Cardiac automatism. The effect of ions and neurotransmitters on the cardiac functions

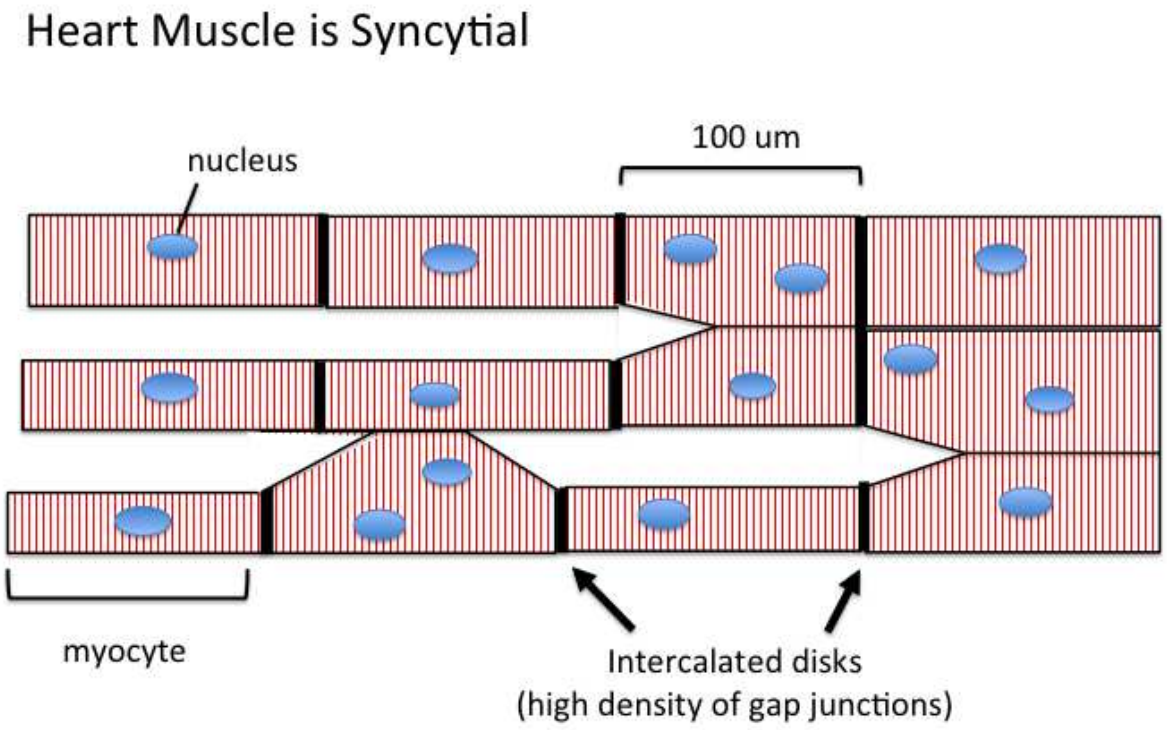
The primary function of the heart is to transfer sufficient blood from the venous system to the arterial side of the circulation under sufficient pressure to maintain the circulatory needs of the body. The heart consists of four chambers which act as two separate pump systems. The right atrium & ventricle (the right heart) pump deoxygenated blood collected from the great veins (superior & inferior vena cava) into the pulmonary circulation, via the pulmonary artery. The left atrium & ventricle (the left heart) pump oxygenated blood received from the pulmonary system into the systemic circulation. The atria, which sit dorsal to the ventricles are relatively thin walled, and their primary functions are to serve as a blood reservoir, and to assist in filling the ventricles with blood. In this sense they serve as "primer pumps". The ventricular chambers have much thicker walls (the left being thicker than the right). They can be thought of as the "power pumps" of the heart since they provide the primary force for pumping blood into the pulmonary and systemic circulations. The pattern with which the heart contracts and relaxes is cyclical and is divided into a period of relaxation (diastole), and a period of contraction (systole). When the heart relaxes during diastole, blood passively drains into the atria, and through them into the ventricles. Contraction of the atria at the end of diastole assists in filling the ventricles. This "atrial kick" contributes ~10% to the cardiac output. When the ventricles contract at the start of systole, the increase in pressure causes the closure of the tricuspid and mitral valves between the ventricles and atria (associated with the first heart sound, S1). The further increase in pressure that occurs after the tricuspid & mitral valves close causes the pulmonary and aortic valves to blow open, allowing the ejection of blood into the pulmonary and systemic circulation. Approximately 70ml (~60% of the blood in the ventricles at the end of diastole) gets ejected into the circulation during systole.

