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Contributions of cellular electrophysiology to the understanding of the electrocardiogram

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Summary. The understanding of cardiac action potential and membrane currents has broadened the theoretical foundation and enhanced the clinical usefulness of the electrocardiogram. An improved understanding of the morphology of the electrocardiographic waveform has resulted from: correlations between V_{max} of depolarization and QRS complex, plateau of the ventricular action potential and S-T segment, terminal repolarization and T-wave, from definitions of action potential differences responsible for the T-wave, and recordings of action potential alternans. Cellular electrophysiology has contri-

buted to the understanding of certain mechanisms of cardiac standstill. Many disturbances of conduction and refractoriness associated with ventricular arrhythmias can be attributed to the following derangements at the cellular level: slowing of terminal repolarization, development of diastolic depolarization in fibers with stable resting membrane potential, after-depolarizations, currents of injury resulting from non-uniform polarization, increased dispersion of action potential durations, and co-existence of slow conduction and short premature action potentials.
Key words. V_{max}; repolarization; diastolic depolarization; cardiac arrhythmias.

The understanding of the electrocardiogram requires understanding 1) the cardiac action potential; 2) the sequence of cardiac activation and recovery; and 3) the properties of the volume conductor. At the time of the first recording of cardiac action potentials[6, 33] electrocardiography was already a mature diagnostic technique based on sound theory buttressed by a wealth of clinical and pathological correlations. In his foreword to Dr Lepeschkin's textbook 'Modern Electrocardiography'[17], Franklin N. Wilson singled out two comprehensive monographs: 'The Mechanism and Graphic Registration of the Heart' by Sir Thomas Lewis (the last edition in 1925), and 'Unregelmässige Herztätigkeit' by Wenckebach and Winterberg, published in 1927. About 1000 references are cited in each of these two textbooks. Lepeschkin's textbook[17] lists 10,000 references covering the literature up to May, 1950.

At the time that Lepeschkin was preparing his textbook, the resting and action potential were explained in terms of Bernstein's membrane theory, the shape of action potential was deduced from the records of monophasic action potentials (MAP) recorded with suction electrodes, and the theoretical model of the electrocardiogram (ECG) was derived from superposition of MAP's. There was also good understanding of the current of injury, the self-sustained depolarization, the repolarization course, and the spread of excitation in both the conducting system and in the myocardium.

With such background it is not surprising that the microelectrode studies did not 'revolutionize' electrocardiography to the extent that they affected membrane physiology. This is not to say, however, that the contributions of cellular electrophysiology to electrocardiographic theory and practice were insubstantial. Each new step toward better understanding of cardiac action potential and membrane currents generated new knowledge that became directly applicable to the interpretation of electrical activity recorded from the entire heart or one of its components. The purpose of this article is to present an electrocardiographer's view of the input of cellular electrophysiology into clinical electrocardiography[23]. While focusing on new explanations and corrections of erroneous concepts, I will also cite examples of clinical investigations stimulated by cellular electrophysiology.

General correlations

Electrocardiogram recorded from the body surface registers atrial depolarization (P-wave), ventricular depolarization (QRS complex) and ventricular repolarization (ST-segment and T-wave). Atrial repolarization (T_a-wave) may also be recognizable occasionally. Introduction of electrodes into the heart enables the recording of local electrograms including His bundle potential. Some success has been achieved also in recording His bundle electrograms from the body surface using computer-assisted signal averaging technique. The P-wave and the QRS complex represent atrial and ventricular depolarizations corresponding to the respective upstrokes of atrial and ventricular action potential; the ST-segment corresponds to the plateau phase, and the T-wave to the terminal phase of venticular repolarization. It appears that neither the overshoot nor the spike (phase 1) make contributions to the morphology of the ventricular complex recognizable. Conversely, an electrocardiographic deflection U-wave that follows the T-wave appears to be unrelated to the morphology of the ventricular action potential.

The isoelectric portion of the PR interval reflects slow conduction in the AV node. When the impulse bypasses the AV node, the isoelectric segment between the onset of P and the onset of QRS decreases from about 180 ms to about 40 ms. The conduction through the bundle branches and Purkinje network is about 3–4 times faster than through the myocardium. Therefore, when an impulse is blocked in the conducting system (bundle branch block), spread of activation through the muscle across the septum increases the normal QRS duration by about 30%. Similar increase in QRS duration occurs when an impulse conducted through atrio-ventricular bypass tract propagates through a portion of ventricular myocardium before it reaches the conducting system. Another example of a wide QRS complex caused by engagement of ventricular myocardium into the conduction pathway is an ecotopic ventricular complex originating distal to the bifurcation of the His bundle. The duration of the normal QRS complex depends on the depth of penetration of the Purkinje network and on the mass of ventricular myocardium. Proportional to the mass, the QRS duration is 35 ms in rabbit, 55 ms in dog, 40–50 ms in newborn human, 80–100 ms in adult human with normal heart, and 100–110 ms in adult with a hypertrophied heart. In larger animals e.g. horse, cow, or elephant, QRS duration is only slightly longer than in man, presumably owing to deeper penetration of the myocardium by the Purkinje network.

