Cardioactive Drugs

A Pharmacologic Basis for Practice

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Preface

Herzwirksame Pharmaka, written by Hansjörg Simon, was first published in German in 1972. When I recommended that an English-language edition of this work would fill an emerging need in American cardiologic practice, I little realized that its preparation would fall to my lot and that it would occupy many months of late-night thesaurus thumbing, introduce to me new disciplines of pharmacology and electrophysiology, and provide the opportunity to make a new and firm friend of its author, Dr. Hansjörg Simon.

Cardioactive Drugs, the title under which the American edition appears, has done all these things for me. Mainly, however, it has provided me with the satisfaction of knowing that, after the reams and reams of European and investigational American literature that have clogged the cardiological journals in the last years, there is now a concise, practical volume to orient the physicians of this country to the therapeutic revolution about to begin. More cardioactive drugs will become available in the next year or so than have ever been available before. This book introduces those drugs to the practitioner.

My thanks go to my wife, Elaine, who bore with me during the gestation of *Cardioactive Drugs,* and to my daughters Lisa, Leslie and Nanette, who assisted in the indexing and proofreading; to my secretary, Mrs. Clarke, who typed and retyped the copy; to Mr. Braxton Mitchell of Urban & Schwarzenberg, who showed infinite patience; and to Dr. Simon, who came to New York to work with me on the translation and the updating of the information.

The book includes some illustrations and tables not in the German edition, and some passages reflecting the American usage of particular drugs when it differed from the German experience, but the work is substantially and essentially unchanged from Dr. Simon's *Herzwirksame Pharmaka.*

It is presented to serve the same purpose.

Dennis A. Bloomfield

Contents

Chapter 1

Electrophysiology and Hemodynamics

The effective use of drugs that act on the heart requires a knowledge of their pharmacological, hemodynamic, and electrophysiological properties. This monograph considers these fundamentals with regard to the important current and emerging cardiac drugs, together with their side effects, indications, dosage, and compatability.

Electrophysiology

The recent introduction into clinical medicine of intracardiac electrophysiology and electrocardiography, including His-bundle recordings, has facilitated both the understanding of rhythm disturbances and the development of rational drug treatment. These techniques permitted the description and the understanding of the interaction between excitability, automaticity, refractoriness, and conduction in the heart and provided the interpretation of the mechanism of both origin and cessation of arrhythmias.

The basic approach to this subject, furthermore, presupposes a fundamental understanding of the function and control of the heart and the necessary points of information are provided in the following brief review of cardiac electrophysiology and hemodynamics.

Basis of Excitation

The basis of excitability of the cells of both the pacemaker and excitation-conducting systems of the heart is the property of the cell membranes to spontaneously increase their permeability to sodium and potassium ions. This leads to changes in potential between the intracellular and the extracellular space, and these changes are accompanied by corresponding mechanical effects. The cardiac cycle is reflected in these changes in transmembrane potential and can be subdivided electrophysiologically into several phases (Fig. 1.1). It is characteristic of the myocardial cells, as of others, that the potassium concentration in the interior of the cell is far higher than in the extracellular space. The opposite is true of sodium ion concentrations. The corresponding potentials are – 90 mV for potassium (the interior of the cell is negative with respect to the exterior) and +60 mV for sodium (the interior of the cell is positive with respect to the exterior). Permeability and conductivity in the resting state are much higher for potassium than for sodium, so that the resting potential is determined by the potassium concentration gradient (Fig. 1.2). Changes in the extracellular potassium concentration lead to corresponding changes of the membrane potential, such that the potential decreases when the extracellular potassium increases, and vice versa.

The permeability for sodium ions increases suddenly when depolarization occurs and the action potential begins with the transmembrane potential rapidly becoming positive (Fig. 1.3, Phase 0). Transiently, the membrane potential is determined by the sodium potential, so that up to +20 mV instead of −90 mV is measured (Phase 1). The increased Na^+ permeability, however, is short-lived and the transmembrane potential quickly begins to recover. There is a short, rapid decrease in potential, passing into an almost plateau-like phase (Phase 2) in which only a small or zero membrane potential can be determined. An inward calcium ion current appears to have the greatest responsibility for this plateau phase. The conductivity for potassium ions then increases (repolarization, Phase 3) and finally returns to its initial value towards the end of the action potential (Phase 4).

