An A-Z of Ions and the Heart

Lead Article

Ion channels and transporters and cardiac arrhythmias - H. A. Fozzard 199

Expert Answers to Three Key Questions

Do drugs have a future in the management of sudden cardiac death? - S. M. Cobbe 217

How do we treat arrhythmias in heart failure? - D. M. Roden 225

Has our new understanding of the mechanisms of atrial fibrillation helped in its treatment? - S. Nattel 233

Fascinoma Cardiologica

Plants and the heart: John Ryan’s receptor - A. Banerjee 239

Summaries of Ten Seminal Papers - M. J. Curtis 243

Circus movements within the AV node as a basis for supraventricular tachycardia as shown by multiple microelectrode recording in the isolated rabbit heart - M. J. Janse and others

A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell - S. Sicouri, C. Antzelevitch

Membrane current through adenosine-triphosphate-regulated potassium channels in guinea-pig ventricular cells - A. Noma, T. Shibasaki

Early afterdepolarizations: mechanism of induction and block. A role for L-type Ca^{2+} current - C. T. January, J. M. Riddle

The Sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms - Task Force of the Working Group on Arrhythmias of the ESC

Molecular determinants of state-dependent block of Na^{+} channels by local anesthetics - D. S. Ragsdale and others

Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity - C. Jiang and others

Molecular mechanism for an inherited cardiac arrhythmia - P. B. Bennett and others

The structure of the potassium channel: molecular basis of K^{+} conduction and selectivity - D. A. Doyle and others

A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results - B-Blocker Heart Attack Research Group

Bibliography of One Hundred Key Papers 255
THE ORIGIN OF CARDIAC ELECTROGENESIS, THE ECG, AND ARRHYTHMIAS

The heart as an electric generator

In order to understand the cardiac electrical system, we must consider the heart as a highly structured multicellular pump. Proper pump function requires that each cardiac chamber contract and relax synchronously. The walls of each chamber are composed of thousands of separate muscle cells, so that synchrony of contraction and relaxation requires a powerful and fast cellular communication system—the conducted action potential. Each individual muscle cell is circumscribed by a membrane that is populated by ion channels and transporters. These marvelous intrinsic membrane proteins orchestrate the many phases of the cardiac action potential and its surface equivalent, the electrocardiogram. Most of the important ion channels and transporters have been cloned, allowing structural insight into their molecular machinery. Cardiac disease is reflected in primary or secondary changes in the function or distribution of these membrane proteins. Most cardioactive drugs target these proteins, and some of the drugs play an important role in the modern treatment of cardiac arrhythmias, ischemia, and heart failure. This article introduces these critical proteins. Drugs that directly block critical ion channels or transporters, such as those for Na⁺, K⁺, and Ca²⁺, also have serious undesirable effects, including proarrhythmia. Consequently, several critical clinical questions arise from this discussion. Future drug development may need to target other channels or modulate channel function in different ways.

**Keywords:** cardiac rhythm; pacemaker; atrial fibrillation; heart failure; ion channel; ion transporter; action potential; antiarrhythmic drug

**Address for correspondence:** Harry A. Fozzard, MC6094, University of Chicago Hospitals, 5841 S. Maryland Ave, Chicago, IL 60637, USA (e-mail: foz@hearts.bsd.uchicago.edu)
tricular (A-V) node, His–Purkinje system, and atrial and ventricular muscle, each with characteristic electrical properties. The coordinated action potential of the whole heart summate to generate electrical potentials that can be recorded as the clinical electrocardiogram (ECG). The cardiac electrical system also provides an autonomous pacemaker that is modulated by the nervous system. This remarkable electrical system is complex and provides a host of opportunities for malfunction and arrhythmia. These arrhythmias can be inconvenient or they can be lethal, since even a brief disruption of the circulation is incompatible with life. This article describes the major molecules that function as membrane transporters and ion channels, discussing their roles in integration of the electrical system in health and disease. In some cases, these membrane molecules are defective and cause arrhythmias directly, as in the long QT syndrome. Alternatively, adaptation of normal ion channels and transporters to hypertrophy, ischemia, or heart failure can be inappropriate, setting the stage for arrhythmia. These transporters and ion channels are also the targets of many potent and occasionally harmful cardiac drugs. This is an explosively growing area of research at this time, and our discussion is designed to assist in understanding and using the wonderful new knowledge and tools that we will have in the next decade.

**Excitability and conduction**

**Resting potential**

All animal cells have a negative potential intracellularly compared with the extracellular solution, usually -60 to -90 mV. It is close to the potential for K+, defined by Nernst’s equation:

$$E_K = \frac{RT}{zF} \ln \left( \frac{[K_o/K_i]}{[K]} \right)$$

where $E$ is the potential, $R$ the absolute gas constant expressed in electrical units, $T$ the absolute temperature (kelvin), $z$ the valence, $F$ the faraday, $\ln$ the natural logarithm, and $K_o$ and $K_i$ the potassium ion concentrations on the two sides of the cell membrane. The resting potential results from the large concentration gradient of K+ between the outside ($\approx$ 4-5 mM) and the inside of the cell ($\approx$ 140 mM) and permeability of the resting membrane to K+. Therefore, the resting potential can be made more negative (hyperpolarized) by lowering outside K+, or it can be made less negative (depolarized) by accumulation of outside K+, as occurs in renal failure or ischemia. The resting potential is always somewhat positive to $E_K$ because the membrane is not perfectly selective for K+. Consequently, the membrane potential can also change by alteration in the membrane permeability to K+.

**Action potential**

The action potential is a sudden transient depolarization that is propagated along cells by flow of cytoplasmic current and between cells by current flow through gap junctions. Depolarization (phase 0, upstroke) occurs by entry of positively charged ions down their electrochemical gradient, reversing the membrane electrical potential to inside levels of +10 to +30 mV. Na+ carries the transient depolarizing current for atrial, ventricular, and His–Purkinje cells, and Ca2+ carries the transient current for S-A and A-V nodal cells (Figure IA). The basal inward rectifier K+ channels set the resting potential. They close upon depolarization, so that even after the primary depolarizing current ceases, the cell remains depolarized. After partial repolarization caused by a transient K+ current (phase 1), the potential settles to a rather steady level near +10 to -20 mV for several hundred ms (phase 2, plateau). During the plateau, Ca2+ channels open in myocytes and allow some Ca2+ to enter the cytoplasm to activate contraction. Finally, delayed rectifier K+ channels open, repolarizing the membrane with the help of the reopened inward rectifier K+ channels (phase 3, rapid repolarization). In pacemaker cells, a combination of closure of the delayed rectifier K+ channels and opening of a special hyperpolarizing-activated nonspecific current channel result in progressive depolarization to threshold for the action potential’s depolarizing channels (phase 4, pacemaker).

**Cell diversity**

Action potentials in various parts of the heart are not identical, either in the excitatory phase or in repolarization. In atrial and ventricular muscle and the His–Purkinje cells, Na+ channels are found with high density, and, because their activation kinetics are rapid, they generate a large current that results in high conduction velocity of the activation wave front. S-A and A-V node cells obtain their excitatory current from Ca2+ channels. The membrane density of these channels is less, their single channel current is smaller, and they activate more slowly, so the intensity of the Ca2+ inward current is much less than that of the Na+ current, and conduction velocity is much slower. For obvious reasons, drugs that block Ca2+ channels can be expected to delay activation in the S-A node and to slow conduction in the A-V node.

The plateau of the action potential is necessary to give the muscle time to relax. Plateau duration also influences the amount of Ca2+ in the cell available for release during the next contraction. Plateau duration is determined by the time required for the delayed...
rectifier K⁺ channels to develop more outward current than the inward current from the small residual Na⁺ and Ca²⁺ currents, depending on the membrane density and distribution of these channels. This density is not the same in different parts of the heart, so that time to repolarization also differs (Figure 1B).

Atrial and ventricular cells have the largest density of inward rectifier K⁺ channels, giving them a stable resting potential. S-A node cells have almost none of these K⁺ channels, so that the K⁺ current holding the cells at resting potential is small. There are two complementary processes that generate the pacemaker current. First, the K⁺ current developed during a preceding action potential is composed mostly of the delayed rectifier current, and this current decays over the next few seconds after repolarization. A small inward Na⁺ current is present in diastole. The falling K⁺ current in the face of a small, but steady, Na⁺ current generates the pacemaker potential. Second, there is a

**The pacemaker**

The heart generates its own rhythm, although the autonomic nervous system modifies the pacemaker rate. Cells of the S-A node do not have a stable resting potential, but gradually depolarize to threshold for their excitatory inward Ca²⁺ current. They have few or no inward rectifier K⁺ channels, so that the K⁺ current holding the cells at resting potential is small. There are two complementary processes that generate the pacemaker current. First, the K⁺ current developed during a preceding action potential is composed mostly of the delayed rectifier current, and this current decays over the next few seconds after repolarization. A small inward Na⁺ current is present in diastole. The falling K⁺ current in the face of a small, but steady, Na⁺ current generates the pacemaker potential. Second, there is a
special hyperpolarization-activated pacemaker channel that opens upon hyperpolarization into the range of the pacemaker potentials. Although nonselective for Na\(^+\) and K\(^+\), the channel functions as if it were an Na\(^+\) channel. This Na\(^+\) current increases over several seconds, depolarizing the membrane. This channel type is also found in other cardiac cells, where it may play a role in some arrhythmias.

A-V node cells and those of the His–Purkinje system can also generate spontaneous pacemaker potentials, but their rates are slower than the dominant S-A node pacemaker rate. The S-A node is particularly well supplied with sympathetic and vagal nerves, with a smaller density in the A-V node. Sympathetic activity releases norepinephrine, which activates adenyl cyclase to produce more cyclic adenosine monophosphate (cAMP). The cAMP directly affects the hyperpolarization-activated channels to shift their voltage range of opening, accelerating the pacemaker potential and speeding the heart rate. Vagal nerve activity releases acetylcholine, which acts through its receptor to slow the rate by two mechanisms. First, the adenyl cyclase enzyme is slowed, reducing the production of cAMP. Second, a special inward rectifier channel is opened, increasing the K\(^+\) current.

**ECG**

The ECG is a recording of the net cardiac electrical events, reflected as electrical potential differences on the body surface. The reason that an organized electrical signal can be detected on the body surface is that atrial and ventricular muscle mass is large enough and synchronization of their depolarization and repolarization is sufficiently good that the single cell events summate. The S-A node mass is too small to generate a surface signal, although it can be detected by catheter electrodes. Atrial depolarization generates the P wave. Dilatation prolongs the conduction path, causing greater overlap (peaking) in the event of right atrial dilatation, or lengthening in the event of left atrial dilatation.

The P-R (P-Q) interval is an estimate of the time for conduction of the action potential through the A-V node and His–Purkinje system, which are also too small to generate surface signals. About half of the interval is A-V node and half is His–Purkinje conduction time, the latter having the fastest conduction velocity in the heart. Ventricular activation begins on the left side of the mid-septum, because it is the shortest conduction path from the His bundle. Next is activation of the right side of the septum and activation of the subendocardial ventricular muscle of the apex and free wall. The latter wave front advances through the ventricular wall toward the epicardium, obscuring the normal right ventricular activation signal. The aortic outflow tract is activated last because it does not have Purkinje connections. The ORS shape is then the measure of the sequence of left ventricular activation reflected in various leads on the surface. Its duration reports the effectiveness of the His–Purkinje system in synchronizing activation of this large mass of muscle.

After completion of ventricular activation, all of the ventricular muscle is depolarized, generating the action potential plateau. The surface signal disappears due to the lack of potential differences in the heart (Figure 1).\(^3\) Repolarization in the left ventricle begins in the epicardial muscle, even though it is depolarized after the endocardium, because it has shorter action potentials. This produces the T wave, which is concordant in most leads because the direction of the repolarization wave is opposite to the depolarization wave. The QT interval is our best surface measure of duration of the ventricular action potential. The QT interval is not the same in every lead because of local repolarization patterns, and it varies with the heart rate. Atrial repolarization is normally obscured by the ORS, and is seen only during tachycardia.

**CARDIAC ION CHANNELS**

Ion channels are intrinsic membrane glycoproteins that form gated pores for the passive downhill movement of ions across the impermeable membrane lipid bilayer. Channels have five important characteristics (Figure 2):\(^6\)

- **Pore.** Ion channels form hydrophilic low-energy pathways (pores) for ions to cross the hydrophobic membrane.
- **Selectivity.** The pore contains a selectivity region that specifies which ion or ions are allowed to pass, eg, the K\(^+\) channel allows K\(^+\) to permeate at a high rate, but excludes Na\(^+\), Ca\(^{2+}\), and Cl\(^-\).
- **Gating.** Most channels are gated, meaning that they can be open or closed.
- **Gating sensors.** The gates are either controlled by the membrane electric field (voltage-dependent), requiring a voltage sensor, or by binding of ligands, requiring a ligand binding site.
- **Drugs.** Drugs or toxins can bind to and alter the function of the channels, or modulate them through second messengers.
It is possible to characterize the voltage-gated ion channels by whole cell current or by recording the intermittent current through a single ion channel by a patch clamp method. Channels have a characteristic single channel conductance. For example, the single Na⁺ channel conductance under physiological conditions is about 20 pS (pico [10⁻¹²] siemens). This conductance means that a single open Na⁺ channel allows Na⁺ ions to enter at a rate of about 10 million ions/second. This very high rate means that a channel has less than 100 ns (nanoseconds) to identify and transport an Na⁺ ion. Channels open intermittently, with average open times from parts of a millisecond to seconds.

Many channels have now been cloned, so that we know their amino acid sequences. They have hydrophobic segments that are threaded through the membrane. The typical primary structural unit (called the α-subunit) of voltage-gated channels has six transmembrane segments. Voltage-gated K⁺ channels are formed by four of these six-transmembrane segment proteins, assembled around a central pore (Figure 3C, E). Voltage-gated Na⁺ and Ca²⁺ channels have

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**Figure 2.** Representation of a voltage-gated ion channel, illustrating its location as a transmembrane protein forming a pore. The pore has a selectivity region and gates that are controlled by intrinsic voltage sensors. P, phosphorylation site.


**Figure 3.** Topology of several ion channel proteins. A. Typical β-subunit, with single transmembrane segment, the N-end outside and the C-end inside. B. Inward rectifier α-subunit channel topology, showing the invaginated extracellular P loop. C. Typical six transmembrane segment voltage-gated K⁺ channel α-subunit. D. Four covalently linked domains typical of Na⁺ and Ca²⁺ channel α-subunits. E. Formation of the pore by four subunits or domains.

<table>
<thead>
<tr>
<th>Channel/transporter name</th>
<th>Abbreviation</th>
<th>Charge carrier</th>
<th>Genes</th>
<th>Physiological activators/modifiers</th>
<th>Clinical/physiologically used blockers</th>
<th>Physiological roles</th>
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<td><em>I</em>\text{Na}</td>
<td>Na(^+)</td>
<td>h1</td>
<td>Depolarization</td>
<td>Local anesthetics, eg, lidocaine,</td>
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<td>Ca(^{2+})</td>
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<td>Verapamil, dihydropyridines, (\beta)-blockers</td>
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<td>(\alpha_{1H})</td>
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<td><em>I</em>(_f)</td>
<td>K(^+)</td>
<td>Kir2 1</td>
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<td>(\beta)-blockers</td>
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<td>K(^+)</td>
<td>Kir3.1 3 Kir3 4 (GIRK1, CIR)</td>
<td>Vagal stimulation (acetylcholine)</td>
<td>Atropine</td>
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<td>Cx43</td>
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<td>CFTR</td>
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<td>Digitalis</td>
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<td>(\alpha_1) (\alpha_2) (\beta)</td>
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<td>(\alpha_1) (\alpha_2) (\beta)</td>
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<td>Stores Ca(^{2+}) for contraction</td>
<td>Maintenance of Ca(^{2+}) balance, can depolarize the membrane</td>
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<td>NHE1</td>
<td>Intracellular acidosis</td>
<td>Amiloride</td>
<td>Maintains intracellular pH</td>
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Table 1. Ion channels and transporters.
four similar six-transmembrane segments covalently connected into a single molecule, which assembles the four domains around the central pore (Figure 3D, E). Ligand-gated K⁺ channels typically have only two transmembrane segments, but still form a pore by assembly of four proteins (Figure 3B). Several channels have secondary β-subunits (Figure 3A), which alter their processing and assembly within the cytoplasm, their targeting and stability in the surface membrane, and their gating and pharmacological properties. Table 1 lists the various ion channels and transporters, the ions they transport, their molecular identity if known, and various functional characteristics.