Slow conduction

Depolarization

Many electrocardiographic manifestations of slow conduction can be explained by slow impulse propagation when the sodium channel is incompletely reactivated i.e. incompletely repolarized myocardium[8], or partly inactivated i.e. during diastolic depolarization[21].

The concept that conduction is slowed or blocked when premature depolarization takes place in an incompletely repolarized myocardium, is useful in interpretation of the ECG changes. This may be due to a short coupling of the premature impulse, long duration of action potential preceding the premature impulse, or both. This mechanism also explains the so-called Ashman phenomenon, i.e. a conduction delay or block in one of the bundle branches (usually right) when a supraventricular impulse following a short cycle is preceded by an impulse with a long cycle. The block is attributed to the onset of depolarization before the end of preceding long action potential engendered by the long cycle. Slow aberrant conduction also occurs when the cycle length is shorter than the duration of action potential at some site of the conducting system. This occurs frequently at rapid rates and the resulting supraventricular tachycardia has a wide QRS complex resembling an ectopic ventricular tachycardia.

Another cause of slow conduction and conduction block is generalized depolarization, best exemplified by hyperkalemia[8]. A typical pattern of hyperkalemia results in uniform widening of the QRS complex without change in shape, and there is a rough correlation between plasma K concentration and duration of the QRS complex[22] (fig. 1). Consistent with slowing of atrial conduction is the progressive widening of the P-wave. P-wave disappears in the electrocardiogram at concentrations 8–10 mM when the conduction in the ventricular myocardium is still preserved. Thus, ventricular muscle fibers are more resistant to the depolarizing effect

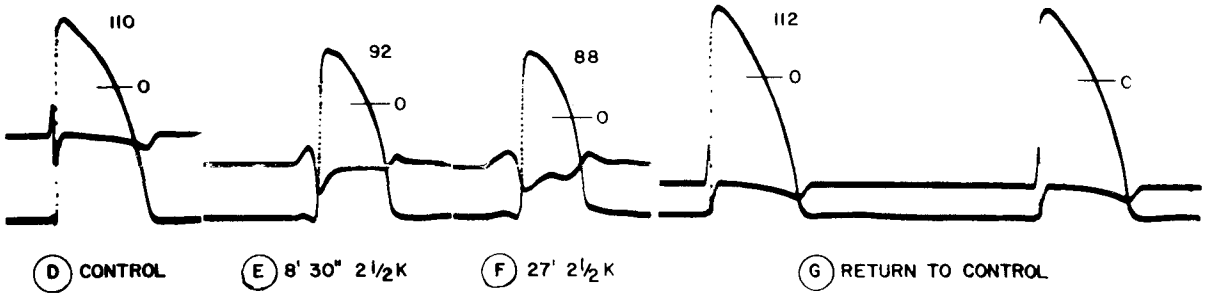

Figure 1. Effect of perfusion with 12.0 mM potassium solution on the ventricular action potential and electrocardiogram in an isolated perfused rabbit heart. Note widening of the QRS complex and lengthening of the interval from the onset of QRS to the onset of action potential. The numbers show action potential amplitude in mV. The QRS duration in D = 44 ms, in E = 138 ms, in F = 210 ms, and in G = 44 ms. Upstroke of action potential is retouched. From Gettes et al.[8] with permission.

of high K than the atrial myocardium. Even more resistant are the S-A node and the His bundle[29]. Therefore, one assumes that when atria become non-excitable, the impulse originating in the S-A node is conducted through depolarization-resistant specialized atrial tracts, A-V node and His bundle. There is experimental evidence that sino-ventricular conduction can occur in the presence of sino-atrial block[9].

Hyperpolarization

Studies of Weidmann[32] and others[8] have established that at low $(K^+)_o$, the resting membrane potential deviates progressively from the equilibrium potential for K (E_K), and that at very low K concentrations hyperpolarization gradually reverts to depolarization to about −30 to −40 mV. The lowest plasma K concentration in man is about 1.0 mM. At this stage, both the P-wave and the QRS complex are still well preserved, and from the correlations of the transmembrane action potential with the ECG in the rabbit heart one may assume that the ventricular muscle is hyperpolarized. Of interest is that at this stage, the QRS duration is increased, a finding that suggests slowing of conduction in hyperpolarized myocardium. This may be due to the increased difference between resting membrane potential and threshold potential.

Antiarrhythmic drugs

Weidmann showed that local anesthetics decrease V_{max} without changes in the resting membrane potential[30]. Experimental studies showed that the depression of conduction in diseased myocardium by antiarrhythmic drugs was greater than in normal myocardium, a finding assumed to be due to the shift of the sodium channel inactivation curve to less negative membrane potentials[30].