Maintenance of the potassium- and sodium-concentration gradients, necessary for establishing the potassium and sodium equilibrium potentials, is in the long term ensured by the sodium-potassium pumps located in the cell membranes. The energy required to operate the pumps is provided by the splitting of energy-rich phosphates in the cell membrane in the presence of the enzyme "membrane ATPase."

Investigations carried out in recent years have examined the role of calcium ions in the action potential. The myocardial fibers of the pacemaker system (sino-atrial and atrio-ventricular nodes) appear to depend on the slower calcium conductance for depolarization in contrast to other myocardial fibers which depend on fast sodium conductance. The calcium-dependent channels have a less

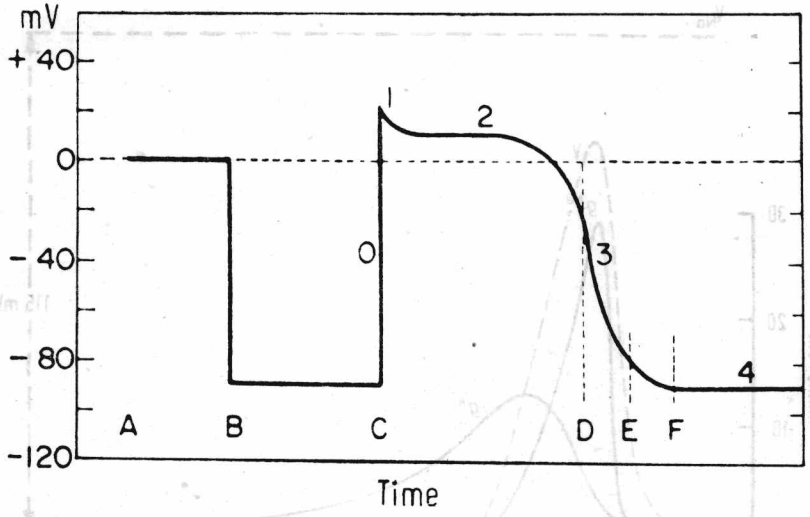

Fig. 1.1 Representation of different phases of the excitation process, measured at a single cell with an intracellular microelectrode. The microelectrode is located outside the cell from A to B, and is inserted intracellularly at B. The action potential is derived from the cell at C. The action potential phases (0–4) are indicated as CD—absolute refractory period, DE—relative refractory period, EF—supernormal phase. (After Berne and Levy, *Cardiovascular Physiology*, C. V. Mosby Co., St. Louis, 1964.)

negative transmembrane potential (−60 to −70 mV) and a slower action potential upstroke. It is mainly the slow inward calcium current in the early phase of the action potential that is instrumental in initiation of arrhythmias and has, therefore, therapeutic implications with regard to the calcium antagonist drugs.

Cells with pacemaking ability are characterized by a maximum diastolic potential of short duration followed by spontaneous diastolic depolarization (Fig. 1.4). This slow depolarization proceeds until the threshold potential has been reached, at which stage spontaneous, rapid depolarization (Phase 0) is initiated.

The Absolute Refractory Period. During Phases 1 and 2, there is a period of absolute refractoriness during which the fiber cannot be restimulated to produce a further depolarization.

The Relative Refractory Period. During Phase 3 of the action potential, excitation of the myocardial cell is possible only with a strong stimulus. In summary, the total refractory period, comprising the absolute and the relative periods, occurs from the beginning of depolarization (R peak) to the end of repolarization (T peak) (Fig. 1.5). It is shortened in diffuse inflammation or fibrosis (myocarditis or severe arteriosclerotic heart disease) where the electrical