The coordinated and synchronized contraction of the muscle cells in each chamber of the heart that occurs during each cardiac cycle of systole and diastole is achieved by a regular pattern of excitation that precedes each contraction. The normal pattern of excitation begins with the spontaneous appearance of action potentials in the Sinoatrial node (SAN), which spontaneously generates action potentials at a frequency of 60-100 per minute. These action potentials spread rapidly through the left and right atria, and into the upper region of the atrioventricular node (AVN). Conduction through the AVN is slow, requiring more than a hundred milliseconds. This delay provides enough time for the atria to contract and assist in filling the ventricles with blood before they are stimulated to contract. Once the impulse exits the distal end of the AVN it enters the bundle of His, which subsequently divides into left and right bundle branches that lie beneath the endocardial surface on each side of the ventricular septum. Each bundle branch spreads downward from the base of the ventricle to the apex. These branches continuously divide into smaller Purkinje fibers that spread out and cover all parts of the ventricular endocardium. Conduction through the His-Purkinje system is very rapid, resulting in an "almost" simultaneous

stimulation of all muscle cells in both chambers. This causes them to contract at almost the same point in time. This coordinated contraction produces a reduction in ventricular volume that ejects blood across the valves into the pulmonary and systemic circulations.

In contrast to skeletal muscle, cardiac muscle fibers are made up of many individual muscle cells connected in series with each other by one or more “intercalated discs”. At the molecular level, intercalated discs consist of a group of gap junctions that provide a low-resistance electrical coupling between myocardial cells (atrial or ventricular). This design allows the electrical currents produced by an action potential in one cell to excite (depolarize) neighboring cells to threshold, so that the excitation wavefront spreads through cardiac muscle (atrial or ventricular) in the direction that muscle fibers are oriented. Such cell-to-cell communication is necessary for producing a coordinated contraction of muscle cells within each cardiac chamber.

Gap junctions also permit the spread of metabolic or second messenger signals between cells. Gap junctions can “close” under pathological conditions commonly produced during myocardial ischemia (e.g. chronic depolarization of neighboring cells, low pH_i, high Ca_i). An increase in gap junctional resistance can slow conduction, but may also help protect healthy myocardium from being damaged by a neighboring region of myocardial ischemia by physically isolating healthy cells from ischemic cells which have pathologically low pH_i, high Ca_i and depolarized resting potentials (analogous to closing the water tight doors to isolate the damaged region of a ship struck by a torpedo).



The spread of depolarization and repolarization that takes place during each heartbeat produces voltage changes that can be measured using electrodes placed on the surface of the body. When measuring the voltage changes along the frontal plane between the right and left arm (lead I), a voltage profile is observed. The initial spread of depolarization across the right and left atria produces a voltage deflection called the P wave. The delay in conduction that takes place in the AV node produces a prolonged isoelectric pause after the P wave which comprises a major part of the PR interval. Changes in conduction time through the AV node, which can result from changes in autonomic tone, drug effects, or heart disease, will result in changes in the PR interval. The depolarization of the ventricular myocardium is detected as the QRS complex, with the initial downward deflection (Q wave) reflecting initial depolarization of the septum prior to depolarization of the rest of the right & left ventricles. Depolarization spreads from the endocardium (where the Purkinje fibers terminate) outward to the epicardium. Factors that affect the normal spread of depolarization in the ventricular myocardium (sodium channel blocking drugs, myocardial ischemia, hyperkalemia) will widen the QRS duration. The T wave reflects ventricular repolarization, and the QT interval reflects the time for complete ventricular repolarization. While the QT interval also includes the QRS interval (the time for ventricular depolarization), clinically there are times when the QRS becomes oddly shaped, and fuses with the T wave, making it impossible to distinguish the end of the QRS with the beginning of the T wave. Hence the QT interval is used as a convention to measure the time it takes for the ventricle to repolarize after the onset of depolarization.