### Voltage-gated channels

**The Na⁺ channel**

Na⁺ channels are the basis of excitability in atrial, ventricular, and His–Purkinje cells. These voltage-dependent channels open in response to depolarization of 15 to 20 mV from the resting potential and allow the flow of Na⁺ into the cell, further depolarizing it. This channel opens upon depolarization, then closes after a millisecond or so. The complex dependence of activation and inactivation on membrane potential was first characterized by Hodgkin and Huxley, who developed a model that summarized the gating states of the channel into closed (C) at the resting potential, but available for opening, open (O), and inactivated (I). With depolarization, the channel gates open from C to O, and the channel then inactivates to I. The channel will remain shut until the membrane is repolarized, when recovery can occur from I to C. Normally, the Na⁺ channel is inactivated during the cardiac action potential plateau, but there is a small amount of Na⁺ current that contributes to maintenance of the plateau (“window current”).

The channel is 20 times more selective for Na⁺ over K⁺, and Ca²⁺ cannot permeate the channel. Only one Na⁺ channel isoform is so far been clearly identified in the heart. The principal α-subunit consists of about 2000 amino acids and has 24 transmembrane segments, organized into four homologous, but not identical, domains of six α-helical transmembrane segments called S1 through S6. This α-subunit forms the pore and its selectivity filter, the gates and their voltage sensors, and the drug binding sites. The fourth transmembrane segment of each domain contains positively charged amino acids at almost every third position, representing the channel’s voltage sensor. Subsequently, it has become clear that this is a motif in every voltage-dependent channel. The pore is formed by the four domains folding around a central channel, lined mostly by the S6 segments. The extracellular segment between S5 and S6 of each domain, called the P loop, folds back into the pore to form the outer vestibule and the selectivity filter. The P loops are nearly identical in all isoforms of Na⁺ channels, forming the narrow selectivity filter. The fast inactivation gate is found in the cytoplasmic linker between domains III and IV, another part of the molecule almost identical in all the isoforms. A small β-subunit with only one transmembrane segment is important to skeletal and brain Na⁺ channels, affecting gating kinetics and membrane stability. However, it is not yet clear if this subunit is normally expressed in heart cells.

The Na⁺ channel is the target of several natural toxins and clinically used drugs. Tetrodotoxin and saxitoxin are highly specific and high-affinity blockers of the channel. The local anesthetic class of antiarrhythmic drugs, such as lidocaine, quinidine, block this channel by binding to a site on the S6 segment in the pore just cytoplasmic to the selectivity filter. Their blocking affinity is influenced by the gating state of the channel, producing the typical clinical phenomenon of “use dependence.” In practical terms, this means that the channel is not blocked by these drugs until it opens and/or inactivates. Consequently, during rapid arrhythmias such as ventricular tachycardia, the channel cycles through the O and I states more frequently and drug block increases.

The Na⁺ channel is one of the causes of the familial long QT syndromes (LQT), which result from mutations that increase the fraction of channels that are open during the action potential plateau. It is also possible that inapparent mutations in the Na⁺ channel set the stage for drug-induced polymorphic ventricular tachycardia.

**Ca²⁺ channels**

- **L-type Ca²⁺ channels.** L-type Ca²⁺ channels, found in all cardiac cells and in vascular smooth muscle cells, are also called dihydropyridine receptors, because this commonly used drug blocks that channel type with high affinity. The channels are activated during the action potential by depolarization beyond -50 or -40 mV by the Na⁺ channels. In S-A and A-V node cells, there are few or no Na⁺ channels, so the upstroke of action potentials in those cells is produced by opening of the L-type Ca²⁺ channels. These channels are also obviously activated in atrial, ventricular, and His–Purkinje cells at plateau voltages, where they produce a Ca²⁺ current that maintains the plateau.
and triggers release of Ca$^{2+}$ for contraction. Intensity of the Ca$^{2+}$ current is much less than that of the Na$^+$ current, resulting in slower conduction velocity for the S-A and A-V node action potentials. The channel is highly selective for Ca$^{2+}$, relative to Na$^+$ and K$^+$, and it is blocked by other divalent ions such as Mg$^{2+}$. The L-type Ca$^{2+}$ channel is strongly modulated by the sympathetic nervous system. Either norepinephrine released from cardiac sympathetic nerve endings or circulating epinephrine greatly increase basal Ca$^{2+}$ current through the cAMP cascade. The adrenergic neurotransmitter binds to adrenergic receptors on the surface membrane, which release G-proteins. The α-subunit of the G protein binds to and stimulates the membrane-bound enzyme adenylyl cyclase, which increases production of cAMP. The cAMP binds to a soluble protein kinase A, activating it to cause phosphorylation of the L-type Ca$^{2+}$ channel complex. This phosphorylation shifts the channel into a kinetic mode where its probability of opening is greatly increased. The Ca$^{2+}$ current is enhanced, increasing both conduction in atrial and ventricular cells and firing frequency and conduction velocity in the S-A and A-V nodes.

The cardiac L-type Ca$^{2+}$ channel is composed of four subunits. The principal α1-subunit makes the channel pore. It resembles the Na$^+$ channel α-subunit in having about 2000 amino acids and 24 transmembrane segments organized into four homologous domains, each with the characteristic S4 segments of voltage-gated channels. Between the S5 and S6 segments of each domain is the extracellular P loop, which folds back into the pore to form the outer vestibule and selectivity filter of the channel. The α,β subunit pair of subunits is a single gene product that is split posttranslationally. The β-subunit is entirely intracellular, and it interacts with the cytoplasmic linker between domains I and II of the α-subunit alters channel kinetics. The L-type Ca$^{2+}$ channel is the target for a number of clinically important drugs, all of which interact with the pore-forming parts of the α-subunit. In addition, it probably contributes significantly to genesis of polymorphic ventricular tachycardia.

- **T-type Ca$^{2+}$ channels.** A second class of voltage-gated Ca$^{2+}$ channels is called T-type. These Ca$^{2+}$ currents are activated by depolarization to threshold levels around −70 mV, much negative to that for L-type channels. They then rapidly inactivate, making the current transient. This current is typically 1/4th to 1/10th the size of L-type currents in atrial and ventricular cells. It is relatively resistant to the dihydropyridine drugs, and intracellular Ca$^{2+}$ does not inhibit it. The current is more prominent in neonatal cells and is increased in ventricular cells of hypertrophied hearts. The principal physiological role for this current in adult cells appears to be to contribute to the pacemaker potential in the S-A node.

**K$^+$ channels**

- **Transient outward family of channels.** Early electrophysiological studies demonstrated a rapidly activating and inactivating outward current (I$,w$) in cardiac cells that was partly responsible for the rapid repolarization from the upstroke of the action potential (phase 1). This K$^+$ current is enhanced by phosphorylation and blocked by 4-aminopyridine. When K$^+$ channels were first cloned, it was quite difficult to determine the molecular basis for this K$^+$ current. It now seems likely that the K$^+$ part of human I$,w$ is mostly produced by the Kv4 2/4 3 proteins (KCND2/3) in the epicardium and by Kv1.4 (KCNA4) in the endocardium. This difference in K$^+$ channels expressed in the epicardium and endocardium explains why the epicardium has a shorter action potential because of more rapid epicardial repolarization. The Kv4 2/4 3 channels recover rapidly and are available to accelerate recovery in action potentials at physiological rates, whereas the Kv1 4 channels recover slowly and are mostly inactivated at physiological rates. These channels change their expression in cardiac hypertrophy, probably explaining the T-wave changes in left ventricular hypertrophy.

Both Kv4 2/4 3 and Kv1 4 channels are of the six-transmembrane-segment type and have the typical charged S4 that is found in all voltage-dependent channels. The Kv1 4 channels have rapid repolarization produced by what is called the “ball-and-chain” mechanism. The long cytoplasmic N-terminal end has a hydrophobic segment that acts as a plug to the pore, producing rapid inactivation. On the other hand, the Kv4 2/4 3 channels inactivate by a different mechanism called “C-type,” in which the outer mouth of the pore closes. This difference provides a basis for designing drugs that will affect one type and not the other.

- **HERG delayed rectifier channel.** The plateau of the cardiac action potential is terminated both by a gradual fall in outward Na$^+$ and Ca$^{2+}$ current and by a rise in K$^+$ current. The K$^+$ current is called delayed rectifier current because it increases with time upon depolarization beyond the resting potential. Two kinds of delayed rectifier K$^+$ currents were originally identified on the basis of different sensitivity to K$^+$ channel blocking.
drugs—one that activated rapidly ($I_{Kr}$) and the other that activated slowly ($I_{If}$). $I_{Kr}$ was found to be generated by a unique type of K$^+$ channel called HERG (human ether-a-go-go-related gene). It is a six-transmembrane-segment K$^+$ channel like the others, but significantly different at the amino acid level. It has quite unusual voltage-dependent gating. The channel activates quickly upon depolarization, but inactivates faster, so that the current is quite small at first. Then, during the gradual repolarization of the action potential, this channel recovers and opens to provide large repolarizing currents for phase 3. The main subunit probably also has a secondary β-subunit that influences its voltage dependence and perhaps its drug sensitivity. Mutations of the gene responsible for coding this channel are responsible for LQT3, one of the types of familial long QT syndrome that is manifested by long QT intervals and poor QT shortening in response to tachycardia. It can be blocked by the class III drug dofetilide.

- **KoLQT1 (KCNQ1) delayed rectifier channel.** This channel was first cloned from a family with the long QT syndrome, and it clearly had the typical amino acid pattern of voltage-gated K$^+$ channels. The cloned protein generates typical $I_{Kr}$ currents when expressed with a β-subunit called minK, a single-transmembrane-segment protein. This current gradually develops during the action potential plateau, repolarizing it into the voltage range where HERG and the inward rectifier current open and terminate the action potential. It is a prime target of Vaughan–Williams class III antiarrhythmic drugs.

**Figure 4.** Representation of a 2-transmembrane segment K$^+$ channel (M1 and M2). Two of the four subunits are shown with their P loops forming the selectivity region. This schematic is from the bacterial KcsA channel. Redrawn from ref 21, with permission: Doyle DA, Cabral JM, Pfuetzner RA, et al. The structure of the potassium channel: molecular basis of K conduction and selectivity. Science. 1998;280:69-77. Copyright © 1998, American Association for the Advancement of Science, USA.

### Hyperpolarization-activated (pacemaker) channel

A specific pacemaker channel has been found in all cardiac cells, called the hyperpolarization-activated channel or the $I_f$ or $I_{If}$ channel ("f" stands for “funny,” and "h" for “hyperpolarization-activated"). This channel has a small single channel conductance, and it is monovalent cation–selective, but it does not discriminate between Na$^+$ and K$^+$. It is shut during the action potential plateau, but opens upon hyperpolarization to potentials negative to -60 mV. It is voltage-dependent, but in the opposite direction to the other voltage-gated channels. The probable molecular basis of this hyperpolarization-activated current is a protein called hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel. Three isoforms have been cloned so far, with HCN2 and 4 present in heart and brain. It is a six-transmembrane-segment protein with an S4 that contains positive charges, but organized in a different manner to the classic voltage-gated channels. It has the typical K$^+$ channel selectivity filter sequence in its P loops. When expressed in noncardiac cells, this channel shows most of the physiological and pharmacological properties of the pacemaker channel, including direct gating by cAMP without phosphorylation. With this molecule available, we should soon have specific drugs to regulate its kinetics. This should give us a tool to modify the pacemaker rate, where that could be of therapeutic value.

### Ligand-gated channels

**Inward rectifier K$^+$ channel**

The K$^+$ channel that sets the membrane resting potential is a member of a special family of K$^+$ channels called inward rectifiers, or Kir. The name inward rectifier means that they only allow K$^+$ currents through the channel when the cell membrane potential is negative to the K$^+$ electrochemical equilibrium, but are blocked at potentials 5 to 10 mV positive to the resting potential, preventing large K$^+$ currents out of the cell that would occur if the channel were open. The importance of this inward rectifier property in the heart is that these K$^+$ channels have a high conductance near the resting potential, holding it near the K$^+$ Nernst potential, but they shut down during the action potential plateau. These channels are not intrinsically voltage-dependent, but are blocked by multivalent ions as a function of the electric field. This block can be modified by outside K$^+$, reducing inward rectification, and shortening the action potential at higher K$^+$. The Kir family of channels are composed of 400 to 500 amino...
acids, and they have only two transmembrane segments that resemble S5 and S6 of the Kv family (Figure 4, see page 207). Between the two transmembrane segments is a P loop characteristic of the pore of K+-selective channels. The isoform responsible for the resting potential in heart is Kir2.1. The mechanism of channel block when the electric field is less than the K+ Nernst potential is either binding of intracellular Mg2+ (typically, 2-3 mM) to a site in the C-terminus or entry of polyamines into the pore from the cytoplasm. Raising outside K+ increases K+ conductance by reducing Mg2+ or polyamine block, thereby shortening the cardiac action potential. This channel also contributes to phase 3 rapid repolarization. As the plateau potential gradually becomes more negative, it enters the region where block of the inward rectifier is relieved, allowing the channel to speed repolarization.

**Muscarinic K+ channel**

Another member of the Kir family is the channel that is responsive to vagal nerve activity. Acetylcholine released at vagal nerve endings binds to a special seven-transmembrane-segment receptor in the cardiac cell membrane, releasing G protein from its binding to the receptor. G protein is composed of three subunits called α, β, and γ. The βγ subunits as a dimer then bind to an inward rectifier K+ channel, gating it open. The responsible Kir isoform is composed of Kir3.1 and Kir3.4 subunits. Activation of this channel in S-A nodal cells leads to a large steady repolarizing current that opposes the pacemaker depolarization, prolonging the time to the next action potential or causing standstill.

**ATP-gated K+ channel**

Another important member of the inward rectifier family is the ATP-gated K+ channel, providing a way to link cell metabolism to channel function. It has long been known that during ischemia or hypoxia there is a large increase in K+ conductance. The conductance of this highly K+-selective and voltage-independent channel is ≈25 pS under physiological ionic conditions, and the cardiac cells have very large numbers of these channels in their surface membranes. Although requiring some MgATP to open, it is shut by cytoplasmic ATP The Kd for ATP inhibition of the channel is about 30 µM. It is quite logical that the fall in cytoplasmic ATP during ischemia activates these channels, leading to large repolarizing currents during the cardiac action potential plateau and dramatically shortening it. However, the action potential shortening of ischemia occurs at cytoplasmic ATP levels of several mM, well above the Kd for channel opening. Because there are so many ATP-sensitive K+ channels in the cardiac membrane, opening of only a few percent of them would be sufficient to terminate the plateau. In addition, the channel is sensitive to the ADP/ATP ratio and to pH, so that the experimental Kd for pure ATP is misleading under pathophysiological conditions.

The pore is formed by four Kir6.2 molecules, but four SUR2 molecules are required for normal function. SUR2 is a much larger protein with probably 11 transmembrane segments organized into three domains. SUR2 is also called the sulfonylurea receptor. The homologous channel in the pancreatic islet β-cells is blocked by sulfonylurea drugs, which are clinically useful in the treatment of diabetes. The cardiac channel is much less sensitive to these drugs, but experimentally they have been shown to prevent shortening of the action potential plateau in cardiac ischemia. No cardiac diseases are known to be associated with abnormal function of the ATP-sensitive K+ channel. However, an ATP-gated K+ channel is also found in the inner membrane of mitochondria, where it seems to play a role in ischemic preconditioning.