The demonstration of the use-dependent properties of the sodium channel block has been very helpful in the interpretation of the ECG in patients treated with sodium channel-blocking antiarrhythmic drugs[11, 14]. For instance, the absence of QRS widening during treatment with lidocaine (even at high concentrations) was attributed to a lesser depression of V_{max} by lidocaine than by other antiarrhythmic drugs. Yet, the in vitro studies showed that at comparable drug concentration, lidocaine depressed V_{max} to the same or to a greater extent than other drugs. However, the rapid recovery from V_{max} block in the presence of lidocaine resulted in dissipation of block between depolarizations at normal heart rates. Yet, it can be shown that lidocaine produces considerable widening of the QRS complex during very rapid tachycardia, or in the early extrasystoles.

Studies in animals and humans have shown that under many other conditions, the in vitro observed effects of sodium channel blocking drugs on the V_{max} were predictive of the time- and voltage-dependent QRS changes in vitro. This is in keeping with the findings of Buchanan et al.[4] that changes in V_{max} induced by antiarrhythmic drugs were proportional to changes in the square of conduction velocity.

Slow channel-dependent conduction

The discovery of the slow inward current explained the slow depolarization in the SA node and in the central portion of the AV node, and the effect of slow channel blocking drugs on the conduction and refractoriness in these structures. These drugs have been useful as pharmacologic probes identifying an unknown mechanism of impulse propagation. For instance, in a case of very slow conduction, lack of suppression by slow channel blocking drugs coupled with suppression by tetrodotoxin implies that the slow conduction in question is not caused by slow channel-dependent depolarization. Similar deductions have been made with regard to slow channel-dependent automaticity in the ventricular myocardial fibers depolarized to a level at which rapid sodium channel is inactivated[13]. We postulated that if the abnormal slow channel-dependent automaticity was responsible for the ectopic activity in depolarized ventricular myocardium, such activity would be suppressed by the slow channel blocking drugs. The lack of important antiarrhythmic effect of the slow channel blocking drugs in the clinical setting of acute or chronic myocardial ischemia has made it unlikely that slow channel dependent automaticity in the depolarized myocardium is responsible for arrhythmias in this setting.

Another type of ectopic activity that was expected to be suppressed by decrease of slow channel blocking drugs is the triggered automaticity originating in pacemaker fibers as a result of a probable increase in intracellular calcium concentration. Indeed, triggered automaticity remains a viable concept of arrhythmia mechanism in a group of patients in whom slow channel blocking drugs suppresses ectopic tachycardias precipitated by 'overdrive acceleration' e.g. an increase in heart rate during exercise.

Relation between plateau of ventricular action potential and ST-segment

The lack of potential differences during plateau accounts for the isoelectric ST-segment. When the plateau becomes short or absent e.g. during tachycardia, at low (K^+), or in the presence of digitalis, the slope of ST-segment ceases to be flat i.e. ST-segment deviates from the baseline[22]. This may be caused also by the superposition of atrial repolarization on the ST-segment whent the PR interval is short[22]. Other common causes of ST-segment deviation from the baseline include hypertrophy, conduction disturbances and pre-excitation, presumably due to asynchrony of repolarization. None of the above ST-segment deviation achieves the magnitude of ST-segment depression or elevation occurring during myo-

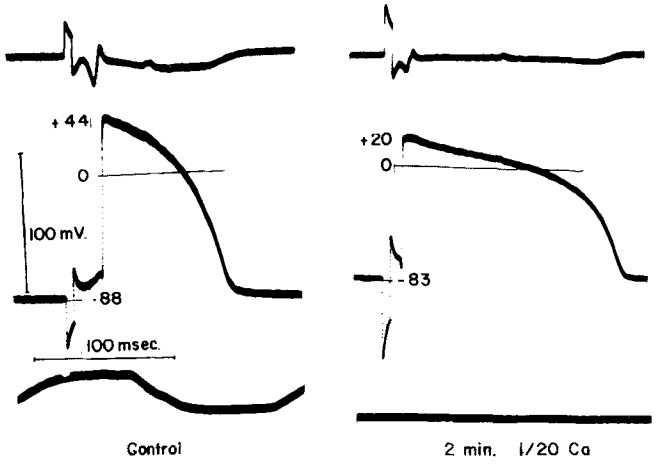

Figure 2. Ventricular action potential, electrocardiogram and contractile force in isolated rabbit heart perfused with low Ca (0.24 mM) Krebs-Henseleit solution. A 5 mV depolarization is associated with a 24 mV decrease in overshoot. Note parallel lengthening of the plateau of the action potential and the ST-segment while visible contraction is abolished. From Surawicz[22] with permission.

cardial ischemia[15], and attributed to 'injury' current resulting from differences in resting membrane potential (diastolic current of injury) and action potential amplitudes (systolic current of injury).

