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Aspects of Myocardial Physiology

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Summary

This article describes in more detail the physiology of the cardiac action potentials (nodal and Purkinje cell), the mechanics of the cardiac cycle and the control of coronary artery perfusion.

CARDIAC ACTION POTENTIALS

Action potentials (APs) are sequential changes in transmembrane potential that occur as a result of activity of ion channels, resulting in the propagation of electrical impulses in excitable cells. The heart has a multicellular structure but behaves like a syncytium because the individual muscle cells communicate with their neighbours through gap junctions, which provide low resistance pathways for easy movement of action potentials between cells. The cardiac action potential (~250ms) is much longer than those of nerve or skeletal muscle (~1-3ms). This is due to a prolonged plateau phase caused by calcium ion influx. Two types of action potential occur in the heart: The fast response, found in heart muscle and Purkinje fibres (Figure 1) and the slow response, found in pacemaker tissues such as the sinoatrial and atrioventricular nodes (Figure 2).

The fast response (Figure 1)

The resting potential of cardiac muscle and Purkinje fibres is about -90mV (interior negative to exterior). An AP is initiated when the membrane is depolarised to a threshold potential of about -65mV. The initial depolarisation originates from transmission from an adjacent cell via gap junctions.

Phase 0 - Rapid depolarization

The inward current caused by opening of fast Na⁺ channels becomes large enough to overcome the outward current through K⁺ channels resulting in a very rapid upstroke.

Phase 1 - Early incomplete repolarisation

Due to inactivation of fast Na⁺ channels and efflux of K⁺ ions.

Phase 2 - Plateau phase

A period of slow decay mainly due to Ca²⁺ entering the cell via L-type (L=long lasting) Ca²⁺ channels which are activated slowly when the membrane potential is more positive than about -35mV. This is balanced by K⁺ efflux through various K⁺ channels. Calcium entry during the plateau is essential for contraction; blockers of L-type Ca²⁺ channels (e.g. verapamil) reduce the force of contraction.

Phase 3 - Rapid repolarisation

Ca²⁺ influx declines and the K⁺ outward current becomes dominant, with an increased rate of repolarisation.

Phase 4 - Electrical diastole

Resting membrane potential is restored.

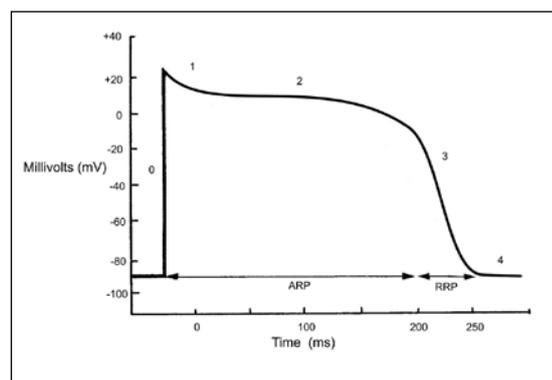


Figure 1. The fast response (Purkinje fibre) action potential; ARP – absolute refractory period, RRP – relative refractory period

The slow response (Figure 2)

These cells spontaneously depolarise and are said to have *automaticity*. Phases 1 and 2 are absent.

Phase 4 - Prepotential or pacemaker potential

There is no depolarisation plateau and the cells have an unstable resting membrane potential during this phase; they gradually depolarise from -60mV to a threshold of -40mV due to a slow continuous influx of Na⁺ ions and a decreased efflux of K⁺ ions. A Ca²⁺ current, due to the opening of T-type (T=transient) Ca²⁺ channels, completes the pacemaker potential.

Phase 0 - Depolarisation

When the membrane potential reaches threshold potential, the L-type calcium channels open, causing Ca²⁺ influx and an AP is generated.

Phase 3 - Repolarisation

Due to efflux of K⁺.

Norepinephrine and epinephrine (mediated via β_1 -receptors) increase the slope of phase 4 by increasing

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Ca²⁺ influx, therefore increasing the heart rate. Ca²⁺ influx also increases the force of contraction. Acetylcholine (mediated via M2 receptors) decreases the slope of phase 4 by increasing K⁺ efflux and causing hyperpolarisation (increased negativity within the cells). This makes the conduction tissue much less excitable so it takes longer to spontaneously reach the threshold level. This results in a decrease in heart rate. The intrinsic rate of the SA node is 100 per minute, however vagal tone decreases this to about 70 beats per minute.