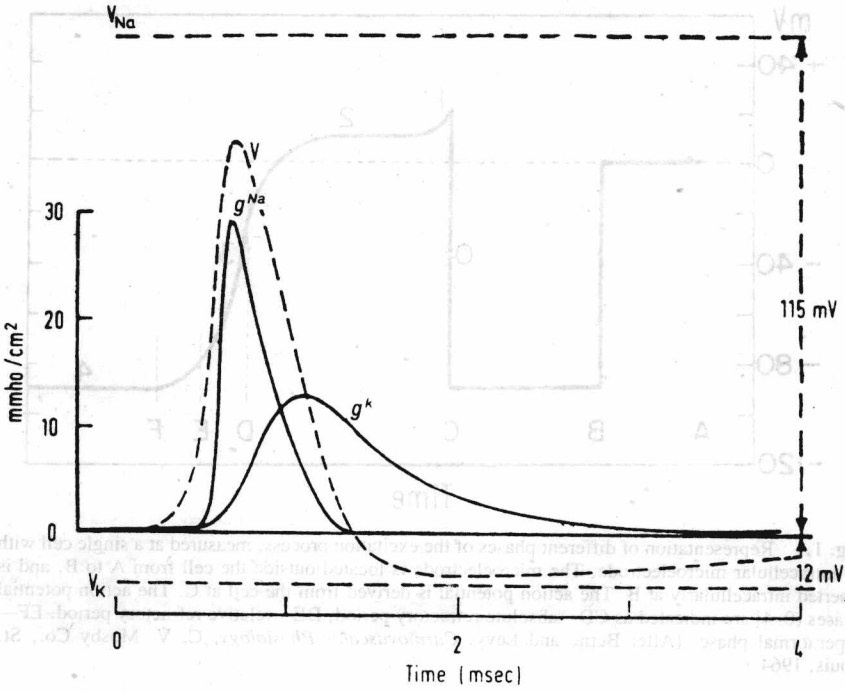

Fig. 1.2 Alterations in membrane permeability for sodium (gNa) and potassium (gK) during the action potential of a toad giant axon (V). Peak conductivity is early for sodium, late for potassium. (After Hodgkin, A. L. and Huxley, A. F., *J. Physiol.* 117:500, 1952.)

pathways can be considered fragmented, or where there is increased cellular permeability for potassium, as in vagal stimulation or under the influence of acetylcholine. This may lead to extrasystoles or fibrillation. Glycosides cause a lengthening of the refractory period, resulting in a decreased heart rate.

The Vulnerable Phase. This period lies within Phases 2 and 3 of the repolarization (Fig. 1.5). It lasts for approximately 20 to 30 msec, and corresponds to the ascending limb of the T wave in the ECG. A strong electric stimulus or a prematurely occurring extrasystole (R-on-T phenomenon) may trigger depolarization in this phase, not infrequently causing ventricular fibrillation (Fig. 1.6).

The Supernormal Phase. Following repolarization, there is a very short period of increased excitability, such that even weak stimuli can trigger depolarization (Fig. 1.5).