**Ryanodine receptor (Ca2+-release channel)**

This channel is found inside the cell and is important for contraction. Most of the Ca2+ that initiates contraction is derived from the sarcoplasmic reticulum. The latter is a specialization of the endoplasmic reticulum that encases the sarcomeres in a network of membrane-enclosed compartments. The ventricular myocyte surface membrane is invaginated into narrow T-tubules, which bring the surface membrane close to the contractile machinery. The sarcoplasmic reticulum adjacent to the surface membrane is called the terminal cisternae. It is an intracellular store for Ca2+, which is in mM concentrations through buffering of Ca2+ by an intracisternal calcium-binding protein. When Ca2+ enters the cell through the surface Ca2+ channels, located near the terminal cisternae, this transmembrane Ca2+ binds to a channel in the cisternae called the ryanodine receptor or the Ca2+-release channel. During the normal contractile cycle, this binding of Ca2+ triggers the channel open and allows release of stored Ca2+ into the cytoplasm, where it activates contraction.

The Ca2+-release channel is the largest channel yet cloned. It is formed by four principal subunits, each of which includes about 5000 amino acids. Each subunit has a very large N-terminal end in the cytoplasm and four transmembrane segments that contribute to the pore through the sarcoplasmic reticulum membrane. The cardiac isoform (RYR2) is about 65% identical to
the skeletal muscle isoform (RYR1). In contrast to skeletal muscle, the channel has no direct connection to the surface membrane Ca^{2+} channels, so that its opening is entirely dependent on the Ca^{2+} current. The four-subunit complex is so big that its shape can be seen with an electron microscope. There is a large central pore and four exit pores to the cytoplasm. The channel is not very selective and has a large single channel conductance of about 100 to 150 pS under approximately physiological conditions. Its Ca^{2+}-sensitivity is enhanced by caffeine and several volatile anesthetics. In addition, phosphorylation by protein kinase A, secondary to adrenergic stimulation, enhances Ca^{2+} release. No diseases are known to be the result of malfunction of this channel in the heart.

**Other channels**

The gap junction channel

Cardiac cells are coupled electrically by nonselective ion channels that form large connections between the cytoplasm of one cell and its neighbor. Clusters of these gap junctions can be seen at the intercalated disks, although they also make side-to-side cell connections. Early physiological experiments showed they are the path for electric current to flow from one cell to another, providing the synchrony so necessary for coordinated electrical and contractile function. Each hemichannel is formed by six connexins (Cx), producing a large channel between the cells. Each connexin is a four-transmembrane-segment protein with a small cytoplasmic N-terminus and a longer cytoplasmic C-terminus that contains putative phosphorylation sites. The principal cardiac isoform of connexin is Cx43 (the protein weighs 43 kd), which is expressed in ventricular cells, and Cx40 is found in His–Purkinje cells. Gap junction single channel conductance is 50 to 300 pS, depending on isoform and conditions. If cardiac muscle is damaged by ischemic injury or by surgery, the gap junctions between the healthy and the damaged cells close, as high extracellular Ca^{2+} diffuses into the damaged cell. Expression of gap junction mRNA has been shown to change in response to cardiac hypertrophy and to ischemia, so it is possible that gap junctions are important in the genesis of arrhythmias associated with these conditions.

**Cl\(^-\) channels**

There are two types of Cl\(^-\) channels that are definitely found in heart cells. One is activated by adrenergic stimulation and the other by intracellular Ca^{2+}. Adrenergic activation of adenyl cyclase leads to the increased production of cAMP and to activation of protein kinase A. This kinase phosphorylates a Cl\(^-\) channel called CFTR (cystic fibrosis transmembrane conductance regulator). The cardiac form of CFTR is a splice variant of the epithelial type that omits some 30 amino acids in
a cytoplasmic loop. This channel protein has about 1400 amino acids and has two sets of six transmembrane segments. Gating occurs over seconds, so that during the action potential the channel is either open or shut. Opening of this 13-pS channel has little effect on the resting potential because of its rectifier properties, but it produces a significant hyperpolarizing current during the plateau of the action potential and shortens it.

The second type of Cl\(^{-}\) channel generates a transient outward current early in the action potential, which coincides with the intracellular Ca\(^{2+}\) transient. Its molecular identity is not yet clear. During ischemia, cardiac cells swell, and cells must have some mechanism to prevent excessive swelling and damage. Hypotonic stress of cardiac cells has been shown to activate a Cl\(^{-}\) current. The molecular mediator of this swelling-activated current has not yet been resolved. There are no currently used cardiac drugs that target Cl\(^{-}\) channels, but such drugs could potentially influence the duration of the refractory period, affect response to ischemia, and possibly alter the pacemaker rate.

ION TRANSPORTERS

Introduction

Cardiac cells must maintain balance of Na\(^{+}\) and K\(^{+}\), Ca\(^{2+}\), and H\(^{+}\). K\(^{+}\) must be kept high in cells to generate the negative resting potential. Na\(^{+}\) must be kept low so that Na\(^{+}\) entry can provide the action potential as a
The sarcolemmal Na\(^+\),K\(^+\) pump

The Na\(^+\),K\(^+\) pump exists in almost every animal cell and creates the intracellular environment necessary for many cellular functions. It sets the conditions for the heart cell’s resting membrane potential by maintaining K\(^+\) high and Na\(^+\) low in the cytoplasm.\(^25\) The Na\(^+\) electrochemical gradient and membrane potential also set the balance for the Na\(^+\)/Ca\(^2+\) exchanger to keep resting cytosolic Ca\(^{2+}\) levels low.

The Na\(^+\),K\(^+\) pump consists of an α- and β-subunit dimer (Figure 6).\(^{26}\) The larger α-subunit of about 1000 amino acids subserves the main functions of Na\(^+\) and K\(^+\) transport through ATP hydrolysis. It probably has 10 transmembrane segments, similar to other membrane pumps, with a large regulatory domain in the cytoplasm. The smaller β-subunit appears to influence the location and stability of the α-subunit in the membrane, and may also play other regulatory roles. There are three isoforms of the α- and β-subunits found in the heart. They differ in their K\(_{\text{d}}\) for Na\(^+\) activation, thereby affecting the resting intracellular Na\(^+\) level, and in their sensitivity to block by digitalis.

The transporter has a stoichiometry of 3 Na\(^+\) out and 2 K\(^+\) in per cycle, using 1 ATP. The charge imbalance means that the pump is rheogenic, moving one positive charge outward with each cycle and rendering that step voltage-dependent. Only under conditions of substantial cellular Na\(^+\) load has the Na\(^+\),K\(^+\) pump current been shown to affect the membrane potential significantly. One circumstance where a hyperpolarizing current can be seen is after a rapid series of action potentials, raising Na\(^+\) within the cell. Following the tachycardia, the hyperpolarizing pump current suppresses spontaneous pacemaker firing rates, a process called overdrive suppression of pacemakers.

The number of pumps can be altered by increased transcription stimulated by elevated cytoplasmic Na\(^+\) or low extracellular K\(^+\). Evidence about pump regulation by β-adrenergic activators such as norepinephrine has been controversial. Digitalis specifically blocks the Na\(^+\),K\(^+\) pump, leading to an increase in intracellular Na\(^+\). Via the Na\(^+\)/Ca\(^{2+}\) exchanger, more Ca\(^{2+}\) is left in the cell for contraction, producing the positive inotropic effect of digitalis. Endogenous digitalis-like molecules have been identified, and it is possible that they play a role in hypertension.

**SERCA, the calcium pump of the sarcoplasmic reticulum, and phospholamban**

The calcium pump of the sarcoplasmic reticulum (SERCA [sarcoendoplasmic reticulum Ca\(^{2+}\)-transporting ATPase]) pumps 2 Ca\(^{2+}\) into the SR in exchange for 2 H\(^+\) and with the hydrolysis of 1 ATP. It is a single molecule of about 1000 amino acids. There are 10 transmembrane segments, probably α-helices, with the N- and C-termini and the bulk of the protein on the cytoplasmic side of the sarcoplasmic reticulum membrane. The membrane has a very high concentration of these pumps, permitting the rapid transport of Ca\(^{2+}\) that is needed to produce relaxation in the muscle.

Under normal conditions, the rate of relaxation of cardiac muscle is closely related to the fall in intracellular Ca\(^{2+}\), which is itself directly related to the sarcoplasmic reticulum calcium pump rate. Associated with the pump is a second phosphoprotein called phospholamban. This calmodulin-like protein binds to SERCA. In its unphosphorylated state it impedes the Ca\(^{2+}\) transport rate, and phosphorylation of phospholamban relieves this inhibition, accelerating the pump rate. Phospholamban is phosphorylated by protein kinase A, which is activated by the cAMP cascade regulated by adrenergic receptor activation. Its phosphorylation is the mechanism of faster relaxation of heart muscle that is produced by the adrenergic mediators norepinephrine and epinephrine.

In heart failure, the Ca\(^{2+}\) transient is prolonged and relaxation is slowed. This is in part the result of reduced expression of SERCA. Some changes in phospholamban expression have also been seen in animal models of heart failure. The changes in expression level presumably are an effort by cardiac cells to increase the intracellular levels of Ca\(^{2+}\), so as to restore contraction strength and relieve the heart failure, but unfortunately at a cost of inadequate relaxation and consequent diastolic dysfunction. No genetic diseases of cardiac SERCA or phospholamban have yet been reported.
The Na+/Ca2+ exchanger was demonstrated by isotopic studies to be a potent means of transporting to the outside the Ca2+ that enters through Ca2+ channels during the action potential. It also probably can contribute some Ca2+ entry for activation of contraction at the beginning of the action potential. The Na+/Ca2+ exchanger protein of about 1000 amino acids appears to have 11 transmembrane segments, with the N-terminal end in the extracellular solution and a large regulatory cytoplasmic segment between the 5th and 6th segments. Only one isoform of the exchanger is reported for heart cells.

Under conditions when the cell membrane is normally polarized, the Na+/Ca2+ exchanger transports 3 Na+ into the cell, thereby priming the transporter to move 1 Ca2+ out of the cell. The energy for efflux of Ca2+ against its steep electrochemical gradient is found in the Na+ gradient, which is maintained separately by the Na+,K+ pump. However, this implies that 3 positive charges enter the cell in exchange for removal of 2 positive charges, making the pump rheogenic and sensitive to the membrane potential. When Ca2+ rises as a result of entry through Ca2+ channels and subsequent release from the sarcoplasmic reticulum, the exchanger rapidly pumps Ca2+ out of the cell. The rheogenic property of the exchanger means that it can generate a transmembrane current. Under normal conditions, this current is too small to affect cardiac electrogenesis, but during Ca2+ overload, such as may occur with block of the Na+,K+ pump in digitalis excess, this current might be large enough to be arrhythmogenic by producing delayed afterdepolarizations.

When the cardiac cells are ischemic, they must draw on anaerobic glycolysis for ATP, generating protons from dissociation of lactic acid. This leads to a fall in intracellular pH and a shutting down of contraction and other metabolic functions. It has been suggested that this shutdown may help the cell survive ischemia. This has led to studies showing that block of the Na+/H+ exchanger does prolong survival during ischemia and speed recovery after reperfusion.

**THREE KEY QUESTIONS**

Ion channels and transporters are the substrate for the cardiac electrical system. Consequently, arrhythmias represent malfunction of these membrane proteins or alteration in their expression in the heart. However elegant the scientific insights revealed by the study of ion channels and transporters, the critical question remains how we can translate the knowledge into better clinical care. Drug and device manipulation of the cardiac electrical system has been both exciting and frustrating. Among the many questions raised by this work, this issue of Dialogues will discuss three examples important to current cardiac care. Lethal arrhythmias are the cause of death in over half of cardiac patients. Stuart Cobbe will address the question “Do drugs have a future in the management of sudden cardiac death?” Heart failure is more than contractile dysfunction, and arrhythmias contribute substantially to its morbidity and mortality. Dan Roden will discuss “How do we treat arrhythmias in heart failure?” Finally, our present success in delaying arrhythmic death has led to a dramatic increase in atrial fibrillation, reducing the quality of life of cardiac patients and revealing the inadequacy of present clinical management. Stanley Nattel will ask the question “Has our new understanding of the mechanisms of atrial fibrillation helped in its treatment?” We expect the next decades will bring new and powerful ways of regulating ion channels and transporters.
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ventricular fibrillation and pulseless ventricular tachycardia are the commonest initiating arrhythmias at the time of sudden death, although a significant minority of deaths are due to asystole or electromechanical dissociation. Since sudden death is commonly arrhythmic, it is logical to attempt prevention by an antiarrhythmic strategy. The “holy grail” of clinical electrophysiology has been to develop methods for the prediction of sudden death in individuals at risk and for its prevention.

DRUGS IN THE MANAGEMENT OF SUDDEN DEATH—NEMESIS?

Sodium current ($I_{Na}$) blockade

Until the end of the 1980s, most interest among electrophysiologists centered on class I antiarrhythmic drugs, which block the rapid inward sodium current $I_{Na}$. Clinical evaluation of antiarrhythmic drugs was based on their ability to terminate spontaneous ventricular tachycardia, prevent its reinduction by programmed stimulation, and/or suppress ventricular premature beats on ambulatory monitoring.

The electrophysiology community has come relatively lately to embrace the concepts of evidence-based medicine and large-scale randomized trials. Early studies of the efficacy of class I antiarrhythmic drugs in the prevention of sudden death and all-cause mortality were based on empirical treatment of patients during or after acute myocardial infarction. None of these trials showed evidence of benefit. The trials were open to criticism because the sample size was inadequate, patient cohorts were not selected for high risk of sudden death, and there was no attempt to prove that the drugs under investigation were able to suppress arrhythmias in the patients studied.

Suppression of ventricular premature beats

The Multicenter Postinfarction Program identified impaired left ventricular ejection fraction and the presence of frequent ventricular premature beats or nonsustained ventricular tachycardia on ambulatory ECG monitoring as independent predictors of sudden death and all-cause mortality following infarction. The presumed causal role of these asymptomatic arrhythmias as the trigger for ventricular tachycardia or fibrillation led many cardiologists to use class I drugs routinely in an attempt to prevent sudden death in postinfarction patients, and, by extension, in all patients with such arrhythmias.

The result of the Cardiac Arrhythmia Survival Trial (CAST) demonstrated the failure of this approach. Despite
effective suppression of ventricular ectopy by flecainide or encaïnide at baseline, active drug therapy resulted in an increased risk of sudden death or cardiac arrest. The increase in relative risk was greater in lower-risk subjects with relatively well-preserved left ventricular function, but the absolute excess mortality was greatest in patients with poorer ventricular function.

**Potassium current (I_{Kr}) blockade**

As a result of CAST, the focus of drug development switched from ventricular premature beat suppression with class I agents to the prolongation of ventricular depolarization by class III drugs, which inhibit the rapid component of the outward potassium current (I_{Kr}). The prototype agents, amiodarone and dl-sotalol (see below), have complex actions, including β-adrenoceptor antagonism, which make the basis of their clinical efficacy difficult to establish. Several “pure” class III agents were subsequently developed, of which dl-sotalol and dofetilide have been studied in large-scale randomized trials.

The Survival With ORal D-sotalol (SWORD) trial investigated the use of dl-sotalol in subjects with left ventricular dysfunction (ejection fraction <0.40) following recent or remote myocardial infarction, without other stratification for arrhythmic risk.³ The trial was stopped early after the finding of a significant excess in all-cause mortality (relative risk [RR], 1.65; 95% confidence interval [CI], 1.15-2.36), attributable to a 77% increase in the relative risk of presumed arrhythmic death.

The Danish Investigation of Arrhythmia and Mortality ON Dofetilide trials (DIAMOND) compared the selective I_{Kr} blocker dofetilide with placebo in two separate populations, a postinfarction group and patients with heart failure.⁴ In contrast to SWORD, therapy was initiated in hospital under telemetric ECG monitoring, and patients developing torsade de pointes or major QT interval prolongation during this phase were withdrawn. Possibly as a result of these precautions, DIAMOND differed from SWORD in that there was no increase in total or arrhythmic death, but nor was there any reduction in mortality.

**Proarrhythmia**

The results of CAST and SWORD proved in the most graphic way that antiarrhythmic drugs were capable of increasing the risk of lethal arrhythmia. Such behavior, termed proarrhythmia, had been observed previously in the context of acute drug administration, electrophysiological testing, or within the first few days of commencing drug therapy. However, the survival curves of the active and placebo groups in CAST
and SWORD (Figure 1) separated progressively, indicating that the excess risk of antiarrhythmic drug therapy persists throughout the period of follow-up.