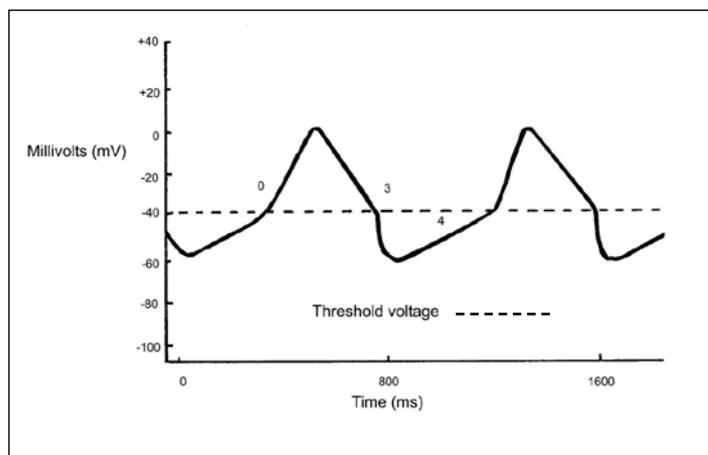


Figure 2. The slow response (sinoatrial node) action potential

Refractory periods

During the absolute refractory period (ARP) (Figure 1) the cardiac cell is totally inexcitable. During the following relative refractory period (RRP) there is a gradual recovery of excitability. A supramaximal stimulus can elicit an AP in the RRP. This AP, however, has a slower rate of depolarisation, a lower amplitude and shorter duration than normal and, therefore, the contraction produced is weaker. Peak muscle tension occurs just before the end of the ARP and the muscle is halfway through its relaxation phase by the end of the RRP. The long refractory period protects the ventricles from too rapid a re-excitation, which would impair their ability to relax long enough to refill sufficiently with blood. Unlike skeletal muscle, two contractions cannot summate and a fused titanic contraction cannot occur.

THE CARDIAC CYCLE

The cardiac cycle refers to the relationship between electrical, mechanical (pressure and volume) and valvular events occurring during one complete heartbeat (Figure 3).

Isovolumetric ventricular contraction (early systole)

The action potential is conducted through the AV node, down the bundle of His, across both ventricles and ventricular depolarisation occurs. This is the QRS complex of the ECG. Ventricular contraction causes a sharp rise in ventricular pressure, and the AV valves close (first heart sound) once this exceeds atrial pressure, preventing backflow into the atria. Ventricular pressure increases dramatically with no change in ventricular volume. During this initial phase of ventricular contraction pressure is less than in the pulmonary artery and aorta, so the outflow valves remain closed - the ventricular volume does not change.