Changes in heart rate predominantly affect the duration of plateau whereas the slopes of terminal repolarization are nearly superimposable at all heart rates. Also at low Ca^{2+} concentrations and low temperatures, the predominant effect on the action potential is lengthening of the plateau, reflected in the ECG as lengthening of the ST-segment and QT interval without appreciable changes in the T-wave duration. Figure 2 shows the effect of low $(Ca^{2+})_o$ on the simultaneously recorded ventricular action potential, ECG and contractile force in isolated, perfused rabbit heart. Lengthening of the ST-segment parallels lengthening of the plateau whereas phase 3 and T-wave are not appreciably changed. Of interest is the marked decrease in the overshoot, presumably reflecting increase in i_{si}. However, this effect is not recognizable in the ECG.

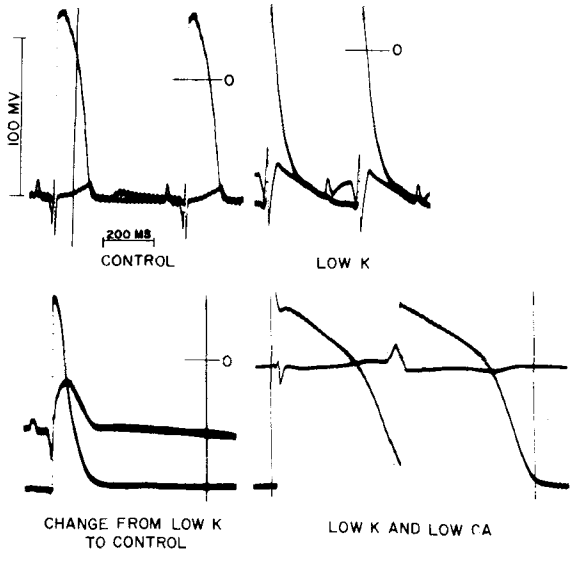

Figure 3. Examples of simultaneously recorded action potentials from the surface of right ventricle and electrocardiogram in isolated perfused rabbit heart. Note that in the top two tracings the repolarization slopes of the action potential and T-wave are identical. Also the slopes are similar in the lower tracing on the left. The lower right tracing shows that a prolonged duration of phase 2 corresponds in time to the prolonged ST-segment in the electrocardiogram. From Surawicz, B., Am. J. Cardiol. *13* (1963) 656–662, with permission.

Relation between the slope of terminal repolarization and ST-segment, T-wave and U-wave in the electrocardiogram

In the isolated rabbit hearts changes in the slope and duration of the terminal repolarization in the ventricular action potential were remarkably similar to changes of repolarization in the simultaneously recorded ECG. Also, the duration of the ventricular complex in the ECG, i.e. the QT interval was similar to that of the single action potential on the ventricular surface. Representative examples are shown in figure 3. Both in control and during perfusion with low K solution the slopes of terminal repolarization in the action potential and the electrocardiogram are nearly identical even though in control the T-wave descent is steep, whereas at low K concentration, the slowly decending repolarization continues throughout the entire cycle. In the human electrocardiogram, changes in shape and duration of ventricular action potential cause a depression of the ST-segment, a decrease in the T-wave amplitude, and an increase in the U-wave. As long as the T-wave and the U-wave are separated by a notch, the duration of QT interval is unchanged (fig. 4). In more advanced stages, the T-wave and U-wave are fused and an accurate measurement of the QT interval is not possible[22]. Figure 3 shows also that after the change from low to normal K concentration, ventricular action potential becomes short[25], and that this is associated with a parallel shortening of the QT interval. Superfusion with solution deficient in both K^+ and Ca^{2+} causes lengthening of plateau and slowing of terminal repolarization (fig. 3). The corresponding ECG changes consist of ST-segment lengthening and decreased T-wave amplitude. Similar correlations between repolarization changes in the action potential and electrocardiograms were found with changes in temperature and administration of digitalis and antiarrhythmic drugs. Some of these changes were confirmed in correlations of the electrocardiogram with monophasic action potential in man[20].

Digitalis shortens plateau and slows the terminal repolarization of the ventricular action potential. These changes are associated with shortening and depression of the ST-segment, lower T-wave amplitude and shortening of the QT interval. Quinidine prolongs plateau, slows the terminal repolarization, and lengthens the ventricular muscle action potential[8]. These changes are associated with lengthening of ST-segment, lower T-wave amplitude and lengthening of the QT interval. Tall, narrow and pointed T-waves in patients with hyperkalemia[22] are attributed to a more rapid terminal repolarization caused by increased gK[31].

