# Initiation and regulation of the heartbeat

Emrys Kirkman

## Abstract

The heart has all the components necessary to initiate and maintain a regular heartbeat, without the need for external influence. Thus, a transplanted heart without nervous connection, or a heart completely removed from the body, if adequately perfused with oxygen, beats rhythmically. In the normal intact body, the function of the nervous and humoral regulation is to modulate the activity of the heart, though some aspects of modulation are intrinsic properties of cardiac muscle.

**Keywords** Action potential; pacemaker cells; sinoatrial node

**Royal College of Anaesthetists CPD Matrix:** 1A01

## Learning objectives

After reading this article, you should be able to:

- explain the process of electrochemical coupling in the heart
- describe the role of actin, myosin, tropomyosin, troponin and ATP in cardiac muscle contraction
- explain the mechanism underlying the effect of the sympathetic nervous system on the force of cardiac muscle contraction

## Origin of the heartbeat: pacemaker cells

Cardiac muscle fibres can be grouped broadly into three main functional categories:

- pacemakers, which initiate the heartbeat by spontaneously generating action potentials
- conducting fibres, which spread the action potentials throughout the heart in an ordered manner to ensure efficient pumping
- myocardial fibres (most fibres), which produce the force needed to pump blood round the body.

Some of the conducting fibres are also capable of generating action potentials spontaneously, though they do not do so under normal circumstances. The force-producing (myocardial) fibres are normally incapable of spontaneous action potential generation, although under abnormal conditions (e.g. following a period of ischaemia) they may acquire the property and cause problems such as arrhythmias.

The two main groups of pacemaker cells in the heart are found in the sinoatrial (SA) and atrioventricular (AV) nodes (Figure 1). Normally, those of the SA node dominate and the rate and rhythm of the heart is dictated by that of the SA node. However, if the SA node fails, or electrical conduction between the atria and ventricles is blocked, then the AV node pacemaker cells assume control and pace the heart. If the AV node fails, other pacemakers lower in the hierarchy can assume the role of heartbeat generation, though the spread of the heartbeat may be grossly abnormal.

In the human heart, the SA node lies in the groove where the superior vena cava joins the right atrium (Figure 2). The SA node contains two histologically distinct fibre types:

- small round cells with few organelles and contractile proteins
- longer elongated cells, which look intermediate between the small round cells and the atrial force-producing cells.

The small round cells are thought to be the pacemakers. Detailed mapping of the atrial surface reveals that there are two to three sites of automaticity within 1–2 cm of the SA node. It is suggested that these sites, together with the SA node, act as the normal atrial pacemaker complex. At times, all of the loci may produce action potentials simultaneously, while at other times the primary focus of activity shifts from one group to another, depending on the prevailing level of autonomic activity.

## Resting membrane potential, pacemaker potential and action potentials

The key to understanding action potentials and pacemaker activity is to be able to explain the resting membrane potential and the factors that influence it. If an electrode is inserted into a living cell, an electrical potential difference is usually found to exist between the inside and the outside; the inside being negative with respect to the outside. A reduction in this potential difference (i.e. if it moves towards zero) is termed a depolarization, while an increase in difference beyond the resting level (inside becomes more negative) is called a hyperpolarization. Excitable tissue (cardiac muscle is an example) has an additional property: if the membrane is depolarized to a specific level (the threshold) a chain of events ensues that leads to a further depolarization and reversal of polarity (inside becoming positive) before the membrane eventually repolarizes back to the resting level (Figure 3). This is an action potential. The potential-time characteristics (shape) of the electrical changes occurring during an action potential are different in pacemaker cells (Figure 3a) and force-producing myocytes (Figure 3b). A key difference is that the pacemaker cells at rest display a slow spontaneous depolarization to threshold and therefore an automatic generation of action potentials. This slow depolarization is known as a pacemaker potential or prepotential. Force-producing myocardial fibres do not display a pacemaker potential; their resting membrane potential is stable and they require an external stimulus, normally a depolarization from a neighbouring cell, to attain threshold and generate an action potential.

### Resting membrane potential

The origin of the resting membrane potential is the chemical concentration gradients of ions across the cell membrane and the selective permeability of the membrane to these ions. With regard to pacemaker activity, the two main ions are potassium ($K^+$)

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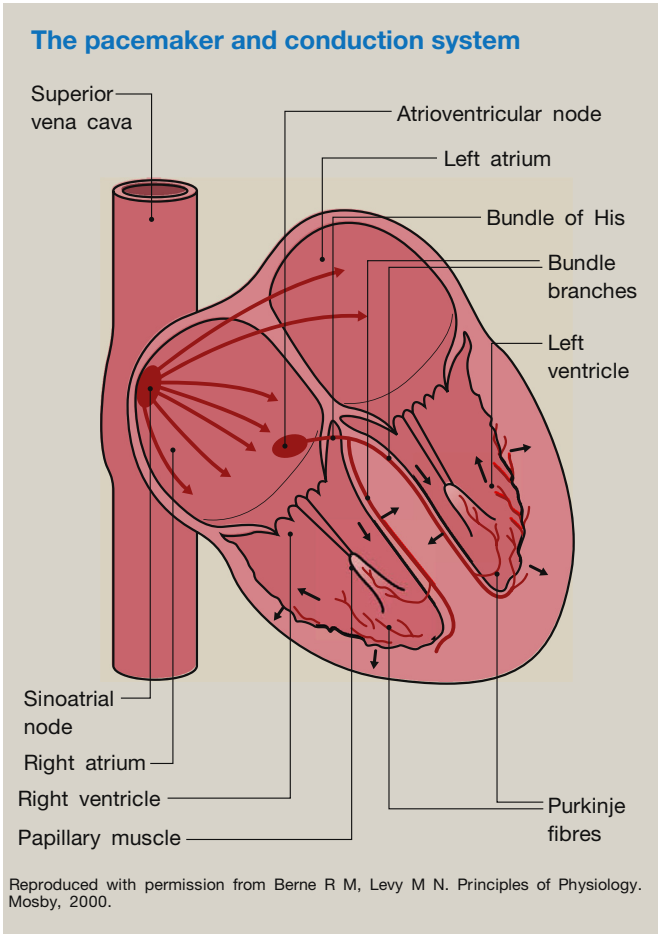