One possible explanation for the increased risk on active therapy in CAST and SWORD was that impaired left ventricular function predisposed to proarrhythmia. Class Ic drugs have negative inotropic effects, and there may be changes in drug distribution in heart failure. Hypertrophy and remodeling in the ventricular myocyte may result in lengthening of action potential duration, which is further exacerbated by drug-induced potassium channel (\(I\text{\textsubscript{K}}\)) blockade and by the influence of diuretic-induced hypokalemia and hypomagnesemia, resulting in the development of acquired long QT syndrome.

An additional proarrhythmic mechanism in CAST and SWORD may have been the effect of ischemia or reinfarction. The effects of class I drugs in slowing intracardiac conduction are enhanced by ischemia, resulting in the development of new areas of slowed conduction or unidirectional block, predisposing to reentry. The lengthening of the cardiac action potential by class III agents is abolished during ischemia, increasing the dispersion between the ischemic and normal areas of the ventricle.

**Programmed ventricular stimulation**

Sadly, the CAST episode is not the only example in the history of electrophysiology where observational data and lack of rigorous controlled trials have led to inappropriate management. Patients who have experienced an episode of ventricular tachycardia or fibrillation remote from the setting of acute myocardial infarction are at high risk of recurrent arrhythmia and sudden death when treated empirically with antiarrhythmic drugs. Sustained ventricular tachyarrhythmia can usually be induced in these patients by programmed stimulation, indicating the presence of a fixed arrhythmia substrate. Following administration of antiarrhythmic drugs, arrhythmia is no longer inducible in a proportion of patients. In prospective observational studies, patients in whom an “effective” drug was identified and administered during follow-up had a lower risk of recurrent arrhythmia or sudden death than those in whom no effective drug could be identified. In view of the consequences of arrhythmia recurrence, no placebo-controlled trials of electrophysiologically guided antiarrhythmic drug therapy have been performed, for ethical reasons. It is noteworthy that \(\beta\)-adrenoceptor blockers, which are generally ineffective in the prevention of arrhythmia induction, were equally effective in preventing sudden death in comparison with electrophysiologically guided antiarrhythmic drug treatment in patients with ventricular tachyarrhythmias.

The largest comparative study of antiarrhythmic drug therapy in patients with ventricular tachyarrhythmias demonstrated that \(dl\)-sotalol was superior to other conventional (mostly class I) drugs in the sup-

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Amiodarone in prevention of sudden death

Growing disillusionment with class I and selective class III agents has led to increased interest in amiodarone, despite its non-cardiac toxicity. Several placebo-controlled trials of empirical amiodarone in asymptomatic patients after myocardial infarction or with congestive heart failure have been reported and subjected to meta-analysis. The European and Canadian Myocardial Infarction Amiodarone Trials (EMIAT and CAMIAT; see 9 for references) studied postinfarction patients with reduced left ventricular ejection fraction or increased ventricular ectopy. Both studies showed a reduction in arrhythmic events, but no significant effect on all-cause mortality. Among the larger trials in heart failure, the Gruppo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina trial (GESICA) showed a significant reduction in total mortality, due to equal effects on sudden and nonsudden death. However, GESICA was an open-labelled study, and contained a low proportion of patients with heart failure due to coronary artery disease. The Congestive Heart Failure—Survival Trial of Antiarrhythmic Therapy (CHF-STAT), in contrast, showed no significant benefit of amiodarone on either sudden death or all-cause mortality in a patient cohort predominantly with ischemic heart disease. Meta-analysis of all amiodarone trials showed a highly significant reduction in sudden death of about 30% (odds ratio [OR], 0.71; 95% CI, 0.59-0.85), but the reduction in all-cause mortality of around 13% was only of borderline significance (OR, 0.87; 95% CI, 0.78-0.99).

Amiodarone has multiple actions, including \( I_{Na} \) blockade, noncompetitive adrenergic antagonism, and calcium channel blockade, in addition to its effects on \( I_{Kr} \). It is not possible to identify from these studies which component may be responsible for its effect. Overall, the benefit of amiodarone in these trials is less than that achieved by conventional \( \beta \)-adrenoceptor blockade (see below), although retrospective subgroup analyses in CAMIAT and EMIAT suggest that patients treated with both amiodarone and \( \beta \)-adrenoceptor antagonists may show reduced cardiac mortality. From a clinical standpoint, the benefits of amiodarone on all-cause mortality are not large enough to justify its widespread use in low-risk groups.

Calcium channel blockers

Many experimental studies have implicated intracellular Ca\(^{2+}\) overload in the genesis of ventricular arrhythmias in acute myocardial infarction. As a result, it might be expected that Ca\(^{2+}\) channel blockers would be of benefit in the prevention of sudden death. Unfortunately, the results of randomized clinical trials have not confirmed this hypothesis. Meta-analysis has indicated, in fact, a trend towards an increase in total mortality in patients randomized to Ca\(^{2+}\) channel blockers after myocardial infarction. Studies in heart failure have not shown any consistent benefit. In one trial, there was a reduction in sudden death and total mortality in patients with nonischemic heart failure, but no evidence of benefit in ischemic cardiomyopathy. There are a number of possible reasons for the lack of benefit of Ca\(^{2+}\) channel blockers: (i) the drugs have an intrinsic negative inotropic action; (ii) short-acting dihydropyridine Ca\(^{2+}\) antagonists produce peripheral vasodilatation, which may result in reflex tachycardia and can exacerbate ischemia; and (iii) the coronary vasodilator properties of these agents may also, at least in theory, provoke ischemia by an intracoronary steal mechanism.

Implantable cardioverter-defibrillators

The apparent death blow to the concept of preventing sudden cardiac death by antiarrhythmic drugs may have been dealt by the recent randomized trials comparing antiarrhythmic drug therapy (mostly amiodarone or sotalol) with the implantable cardioverter-defibrillator in patients at genuine high risk of arrhythmic death, or in survivors of life-threatening ventricular tachyarrhythmias (Figure 2). The important details are presented in Figure 3. A recent meta-analysis of the three trials involving patients with previous life-threatening ventricular tachyarrhythmias demonstrated a relative risk reduction in all-cause mortality of 27% (RR, 95%; CI, 11% to 41%).
Despite the disappointing results in trials of antiarrhythmic drugs, strong evidence has accumulated that the risk of sudden death can be reduced by drug therapy. In Western societies, atherosclerotic coronary artery disease and its complications are the most important underlying causes of sudden death. Interventions to reduce the risk of development or progression of coronary disease may therefore have important “downstream” effects, by preventing the immediate precursors of sudden death such as myocardial ischemia/infarction, catecholamine release, or heart failure.

**Lipid lowering**

The Scandinavian Simvastatin Survival Study (SSSS)\(^1\) and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID)\(^2\) trials reported a reduction in all-cause and cardiac death, as well as in recurrent myocardial infarction. In both studies, the proportional reduction in sudden death was comparable to the overall effect on cardiac mortality.

**Antiplatelet therapy**

Meta-analysis of randomized placebo-controlled trials of antiplatelet therapy\(^3\) has confirmed a consistent pattern of benefit among “high-risk” patients, ie, those with evidence of existing vascular disease. This includes patients with stable and unstable angina pectoris and acute and remote myocardial infarction. A risk reduction of about one third in the incidence of nonfatal myocardial infarction and vascular death was found. The effect of antiplatelet therapy on sudden death was not reported separately, but it is likely that a similar proportional risk reduction occurs. The role of antiplatelet therapy and anticoagulation in reducing overall mortality and sudden death in heart failure remains undefined and is the subject of ongoing clinical trials.

**Figure 2.** Survival curve for the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial.\(^4\)


**Figure 3.** Comparison of the effect of implantable defibrillator versus antiarrhythmic therapy in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)\(^5\), the Multicenter UnSustained Tachycardia Trial (MUSTT)\(^6\), the Antiarrhythmics Versus Implantable Defibrillators (AVID)\(^7\) trial, and the Canadian Implantable Defibrillator Study (CIDS)\(^8\). Values above each column represent 3-year all-cause mortality.

Abbreviations: AA, antiarrhythmic; ICD, implantable cardioverter-defibrillator; RR, risk reduction.
Thrombolytic therapy

Thrombolytic therapy has been shown to reduce the relative risk of death in the acute phase of myocardial infarction by about 20%. Meta-analysis of 15 randomized trials showed no reduction in the risk of ventricular fibrillation in the first 24 hours, but the odds ratio for development of ventricular fibrillation at any time during hospital admission was 0.82 (95% CI, 0.76 to 0.90; \( P < 0.001 \)). Various studies have reported a reduction in the prevalence of late potentials or inducibility of ventricular tachycardia, which suggests that thrombolytic therapy may prevent development of the substrate for recurrent tachyarrhythmias.

**\( \beta \)-Adrenoceptor blockade**

\( \beta \)-Adrenoceptor blockade in survivors of recent myocardial infarction reduces not only the risk of reinfarction but also of sudden death (Table I). Drugs with intrinsic sympathomimetic activity appear not to confer any survival advantage. In contrast, there is no evidence of heterogeneity between the results obtained with \( \beta_1 \)-selective compared with nonselective blockers. Although patients with uncontrolled heart failure were excluded from these trials, retrospective subgroup analyses of patients with cardiomegaly or heart failure complicating the acute infarction showed that the relative risk reduction in sudden cardiac death and total mortality was as great as in lower-risk patients. The absolute benefit of treatment was therefore greater.

In recent trials, \( \beta \)-adrenoceptor blockade has achieved significant reductions in total and sudden death in patients with congestive heart failure.

**Table I. Outcome of \( \beta \)-blocker trials.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Drug</th>
<th>RR (%)</th>
<th>95% CI</th>
<th>( P )</th>
<th>RR (%)</th>
<th>95% CI</th>
<th>( P )</th>
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<tbody>
<tr>
<td>POST-EMI</td>
<td>1977</td>
<td>Practolol</td>
<td>44</td>
<td>14 - 64</td>
<td>&lt;0.02</td>
<td>23</td>
<td>4 - 41</td>
<td>NA</td>
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<tr>
<td>Norwegian</td>
<td>1981</td>
<td>Timolol</td>
<td>51</td>
<td>31 - 65</td>
<td>&lt;0.001</td>
<td>39</td>
<td>19 - 49</td>
<td>0.0001</td>
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<tr>
<td>BHAT</td>
<td>1982</td>
<td>Propranolol</td>
<td>28</td>
<td>1 - 47</td>
<td>&lt;0.05</td>
<td>26</td>
<td>9 - 40</td>
<td>&lt;0.005</td>
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<tr>
<td>Norwegian</td>
<td>1982</td>
<td>Propranolol</td>
<td>51</td>
<td>2 - 76</td>
<td>&lt;0.038</td>
<td>31</td>
<td>11 - 58</td>
<td>NS</td>
</tr>
<tr>
<td>CIBS II</td>
<td>1999</td>
<td>Bisoprolol</td>
<td>44</td>
<td>20 - 61</td>
<td>&lt;0.0011</td>
<td>34</td>
<td>19 - 46</td>
<td>&lt;0.0001</td>
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<tr>
<td>MERIT-HF</td>
<td>1999</td>
<td>Metoprolol</td>
<td>41</td>
<td>22 - 55</td>
<td>&lt;0.002</td>
<td>34</td>
<td>19 - 47</td>
<td>&lt;0.0001</td>
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**Table II. Outcome of ACE-inhibitor trials.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Drug</th>
<th>RR (%)</th>
<th>95% CI</th>
<th>( P )</th>
<th>RR (%)</th>
<th>95% CI</th>
<th>( P )</th>
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<tr>
<td>SOLVD Rx</td>
<td>1991</td>
<td>Enalapril</td>
<td>10</td>
<td>-17 - 21</td>
<td>NS</td>
<td>16</td>
<td>5 - 26</td>
<td>&lt;0.0036</td>
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<tr>
<td>SOLVD Prev</td>
<td>1992</td>
<td>Enalapril</td>
<td>7</td>
<td>-22 - 30</td>
<td>NS</td>
<td>8</td>
<td>-8 - 21</td>
<td>NS</td>
</tr>
<tr>
<td>SAVE</td>
<td>1992</td>
<td>Captopril</td>
<td>16</td>
<td>-8 - 34</td>
<td>NS</td>
<td>19</td>
<td>3 - 32</td>
<td>0.019</td>
</tr>
<tr>
<td>AIRE</td>
<td>1993</td>
<td>Ramipril</td>
<td>30</td>
<td>7 - 44</td>
<td>0.01</td>
<td>27</td>
<td>11 - 40</td>
<td>0.002</td>
</tr>
<tr>
<td>TRACE</td>
<td>1995</td>
<td>Trandolapril</td>
<td>24</td>
<td>2 - 41</td>
<td>0.03</td>
<td>22</td>
<td>9 - 33</td>
<td>0.001</td>
</tr>
<tr>
<td>HOPE</td>
<td>2000</td>
<td>Ramipril</td>
<td>38*</td>
<td>6 - 59</td>
<td>0.02</td>
<td>16</td>
<td>5 - 25</td>
<td>0.005</td>
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</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; NA, not available; NS, non significant; POST-MI, post–myocardial infarction; RR, risk reduction. Names of studies: see Study Acronyms box.
failure. The effect on sudden death is considerable, with risk reductions in the range of 41% to 55%.

### Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been investigated in long-term clinical studies of nearly 13,000 patients with left ventricular dysfunction or heart failure. The principal benefit is in the prevention of progression of heart failure. However, all of the studies except the COoperative North Scandinavian ENalapril SUrvival Study (CONSENSUS) show some reduction in the incidence of sudden unexpected death (Table II), and in the Acute Infarction Ramipril Efficacy (AIRE) and TRAndolapril Cardiac Evaluation (TRACE) studies, the reductions in sudden death are statistically significant. Recently, the Heart Outcomes Prospective Evaluation (HOPE) trial also reported a reduction in cardiac arrest (RR 0.62, \(P=0.02\)) and cardiovascular mortality (RR 0.74, \(P=0.001\)) in patients with known vascular disease or diabetes who did not have left ventricular dysfunction.

### Aldosterone antagonism

Stimulation of the renin-angiotensin-aldosterone system in heart failure results in increased plasma levels of aldosterone, which are not suppressed by chronic ACE-inhibitor therapy. The Randomized Aldactone Evaluation Study (RALES) demonstrated that spironolactone reduced both death due to progressive heart failure and sudden death. The reason for the latter effect may include avoidance of hypokalemia and regression of cardiac interstitial hypertrophy, which is stimulated by aldosterone and may predispose to reentrant arrhythmias.

### Inhibition of sodium–hydrogen exchange

Acute ischemia results in the rapid development of intracellular acidosis, which, by activation of the sarcolemmal Na\(^+\)/H\(^+\) exchanger, results in Na\(^+\) influx. Since sarcolemmal Na\(^+\)/K\(^+\) ATPase is inhibited in ischemia, the normal route of Na\(^+\) extrusion is inhibited, resulting in an increased concentration of Na\(^+\). This, in turn, produces an increase in Ca\(^{2+}\) concentration, via the Na\(^+\)/Ca\(^{2+}\) exchanger. Intracellular Ca\(^{2+}\) accumulation predisposes to ventricular arrhythmias during both ischemia and reperfusion. Specific inhibitors of Na\(^+\)/H\(^+\) exchange such as HOE-694 and cariporide have been studied in animal models of acute ischemia and reperfusion. These agents have no direct electrophysiological actions, but reduce the incidence of ventricular fibrillation, as well as preserving contractile function and reducing infarct size, presumably by virtue of preventing Ca\(^{2+}\) overload. The role of inhibition of Na\(^+\)/H\(^+\) exchange in acute coronary syndromes is currently under investigation, but a recently presented trial failed to document significant reduction in death or myocardial infarction.

### CONCLUSIONS

The future of drugs in the prevention of sudden cardiac death is bright—but that future lies in primary and secondary prevention of coronary artery disease and its consequences. Antiarrhythmic drugs seem likely, for the foreseeable future, to be used in an adjunctive role in combination with implantable cardioverter-defibrillators. Amiodarone and sotalol will continue to be used if device therapy is not feasible owing to cost restraints or comorbidity.

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How do we treat arrhythmias in heart failure?