T-wave mechanisms

In the normal electrocardiogram, the polarity of the T-wave is concordant with QRS and the angle between the QRS axis and T axis is less than 60°. This indicates that the uncancelled repolarization potentials (96% of ventricular repolarization is believed to undergo cancellation) forming the T-wave are longer in some regions of the ventricle depolarized early with respect to some regions undergoing later repolarization. Although the general order of recovery is roughly the same as the order of activation, QRS area is seldom zero even in the local electrograms when the records are made with closely spaced electrodes. We[2] correlated the activation sequence and the duration of monophasic action potentials on dog ventricular surface, and found consistently shorter MAP's at

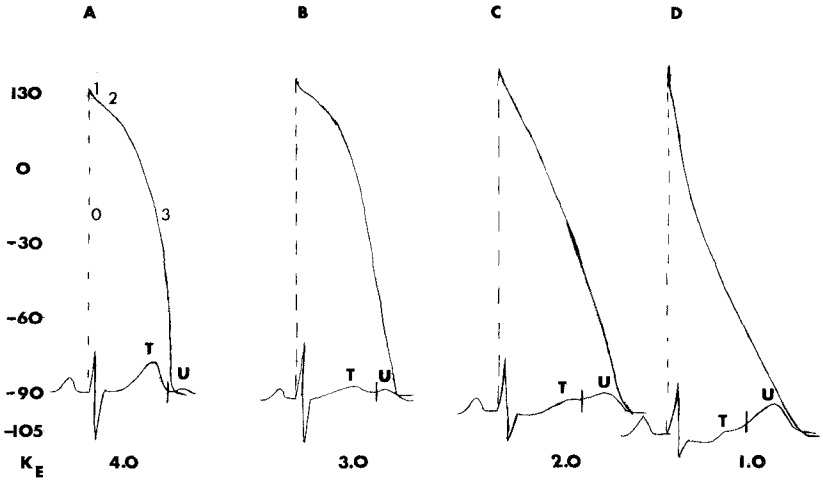

Figure 4. Diagram of ventricular action potential (AP) superimposed on the electrocardiogram at extracellular K (K_E) concentrations decreasing from 4.0 to 1.0 mM (abscissa). The numbers on the ordinate show levels of membrane potential in mV. Note the progressive shortening of phase 2, lengthening of phase 3, and hyperpolarization. The corresponding changes in the electrocardiogram consist of decreasing T-wave and increasing U-wave amplitide i.e. shift of main repolarization wave from systole to diastole. End of systole is indicated by a small vertical line after the end of T. From Surawicz[22] with permission.

the sites activated later, i.e. the base vs the apex. From these and similar studies of the effective refractory periods it appears that T-wave polarity is determined by the differences in the duration of action potentials between very closely adjacent areas, and also differences between action potential durations at more distant areas of the ventricles. The electrophysiologic mechanism of the regional differences in ventricular action potential durations is not known.

A number of pathological and functional derangements can cause an abnormal direction of T-wave vector, manifested by T-wave inversion in one or more of the standard limb or anterior precordial leads. In the absence of any change in the sequence of activation this finding indicates an altered relation between action potential durations in some portions of the ventricle. To define the magnitude and the extent of AP duration changes responsible for T-wave inversion in the ECG, we studied the effect of isoproterenol-induced MAP shortening on the amplitude and polarity of the T-wave[3]. Infusion of isoproterenol into a coronary artery or one of their branches shortened MAP in the regions perfused by the appropriate vessel. The region in which the MAP was shortened could be determined by weighing the perfused portion of the heart. The average MAP shortening induced by isoproterenol ranged from 12–18 ms. Such shortening altered the T-wave direction, even if MAP changes were confined to less than 10% of ventricular myocardium. From these observations we concluded that T-wave is a sensitive but non-specific indicator of abnormalities of repolarization[3]. We also investigated the effect of isoproterenol on T-wave in man, and deduced from the effects on rate, T-wave, and QT interval, that T-wave inversion could be caused by a 20-ms increase in the duration of repolarization in some regions of the ventricular myocardium[5].