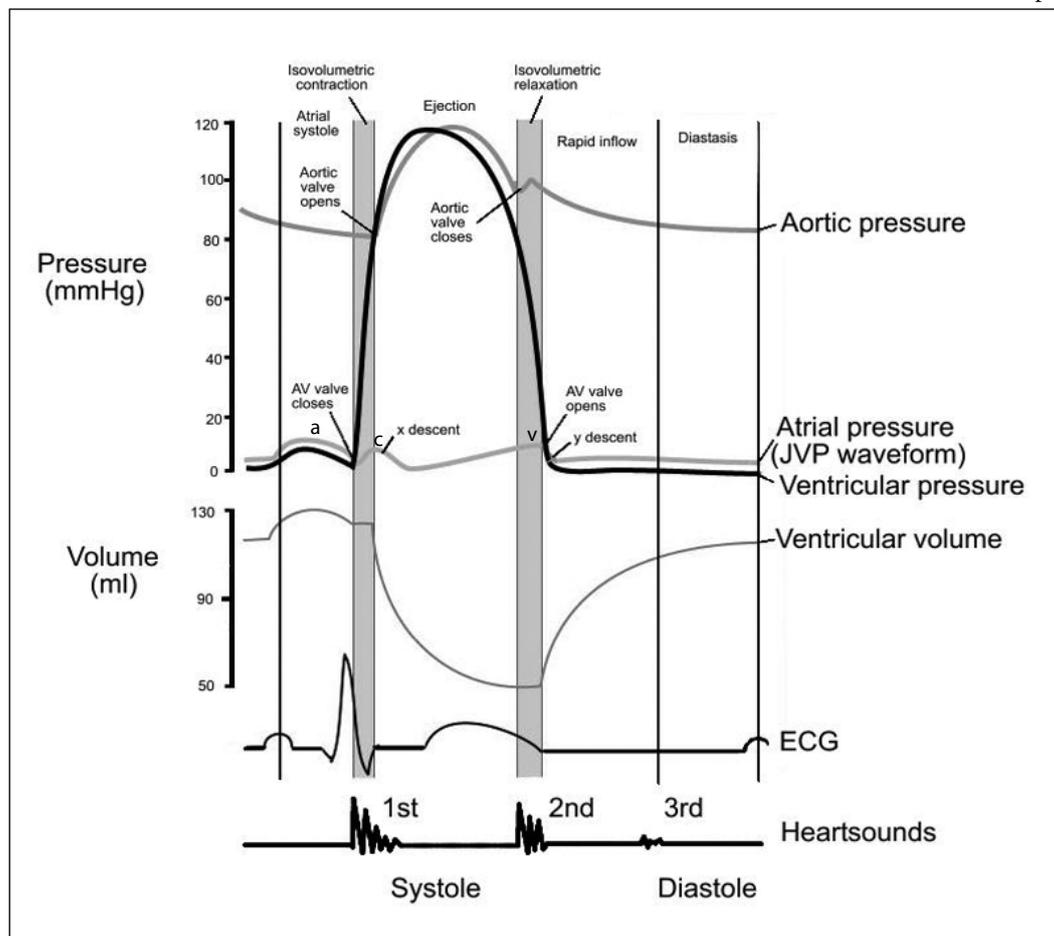


Figure 3. Events of the cardiac cycle

The increasing pressure causes the AV valves to bulge into the atria, resulting in the 'c' wave of the central venous pressure trace.

Ejection (systole)

The semilunar valves open as ventricular pressure exceeds aortic blood pressure. Approximately two thirds of the blood in the ventricles is ejected into the arteries. Flow into the arteries is initially very rapid (**rapid ejection phase**), but subsequently decreases (**reduced ejection phase**). The stroke volume (SV) is the volume of blood ejected from each ventricle in a single beat and the ejection fraction is SV/EDV (end diastolic volume). Arterial blood pressure rises to its highest point (systolic blood pressure). During the last two thirds of systole, before the AV valves open again, atrial pressure rises as a result of filling from the veins, resulting in the 'v' wave of the central venous

pressure trace. Active contraction ceases during the second half of ejection, and the ventricular muscle repolarises. This is the T wave of the ECG. Ventricular pressure during the reduced ejection phase is slightly less than in the artery, but blood continues to flow out of the ventricle because of momentum (**protodiastole**). Eventually, the flow briefly reverses, causing closure of the outflow valve and a small increase in aortic pressure, the **dicrotic notch**.

Isovolumetric relaxation (early diastole)

The ventricles relax and the ventricular pressure falls below arterial blood pressure. This causes the semilunar valves to close causing the second heart sound. The ventricular pressure falls with no change in ventricular volume. When ventricular pressure falls below atrial pressure, the AV valves open and the cycle begins again.

Passive filling (early diastole)

The atria and ventricles are relaxed and ventricular pressure is close to zero. The atrioventricular (AV) valves are open and the semilunar valves are closed. Blood flows from the great veins into the atria and ventricles. About 80% of ventricular filling occurs during this phase consisting of an initial **rapid filling** phase followed by a slower filling phase (**diastasis**).

Atrial contraction (late diastole)

A wave of depolarisation, beginning at the sinoatrial (SA) node, spreads across both atria and reaches the AV node. This is the P wave of the ECG. The atria contract and atrial pressures increases producing the 'a' wave of the central venous pressure trace. Blood continues to flow into the ventricles and ventricular pressure increases slightly. The atrial contribution to ventricular filling increases as heart rate increases and diastole shortens, and there is less time for passive filling. Ventricular