Cardiac action potentials have a complex shape that is distinctly different, and of much longer duration compared to those recorded from nerve or skeletal muscle. By convention the cardiac action potential is subdivided into 5 distinct phases (0 through 4). The phases are designated:

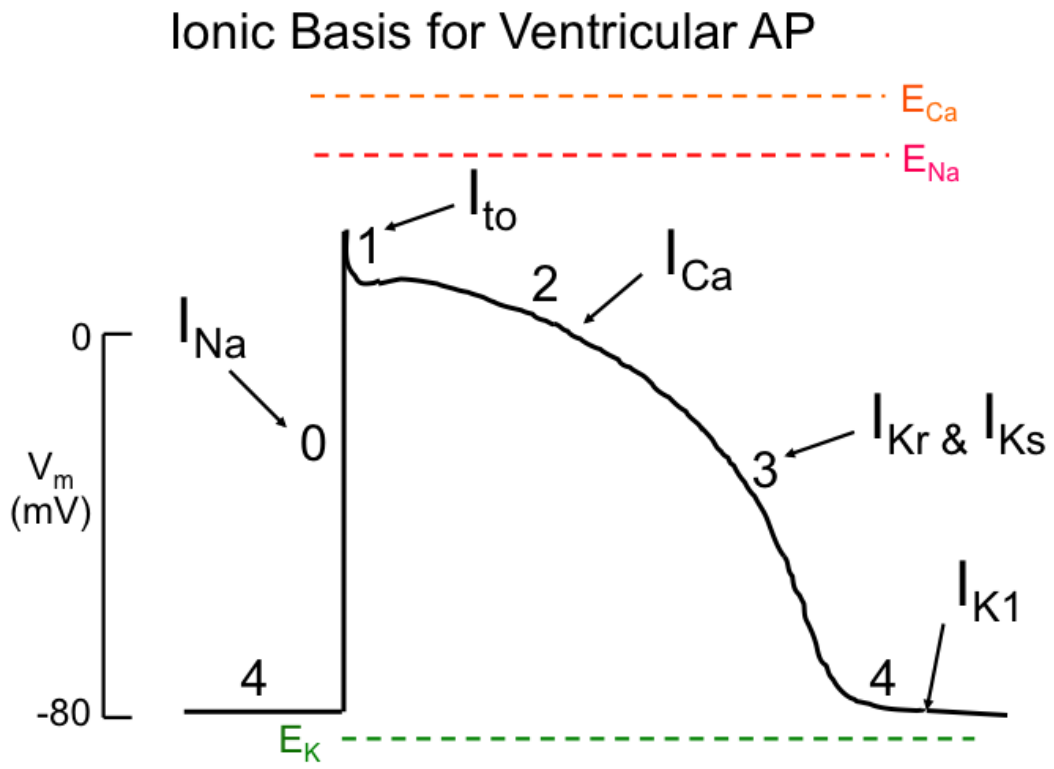
phase 0 (action potential upstroke)

phase 1 (notch or rapid repolarization phase)

phase 2 (plateau phase)

phase 3 (period of rapid repolarization)

phase 4 (diastolic period)



These different phases of the action potential result from the opening and closing of different voltage sensitive channels that selectively conduct different ions. This results from the fact that cells in different regions express varying densities of the various ion channels that regulate the shape of the cardiac action potential. Because of these differences in ion channel expression, cells from other regions differ from ventricular myocytes in that they lack a clear plateau phase (e.g. SA node), or have a small or absent phase 1 component (e.g. SA node, ventricular endocardium), exhibit automaticity (SA node, AV node, Purkinje fibers), or have a slow Ca-mediated upstroke (SA and AV nodes) (Figure 5). Differences in ion channel expression also causes the duration of the action potential in atrial cells to be much shorter (~1/3rd the duration) than for action potentials in the ventricular myocardium or Purkinje fibers.

The cardiac action potential gains its peculiar shape from the opening and closing of different voltage sensitive channels. The flux of ions through each channel drives the membrane potential toward the equilibrium potential for that species of ion. For example, when cardiac cells are left unstimulated (phase 4), the only channel type that opens on a regular basis is an “inwardly rectifying” K-selective channel which produces a K current called IK1 (the first discovered cardiac K current).

The selective permeability of the resting membrane to K ions causes the potential difference across the resting cell membrane to approach the equilibrium potential for K ions (EK ≈ -95) (Figure 6). In contrast, when heart cells are partially depolarized by an invading action potential, these K channels close, and a large number of excitable Na channels transiently open. This drives the membrane potential towards the equilibrium potential for Na ions (ENa ≈ +60) and produces the action potential upstroke (phase 0). Almost all Na channels become rapidly inactivated within ~1 msec at normal body temperature. However, a small (~1%) fraction of Na channels do not fully inactivate and contribute to maintenance of the plateau phase of the ventricular action potential. This non-inactivating component can be blocked by Na channel blocking drugs (e.g. lidocaine).