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Congestive heart failure (CHF) is the commonest discharge diagnosis in the United States, and it has been estimated that 1% of the population has symptomatic heart failure. This is a serious diagnosis, with a mortality rate—50% in 5 years—exceeding many malignancies. Death is most often sudden in CHF, so the question naturally arises as to whether antiarrhythmic or other therapies designed to prevent sudden death may have a role in the management of patients with CHF.1

In the reasonable (but unproven) assumption that sudden death in congestive heart failure (CHF) is primarily due to arrhythmia, four management strategies are employed: (i) treatment to prevent reversible causes of arrhythmia; (ii) β-blockade and angio-tensin-converting enzyme inhibition (included in strategy 1, but directly useful by inhibiting sympathetic-renin-angiotensin activation, a common maladaptive response in CHF); (iii) antiarrhythmic drugs (in selected cases, eg, amiodarone to maintain sinus rhythm after conversion of atrial fibrillation; and (iv) an implanted cardioverter-defibrillator device, an increasingly valid option in high-risk patients. New approaches may be gene-based, such as the discovery of an association between arrhythmia and reduced Kr4.3 gene expression. Continuing application of molecular techniques will identify further instances of altered gene expression in CHF and new therapeutic options.

**Keywords:** cardiac arrhythmia; congestive heart failure; antiarrhythmic drug; amiodarone; defibrillation

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<table>
<thead>
<tr>
<th>SELECTED ABBREVIATIONS AND ACRONYMS</th>
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<tr>
<td><strong>AVID</strong></td>
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<tr>
<td><strong>CABG</strong></td>
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<td><strong>CaM kinase</strong></td>
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How do we treat arrhythmias in heart failure?

Although many ACE inhibitors have been shown to reduce mortality in heart failure, their specific effects on arrhythmic death or sudden death are less consistent, with only some trials reporting a reduction in sudden death.9,10 More recently, the aldosterone receptor antagonist spironolactone has been shown to markedly reduce mortality (due to progressive heart failure as well as to sudden death) in patients with advanced disease already treated with digoxin, diuretics, and ACE inhibitors.11 The dose used was low, and the mechanism underlying this effect is uncertain. Multiple large trials have now demonstrated that digoxin does not alter long-term mortality in heart failure, but does reduce hospitalizations.12 Because other agents with positive inotropic effects almost uniformly increase mortality, digoxin remains a mainstay in the management of patients with heart failure.

ANTIARRHYTHMIC DRUGS

IN HEART FAILURE

With the few exceptions described below, antiarrhythmic drugs have not been specifically tested in patients with heart failure. However, they have been tested in patients judged to be at high risk for sudden death, because of a history of myocardial infarction or the presence of ventricular extrasystoles or left ventricular dysfunction. In the Cardiac Arrhythmia Suppression Trial (CAST), encainide and flecainide increased mortality in patients convalescing from acute myocardial infarction. Interestingly, the deleterious effects of these agents were uniform across patient groups, and in fact were no worse among patients with heart failure or low ejection fraction compared with those with preserved ventricular function.13 The dextrorotatory isomer of sotalol, d-sotalol, a rapid delayed
rectifier potassium channel ($I_{Kr}$)-specific QT-prolonging agent, was tested in patients with recent or remote myocardial infarction and ejection fractions <40% in the Survival With ORal D-sotalol (SWORD) trial. Among patients with myocardial infarction, d-sotalol markedly increased mortality in those with relatively preserved left ventricular function (ejection fraction 31% to 40%), while it was relatively outcome-neutral in those with more severe left ventricular dysfunction. Among those with recent myocardial infarction, the increase in mortality with d-sotalol was more uniform across ejection fractions.

This generally distressing ineffectiveness of antiarrhythmic drugs in reducing mortality in “high-risk” patients is mirrored by therapies developed to improve contractility. For example, both milrinone and vesnarinone (phosphodiesterase inhibitors) acutely improve contractility, but both increase mortality during long-term therapy. Interestingly, the excess mortality appears to be largely arrhythmic. In the large VESnarinone Trial–II (VEST-II), death due to pump failure was equivalent in the placebo, 30-mg, and 60-mg groups, but the higher doses of drug increased the number of patients dying suddenly. This likely reflects the fact that vesnarinone increases cyclic-AMP-dependent protein kinase (PKA), which not only improves contractility, but also likely engages arrhythmogenic mechanisms, perhaps related to increased intracellular calcium. Whether drugs can be developed to improve contractility without causing arrhythmias is an open question. One strategy, “sensitizing” the contractile apparatus to normal intracellular concentrations of calcium, has some promise in this regard. Two antiarrhythmics have been shown to be outcome-neutral, or possibly even beneficial, in patients with CHF. These are dofetilide, an $I_{Kr}$-specific QT-prolonging agent, and amiodarone, an agent with a wide variety of pharmacologic effects, including a prominent sympatholytic effect. An early Argentinian trial, Gruppo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA), reported a marked beneficial effect of amiodarone on overall survival in patients with reduced ejection fraction. By contrast, a US study, the Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy (CHF-STAT), showed no effect of amiodarone on total mortality. There was, however, a trend to a decreased mortality among patients with nonischemic cardiomyopathy (a relatively large group in GESICA) in CHF-STAT.

Dofetilide was tested in the Danish Investigation of Arrhythmia and Mortality ON Dofetilide (DIAMOND) trials. These were two large randomized trials, one conducted in patients with recent myocardial infarction and the second in patients with recent hospitalization for heart failure. In both trials, dofetilide was absolutely outcome-neutral: in DIAMOND-CHF, mortality at 3 years was 311/762 in patients randomized to receive dofetilide versus 317/756 among those receiving placebo, and the corresponding numbers for those in DIAMOND-MI were 230/749 versus 243/761. Since dofetilide and d-sotalol have extremely similar pharmacologic characteristics, it seems likely that differences in trial design account for the differences in outcomes between DIAMOND and SWORD. The only recognized toxicity from these agents is their propensity to cause torsades de pointes, in a dose-related fashion for both agents. The SWORD design included enrollment of relatively low-risk patients (in whom benefit would be difficult to demonstrate, so any case of torsades de pointes might skew the outcome) and forced titration, often in an outpatient setting, to relatively high dosages. The DIAMOND design, by contrast, enrolled sicker patients (who had a greater chance of benefit from the drug), and employed careful in-hospital dose titration. In DIAMOND-CHF, torsades de pointes occurred in 25/762 patients, and, in DIAMOND-MI, in 7/749 patients. None of the 1517 patients were enrolled in the corresponding placebo arms in DIAMOND and had torsades de pointes. Thus, these data provide objective support for the long-held belief that CHF itself is a risk factor for torsades de pointes.

**ATRIAL FIBRILLATION IN HEART FAILURE**

Further analysis of the DIAMOND databases showed no difference in arrhythmic death, a prespecified end point. One interesting exploratory analysis showed that among patients in DIAMOND-CHF, there was a highly statistically significant ($P<0.001$) reduction in the rate at which patients receiving dofetilide were rehospitalized for worsening heart failure. This difference was not seen in patients enrolled in DIAMOND-MI. Further analysis suggests that this beneficial effect relates to the efficacy of dofetilide in maintaining sinus rhythm in patients with heart failure. Among patients who entered the DIAMOND trials with atrial fibrillation, 79% of those randomized to dofetilide were in sinus rhythm at 12 months versus only 42% of those randomized to placebo ($P<0.001$). Importantly, it was only in patients entering the trial in atrial fibrillation that a beneficial effect of dofetilide on rehospitalization rates for heart failure was observed.
How do we treat arrhythmias in heart failure?

Roden

Some patients who convert to normal rhythm on amiodarone, compared with those in whom atrial fibrillation was permanent, had a better 1-year survival with amiodarone therapy. Patients receiving permanent atrial fibrillation had a higher mortality rate, with a 1-year mortality rate of 52% versus 71% for those who converted to normal rhythm on amiodarone. In a study of 90 patients with advanced heart failure, the mortality rate of those who converted to normal rhythm was significantly lower than that of those who maintained atrial fibrillation. On 315 patients entered the CHF-STAT database, those with atrial fibrillation (52%, n=75) versus those with sinus rhythm (71%, n=315) at baseline had a worse 1-year survival. Among 4500 patients in the AVID trial, when sinus rhythm was present at entry, the mortality rate was significantly lower in patients treated with amiodarone than in those treated with placebo (18.5% versus 26.7%, p<0.001). Among 367 patients treated for atrial fibrillation, those who converted to normal rhythm had a 1-year mortality rate of 52% versus 71% for those who maintained atrial fibrillation. Taken together, these data provide support for the idea that maintaining sinus rhythm may have a long-term beneficial effect on pump function in patients with heart failure. Further support for this concept also comes from an analysis of the CHF-STAT database, which showed a higher mortality rate among 71% of patients entering CHF-STAT with atrial fibrillation, mortality rate was significantly better among those who converted to normal rhythm than those who maintained atrial fibrillation.

Implanted Cardioverter/Defibrillators

Thus, antiarrhythmic drugs have been ineffective (or worse) in reducing mortality among patients with CHF. A number of trials have examined a potential role for the implanted cardioverter/defibrillator device (ICD) to reduce mortality among high-risk patients, including patients with CHF. One of the earliest trials was the Multicenter Automatic Defibrillator Implantation Trial (MADIT), which compared “conventional” antiarrhythmic therapy (usually amiodarone) with ICDs in a small group of patients (n=196) with preserved functional class (NYHA class I, II, or III), nonsustained ventricular tachycardia on a Holter monitor, inducible ventricular tachycardia at electrophysiologic testing persisting after intravenous propranolol, and no indication for revascularization. The primary end point was total mortality, and the patients randomized to receive an ICD had significantly lower 2-year mortality than those randomized to “conventional” therapy. Another trial, Amiodarone Vs Implantable Defibrillators (AVID), studied a larger number of patients (1016) with reduced ejection fraction (<40%) resuscitated from ventricular fibrillation or presenting with ventricular tachycardia and syncope. Patients were randomized to receive an ICD or antiarrhythmic drugs, again usually amiodarone. The primary end point was total mortality and, as in MADIT, patients randomized to receive an ICD had a significantly lower mortality. In MUSTT, patients deemed to be at risk for sudden death first underwent programmed electrical stimulation. Patients with inducible arrhythmia by this evaluation were randomized to standard medical therapy (but no antiarrhythmics) versus therapy (drug or ICD) designed to suppress arrhythmia. A recent trial, the Multicenter Un-Sustained Tachycardia Trial (MUSTT), provided further evidence for a benefit of ICD therapy (independent of β-blockade) among “high-risk” patients. High-risk patients in MUSTT were defined as those with coronary disease, reduced ejection fraction (<40%), and asymptomatic nonsustained ventricular tachycardia. In MUSTT, patients deemed to be at risk for sudden death first underwent programmed electrical stimulation. Patients with inducible arrhythmia by this evaluation were randomized to standard medical therapy (but no antiarrhythmics) versus therapy (drug or ICD) designed to suppress arrhythmia. Patients without inducible arrhythmia were followed in a registry. The primary end point was survival among patients randomized to specific antiarrhythmic therapy versus those receiving standard medical therapeutics.
In this comparison, patients randomized to receive antiarrhythmic therapy did have a better outcome ($P=0.043$) than those receiving “standard” therapy. However, this outcome was driven exclusively by a benefit among patients in the arrhythmia treatment group who received an ICD. In fact, survival was worse among patients receiving antiarrhythmic drugs than those receiving standard medical therapy (but no drugs). The difference between the latter two groups was not statistically significant, and the assignment to ICD or drugs was not randomized. However, β-blocker use was significantly higher among patients receiving standard medical therapy than even among those receiving ICDs.

One large trial, the Coronary Artery Bypass Graft (CABG) Patch Trial, has failed to show a benefit of ICD versus standard therapies.29 CABG was conducted in patients undergoing coronary artery bypass grafting who received standard postoperative therapy and were randomized to ICD or no ICD. The finding of no difference has been taken by some to suggest that episodes of myocardial ischemia are important triggers for VT/VF events in patients with ICDs, even in the absence of detectable ischemia.

Taken together, the weight of emerging data strongly suggests that survival in “high-risk” patients with heart disease can be improved by use of ICDs. This reflects the fact that ICD technologies have evolved over the past 20 years to the point that the devices are simple to use, carry minimal morbidity (and virtually no mortality) with their placement and use, and are extraordinarily effective at recognizing and terminating sustained ventricular tachyarrhythmias, both VT and VF. Given these characteristics, it is hardly surprising that ICDs come out “ahead” of drugs that have much less predictable efficacy and a litany of side effects during short-term and long-term use. Two questions will become important in ICD use over the next decade or two. First, it will be important to define subsets of patients in whom benefit is greatest. The current state of the art would suggest that even patients at moderate risk of sudden death might benefit from ICD placement, although the numbers required to treat become enormous as lower-risk patients are evaluated. Because of this, randomized trials to determine efficacy of ICD therapy in moderate-to-low-risk subsets are not likely to be performed. The second, equally pressing and related, question for society is to define the criteria under which these relatively expensive devices will be implanted prophylactically.

![Figure 1](image_url). Membrane currents (left) and calcium transients (right) recorded in rabbit ventricular myocytes using short or long action potential (AP) waveforms as the command pulses (top, panels A and B). Intracellular calcium concentration was higher with the long action potential clamp (right). Under this condition, membrane current displayed a postrepolarization inward current (arrow, panel A, bottom), the arrhythmogenic “transient inward” current. This was absent with the voltage clamp experiment using the short action potential command (panel B). This arrhythmogenic inward current was abolished by inhibiting calcium-calmodulin–dependent (CaM) kinase, but not by inhibiting cyclic-AMP-dependent protein kinase (PKA) or protein kinase C (PKC). Reproduced from ref 34: Wu Y, Roden DM, Anderson ME. Calmodulin kinase inhibition prevents development of the arrhythmogenic transient inward current. Circ Res. 1999;84:906-912. Copyright © 1999, American Heart Association.
NEW TARGETS?

It seems likely that death due to arrhythmias in patients with CHF has multiple mechanisms. Nevertheless, evolving molecular genetic thinking in this area has defined a number of common homeostatic perturbations that may promote arrhythmias in this disease. For example, ventricular action potentials are consistently prolonged in animal models of heart failure and in patients. A common underlying finding is reduced transient outward current (Ito), with resultant reduced phase I “notch.” Changing the voltage at which the phase I notch ends, in turn, likely increases current through normal L-type calcium channels, prolonging action potential duration. Altered expression of the sodium-calcium exchanger has also been reported. Expression of Kv4.3 likely underlies Ito, and reduced expression of this gene has been found in heart failure models. Action potential prolongation that occurs in heart failure (as well as that seen in other settings such as the congenital long QT syndromes) likely increases intracellular calcium and can thereby be arrhythmogenic, by activating calcium-dependent signaling processes within the cell. One such arrhythmogenic system is calcium-calmodulin–dependent kinase (CaM kinase). CaM kinase is activated when action potentials are prolonged, and some data suggest this activation is highly arrhythmogenic by generating calcium-dependent transient inward current.

It seems likely that continuing application of molecular techniques to the syndrome of CHF will provide further descriptions of altered gene expression in heart failure. The extent to which these changes are adaptive (eg, to support contractility in the failing heart) or maladaptive (eg, to result in arrhythmias) will be interesting to unravel. Obviously, the identification of a maladaptive arrhythmogenic response would provide an entirely new target for antiarrhythmic drugs in this highly lethal condition.

PUTTING IT ALL TOGETHER

The answer to the question of how to treat arrhythmias in heart failure then follows from available data. All patients with the syndrome of heart failure should receive therapies known to reduce morbidity and mortality, including those due to arrhythmias; the most important of these therapies are digoxin, β-blockade, ACE inhibition, and the aldosterone receptor antagonist spironolactone. Prophylactic antiarrhythmic drugs are not indicated in patients with CHF, and some antiarrhythmic drugs should be avoided entirely. Among patients with atrial fibrillation and CHF, soft data suggest that dofetilide or amiodarone may reduce hospitalizations, although they are without effect on long-term mortality. Some data suggest amiodarone may reduce mortality in non-ischemic dilated cardiomyopathies, but other studies have failed to show this result. Among patients with recurrent episodes of symptomatic nonsustained ventricular tachycardia, amiodarone is probably the therapy of choice. Some patient groups that are at very high risk for sudden death can be identified: those with recurrent episodes of sustained monomorphic VT or those resuscitated from an episode of out-of-hospital cardiac arrest. Placement of an ICD device is the preferred therapy in this setting. Patients with very frequent arrhythmias and an ICD will require suppressive drug therapy to prevent frequent discharges of the device, and in practice the drug that is most widely used is amiodarone. An emerging understanding of the molecular basis of arrhythmias in heart failure may provide new targets for drug therapy in this highly lethal condition.

