been a matter of great interest in the search for effective therapies for hypertrophy and heart failure. Glucose-insulin-potassium (GIK) infusion is one such therapy that has been studied extensively over the past 50 years.[29] GIK increases glycolytic flux and ATP generation, reduces fatty acid uptake and metabolism and attenuates ischaemia-reperfusion damage in animal models.[29] Human trials have had mixed results but when GIK is given close to the time of ischaemic insult, outcomes are more promising.[29] Studies in cardiac surgery have shown reduced incidence of low cardiac output syndrome and inotrope use and improved systolic and diastolic function.[30,31] The IMMEDIATE trial compared early infusion of GIK with placebo in patients with suspected acute coronary syndrome. Although there was no benefit shown for the primary outcome of conversion of acute coronary syndrome to myocardial infarction, results of secondary outcomes suggested a reduction in the composite outcome of cardiac arrest and in-hospital death, with lower risk of serious adverse cardiovascular events at 1 year.[32]

## Conclusions

Cardiomyocytes are uniquely adapted to fulfil their purpose at the centre of the circulatory system. Our understanding of the myriad pathways and mechanisms that characterise their function in health and disease is constantly growing. With an increasing elderly population, anaesthetists increasingly encounter patients with chronic heart disease. Our interventions in operating theatres and the ICU can have a

profound effect on the circulation, therefore understanding cardiac physiology remains core knowledge for our practice.

## Declaration of interests

PMH is editor-in-chief of *BJA Open* and an editorial board member of the BJA. The other authors declare no conflicts of interest.

## MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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