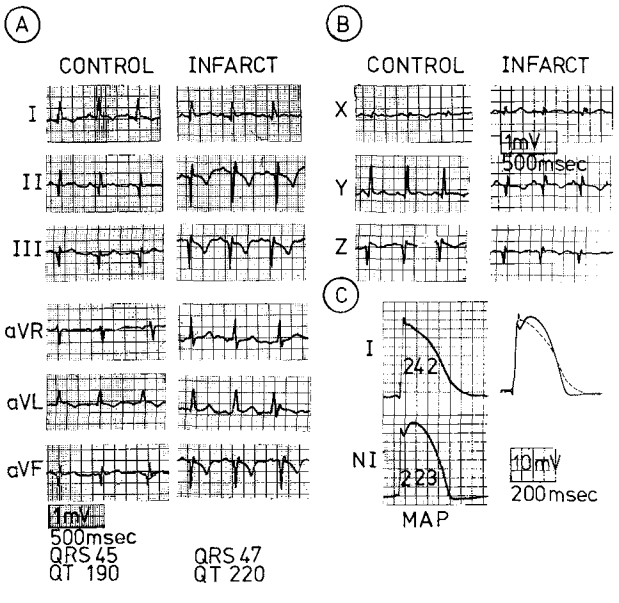

Figure 5. Electrocardiogram of a dog before (control) and 5 days after coronary occlusion (infarct). In A, leads I, II, III, aVr, aVl, aVf and in B, leads X, Y, Z. Note lengthening of QT interval from 190 to 220 ms. Monophasic action potentials (MAP) were recorded from the myocardium at the border of the infarct (I) and from the normal myocardium at a distance from the infarct (NI). Their duration in ms is inscribed within the tracings. On the right, both MAP's are superimposed. Subsequently, similar patterns were recorded in transmembrane action potentials in vitro from tissues excised at the I and NI sites (not shown). From unpublished experiments of C.S. Kuo, D.F. Butler, C.M. Chen, and B. Surawicz.

T-wave abnormalities have been divided into primary, secondary, and combined. The secondary abnormalities result from changes in the sequence of repolarization secondary to changes in the sequence of depolarization without changes in shape or duration of action potentials, whereas the primary changes are caused by changes in shape and/or duration of ventricular action potentials.

The primary changes may be uniform e.g. effects of rate, temperature, generalized hypoxemia, electrolyte abnormalities, and drugs. More often, however, the primary abnormalities of repolarization are not uniform, but localized to a diseased area. An example of such localized abnormality is the post-ischemic T-wave change. Acute ischemia causes depolarization and shortening of ventricular action potential. This is associated with displacement of the ST-segment from the baseline which, in the extreme form, produces a monophasic complex. There is also shortening of the QT interval that appears to be caused by a more rapid slope of terminal repolarization.

Another effect of acute myocardial ischemia may be increased T-wave duration and lengthening of the QT interval.

The assumed mechanism in such cases is delayed repolarization resulting from slow conduction in the ischemic region[15]. The same mechanism, however, is probably not responsible for increased T-wave duration and QT lengthening during chronic stage of infarction, when conduction disturbances are no longer evident in the surface electrocardiogram. Such post-ischemic T-wave abnormalities and QT lengthening after a transmural or a non-transmural myocardial infarction may persist for days, months, years, or remain permanently. They also were present in dogs with a 5–14-day-old myocardial infarction. Using suction electrodes in these animals, we found that electrocardiographic changes were associated with lengthening of MAP's in the regions bordering the infarction scar (fig. 5). This was verified in the records of transmembrane action potentials recorded from the excised strips of tissue in which the MAP lengthening was found. The longer action potentials in the vicinity of the infarction scar differed from normal action potentials in their response to isoproterenol i.e. no shortening or lesser shortening. The possible mechanism of such decreased responsiveness is not known.

Alternans of ventricular repolarization

In a series of unpublished experiments, we observed that alternans of ST-segment, T-wave and QT interval was associated with two types of action potential alternans in the ventricular muscle fibers. In one, the alternans was dependent on critical action potential duration, and in the other on action potential shape. In the former, the long duration of action potential caused subsequent depolarization to occur before the repolarization of the preceding AP was completed. Because of proximity to preceding repolarization, i.e. a short diastolic interval, the subsequent short action potential was followed by a longer diastolic interval, and a longer action potential[10]. With increasing duration of action potential, a lesser increase in rate was required to produce this type of alternans. In the second type, alternans of action potential duration was not dependent on the rate of driving or diastolic interval, but on the changes in plateau amplitude and duration. This was observed at low temperature or in fibers intoxicated with quinidine.

Mechanisms of ventricular safety and vulnerability deduced from combined electrocardiographic and electrophysiologic observations

Electrocardiogram records events occurring in vivo but does not disclose the nature of corresponding abnormalities at the cellular level. Single cell records may explain the mechanism of abnormalities associated with experimentally-induced arrhythmias but they beg the question of their relevance to the in vivo occurring events. This may result in clinical concepts of arrhythmia mechanisms postulating abnormalities at the cellular level that may not exist at all, and electrophysiologic concepts based on laboratory observations postulating clinically non-existing mechanisms.

In this section, I will attempt to explain how certain putative mechanisms of electrical safety and vulnerability of the heart can be deduced from correlating the electrocardiographic observations in vivo with the electrophysiologic observations in vitro.

Stable resting membrane potentials

During diastole, myocardial cells remain at a stable resting membrane potential that is close to the E_K. The importance of this factor in maintaining electrical stability can be illustrated by two examples of arrhythmias occurring when the non-pacemaker fibers acquire diastolic depolarization and become transformed into pacemaker fibers.

It is known that the electric current can induce ventricular fibrillation in a normal heart and restore regular activity to a fibrillating heart. Records in single ventricular fibers[1] have shown that weak electric stimuli depolarize the ventricular fibers to a level at which diastolic depolarization develops spontaneously, and the activity becomes automatic. Stronger electric currents cause a more pronounced depolarization resulting in cardiac standstill enabling restoration of regular activity. These observations suggest that ventricular fibrillation in an electrocuted heart is caused by transformation of non-pacemaker fibers into rapidly discharging pacemaker fibers.