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Has our new understanding of the mechanisms of atrial fibrillation helped in its treatment?

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Notions about the mechanisms underlying atrial fibrillation (AF) go back to the beginning of the twentieth century, when multiple circuit reentry, rapidly discharging ectopic foci, and single-circuit mother-wave reentry with fibrillatory conduction were proposed as alternative hypotheses to account for the characteristic rapid, irregular atrial activity. For many years, multiple-circuit reentry held sway as the dominant conceptual model of AF. Recent research has shown that all of the initially-proposed mechanisms can play a role in AF, depending on the clinical setting, and that atrial tachycardias (epitomized by AF) alter atrial electrophysiology so as to favor multiple-circuit reentry, which then becomes a common final pathway for AF. Recent advances in understanding the mechanisms of AF have important implications for treating the arrhythmia, which the present paper will review.

Keywords: cardiac arrhythmia; antiarrhythmic drug; ion channel; remodeling; pulmonary vein

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SELECTED ABBREVIATIONS AND ACRONYMS

AF atrial fibrillation
CHF congestive heart failure
ERP effective refractory period
NCX Na+, Ca2+ exchanger
TRACE TRAndolapril Cardiac Evaluation

In 1924, Walter Garrey wrote a superb review article summarizing contemporary knowledge of the properties and mechanisms of atrial fibrillation (AF). There were three prevailing conceptual models, illustrated diagrammatically in Figure 1 (next page). Garrey himself was a proponent of the notion of multiple-circuit reentry, in which multiple wavefronts weaved in and out, passing around refractory tissue and maintaining continuous atrial activity. Lewis favored the idea that a single macro-reentry circuit maintained the arrhythmia, with variable conduction through refractory tissue producing the irregular atrial electrocardiographic activity and irregular ventricular response characteristic of the arrhythmia. Others, like Winterburg, believed that rapidly discharging ectopic foci were at the source of AF. Subsequently, Gordon Moe framed his “multiple wavelet hypothesis,” according to which AF was maintained by multiple continuously propagating atrial wavelets, many of which encountered refractory tissue and died out, but enough of which were successful in spawning propagating “daughter wavelets” to maintain the arrhythmia. In fairness, Moe did acknowledge the likelihood of a role for other mechanisms like enhanced ectopic activity, however, the logical appeal of the mechanism that he proposed made it the dominant conceptualization of AF until quite recently.

In the 1970s, Allessie described the “leading circle” mechanism of reentry, which allowed the properties determining the number of circuits that could be accommodated in a tissue to be estimated on the basis of the wavelength for reentry, the minimum reentry circuit size given by the product of conduction velocity and refractory period. Figure 2 shows how the wavelength is thought to determine the minimum size of a reentry circuit. Because a circuit smaller than the wavelength cannot maintain itself, functional reentry will automatically establish itself in the shortest circuit size that maintains activity (the wavelength). If AF is maintained by multiple functional circuits, the minimal circuit size will determine the number...
of circuits the atria will accommodate. If circuit size is increased (eg, by increasing refractory period), the atria will be able to accommodate fewer circuits, and AF is likely to terminate. On the other hand, if conditions are altered so that more circuits can be accommodated (eg, by reducing the wavelength via slowed conduction or decreased refractory period, or by increasing atrial size), AF is more likely to persist. Allessie et al subsequently provided direct experimental evidence for Moe’s multiple wavelet schema and showed that the ability to induce AF in experimental models was related to the wavelength of atrial tissue, with smaller wavelengths allowing more functional circuits and a greater likelihood of AF. Subsequent studies in a vagal model of AF suggested that AF termination by antiarrhythmic drugs is related to their ability to prolong the wavelength and increase the size of apparent reentry circuits beyond critical values required for AF maintenance.

The past several years have seen an unprecedented explosion in our understanding about the mechanisms underlying AF. It is probable that we have learned more about the basic mechanisms of AF over the last 6 years than we did over the preceding century.

Atrial fibrillation–induced remodeling

One key advance in this area was the demonstration that AF alters atrial electrophysiology in a fashion that promotes its own maintenance, a phenomenon that has been referred to as atrial fibrillation-induced remodeling.

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to as “AF begets AF.” The underlying electrophysiological changes have become known as atrial electrical remodeling. In a series of elegant experiments, Allessie’s group showed that simply maintaining AF artificially in goats with normal hearts causes a marked reduction in atrial effective refractory period (ERP) and ERP accommodation to rate, along with a progressive increase in the ability to maintain AF. Other groups subsequently showed that regular atrial tachycardias achieve the same form of remodeling, indicating that the atria respond to a tachycardic stimulus with a series of stereotyped electrical alterations that allow them to respond to a more rapid rate, but at the price of increased vulnerability to AF. Tachycardia-induced AF-promoting alterations can occur over as little as 5 to 15 minutes, with changes continuing to progress over days to weeks.

It has been suggested that tachycardia increases cellular Ca$^{2+}$ loading (Figure 3). Since Ca$^{2+}$ overload can cause cell death, the cell responds by protecting itself via several measures to decrease Ca$^{2+}$ loading: rapid functional changes (Ca$^{2+}$-channel inactivation) and slower genetically-determined decreases in L-type Ca$^{2+}$ and Na$^{+}$ channel expression. The risk to cell viability is minimized by these changes, but action potential duration is decreased by the consequent reductions in Ca$^{2+}$ current (which normally maintains the action potential plateau), resulting in decreased action potential duration, decreased refractory period, reduced wavelength, and an increased susceptibility to AF. The unraveling of these mechanisms has provided potential insights into a variety of clinically important phenomena such as the tendency of regular atrial tachyarrhythmias (like AV reentry, AV node reentry, and atrial flutter) to be associated with AF, the progression of paroxysmal to persistent AF, the resistance of longer-duration AF to antiarrhythmic drug therapy, and the occurrence of atrial mechanical dysfunction following cardioversion of AF.

### The role of pulmonary vein ectopy

A crucially important contribution was provided several years ago by the group of Michel Haissaguerre in Bordeaux, who showed that in many patients with AF, the arrhythmia was triggered by rapid ectopic activity coming from cardiac tissues associated with the pulmonary veins. Not only did Haissaguerre’s group demonstrate the presence of such activity, but they showed that its elimination by focal ablation could result in cure of drug-resistant AF. Subsequent investigators have confirmed Haissaguerre’s findings and it is now believed that ectopic activity from the pulmonary vein region plays a crucial role in many cases of AF, acting in some cases as a primary driver for the arrhythmia (as postulated by some investigators in the early 20th century), and in others as the trigger acting on a vulnerable substrate to induce AF. The fundamental basis for the preferential generation of this activity in the pulmonary vein region remains to be established, but awareness of its importance has already made important contributions to AF management.

### The identification of other substrates for atrial fibrillation maintenance

Certain disease entities, such as congestive heart failure (CHF), are well-known to predispose to AF. Recently, the pathophysiology of AF has been evaluated in detail in an experimental model of CHF. It appears that CHF causes important atrial fibrosis, resulting in conduction abnormalities that promote AF maintenance. Intriguingly, the...

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**Figure 3.** Sequence of events that occur when atrial fibrillation (AF) begins. Because Ca$^{2+}$ enters the cell with each action potential (AP), the ≈10-fold increase in AP frequency caused by AF greatly increases cellular Ca$^{2+}$ loading. Cellular Ca$^{2+}$ loading tends to increase intracellular [Ca$^{2+}$], which, if uncontrolled, would lead to cell death. The cell protects itself by inactivating Ca$^{2+}$ channels (short-term adaptation) and reducing the number of Ca$^{2+}$ channels in the membrane (long-term adaptation). Ca$^{2+}$ loading is reduced, but at the expense of a shorter AP, reduced refractory period, decreased wavelength, and therefore increased risk of AF occurrence and maintenance.
interstitial fibrosis that characterizes the experimental AF model is also seen in association with AF in a variety of clinical conditions, including CHF, mitral valve disease, and senescence. In addition, CHF enhances the current carried by the Na+, Ca2+ exchanger (NCX).17 The NCX exchanges 3 Na+ ions for one Ca2+ ion, thus carrying a net current. When the cell repolarizes after an action potential depolarization, the NCX removes Ca2+ that has entered the cell during the action potential by exchanging it for extracellular Na+. This action results in a net movement of Na+ ions into the cell, tending to depolarize the cell by causing delayed afterdepolarizations and to cause ectopic action potential generation. Thus, NCX upregulation by CHF can contribute to AF by causing ectopy that triggers the arrhythmia.

Synthesis of mechanisms—what does it all mean for clinical practice?

Recent advances have shown us that AF may be due to any of the three mechanisms hypothesized in the early 20th century (Figure 1). However, following the onset of AF by any mechanism, tachycardia-related electrophysiological remodeling will occur, resulting in a decreased wavelength and tending to transform the arrhythmia into multiple-circuit reentry (Figure 4). This likely explains why AF that is persistent becomes more resistant to drug therapy and why AF is particularly likely to recur within the first few days after electrical cardioversion of previously persistent AF. The ionic remodeling caused by atrial tachycardia affects not only ionic currents, but also intracellular Ca2+ handling, with a consequently reduced systolic intracellular free-Ca2+ rise.18 Since the release of Ca2+ in the cytoplasm triggers and determines the systolic contraction, the reduced systolic Ca2+ transient caused by atrial tachycardia accounts for atrial mechanical dysfunction following the cardioversion of AF. The latter is responsible for thromboembolic complications following conversion to sinus rhythm, so this aspect of ionic remodeling is of considerable clinical importance.

Which specific new clinical approaches can be deduced from our recent discoveries of AF mechanisms? The first is that early cardioversion of AF is desirable, in order to minimize the chances of remodeling and maximize the chances of maintaining sinus rhythm. Implantable atrial cardioverters may be quite useful in this regard, by permitting early restoration of sinus rhythm. In fact, these notions have led to the idea that by allowing for reversal of remodeling, “sinus rhythm begets sinus rhythm.” Knowing that remodeling is greatest immediately after cardioversion of long-lasting (>1 week) AF, and reverses over the next few days, points to the idea of applying more intense antiarrhythmic therapy for the few days after cardioversion, the time of greatest risk of AF recurrence. The understanding of the role of enhanced atrial ectopic activity, particularly from the pulmonary vein region, has permitted the development of a curative approach to treating AF by ablating arrhythmogenic foci.15 The concept of remodeling, as depicted in Figure 4, has allowed us to understand that AF may begin with rapid focal discharge and then transform itself into multiple circuit reentry by dint of electrical remodeling, as reported by Hobbs et al.19 In such a case, radiofrequency ablation of a pulmonary vein ectopic focus may completely prevent AF recurrence.

_Tachycardia-induced remodeling occurs following the onset of atrial fibrillation (AF) due to either mother wave reentry or rapid ectopy. Remodeling decreases the wavelength, favoring the transformation of AF due to mother wave reentry or rapid ectopy into multiple circuit reentry. In order to identify the initial mechanism of AF and establish definitive therapy, it may be necessary to stop AF and allow remodeling to reverse itself, thus exposing the initial substrate._

The ablation of automatic foci initiating AF promises to revolutionize AF therapy by opening up the possibility of safe and highly effective nonpharmacologic treatment.

Our increasing understanding of atrial remodeling may allow for the development of new pharmacologic approaches that target the development of the substrate for AF rather than simply the final electrical product. Mibefradil, a drug that blocks...
both L-type Ca\(^{2+}\) channels (which are the target of standard clinical Ca\(^{2+}\) channel blockers like diltiazem and verapamil) and T-type Ca\(^{2+}\) channels (a form of channel with different biophysical properties)\(^{20}\) is able to prevent atrial tachycardia-dependent remodeling quite effectively\(^{21}\) T-type channels carry a transient Ca\(^{2+}\) current that is normally smaller than that carried by L-type channels. However, L-type current is downregulated by AF, so T-type current may be an important continuing source of Ca\(^{2+}\) overload in the presence of AF. Alternatively, some other action (such as K\(^{+}\) or Na\(^{+}\) channel blockade or cytochrome inhibition) may be responsible for the beneficial effects of mibefradil. Mibefradil has been withdrawn from the market because of adverse drug interactions, but the demonstrated possibility of preventing atrial remodeling raises exciting prospects for new approaches in the future. Inhibition of the renin-angiotensin system has been shown to prevent AF-promoting structural remodeling caused by experimental CHF\(^{22}\) This raises the possibility of preventing structural remodeling in order to prevent clinical AF, and may account for the AF-preventing effect of trandolapril observed in the TRAndolapril Cardiac Evaluation (TRACE) study\(^{23}\) Finally, the molecular mechanisms responsible for changes in ion channel expression caused by heart disease are being worked out. New interventions that target changes in the expression of critical ion channel genes have the potential capacity to provide novel therapeutic approaches to AF.

**CONCLUSIONS**

The great advances that have recently taken place in our understanding of AF mechanisms have led to improved understanding of the basis for a variety of clinical properties of the arrhythmia. They have already led to important advances in AF management and will likely lead to additional therapeutic refinements in the years to come.

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In 1748, British ethnobotanist and physician John Ryan, collecting in the West Indies and central Americas, sent back samples of a shrub from the Flacourtiaceae family to botanist M. Vahl, who, as per custom, named the genus *Ryania* (Figure 1). We do not know whether Ryan’s interest was captured by its glossy leaves and faint cinnamon aroma, or by the fact that natives used stem extracts to prepare poisoned arrows and, sometimes, to euthanize enfeebled members of their tribes. Little is known about him except that he was elected Fellow of the Royal Society in 1798.

Plants often make poisons to deter predators, which are usually insects. In the 1940s, Merck chemists K. Folkers and E. Rogers collaborated with entomologists R. E. Heal and coworkers at Rutgers U to assess *Ryania* stem extracts as an insecticide.1 The chemistry of the active insecticide lay with the diterpenoid ryanodol and its pyrrolidinyl derivative, ryanodine.2,3 Ryanodine remains a favorite among ecologically conscious growers of Macintosh apples in upstate New York. Heal and his coworkers4 reported the first pharmacological properties of *Ryania* extracts—slowed insect motility—but did not discuss muscle arrest. In contrast, two reports in *Science*, a few weeks apart, using ryanodine itself, documented rigor in insects.5,6 These early researchers could have scarcely imagined what a complex portal they were investigating. Ryanodine selectively binds the ryanodine receptor (RyR), a large protein that tetramerizes to form a release gate for Ca\(^{2+}\) from sarcoplasmic reticulum (SR) stores. At 563 to 568 kd, RyRs are among the largest proteins known. Three different genes (on chromosomes 1, 5, and 19) encode the RyR1, 2, and 3 isoforms, expressed differentially in the various muscle types. The RyR proteins span the SR membrane and belay the center of intricate macromolecular structures that fulfil the precise Ca\(^{2+}\) release characteristics required of the corresponding type of muscle (eg, cardiac, skeletal, insect). The full ensemble includes proteins on the SR-lumen side (calsequestrin, binding proteins [BiP]) and components in the cytosol face (tacrolimus = FK506 binding protein [FKBP], sorcin). The supramolecular complex surrounding the RyR quatrefoil is at the limit of depiction by electron microscopy, but frequently juxtaposed against dihydropyridine-sensitive Ca\(^{2+}\) channels (visualized as triadic junctions where the monster cytoplasmic domains of the RyRs appear as “feet”).

Ryanodine binds two different areas on the receptor, with opposite effects. The exact site is unknown. Pharmacologically, there is a single high-affinity site that tends to preserve the open conformation, but the conductance is lowered (by about 50%). Add more ryanodine and some 4 to 10 sites are bound that will now jam the receptor shut. Moreover, ryanodine binds the RyR in open conformation, when the muscle is being used and also depends on the Ca\(^{2+}\) concentration and voltage. The 25 carbons of ryanodine form a compact three-dimensional structure. There are several fused 5- and 6-membered rings, and most carbons are chiral. The 9 oxygens are interspersed over the surface creating precise hydrogen bonds with residues lining a pocket on the receptor (Figure 2, next page).