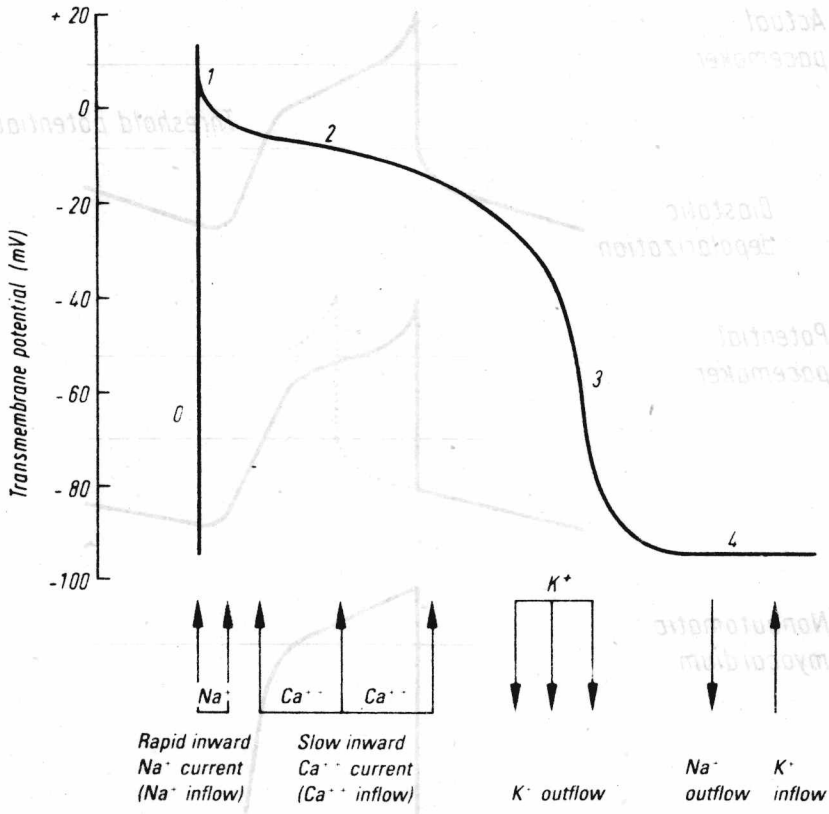

Fig. 1.3 Na^+, Ca^{++}, and K^+ flux during the action potential. The action potential phases are indicated 0–4. The rapid sodium and slow calcium influx is indicated together with the potassium efflux and the return to sodium/potassium transmembrane resting potentials. (From W. G. Nayler, N. C. R. Merrilles, in *Calcium and The Heart*, ed. P. Harris and L. H. Opie, Academic Press, London and New York, 1971.)

Diastolic Depolarization (Phase 4). This phenomenon occurs spontaneously only in the sinus node, in the region of the coronary sinus and in parts of the atrium close to the atrioventricular node, as well as in the His-Purkinje system, and is the cause of automaticity of the heart. The core of the A-V node itself does not possess this property nor does the contractile myocardium except under particular conditions to be discussed later. The steeper the diastolic depolarization, the earlier the threshold potential for triggering an action potential is reached (Fig. 1.7). Catecholamine effect, hypoxia, hypercapnia, and acute increase in myocardial fiber tension are accompanied by an acceleration of this

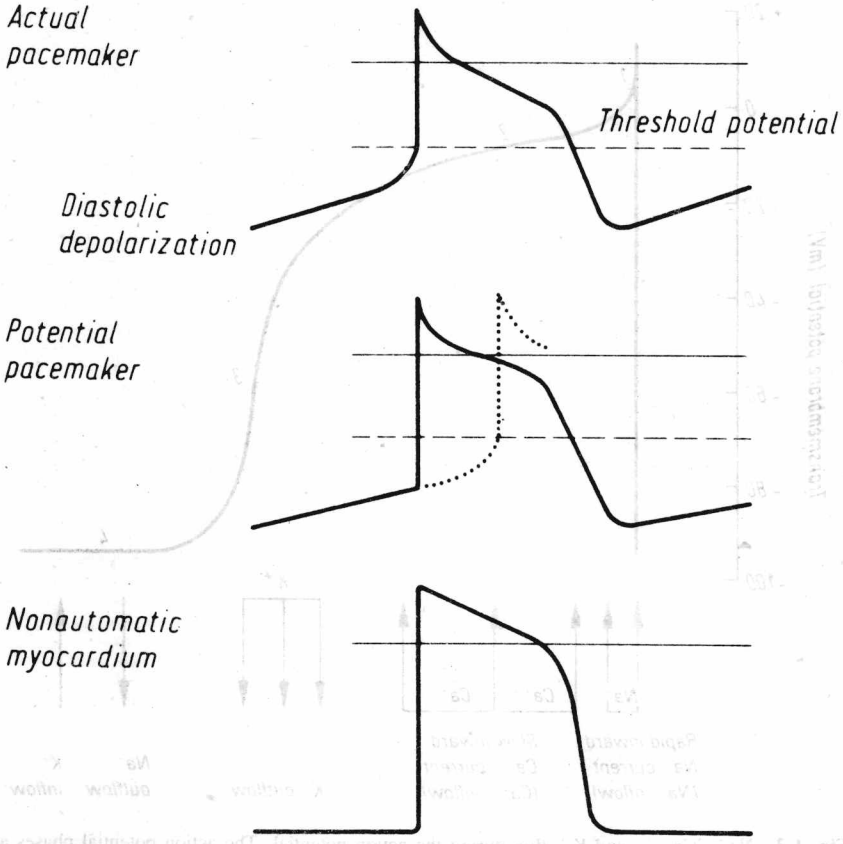

Fig. 1.4 Characteristic response of excitation process in pacemaker tissue and in nonautomatic myocardium. (After H. Antoni, in *Herzrhythmusstörungen*, ed. M. Holzmann, F. K. Schatauer, Stuttgart & New York, 1969.)

process, so that the heart rate increases and extrasystoles are not uncommon. The opposite effect, a decrease of the diastolic depolarization rate, is caused by vagal stimulation, increased serum potassium level, acetylcholine effect, myocardial damage, and the action of most antiarrhythmic drugs.