Other voltage and time-dependent inward and outward currents then become activated in a time-dependent sequence after phase 0. One of the first currents to become activated is the transient outward current (Ito), which produces a phase of rapid repolarization (phase 1). (The charge carrier for Ito is K). The repolarizing effect of Ito is counterbalanced by activation of the L-type Ca current, resulting in a plateau phase (phase 2) of several hundred milliseconds where there is little change in voltage over time. Ca influx is an important "trigger" for excitation-contraction coupling (to be discussed later). A slow inactivation of the Ca-current, combined with activation of additional outward K currents (IKr & IKs) eventually leads to a phase of rapid repolarization (phase 3). The behavior of many of these ion channels can be modulated by the presence of neurotransmitters, drugs and changes in metabolic conditions.

Ionic basis for the resting and action potential in a ventricular heart cell. The action potential is divided into phases 0 through 4. Each phase results from a change in the balance of inward and outward ionic currents that become activated upon membrane depolarization. The primary currents underlying each phase are: phase 0: Na current (INa); phase 1: transient outward K current (Ito); phase 2: L-type Ca current(ICa); phase 3: delayed rectifier K currents (IKr & IKs); phase 4: inwardly rectifying K current (IK1). The change in dominant conductance during each phase produce either net depolarization or hyperpolarization and give the action potential its characteristic shape.

As mentioned above, at rest, healthy cardiac muscle cells have cell membranes that are selectively permeable to K ions, and therefore have resting potentials near the equilibrium potential for K ions (EK ≈ -95 when [K]o = 4 mM) (Figure 6). Hence the resting potential can be predicted by the difference in extracellular and intracellular K concentrations according to the Nernst equation (Figure 8). Hyperkalemia (K]o > 5 mM) will result in a depolarization of the resting potential. Systemic hyperkalemia can occur from abnormalities such as Addison's disease (destruction of adrenal glands – no aldosterone production), renal failure, or treatment with K sparing diuretics. In addition, myocardial ischemia produces a local tissue hyperkalemia that can reach levels of 10-20 mM within a few minutes after the occlusion of a coronary artery (Figure 8). Consequently, a common event during myocardial ischemia is a depolarization of the resting potential.

Automaticity is defined as the ability of heart cells to spontaneously depolarize and generate an action potential. In a normal healthy heart, only cells in the regions of the SAN, AVN, and His-

Purkinje conduction system have the property of automaticity, or the ability to spontaneously depolarize to threshold when left unstimulated. The transmembrane potential in these cells is never stable (never truly “rests”). (Note that healthy ventricular muscle cells, and the majority of atrial muscle cells do not display automaticity.)

Cells that can reach threshold in the shortest amount of time have the greatest automaticity since they can produce action potentials at a more rapid rate than other cells. It is known that the diastolic depolarization that underlies automaticity results from an imbalance between the net inward flux of positive ions (Na or Ca) that act to depolarize the cell vs. the outward flux of positive K ions, which acts to hyperpolarize the cell.

Normally, cells in the SAN have the greatest automaticity (firing rate) and therefore function as the normal pacemaker for the heart. Cells outside the SAN that have the potential for becoming pacemakers are often referred to as latent pacemakers. If automaticity of the SAN becomes depressed or automaticity of cells outside the SAN becomes enhanced and results in the generation of an action potential at a site outside the SAN, this region is referred to as an ectopic pacemaker.

SAN: Cells in the SAN normally beat at a rate of ~70 beats/minute when the body is at rest (and under the influence of a degree of vagal tone). Removal of vagal tone (e.g. which can be achieved by administering atropine, a drug that blocks “muscarinic” acetylcholine receptors) will cause the resting sinus rate to increase to by 20-30 beats/min (but to a smaller extent in elderly patients).

AVN: cells in the AVN have an intrinsic firing rate of 40 to 60 beats/minute, slightly slower than in the SA node.

Purkinje Fibers: cells in the Purkinje fiber region have an intrinsic firing rate of 15 to 40 beats/minute.