**Figure 1**

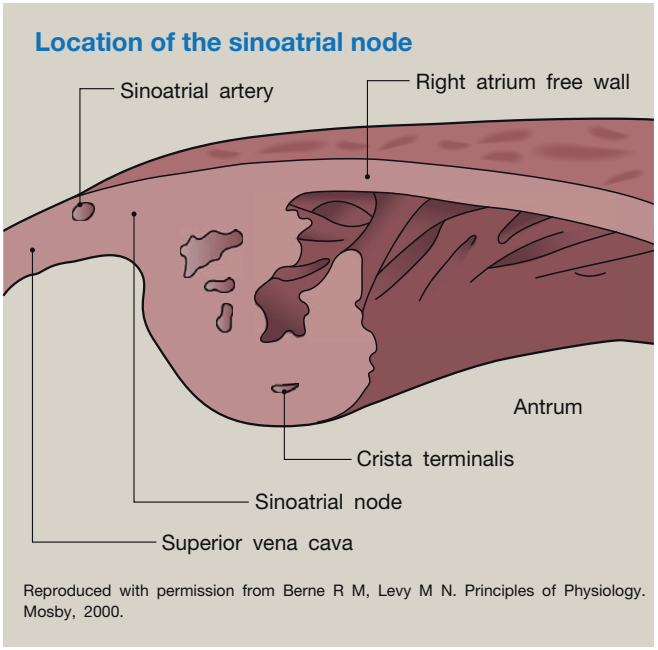


**Figure 2**

and calcium ($Ca^{2+}$), together with some contribution from sodium ($Na^+$). The $K^+$ concentration is much higher inside the cells, while that of $Ca^{2+}$ and $Na^+$ is much higher outside (Figure 4). These ions cross the membrane via channels, which display varying degrees of selectivity for particular ions.

$K^+$ diffuses out of the cell down its concentration gradient. The amount diffusing, as a proportion of the total amount present, is minuscule. However, the movement of the positive ions down their concentration gradient against the resistance of the membrance generates a potential difference, with the inside of the cell becoming negative. This electrical gradient opposes the movement of $K^+$ out of the cell, the negative interior attracting the positive $K^+$ ions. A state of equilibrium is therefore obtained when the electrical gradient is exactly equal and opposite to the chemical gradient. This is the electrochemical equilibrium, and potential difference attained at this point is referred to as the equilibrium potential for that particular ion.

In the case of $Ca^{2+}$ and $Na^+$ the chemical concentration gradient is such that these diffuse into the cell (Figure 4). Thus, the electrochemical equilibria for these ions has the inside of the cell positive (Figure 4). It is possible to calculate the equilibrium potential for any ion, given the concentrations of the ions on either side of the cell membrane, using the Nernst equation. For a positive ion at equilibrium in an environment at 37°C:

$$E_{ion} = -61.5 \log_{10}\left([Ion^+]_i / [Ion^+]_o\right)$$

where $E_{ion}$ is the equilibrium potential for the ion, $[Ion^+]_i$ is the concentration of the ion inside the cell and $[Ion^+]_o$ is the concentration of the ion outside the cell.

For a typical cardiac muscle fibre cell the equilibrium potential for $K^+$, $Ca^{2+}$ and $Na^+$ is shown in Figure 4. Given that each of these ions is attempting to 'drive' the membrane potential to their respective equilibrium potentials, what determines the membrane potential at any given instant? To answer this we must discuss the relative permeability of the membrane to these ions.

Consider an extreme example in which the membrane was permeable only to $K^+$. Under these circumstances, $Ca^{2+}$ and $Na^+$ could not diffuse across the membrane and could not influence its electrical potential. Under 'resting' conditions, the membrane potential is closer to $E_K$ (the equilibrium potential for potassium) than it is to $E_{Ca}$ or $E_{Na}$ because the membrane is more permeable to $K^+$. The resting membrane potential is influenced by the transmembrane chemical concentration difference of a number of ions and the relative permeability of membrane to these ions. This allows us to explain the pacemaker potential and the action potential in the pacemaker cells.

### SA node cells: pacemaker and action potentials

The pacemaker and the action potential are brought about by a change in the relative permeability of the membrane to a range of ions, the most important of which are $K^+$ and $Ca^{2+}$, with some contribution from $Na^+$. This change in membrane permeability occurs because a number of membrane channels for these ions are 'gated' (they can be open and functional, or closed and prevent passage of the ion). The state of some ion channels (open or closed) is dictated by the membrane potential (i.e. they are voltage-gated).

At the start of the prepotential, the permeability to $K^+$ is relatively high, therefore there is an outward movement of $K^+$




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