The response of action and resting potentials to stimulation can only be determined through measurements in the cell itself. Surface electrocardiography and intracardiac His-bundle recording, on the other hand, permit determination of the effects of these parameters on excitability, conduction, and automaticity.

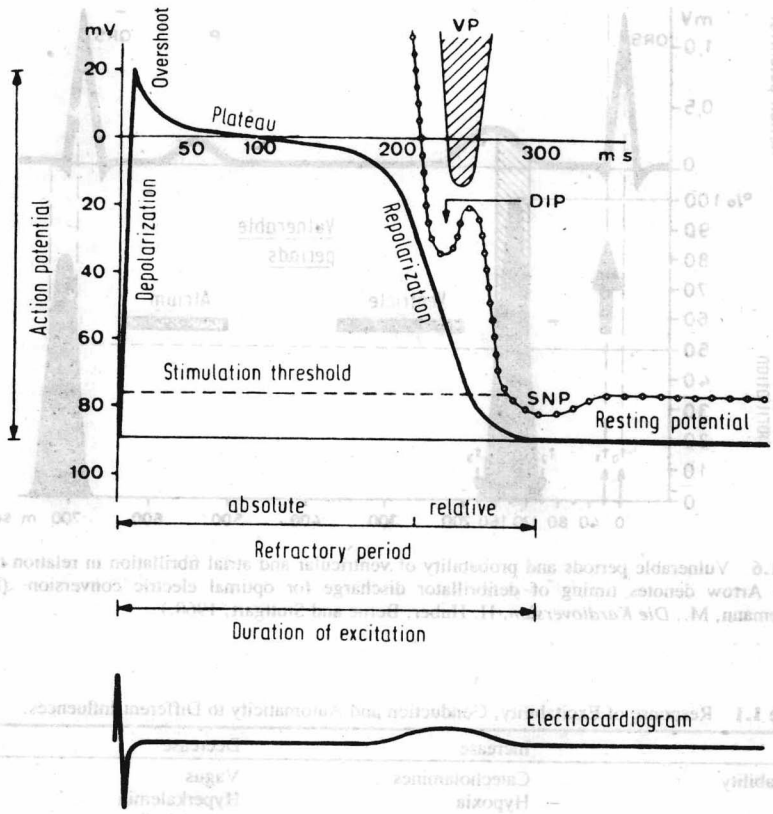

Fig. 1.5 Relationship between action potential and susceptibility to ventricular ectopy. The phases of the action potential are designated depolarization (Phase 0), overshoot (Phase 1), plateau (Phase 2), repolarization (Phase 3), and resting potential (Phase 4) and are measured on the left scale in mV. The refractory periods are shown to coincide with the duration of excitation. The ventricular ectopic stimulation threshold is indicated by open circles during the relative refractory period and coincides with the normal stimulation threshold (dashed line) during Phase 4. The vulnerable phase (VP) corresponds to the transient threshold dip (DIP), and the supernormal phase (SNP) corresponds to the transient increase in threshold negativity. The ECG shows the relation of these periods to the S-T segment and T wave. (From Friedemann, M., *Die Kardioversion*, H. Huber, Berne and Stuttgart, 1968.)

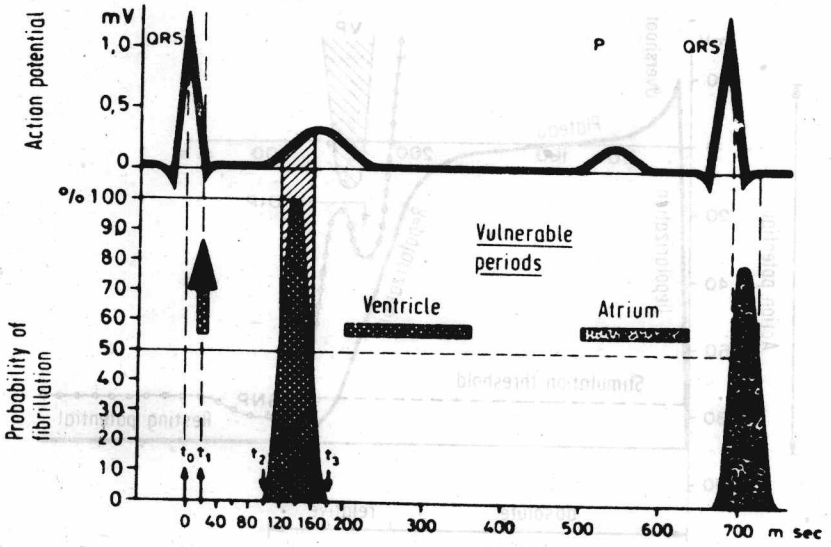

Fig. 1.6 Vulnerable periods and probability of ventricular and atrial fibrillation in relation to the ECG. Arrow denotes timing of defibrillator discharge for optimal electric conversion. (From Friedemann, M., *Die Kardioversion*, H. Huber, Berne and Stuttgart, 1968.)