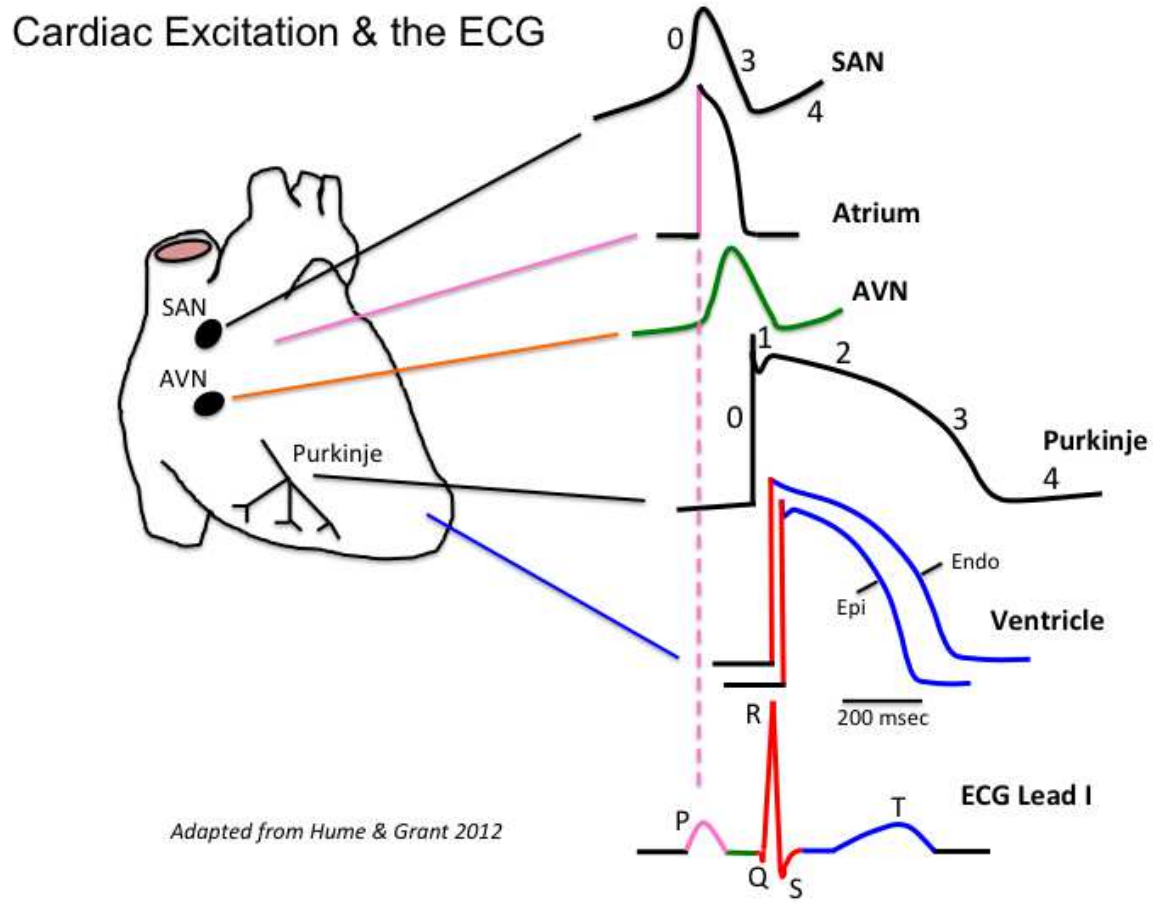
Hypokalemia can thus result in the development of ectopic pacemaker activity by resulting in a steeper slope of phase 4 depolarization. Hyperkalemia does exactly the opposite (i.e. suppresses automaticity). Note that the automaticity of SA nodal cells is relatively unaffected by changes in extracellular potassium concentration compared to Purkinje fibers. Hypokalemia increases Purkinje automaticity.

