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Conduction of the impulse in the ischemic myocardium – implications for malignant ventricular arrhythmias

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Summary. Ventricular arrhythmias occurring consequent to regional disturbances of myocardial perfusion are the most frequent cause of sudden cardiac death. They are related to marked changes of impulse propagation in the ischemic region, which consist of circulating excitation with re-entry. Mapping of the impulse during ventricular tachycardias and ventricular fibrillation shows that the circus movements change their shape and localization from beat to beat. Zones of tissue which block the impulse during one beat may conduct the impulse at a fast rate during the next beat. The main cause underlying this behavior is the depression of the ischemic action potential. This depression is caused by the partial inactivation and the

prolonged recovery of the rapid sodium inward current. In addition to the decrease in resting potential, other factors, such as acidosis, contribute to the inactivation of the inward currents generating the upstroke of the action potential. An increase of coupling resistance between myocardial cells and/or an increase of extracellular resistance appear to be less important for explaining conduction disturbances in acute ischemia.
Key words. Arrhythmias; myocardial ischemia; conduction block.

Introduction

Ventricular fibrillation and ventricular tachycardia are probably the most frequent causes of sudden cardiac death[1]. Such fatal events occur in more than half of the deaths associated with myocardial necrosis, i.e. in more than 50% of 550,000 cases a year in the population of the United States[1].

The sudden transition from a regularly and safely beating heart to the chaotic state of fibrillation has fascinated experimental investigators since the beginning of this century[11,25]. In the setting of experimental myocardial ischemia, Harris et al.[13] were the first to describe the phasic occurrence of ventricular arrhythmias after experimental coronary ligation. The first of three phases, which is identical with the reversible stage of myocardial ischemia, is characterized by the frequent occurrence of malignant arrhythmias. The incidence of ventricular fibrillation and ventricular tachycardias during this period (which corresponds approximately to the first 20 min after experimental coronary artery occlusion) is about 50% in hearts of big animals such as pigs and dogs[35].

After a second phase, when regular sinus rhythm predominates, a third arrhythmogenic phase takes place with frequent single or multiple extrasystoles, most likely of focal origin[34]. For many decades the views on the eventual mechanisms of these arrhythmias were controversial, and two essentially opposing hypotheses; the ectopic, rapidly discharging pacemaker and the circulating excitation with re-entry, were proposed. More recently, it has been demonstrated directly that rapid and arrhythmic ventricular excitation during tachycardias and/or fibrillation is *maintained by circle movements with re-entry*[16]. However, the mechanism of *initiation* has not been completely elucidated as yet. Several possibilities have been suggested, such as ectopic pacemakers, micro-re-entry[7], reflexion-re-entry[4] and excitation by injury currents[16]. None of these can be proven to be consistently responsible for the event initiating the circus movements and it may well be that they co-exist. Nevertheless, there is no doubt that ventricular fibrillation cannot be ini-