Table 1.1 Response of Excitability, Conduction and Automaticity to Different Influences.

	Increase	Decrease
Excitability	Catecholamines	Vagus
	Hypoxia	Hyperkalemia
	Hypercapnia	Acetylcholine
	Hypercalcemia	Antiarrhythmic drugs
	Glycosides	
	Hypokalemia	
Conduction	Catecholamines	Vagus
	Glucagon	Acetylcholine
		Hyperkalemia
		Glycosides
		(Antiarrhythmic drugs)
Automaticity	Catecholamines	Hyperkalemia
	Acidosis	Antiarrhythmic drugs
	Glycosides	
	Hypoxia	
	Hypokalemia	
	Acute increase in myocardial wall tension	

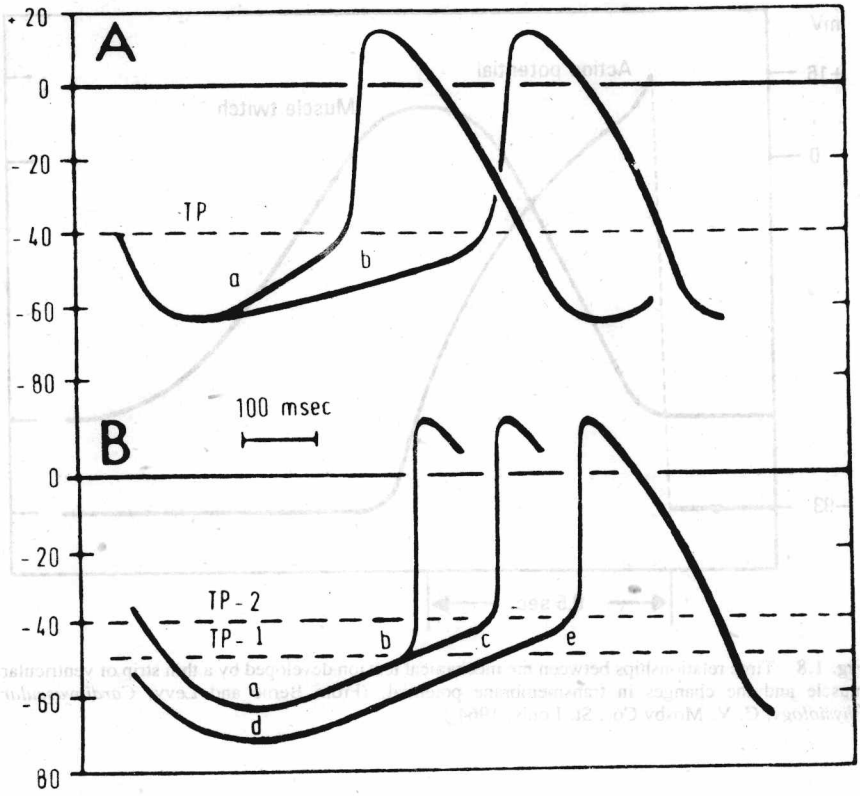

Fig. 1.7 Representation of electrophysiological basis for decrease in pacemaker frequency. (A): Decrease of diastolic depolarization slope from *a* to *b* produces a longer interval before threshold potential is reached. (B): Increase of threshold potential (TP) has the same effect at given diastolic depolarization. (From Berne and Levy, *Cardiovascular Physiology*, C. V. Mosby Co., St. Louis, 1964.)

Table 1.2 Conduction Velocity in Various Parts of the Conducting System.