A more direct evidence of such mechanism stems from observations in isolated rabbit hearts perfused with K-deficient solutions[8,27]. The low K progressively slows ventricular repolarization. This slowing reaches a point at which instead of continuing to repolarize the fiber develops diastolic depolarization at membrane potential[19]. The resulting automaticity of non-pacemaker fibers is associated with the development of ventricular arrhythmias terminating in ventricular fibrillation.

Another cause of an unstable resting membrane potential is an afterdepolarization generated by transient inward current, usually in the presence of digitalis or other conditions associated with increased accumulation of intracellular calcium[28]. Automatic activity may occur when afterdepolarizations reach threshold for spontaneous depolarization. This can be triggered in various types of cardiac fibers by rapid pacing[7]. Electrocardiographic observations suggest that this mechanism is responsible for ectopic rhythms precipitated by digitalis toxicity.

Short relative refractory period

In single ventricular muscle of Purkinje fibers, relative refractory period corresponds to the period of terminal repolarizaiton from the end of inactivation to the onset of full reactivation of the sodium channel, i.e. from about −60 mV to about −85 mV. During this period, threshold of excitability is increased, and conduction of premature impulse is slower than in fully repolarized fibers. The normal course of terminal repolarization in the ventricular muscle is steep which means that the relative refractory period is short, and the time interval available for slow propagation of early premature depolarizations arising during relative refractory period is brief.

A slower slope of terminal repolarization results in longer relative refractory period, and an increase in time available for slow propagation of an early premature impulse. The velocity of terminal repolarization is probably dependent largely on g_K, and slowing of terminal repolarization at low $(K^+)_o$ has been attributed to low g_K. Slowing of terminal repolarization is also caused by a number of antiarrhythmic and psychotropic drugs that prolong the duration of T-wave and increase U-wave amplitude. Slow terminal repolarization may be also present in myocardial fibers bordering the myocardial infarction scar. Ample experimental evidence links lengthening of relative refractory period to slow conduction of premature impulses and aggravation of ventricular arrhythmias.

Uniform polarization

Isoelectric diastolic (TQ) interval indicates uniform resting membrane potential. Localized depolarization produced by topical or intracoronary administration of K^+ salts[18] creates an 'injury' current, manifested in the ECG by displacement of TQ segment[15]. Coronary occlusion also causes regional increase in interstitial K^+ concentration[12], uneven polarization, and displacement of the TQ segment. Characteristically, ventricular arrhythmias including ventricular fibrillation occur more frequently either immediately upon liga-

tion of the coronary artery (occlusion arrhythmias), or upon release (reperfusion arrhythmias) than during sustained occlusion. This suggests that the arrhythmias are generated or facilitated by nonhomogenous depolarization. In contrast to the destabilizing and arrhythmogenic effects of localized depolarization, generalized depolarization results in uniform slowing of conduction without increased propensity to arrhythmias[24].

Small ratio of the impulse propagation time to the duration of ventricular refractory period

Normal duration of the ventricular impulse propagation (the QRS complex) is about 3–5 times shorter than the duration of ventricular action potential, or refractory period. QRS duration is increased in ventricular premature complexes, and the ratio of QRS duration to the duration of refractory period increases progressively with increasing prematurity due to progressive slowing of conduction and progressive shortening of action potential. The combination of slow conduction and short refractory period facilitates re-entry. Ventricular arrhythmias, attributed to re-entry can be induced by premature stimuli of an appropriate strength and duration during relative refractory period. Experimental evidence suggests that under such circumstances, the duration of QRS complex i.e. ventricular propagation time may exceed the duration of the premature action potential at the stimulation site[26]. It appears that the small ratio of the impulse propagation time to the duration of ventricular refractory period is an important safety factor guarding against re-entry.

Small dispersion of repolarization

Large dispersion of repolarization creates conditions similar to long relative refractory period, i.e. increased time interval available for slow propagation of an early premature impulse. Increased dispersion of repolarization may be due to increased differences in activation times, increased differences in action potential duration, or both[16]. Lengthening of ventricular action potential causes lengthening of QT interval in the ECG. This may be associated with increased propensity to serious ventricular arrhythmias. An example of such condition is the congenital long QT syndrome. However, QT lengthening of equal or greater magnitude may be present without an increased risk of ventricular tachyarrhythmias, for example, during hypocalcemia. The postulated difference between these two types of QT lengthening is that low calcium prolongs ventricular action potential uniformly whereas the lengthening of action potential in subjects with congenital long QT syndrome appears to be limited to certain regions of the ventricular myocardium. Therefore, the arrhythmias are not caused by lengthening of QT interval but by increased dispersion of repolarization. We have shown that experimentally induced dispersion of action potential duration facilitates induction of ventricular fibrillation when stimuli applied at a site with short action potential duration propagate slowly during incomplete repolarization at the sites with long action potential duration[16].