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Although ryanodine is considered an alkaloid, the only alkaline nitrogen is in the pyrrole carboxylic substituent at position 3. This side group is easily lost under mildly acidic or oxidizing conditions, yielding ryanodol. The left-hand half of the molecule inserts into a cavity of the RyR with positions 9 and 10 at the mouth of the cleft. While binding affinity to vertebrate receptors is decreased over 1000-fold, ryanodol somehow retains substantial toxicity for insects. Other plants in the Flacourtiaceae and neighboring families also fashion closely similar diterpenes such as cinnzeylanol (3-deoxyryanodol, which has no substituent at the 3 position), found in cinnamon bark.

Opening or closing of internal Ca\(^{2+}\) stores shows variable effects on different insect species. In intact animals and insects, neurons, smooth muscle, skeletal muscle, and cardiac muscle (like insect muscles) are all affected, generating complex physiological behaviors. The full complexity of the excitation-contraction profiles can be attributed to the peculiarity of the receptor phenotype, convoluted by the relative importance of internal Ca\(^{2+}\) stores in regulating free cytosolic Ca\(^{2+}\). Thus, while cardiac muscle shows initial positive inotropy followed by failure of both contractility and relaxation, ultimately leading to flaccid arrest, skeletal muscle goes into rigor.

The cardiac effects of ryanodine were first published by Robert Furchgott (well known for his work on nitric oxide)\(^7\) and Leonard Procita\(^8\) in back-to-back articles in 1956. Using kitten auricles, they observed negative inotropic effects, similar to insect muscle, but different from skeletal muscle.

The mechanistic breakthrough came around 1961 when the availability of radioactive \(^{45}\)Ca allowed Ahmad and Lewis to observe that ryanodine increased Ca\(^{2+}\) transport in and out of cardiac SR fractions. Throughout the 1960s, Fairhurst and Jenden at UCLA (University of California, Los Angeles) spearheaded the discovery of ryanodine’s effects on cardiac Ca\(^{2+}\) handling. The problem attracted other heart luminaries, including Winnifred Nayler, Gerhardt Langer, and Frank Sleator. However, ryanodine only made its official debut in cardiac physiology in 1979, with the publication back to back in *J Pharmacol Exp Ther* of the oft-quoted papers by J. T. Willerson and his junior colleagues Larry Jones and John Sutko.\(^9,10\)

Plants appear to have noted the importance of cyclic Ca\(^{2+}\) release—arrest the heart muscle and the pest is dead. Coffee beans (xanthines), poppy pods (verapamil), and fungi (cyclosporins) have each sought and found marvelously complex ring compounds to manipulate the Ca\(^{2+}\)-gating proteins in insect muscles.

Of the millions of plant compounds, ryanodine is one of a few plant products to have identified a receptor. This fact has led to the forgotten John Ryan becoming the only person so far to have been immortalized in receptor lore—thanks to a plant.

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**Figure 2.** Ryanodol molecule at the ryanodine receptor binding site.
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Ryanodine: its alterations of cat papillary muscle contractile state and responsiveness to inotropic interventions and a suggested mechanism of action.
Janske devoted the major part of his life in science to the difficult task of visualizing electrical propagation through the heart during the initiation and maintenance of arrhythmias. The most difficult arrhythmia to work with is ventricular fibrillation (VF). Here, the authors explored an arrhythmia altogether more amenable to analysis.

A rabbit heart supraventricular preparation consisting of the atrioventricular (AV) node without an intact sinoatrial node was stimulated electrically to induce supraventricular tachycardia (SVT). Because the AV node is small, it is possible to record from most of its surface using a small number of electrodes. Nevertheless, the “brush” of ten microelectrodes used in this study represents a major undertaking.

By integrating these recordings it was possible to create a virtual map of propagation in the AV node, and the now familiar isochrones were drawn to show the pattern of activation during SVT, using the upstroke of the action potentials to define the moment of activation. This revealed propagating waves, with velocity defined by the isochrone intervals.

It was shown that a premature stimulus may elicit, block, or reset SVT, depending on whether delivered early or late in the cardiac cycle. Retrograde conduction and decremental conduction were demonstrated, and the patterns were predictable and related to conduction velocity and refractory period. This early mapping strongly hinted at a circus movement of activation—in other words, reentry.

In subsequent years, attempts were made by different investigators to map ventricular arrhythmias using arrays of extracellular electrodes, in some cases located at different depths across the myocardium to visualize transmural propagation.

The skeptic might argue that this was a very expensive and time-consuming exercise to prove what Mines had already shown us in the early part of the last century. Certainly, the deductions of Mines, made using very primitive analysis, were borne out by Janske and the other mappers who followed. The skeptic would probably be wrong, however. In addition to confirming the suspicions of Mines (that reentry is responsible for the maintenance of most if not all complex arrhythmias), the mappers revealed enough about propagation, refactoriness, and conduction velocity to allow others to make better sense of the effects of many antiarrhythmic drugs. The proarrhythmic actions of flecainide, for example, would remain a mystery were it not for an understanding of the numerical determinants of reentry described so precisely in the work of Janske and others.

The area that has not benefited greatly from mapping is the study of the mechanisms of initiation of complex arrhythmias. Is ventricular fibrillation initiated by reentry, an ectopic pacemaker, or by flow of injury current between adjacent diseased and healthy tissue? We still do not really know what goes on in animal hearts, let alone in man.

In the case of these AV node mapping experiments, the evidence for reentry may be seen alongside the data provided by very different experiments concerning the ionic basis of propagation in the AV node. The development of L channel blockers provides a rational therapy for SVT for which an explanation about the mechanism of benefit is now readily understandable.

1971

The “authorized biography” of the recluse US millionaire Howard Hughes is announced, but its authors are imprisoned for fraud; Sierra Leone becomes a republic; and the members of the US table tennis team become the first US citizens to travel to China since the mid-1950s.
A subpopulation of cells with unique electrophysiological properties in the deep subepicardium of the canine ventricle. The M cell

S. Sicouri, C. Antzelevitch


Anatomy in its purest form is regarded by many as a done-and-dusted (if not dead) subject. It is therefore perhaps a surprise to encounter a paper published as recently as 1991, which, in essence, describes an anatomical feature of the heart that had hitherto been overlooked. The M cells (which have nothing to do with M currents) are located in the ventricular deep subepicardium. Sicouri and Antzelevitch discovered these cells by chance while exploring electrophysiological differences between epicardial and endocardial cells. In this paper, these cells were characterized.

The rate of depolarization of these cells is greater than that of cells in the other regions of the ventricular wall that sandwich them, both epicardial and endocardial. This means that conduction velocity in these cells is greater than elsewhere in the heart, with the exception of Purkinje fibers. Values of Vmax reach 150% of those in the endocardium, and almost 200% of values in the epicardium. The action potential duration (APD) of M cells is longer than that of both epicardial and endocardial cells. Moreover, the frequency-dependence of the M cell APD is considerably more pronounced than that of epicardial and endocardial cells, and at very long cycle lengths (5 s), the M cell APD becomes double that of endocardial cells. In other respects, M cells most resemble epicardial cells, expressing a prominent transient outward current ($I_{to}$) with both fast and slow components.

This is a very nice characterization study. However, the discussion section, in places, is perhaps a little bold. Not content with advancing our knowledge of cardiac anatomy, the authors also ventured to suggest that the M cells “contribute importantly to arrhythmogenesis.” At the time, this may have seemed to be a possibility. Cells that exhibit unusually long APDs, especially during bradycardia, would have appeared to have been likely candidates as loci for afterdepolarizations. Also at the time, there was a growing awareness of the link between repolarization and torsades de pointes.

However, my instincts about the role of these cells were, and remain, rather different. Cells that show marked APD prolongation during bradycardia in normal healthy hearts do not seem to me to be the inevitable harbingers of disaster. After all, compared with mild indigestion, for example, ventricular tachycardia and fibrillation do not blight our lives by their ever-present threatened manifestation. In healthy people, these arrhythmias are very rare. Therefore, had I been an author of this work, I suspect that I would have chosen to emphasize that the pattern of conduction and repolarization generated by the presence of M cells is likely to contribute to the maintenance and stability of normal sinus rhythm.

As for our current perception of the role of M cells, pathologic influences such as drug overdose or ischemia may indeed convert M cells from guardians of stability to triggers of arrhythmias. Nevertheless, whether the malignancy of this exceeds that exhibited in other cells (disturbed by the same pathologic influence) cannot be assumed. It is very hard to pinpoint the anatomic focus of ventricular arrhythmogenesis, and even isochronal mapping studies have their limitations. Therefore, it is perhaps unremarkable that the M cell has not emerged as a special drug target for suppression of lethal ventricular arrhythmias.

1991

Jazz saxophonist Stan Getz (Girl from Impanima) dies, aged 64; Mount Pinatubo in the Philippines erupts for the first time in 600 years; and Slovenia and Croatia declare independence from Yugoslavia.
Membrane current through adenosine-triphosphate–regulated potassium channels in guinea-pig ventricular cells

A. Noma, T. Shibasaki

J Physiol. 1985;363:463-480

Having earlier identified a K+ current activated when intracellular ATP levels fall (I_{K-ATP}), in this paper Noma and colleagues used the whole-cell voltage clamp technic to examine the contribution made by I_{K-ATP} to the whole-cell current generated by adenosine triphosphate (ATP) depletion in ventricular cells. The now familiar techniques of chelating Ca^{2+} with ethyleneglycol-bis(β-aminoethylether)-N,N',N,N'-tetracetic acid (EGTA) and blocking the Na+ pump current by dialyzing with Na+-free solution were employed. The characteristics of the whole-cell current were revealed to be very similar to I_{K-ATP}.

The authors inferred that the "I_{K-ATP} channels are responsible for the increase in the outward current and the shortening of the action potential duration under various anoxic conditions."

This paper had less impact on me than Noma’s first I_{K-ATP} paper in 1983. There was an awareness at the time that the action potential duration (APD) shortening that occurs during the first 30 min of regional ischemia may play a key role in the initiation of phase I ischemic arrhythmias. The idea that ischemia switched on a current that profoundly affected repolarization seemed to be an obvious answer to the problem of finding a suitable drug target for prevention of sudden cardiac death. Here was a molecular target that played no role in normal cardiac electrophysiology, but that became functional at the time when lethal arrhythmias appear. For those of us weaned on the concept of pharmacological selectivity driven by pathological markers, this seemed like the answer. This was far better than utilizing frequency-dependence to allow tachyarrhythmia targeting by class I agents (with their inherently dangerous ability to slow conduction). Eureka, we thought.

When the earlier Noma paper was published in 1983, one immediately assumed that the major antiarrhythmic drug research laboratories of the time (eg, Lucchesi, Schwartz, Corr, Euler, Colatsaky, Parratt, Szekeres, Hashimoto) would be busily testing glibenclamide and its analogs for antiarrhythmic activity. There seemed to be little point in adding to the stampede. However, we waited in vain. It was six years before the first full publication concerning prevention of ischemic arrhythmias by an I_{K-ATP} blocker appeared (from Opie’s group), and the effects were not particularly exciting.

It was clear that, by the early 1990s, all the APD shortening evoked by simulated ischemia in single-cell studies could be attributed to I_{K-ATP}. However, as the years passed, it became clear that for every positive report of antiarrhythmic protection by glibenclamide and analogs, there was a negative report. The positive findings appeared as full papers, whereas, rather disappointingly, most of the negative reports appeared as meeting abstracts only. This is the way of the world, with the news that we want to hear being embraced, but the disappointing news being rejected, even in our supposedly dispassionate scientific literature.

So, 15 years after the seminal work of Noma was published, I still await the news that ischemia-induced ventricular fibrillation can be prevented in man by blocking cardiac I_{K-ATP}. It appears that I may have a long wait. Perhaps this will be yet another example of a mechanism of antiarrhythmic action that is "accepted" before there is any evidence of any substantial antiarrhythmic effect that requires explanation. Indeed, in later times it has been proposed that I_{K-ATP} activators may be able to prevent early afterdepolarizations and ventricular fibrillation in ischemic heart disease. How times, and viewpoints, change.

1985

Body of Nazi war criminal Joseph Mengele is located and exhumed;
Claus von Bülow is acquitted on charges that he tried to murder his wife;
and bomb destroys Air India Boeing 747 in flight near Ireland, killing 329
Early afterdepolarizations: mechanism of induction and block. A role for L-type Ca\textsuperscript{2+} current

C. T. January, J. M. Riddle

Circ Res. 1989;64:977-990

This is a very useful paper in my opinion, but for reasons that may not have been initially intended by the authors. Early afterdepolarizations (EADs) are observed in isolated excised bits of cardiac tissue under the influence of certain drugs and toxins. They are capable of initiating repetitive firing of action potentials. They cannot be observed in whole hearts, only inferred, owing to the requirement for, and technical difficulty in obtaining, the necessary electrophysiological evidence. However, the suspicion that EADs contribute to the initiation of certain cardiac arrhythmias is widely held, and by 1988 EADs were regarded as one likely cause of a particular type of ectopy, abnormal automaticity (which is one possible tissue mechanism of arrhythmogenesis in certain settings).

Knowledge of an arrhythmogenic mechanism in a patient is good for one thing—planning how to respond. Thus, to be able to know that EADs are instrumental in initiating a specific type of arrhythmia is of value only if we can also say that EADs are caused by “current X” and are therefore blocked by the “X-blocking class of drugs.” In this regard, one difficulty with EADs at the time (late 1980s) was that it was uncertain whether their initiation was dependent on Na\textsuperscript{+}, K\textsuperscript{+}, or Ca\textsuperscript{2+} current abnormalities. Thus, even if it were the case that EADs were strongly suspected of being responsible for a patient’s arrhythmia, this did not help a great deal in guiding drug selection.

January and Riddle used the classic sheep Purkinje fiber preparation, and voltage clamp protocols. EADs were induced by electrical stimulation and Bay K 8644 (an $I_{Ca-L}$ activator). Depolarization-induced EADs were found to be associated with a transient inward current that showed similar time- and voltage-dependence. Bay K 8644 facilitated these responses, and effects were blocked by nitrendipine, but not tetrodotoxin (TTX), indicating a dependence on $I_{Ca-L}$. The interpretation, that $I_{Ca-L}$ window current participates in EADs seemed reasonable.

The odd thing is this: if Purkinje fiber EADs are clinically relevant and caused by (or at least dependent on) $I_{Ca-L}$, then one would expect a good proportion of clinical ventricular arrhythmias to be susceptible to prevention by verapamil and diltiazem. This is palpably not so. Verapamil is a good suppressor of supraventricular tachycardia involving the AV node, but is not known for its ability to suppress serious ventricular arrhythmias.

This is a bit worrisome. Does it mean that verapamil is incapable of suppressing EADs in vivo? I can see no a priori reason why this should be so. It is a perfectly good drug for treating AV nodal reentry, so it can clearly affect the human heart. It is true that $I_{Ca-L}$ in healthy ventricle is not blocked by verapamil at “clinical” dosage. However, in Purkinje fibers that are experiencing action potential duration extension and EADs, the voltage dependence of verapamil should ensure that $I_{Ca-L}$-blocking activity is enhanced. Therefore, any EADs that are present ought to be correspondingly blocked—if they are $I_{Ca-L}$-dependent. Thus, an alternative and less optimistic explanation is that EADs do not contribute significantly to lethal ventricular arrhythmias in man. In this case, verapamil would not be expected to be much use in prevention of sudden cardiac death, a priori.

This is therefore a potentially very illuminating paper from the skeptic’s viewpoint, albeit not for the reasons that may have seemed immediately apparent at the time.