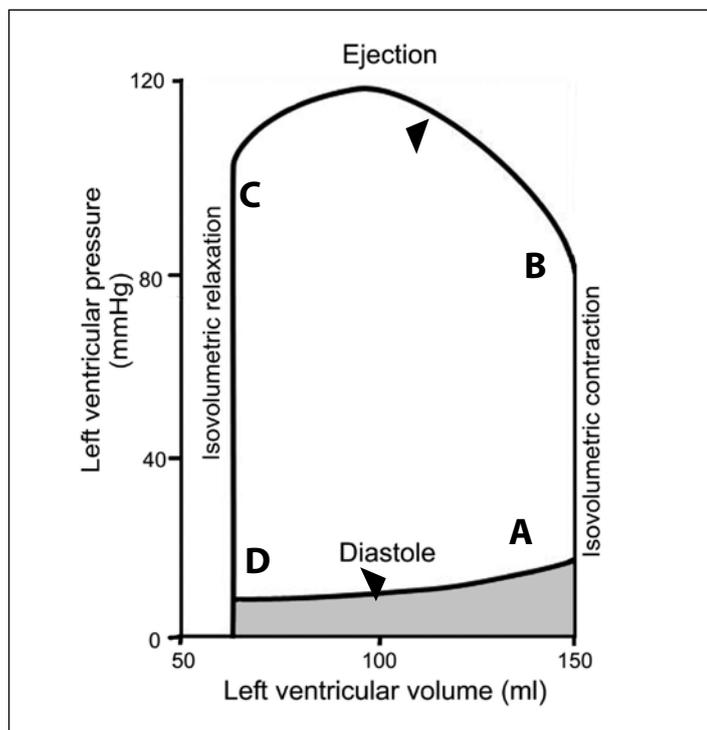


Figure 4. Left ventricular pressure-volume loop during a single heart cycle in a normal adult at rest

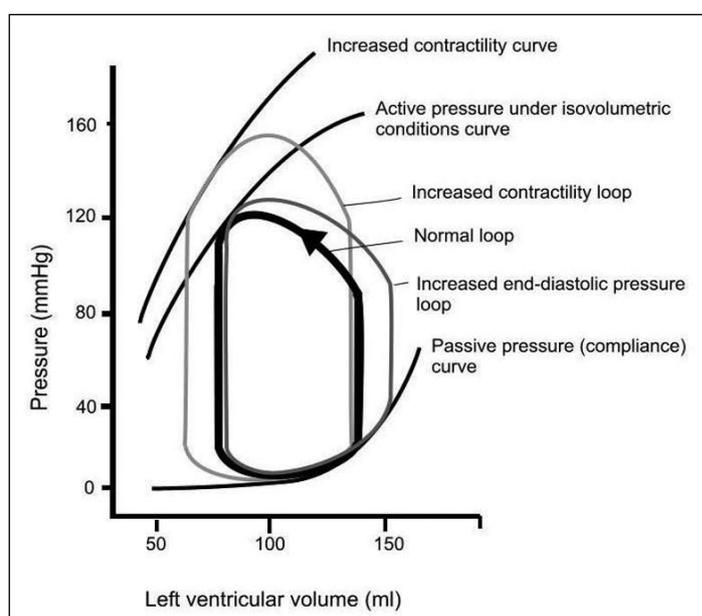


Figure 5. How the pressure-volume loop is affected by the contractility and compliance of the ventricle, and factors that alter refilling or ejection

volume (EDV) = volume of blood in the ventricle at the end of diastole. Arterial pressure is at its lowest at this stage of the cycle.

The X descent of the CVP trace results from atrial relaxation and downward displacement of the tricuspid valve during ventricular systole. The Y descent of the CVP trace is due to atrial emptying as the tricuspid valve opens and blood enters the ventricle.

THE PRESSURE VOLUME LOOP (Figures 4 and 5)

This represents the events of the cardiac cycle. The cardiac cycle proceeds in an anticlockwise direction. (A) End diastole, (B) aortic valve opening, (C) aortic valve closure, (D) mitral valve opening. EDV and end systolic volume (ESV) are represented by points A and C respectively. The area enclosed by the loop represents the stroke work (since work = pressure x volume). The pressure-volume curve in diastole is initially quite flat, indicating that large increases in volume can be accommodated by only small increases in pressure. However, the ventricle becomes less distensible with greater filling, as evidenced by the sharp rise of the diastole curve at large intraventricular volumes.

CONTROL OF THE CORONARY CIRCULATION

Myocardial blood supply is from the right and left coronary arteries, which run over the surface of the heart giving branches to the endocardium (the inner layer of the myocardium). Venous drainage is mostly via the coronary sinus into the right atrium, but a small proportion of blood flows directly into the ventricles through the Thebesian veins, delivering unoxygenated blood to the systemic circulation.