Site	Conduction velocity (mm/sec)
Atrium	1000
Atrioventricular node	200
His-Purkinje system	4000

Table 1.3 Hemodynamic Changes in Heart Failure

Increase	Decrease
End-diastolic pressure (LVEDP)	Rate of pressure rise (dP/dt)
End-diastolic volume (EDV)	Stroke volume (SV)
Heart rate	Cardiac output (CO)
	Ejection fraction (SV/EDV)
	Contractility

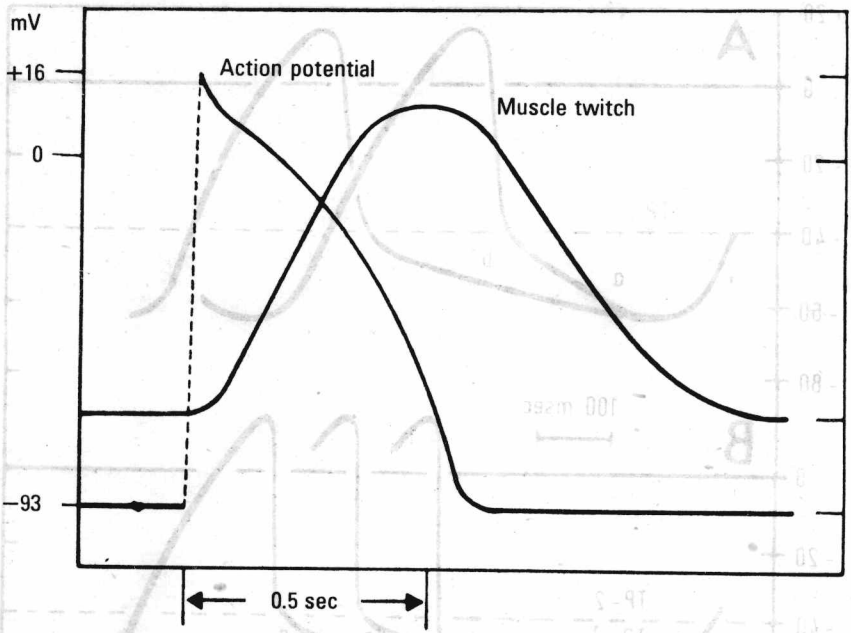

Fig. 1.8 Time relationships between the mechanical tension developed by a thin strip of ventricular muscle and the changes in transmembrane potential. (From Berne and Levy, *Cardiovascular Physiology*, C. V. Mosby Co., St. Louis, 1964.)

Excitability

The myocardium can be excited by natural and artificial stimuli. Figure 1.4 shows the basic form of the excitation process in the pacemaker tissue and in the contracting myocardium, as can be observed through intracellular microelectrode recording. The response to an adequate stimulation is an action potential and subsequent contraction (Fig. 1.8). This response of the myocardium obeys the "all-or-nothing law" which states that an action potential which exceeds the threshold produces a maximal wave of depolarization through the heart, and that no stronger stimuli can produce a greater depolarization. However, the threshold (i.e., the excitability) is subject to large variations during the cardiac cycle as indicated above.

The factors which influence the excitability are shown in Table 1.1. They correspond clinically to variations in heart rate and ectopic activity.

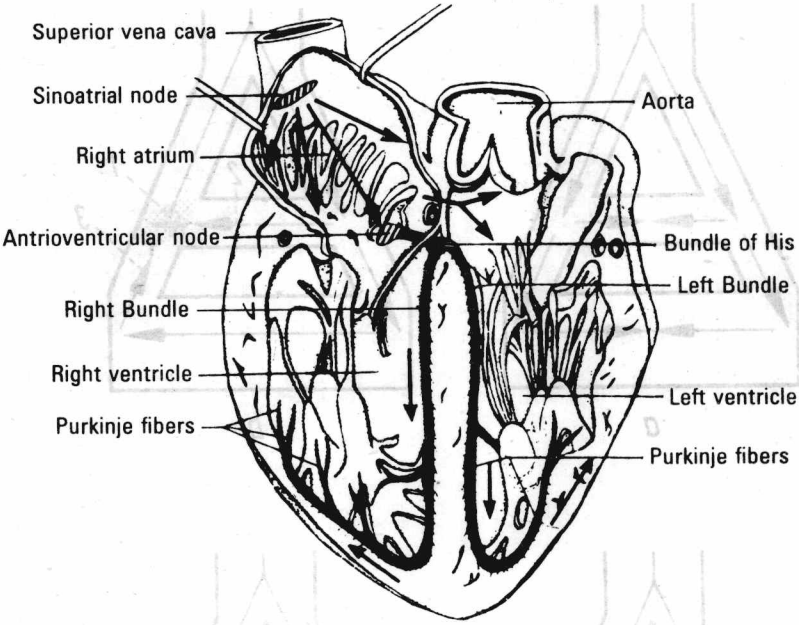

Fig. 1.9 Diagram of the conducting system of the heart.