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1989

Christine Jorgensen, the world’s first transsexual, dies, aged 62; Joe Valdez Caballero, creator of the hard taco shell, dies, aged 81; and Kenya announces worldwide ban on ivory to preserve its elephant herd
The Sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms

Task Force of the Working Group on Arrhythmias of the European Society of Cardiology

Circulation. 1991;84:1831-1851

The Vaughan–Williams classification (VWC) of antiarrhythmic drugs was believed by some in the late 1980s to have outlived its usefulness. The VWC is certainly heterogeneous—some classes are based on molecular actions (class I) and some on tissue actions (class III). Moreover, not all drugs that share a common molecular action share common antiarrhythmic actions (compare verapamil with nifedipine). However, the VWC was intended as a broad-brush system, amenable to extension, and subclassification.

The Sicilian gambit is in fact not a new classification of antiarrhythmic drugs, but a new “approach to classification.” Much of the article provides justification for the new approach. There are excellent reviews of putative molecular targets (ion channels, receptors, and pumps) for existing and hypothetical new drugs, setting the stage for the approach, and a synopsis of hypothetical arrhythmogenic mechanisms, identifying the main tissue mechanisms (reentry, delayed afterdepolarization [DAD], etc.). Then comes a nice innovation—the “vulnerable parameter.” The idea is that if an arrhythmia is caused at the tissue level by, for example, reentry dependent on Ca2+ channels, then the vulnerable parameter is excitability and conduction (a decrease being desired). This in turn is linked to “ionic currents most likely to modulate the vulnerable parameter.” In the present example, $I_{Ca-L}$ was identified. The new approach to drug classification is essentially to relate drugs to vulnerable parameters.

To apply the approach, first we diagnose the arrhythmia. This has a known tissue mechanism (which is defined). For example, ventricular fibrillation (VF) is caused by reentry. Then, knowing the vulnerable parameter, we select a drug that targets it. For VF, we target refractory period (with the aim of prolonging it), and the representative therapeutic drug is bretylium.

The concluding remarks are that in the long term, a physician will be able to diagnose an arrhythmia, understand its mechanism, have knowledge of the vulnerable parameter and, on this basis, select “effective pharmacological therapy.” Therapy will improve as “the number and variety of antiarrhythmic drugs increase.” And “in the meantime” the Sicilian gambit provides a “basis for rational consideration of arrhythmias and their therapy” and “communication among basic and clinical investigators.”

Anybody spotted the flaws in all this yet? First of all, like the VWC, the Sicilian gambit is a hybrid (vulnerable parameters range from Ca2+ overload through EADs to conduction). However, and more importantly, the problem with antiarrhythmic drugs is not that physicians find it tough to choose (among the myriad of available effective antiarrhythmics) the one drug that will cure their patient owing to the absence of a “basis for rational consideration of arrhythmias and their therapy.” The real problem is that for many arrhythmias (especially life-threatening arrhythmias like VF) the available drugs are poorly effective at best and positively harmful at worst (see the Cardiac Arrhythmia Suppression Trial [CAST] and Survival With ORal D-sotalol [SWORD] studies). The Sicilian gambit is therefore identical to the VWC in that it addresses only the drugs that we already have. Moreover, it assumes that correct diagnosis of an arrhythmia defines the underlying mechanism and the ideal therapy. If only this were true.

The Sicilian gambit provides a theoretical basis for drug selection. But, like the VWC, it “suggests we know more than we do.” That, of course, is a drawback of all classification systems and approaches.

1991

Gene Roddenberry, creator of Star Trek, dies of a heart attack at the age of 70; the Russian city of Leningrad officially changes its name back to St Petersburg; and the Nobel Peace Prize is awarded to Aung San Suu Kyi, the Burmese democratic leader held under house arrest.
Molecular determinants of state-dependent block of Na+ channels by local anesthetics

D. S. Ragsdale, J. C. McPhee, T. Scheuer, W. A. Catterall

Science. 1994;265:1724-1728

In this study, it was shown that, by altering the structure of rat brain Na+ channels (by site-directed mutagenesis), it was possible to selectively alter the binding of local anesthetics to the rested, open, and inactivated states of the channel, and the ability of drugs to access their binding site via a hydrophilic pathway.

I like this paper because it reinforces the notion that local anesthetics modulate a specific molecular target (the Na+ channel) rather than vaguely partition into the milieu to perturb function. However, despite the notoriously low eudismic ratios seen for local anesthetic optical enantiomers, I think we did already know that local anesthetics have molecular specificity and are not simply “membrane fluidifiers.” The existence of use-dependence and voltage-dependent unblocking of Na+ channels is sufficient evidence, I would have thought. Still, it’s nice to see someone finding out which bits of the Na+ channel control which aspect of binding and its consequence.

My other main comment, as a pharmacologist, is that I do wonder how this might lead to the development of new drugs. I suppose that if we know the topography of the regions that, when drug-bound, lead to this or that effect, then maybe we could design target-specific drugs. I do believe that pharmaceutical companies employ this approach already (combinatorial chemistry). The problem seems to me to be that in the case of class I antiarrhythmics (also known to some as “local anesthetics”) dozens (probably hundreds) have been tested and the full range of their limited therapeutic utility as drugs for preventing lethal arrhythmias has been well characterized. Thus, although the present paper may reinforce a principle (that the nature of drug actions are dependent on the nature of the molecular target), it does not provide data of specific practical value in the development of antiarrhythmics—because the Na+ channel is a fished-out lake.

But this criticism may be unfair. Although my commentary appears in a cardiological journal, Ragsdale et al appear to be pharmacologists with an interest in how local anesthetics work, not drug hunters in pursuit of novel antiarrhythmics.

A criticism that may be a little less unfair is that the pharmacological probing of the altered Na+ channels here relied upon the use of only two concentrations of only one drug. If a couple of other drugs were found to have their actions altered in a qualitatively different manner, the entire underlying premise (that the experiments here were probing local anaesthetic molecular specificity as a generality) would need to be reconsidered.

My last point is this. Sexy techniques that give lots of lovely descriptive information are fine fodder for journals like Nature and Science. The stated objective of the present paper was “determination of the amino acids that form the local anesthetic receptor site is important for understanding the complex action of these (local anesthetic) drugs…we used site-directed mutagenesis to examine the function of segment IVS6…in local anaesthetic action.” In other words, this is very much an “I wonder what would happen if…” type of paper. There is nothing particularly wrong with that, although I do wish the authors of such papers would tell us what they think the value of their data might be from a pharmacotherapeutic perspective.

The World Health Organization announces that polio has been completely eradicated from the Western hemisphere;

Baseball owners end season and cancel World Series in response to players’ strike;

and the last Allied soldiers bid farewell to Berlin after spending 50 years defending the city.
In this paper, the authors took several generations of 15 families, all with long QT syndrome (LQT), classified individual family members as being symptomatic (expressing arrhythmias) or not, and related this to genotype using polymerase chain reaction (PCR) analysis. Thus, genetic markers were sought to identify the gene for LQT. Two were found in two distinct groups of families. The first marker was \textit{D75483} (the long arm of chromosome 7). In other families, \textit{D75483} was not linked, whereas \textit{D75505} in chromosome 3 was the culprit. These genotypes differed from earlier LQT family linkage in families whose unfavorable mutation appeared to be located in the short arm of chromosome 11 (p15.5 [\textit{LQT1}]). The two new links were termed \textit{LQT2} and \textit{LQT3}.

In a more specific sense, I do wonder about the apparent obsession with the LQT-related condition, “torsades de pointes,” which, in the 1970s, might have appeared to a casual observer to be the most clinically important condition associated with cardiac arrhythmias. Although it is certainly true that drug-induced torsades de pointes is of concern in the realm of drug safety and pharmacovigilance, in the wider world it is surely ischemia-induced ventricular fibrillation that has the far greater relevance to life and death. After all, according to its original definition, torsades de pointes is defined as a syndrome associated with a spontaneously reversible arrhythmia.

Two long QT syndrome loci map to chromosomes 3 and 7 with evidence for further heterogeneity


\textit{Nat Genet.} 1994;8:141-147
This article describes single-channel behavior of mutant Na+ channels from human hearts associated with one form of hereditary long QT syndrome (LQT3). Compared with wild type (WT) channels, the LQT3 channels (∆KPQ) had faster current decay time constants, but incomplete decay after 200 ms, and inactivated at more negative potentials. ∆KPQ also exhibited peculiar multiple reopenings (“bursts”), which were found to result from occasional altered gating behavior. This was suggested to be sufficient to account for a persistence of inward current during action potential plateau in LQT3 that underlies the delay in depolarization.

This is a fine descriptive article. Fortunately the single-channel behavior of ∆KPQ provides a good explanation for LQT3. In this regard, it fits nicely with the “molecules to man” mantra that pervades modern biology.

In a wider context, one might hope that these findings can be utilized in the future therapy of LQT3. From a pharmacological perspective, one might anticipate the development of a drug that targets ∆KPQ selectively, and corrects its behavior. To do this most simply, it would need to shift inactivation to more positive potentials. This sounds like a ∆KPQ-selective class I antiarrhythmic to me. I feel the skeptic in me awakening again.

Available class I antiarrhythmics possess one of a broad range of properties, in terms of lipid solubility, relative affinity for channel states, and binding/unbinding kinetics, and a restricted range of molecular weights. These characteristics define the detail of the drugs’ antiarrhythmic properties. However, despite several decades of detailed electrophysiological study and one-time frenzied activity in pharmaceutical drug discovery, the class I antiarrhythmics have proven to be unsuccessful where it really matters—prevention of lethal arrhythmias. No matter how one tinkers with state-selectivity and binding properties, the enigmatic soma for ventricular fibrillation remains elusive. Thus, I can’t help feeling that I will be long dead before someone synthesizes a truly ∆KPQ-selective class I antiarrhythmic with a profile just right for prolonging the lives of the LQT3 victim.

But what of gene therapy? The skeptic is now wide awake, I’m afraid. The goal of transfecting myocytes in a therapeutically useful manner will be achieved one day. Whether that will be before or after the obscure English soccer team Crystal Palace wins the English soccer Premier League championship may be a matter for lively debate in the decades to come.

However, there are other reasons that make general skepticism about the value of this work seem churlish. This paper does actually serve as a prelude and basis for an important therapeutic advance. To be able to determine whether LQT syndrome is related to a K+ versus Na+ channel defect is now recognized as an important guide to therapy. A pacemaker (fitted when LQT syndrome is the result of a K+ channel defect, in order to prevent the bradycardia that exaggerates the tendency for repolarization delay to occur) would be a positive hazard if the LQT syndrome were to be the product of a Na+ channel defect (i.e., LQT3). In this respect, the paper is of great therapeutic importance. One must hope, therefore, that the medical infrastructure can cope financially with the need to identify the genotype underlying every individual’s LQT, since this would appear to be an essential part of the therapeutic process.

1995

250 passengers are killed in the crash of the Purshottam Express in India; thousands gather at Hiroshima to commemorate the 50th anniversary of the dropping of the first atomic bomb; and Howard Koch, Hollywood screenwriter and cowriter of Casablanca, dies, aged 93.
The structure of the potassium channel: molecular basis of K+ conduction and selectivity


Science. 1998;280:69-77

This is a truly excellent paper, not simply because it changed the way we think about ion channel function, but because it set out to disprove a hypothesis (the most valuable scientific approach, in my view), and succeeded unequivocally.

Prior to 1998, nobody really knew how K+ channels select for K+ over the smaller Na+ ion. A simple physical barrier, like a garden sieve, would be expected to hold back the bigger lumps (K+), rather than the smaller ones (Na+). Part of this confusion related to the fact that people did not know what K+ channel pores actually looked like. The general properties of K+ channels had led investigators to hypothesize that the channels have long pores, such that K+ ions effectively line up in single file when passing through the channel. However, this is inconsistent with the known rapid ionic throughput, which approaches the rate of diffusion (impossible were there to be a queue of ions in a long pore).

To test the long pore hypothesis the authors did some x-ray analysis. They found that the hypothesis was incorrect since the channel pore was in fact the shape of an “inverted teepee” or “cone.”

I became bemused when I attempted to visualize this teepee inversion and realized that if one were to turn the x-ray photo upside down the teepee would cease to be inverted. In membrane biology, how does one decide which way is “up”? However, this turns out to be a trivial issue when one sees the beautiful picture and description of K+ transport by this teepee. And the teepee terminology has now become established. Fortunately, Doyle, rather than Custer was the first author of the work.

Essentially, the selectivity filter fits K+ almost so perfectly that it strips it of its water of hydration rather like two parked vehicles stripping another of it’s wing mirrors as it passes between them. The selectivity filter holds only two K+ ions because it is not very deep. Because K+ ions repel one another, the second one to enter pushes the first one out of the selectivity filter and through the channel. This happens very quickly.

In the case of Na+, its looser fit in the selectivity filter means that it does not lose its water of hydration, and is therefore not attracted to the lining of the filter. So if Na+ happens to diffuse into the pore, it will simply diffuse back out again, whereas K+, having lost its water of hydration, is strangely attracted to the pore walls (at least until it gets bumped on and out by another K+ ion with its newly restricted side rear vision).

I must admit that there is a fair bit of generalization on the balance between “energetic costs and gains” here, and “attractive force… perfectly balanced… by repulsive force,” and I was half expecting a discourse on yin and yang towards the end.

From a pharmacological point of view, the search for new drugs is facilitated whenever a new specific marker is identified. The present paper actually characterizes a non-specific marker, ie, a structural motif common to all K+ channels. Thus, despite the quality of the science, the skeptic in me feels that this is not likely to lead to new drug development.
A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results

Curtis

B-Blocker Heart Attack Research Group

JAMA. 1982;247:1707-1714

From a drug developmental point of view, this paper reaches back into the past, yet still has a very contemporary context, so I have saved it till last. It may come as a surprise to the uninitiated that a class of drug developed in the 1960s for reducing cardiovascular mortality was still being evaluated in the early 1980s for its effects on survival following acute myocardial infarction (MI). The β-Blocker Heart Attack trial (BHAT) evaluated several thousand patients assigned to propranolol or placebo 5 to 21 days after acute MI. Total mortality, assessed after 25 months, was reduced from 9.8% to 7.2%, and sudden cardiac death (as classified blind at a later date by a committee of cardiologists) reduced from 4.6% to 3.3%.

These findings supported the idea that β₁-blocker therapy reduces post-MI death rate and that the benefit is due to β₁-blocker-mediated suppression of ventricular fibrillation (VF). However, this still remains contentious. Although meta-analysis of consecutive clinical trials confirms that post-MI mortality is indeed reduced by β-blockers, other studies have suggested that prevention of cardiac rupture is the basis for improved survival.

Moreover, there could be a very simple, β₁-receptor-unrelated, explanation for the benefit from propranolol in BHAT (and perhaps other studies too). The paper states that significantly more of the placebo group were taking antiarrhythmics. Why were they given antiarrhythmics? In order to suppress ectopic beats—arrhythmias that were presumably and unsurprisingly less common in the propranolol cohort. What was the identity of these antiarrhythmics? There are lots of class I and III agents that suppress ectopic beats, many of which were in use at the time—presumably it was one or more of these drugs (class IV drugs are ineffective). However, we now know that many class I and III antiarrhythmics have an unfortunate adverse effect—lethal proarrhythmia. Thus, it is quite possible that the suppression of death by propranolol in the BHAT study is an artifact—a consequence of the greater use of “antiarrhythmics” in the placebo group, which led to a greater amount of lethal proarrhythmia in this group.

Admittedly, an extrapolation like this can provide an enormous return in speculation on a small investment of fact (to paraphrase Mark Twain). But regardless of the truth about the mechanism of benefit of β₁-blockers, the fact is that neither these antiarrhythmic agents nor any other have reduced MI mortality rates to the extent one would hope and expect from any truly effective drug.

It is easy to justify almost anything in research. For me, the only really valuable biomedical research is that which leads to a therapeutic advance. Ion channels, pumps, and transporters (and the receptors that regulate some of them), as Harry Fozzard explains so eloquently in this issue, form the molecular basis for electrogenesis and conduction in the heart. However, it remains apparent that we are still some way from being able to reconstitute the cardiac channels, receptors, pumps, and regulatory molecules into a model (conceptual, mathematical, or whatever) that allows prediction of the type of drug that will prevent our hearts from killing us. I wonder what it is that we are doing wrong. When the wonder drugs do eventually materialize, all of the ten papers summarized here may be seen to have contributed to their development. On the other hand…
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### Bibliography of One Hundred Key Papers

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