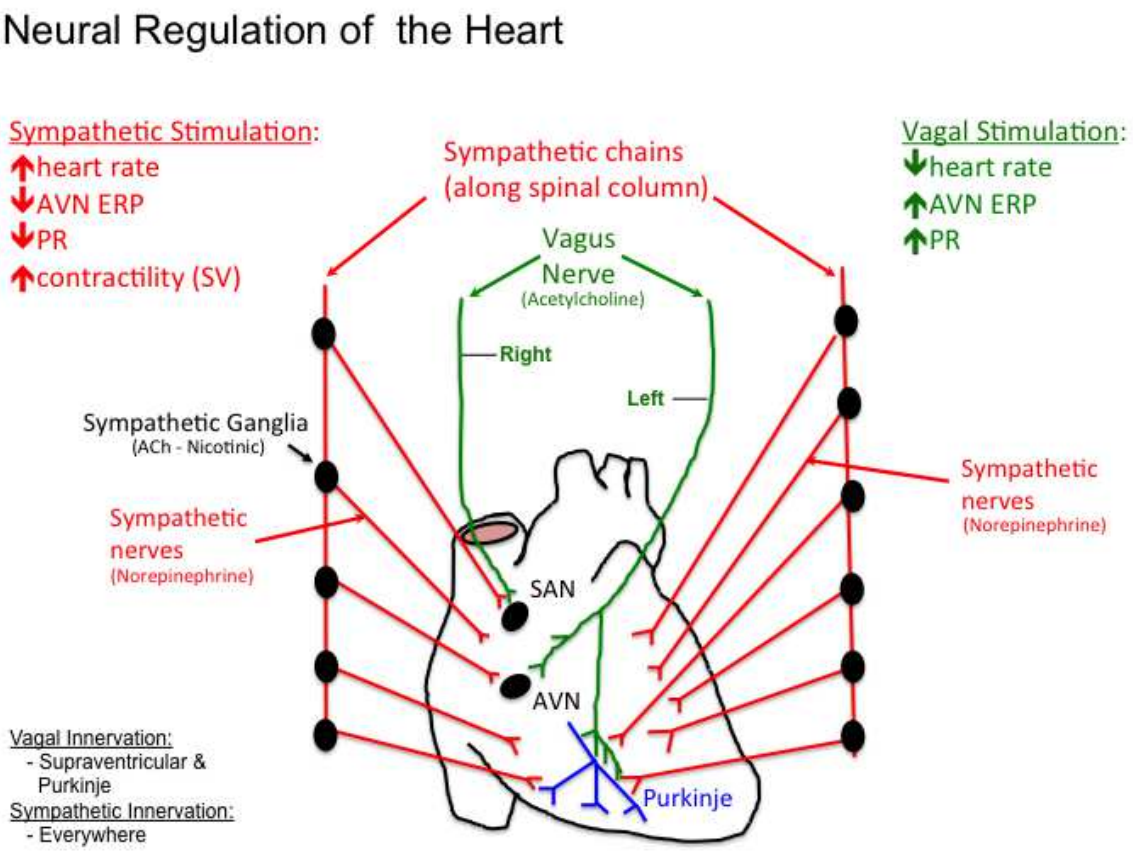
In order for the heart to function as a mechanical pump, the process of electrical stimulation must result in a rise in intracellular calcium that is sufficient to increase the interaction between actin and myosin, resulting in a shortening of myocardial cell length. This process is commonly referred to as “excitation-contraction coupling”. In cardiac cells, the major source for the rise in intracellular calcium that produces contraction is the rapid release of Ca from the sarcoplasmic reticulum (SR). During each heartbeat, the action potential spreads across the surface of myocardial cells, and into invaginations of the cell membrane (T-tubules) that allow excitation to spread into the interior of each myocardial cell. Hence contractility in cardiac tissue is sensitive to both the amount of Ca influx, which regulates Ca-induced Ca release from the SR, as well as

intracellular and extracellular Na concentrations (because of the role of the Na/Ca exchange mechanism in regulating intracellular Ca concentration).

Because the duration of action potentials in the epicardium are shorter than in the endocardium, repolarization occurs first in the epicardium, followed by repolarization in the endocardium (Figure 5). This causes the T wave to have an upright configuration. The surface electrocardiogram can be measured from many different orientations (e.g. the standard clinical electrocardiogram is measured using 12 surface leads) which can be used to pinpoint the nature and extent of various types of cardiac pathology. Additional details will be provided in separate modules.

http://tmedweb.tulane.edu/pharmwiki/doku.php/introduction_to_cardiac_physiology_electrophysiology





ERP: Effective Refractory Period. The time period after an action potential upstroke (or QRS complex in vivo) during which the heart is refractory to stimulation by a physiological stimulus. During this time the heart will not be able to produce a 2nd conducted action potential, if stimulated. (The typical definition of a "physiological stimulus" is an electrical shock delivered at twice the value of the electrical threshold for producing a conducted beat after a long diastolic interval).

Stroke Volume (SV): the volume of blood ejected by the left ventricle in one contraction (normal = 70 ml)