Conduction

The action potential is conducted through local electrical circuits between active and resting membrane sections. The conduction pathway is illustrated in Figure 1.9. From the sinus node the excitation is propagated through the atria by several pathways to the atrioventricular node. Deceleration of the conduction takes place in the atrioventricular node before the excitation is propagated into the bundle of His; this causes a delay between contraction of the atrium and contraction of the ventricle corresponding to the duration of the P-R interval in the ECG. This delay ensures optimum diastolic filling of the ventricle. The septum and the papillary muscles are excited first in the ventricles. This is followed by rapid excitation of the endocardium of both ventricles, and less rapid excitation of the myocardium and the epicardium. Intracardiac recording of potentials from various parts of the right atrium, the bundle of His, and the right ventricle has shown that one or more aberrant pathways between atrium and ventricle may exist in many patients. Such pathways often cause arrhythmia by means of a reentry mechanism.

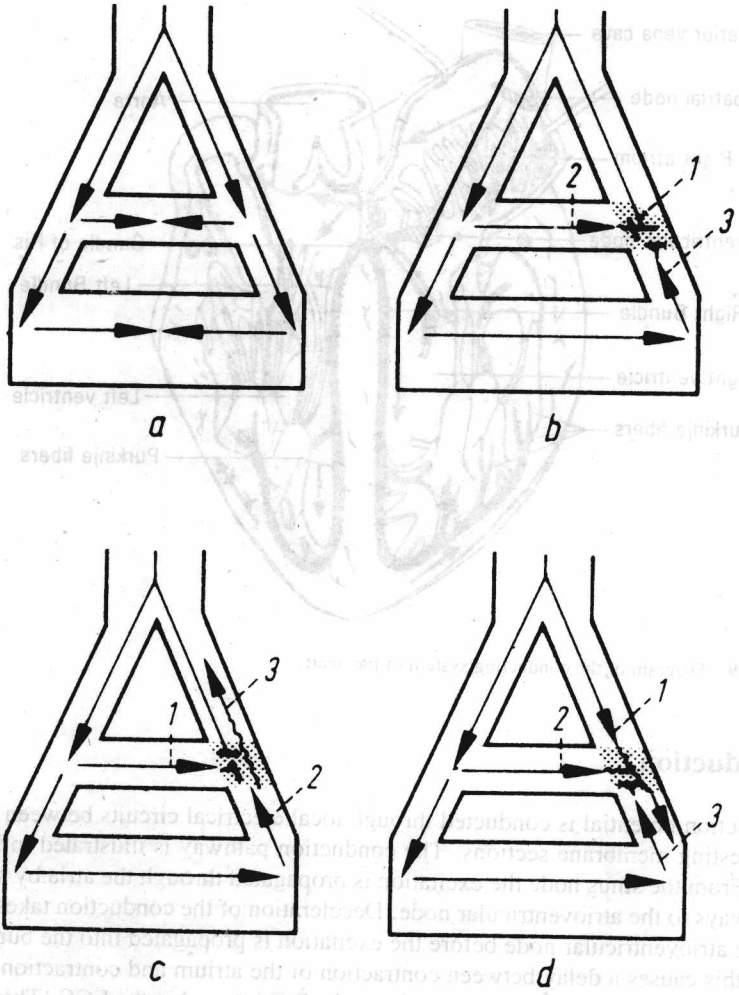

Fig. 1.10 Conduction disturbance and circus movement.
a) Normal conduction conditions. Shaded areas in *b* to *d* indicate damage to Purkinje system.
b) Bidirectional block. Excitations reaching damaged tissue at points 1, 2, and 3 are blocked.
c) Unidirectional block and circus movement. Pulse arriving at 1 is blocked; pulse arriving at 2 is not blocked but starts circus movement (3).
d) Summation of pulses. Coincidence in time of pulses 1 and 2 causes their summation in damaged part of excitation-conducting system, so that transmission becomes possible.
(From O.S. Narula, *His-bundle Electrocardiography*, F. A. Davis Co., Philadelphia, 1975.)