Comment: Figure 6 shows a diagram with abnormalities assumed to create disturbances of conduction and refractoriness. It can be seen that the prevailing disturbance at the cellular level is a non-uniform depolarization which generates or facilitates serious life-threatening ventricular tachyarrhythmias.

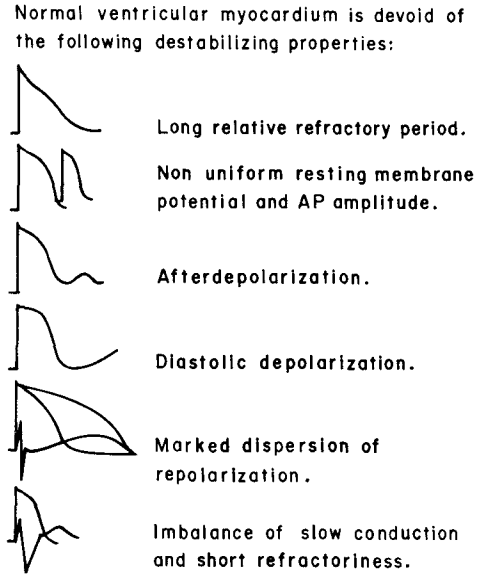

Figure 6. Diagram of putative destabilizing electrophysiologic properties in the ventricular myocardium, known to contribute to serious ventricular arrhythmias. Ventricular action potential and electrocardiogram are superimposed. See text.

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Cell-to-cell communication in the heart: structure-function correlations

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Summary. The communicating cell junctions that ensure the electrical and diffusional continuity of the intracellular space in the heart fibres can be switched from their normal conducting, or opened state, to an exceptional non-conducting, or closed state. This electrical uncoupling is observed after cell injury in the presence of Ca^{2+} ions in the extracellular fluid, after metabolic inhibition and in the presence of aliphatic alcohols (C_6 to C_9). The correlations between electrical uncoupling and gap junction morphology in the heart are briefly reviewed. A decrease of the distance between P-face particles and between the E-face pits has been found in all investigations[3, 10, 16, 18, 55], but the functional significance of this observation is not understood at present. A quantitatively very similar decrease of the average particle diameter (about −0.7 nm) has been measured in glutaraldehyde-fixed sheep Purkinje fibres[16] and in unfixed, quickly frozen rat auricles[18] that had been electrically uncoupled by three different procedures. About half of this decrease was reversible on short-term electrical recoupling (within 20 min). It is concluded that a measurable decrease of the connexon diameter correlates with electrical uncoupling.
Key words. Heart; electrical coupling; electrical uncoupling; communicating junctions; gap junctions.

From a syncytium to a coupled cell system

Up to 1954, physiologists considered the heart as a morphological and functional syncytium of fused cells building up fibres with regularly spaced nuclei but no obvious transversal cell boundaries, and with electrical properties similar to those of skeletal muscle or nerve. This continuous network accounted for the all-or-none propagation of electrical and mechanical activity from any stimulated point. This classical view was seriously questioned by Sjöstrand and Andersson's[56] electron micrographs, in which the heart fibres unequivocally appeared to be built up of single cells entirely separated by their surface membranes, abutting without fusion at the intercalated disks.

These discontinuities in the core conductor of heart fibres had to be taken into account in any explanation of electrical conduction. Silvio Weidmann, who had just showed (1952)[64] that the Purkinje fibres of ungulate hearts have cable properties similar to those of nerve[29] and skeletal muscle[32], despite their well-known cellular structure[48, 58], took up this challenge and started an investigation of the cell-to-cell conduction process in the heart. Weidmann[65] first tried a direct measurement of the cell-to-cell resistance by means of two double-barreled micro-electrodes, one on each side of an intercalated disk. This first attempt was not successful because, as is now understood, electrical transmission across the disk is so efficient that the voltage drop across the cell boundary is smaller than the error inherent in measurements by micro-electrodes. Weidmann[65, 66] then devised an entirely original approach to this problem by loading a thin myocardial bundle in a two-compartment chamber with $^{42}K^+$ over one half of its length, while the other half was continuously washed in a non-radioactive solution. The fibres in the unloaded compartment become radioactive too, and the spatial distribution of $^{42}K^+$ when diffusion equilibrium is approached corresponds to that calculated on the assumption of a cell-to-cell passage of $^{42}K^+$ across an average disk resistance of $3\,\Omega \times cm^2$. The space constant of 1.55 mm measured for the decrease of radioactivity on the unloaded side of the bundle makes improbable the alternative interpretation that loading in the washed compartment could be by way of the extracellular space only.

The same method was applied later to investigate the diffusion of several substances with different molecular weights