The heart at rest receives about 5% of the cardiac output. Coronary blood flow is approximately 250ml.min⁻¹. Oxygen extraction by the myocardium at rest is very high (65%) compared to other tissues (35%). Therefore, the myocardium cannot compensate for reductions in blood flow by extracting more oxygen from haemoglobin. Any increases in myocardial O₂ demand must be met by an increase in

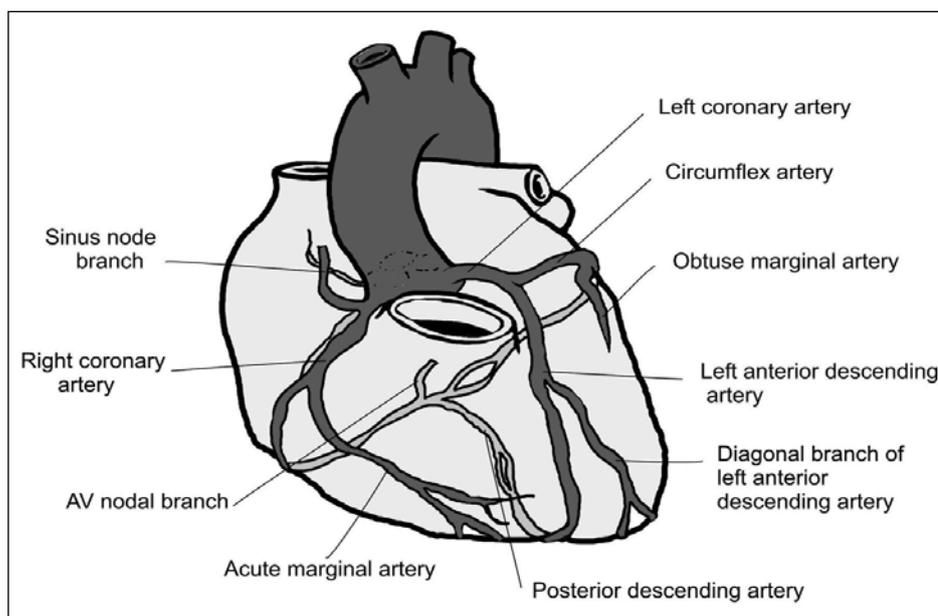


Figure 6. *The anatomy of the coronary arteries*

coronary blood flow. The three main factors influencing coronary flow are **mechanical**, mainly external compression and perfusion pressure, **metabolic** and **neural**.

Coronary artery compression and blood flow

Left coronary arterial blood flow is unique in that there is interruption of flow during systole (mechanical compression of vessels by myocardial contraction) and flow occurs predominantly during diastole when cardiac muscle relaxes and no longer obstructs blood flow through ventricular vessels. Conversely, right coronary arterial flow rate is highest during systole, because the aortic pressure driving flow increases more during systole (from 80 to 120mmHg) than the right ventricular pressure, which opposes flow (from 0 to 25mmHg). As about 80% of the total coronary arterial flow occurs during diastole, a pressure around the aortic diastolic pressure becomes the primary determinant of the pressure gradient for coronary flow. Coronary perfusion pressure is the arterial diastolic pressure minus left ventricular end diastolic pressure ($CPP = ADP - LVEDP$). Increases in heart rate that shorten diastole time for coronary blood flow are likely to increase oxygen consumption more than elevations in blood pressure, which are likely to offset increased oxygen demands by enhanced pressure-dependent coronary blood flow. The myocardium

regulates its own blood flow (autoregulation) closely between perfusion pressures of 50 and 150mmHg. Beyond this range, blood flow becomes increasingly pressure dependent. This autoregulation is due to a combination of myogenic and metabolic mechanisms.

Metabolic factors

The close relationship between coronary blood flow and myocardial oxygen consumption indicates that one or more of the products of metabolism cause coronary vasodilation. Hypoxia and adenosine are potent coronary vasodilators. Others factors suspected of playing this role include $PaCO_2$, H^+ , K^+ , lactate and prostaglandins. Under normal conditions, changes in blood flow are entirely due to variations in coronary artery tone (resistance) in response to metabolic demand.

Neural Factors

The coronary arterioles contain α_1 -adrenergic receptors which mediate vasoconstriction, and β_2 -adrenergic receptors which mediate vasodilation. Sympathetic stimulation generally increases myocardial blood flow because of metabolic factors, and not because of β_2 -adrenergic stimulation. This is shown experimentally when the inotropic and chronotropic effects of sympathetic discharge are blocked by a β_1 selective blocker to reduce metabolic demand, and injection of norepinephrine in unanesthetized animals elicits coronary vasoconstriction. Therefore the direct effect of sympathetic stimulation is constriction rather than dilation of the coronary vessels and highlights the importance of metabolic control.

FURTHER READING

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