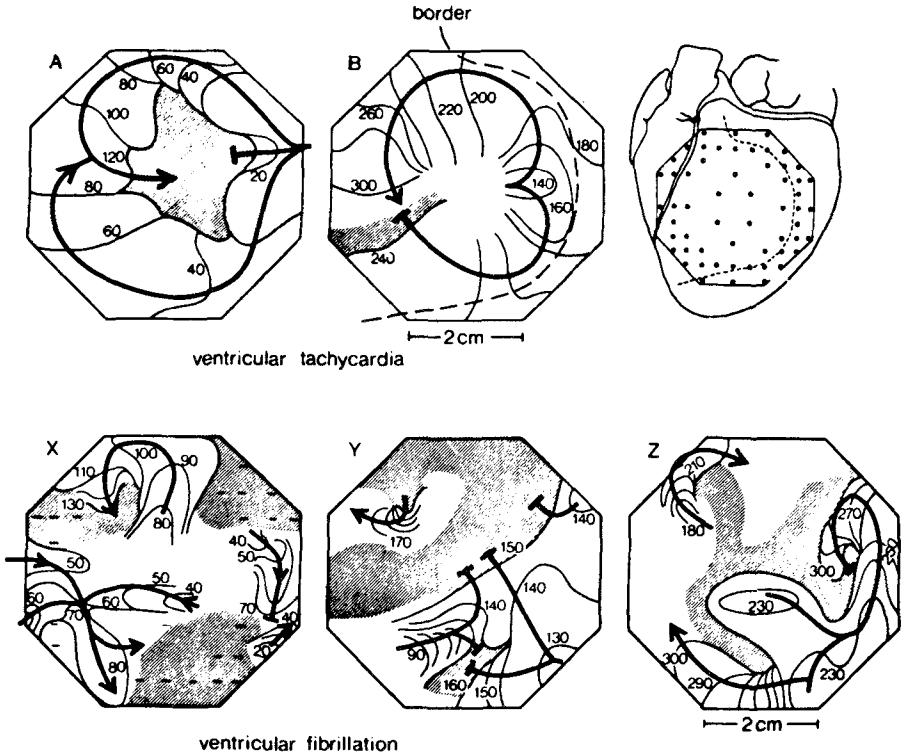

Figure 1. Patterns of activation during a ventricular tachycardia which degenerated into ventricular fibrillation. Recordings were taken 4 min after occlusion of the left anterior descending artery in an isolated perfused pig heart. The upper right panel shows the position of the electrodes on the anterior wall of the left ventricle. The interrupted line denotes the position of the border between the normal and the ischemic zones. Extracellular electrograms were recorded simultaneously from the 60 electrodes and activation or so-called 'isochronic' maps were constructed from the activation time of each electrode. Activation maps during two subsequent beats of a ventricular tachycardia (A and B) are shown on the upper panel. The numbers on the isochrone lines indicate the time of local activation in ms (relative to an arbitrary zero time reference). Isochrone lines are drawn in increments of 20 ms, shadowed areas symbolize zones of conduction block. In A, the epicardial area is invaded from the normal side of the border. Propagation is blocked in the middle and splits in two wavefronts which bypass the block and penetrate retrogradely into the center. Re-entry and re-excitation occurs after 140 ms at the original site. Note the shift of the blocked zone during beat B. The maps X, Y and Z on the lower panel were recorded a few seconds later when the heart was fibrillating. Multiple wavelets were present, fusing and colliding with each other and forming circulating excitation. Again, the zones which block the impulse change their position from beat to beat. (Reproduced with permission by the American Heart Association)[17].

tiated by focal ectopic activity without the presence of severe disturbances in impulse conduction predisposing to circulating excitation. In normal ventricles induction of ventricular fibrillation requires the application of unphysiologically large excitatory currents whose strength exceeds manyfold the normal threshold for local stimulation or the strength of physiological local currents at a propagating wavefront.

The purpose of this review article is to discuss the disturbances of impulse conduction which cause the circus movements in acutely ischemic tissue and to relate them to the changes in cellular electrical activity and to the changes in the passive electrical properties of the tissue.

Circulating excitation with re-entry – relation to changes in conduction velocity and conduction block

The main electrophysiological conditions necessary for re-entry to develop were already described by Mines[29] at the beginning of this century: a) the occurrence of unidirectional conduction block, mostly elicited by a premature stimulus, and b) a shortening of the wavelength of propagation, i.e. of the zone of refractoriness which moves with the wavefront. The length of the propagating wave is given by the product of the refractory period times the conduction velocity. Therefore, either a decrease of conduction velocity and/or a shortening of the refractory period will favor the formation of re-entrant circuits.

Multiple mechanisms, including changes of the passive electrical properties of the tissue and changes in the action potential, have been suggested to underly block formation and/or conduction slowing. One of the pertinent questions is whether and how closely specific electrical changes at a cellular level are related to the changes in the activation pattern typical for a given pathophysiological state. In myocardial ischemia such a typical pattern certainly exists. Figure 1 demonstrates the epicardial excitation during ventricular tachycardial (upper part) and ventricular fibrillation (lower part) as determined from simultaneous extracellular recordings with a multiterminal electrode[17]. In addition to the direct demonstration of circus movement with re-entry, two observations can be consistently made from such isochrone maps. They both characterize the circus movements in acute myocardial ischemia. First, the excitation pattern appears to be irregular; there is no consistency from beat to beat. Sites which block the impulse during one beat (e.g. central zone on map of beat A on the upper panel of fig. 1) conduct the impulse during the next beat (beat B, upper panel of fig. 1). This observation already suggests that the *conduction block is* purely *functional* in nature and excludes, at this stage of ischemia, blocks of fixed location due to complete cellular uncoupling. Second, the circuits are relatively large in diameter (4-7 mm)[21], similarly to those found in isolated rabbit atria[3], although they have rather short resolution times (e.g. 120 ms in beats A and B of fig. 1). This second observation suggests that conduction velocity in ischemia, although decreased, does not fall to the very low values observed e.g. in Purkinje fibers during propagation of Ca^{++}-mediated responses[7,8].

More quantitative information on changes of conduction velocity and conduction block in ischemia has been obtained with epicardial high resolution mapping[21]. In these experiments the propagation pattern was recorded within a small area of tissue (approx. 1 cm^2) by closely spaced extracellular leads and conduction velocities were calculated in parallel and transversely to the main fiber direction,i.e. by taking into account the anisotropic architecture of the tissue. Both the longitudinal and the transverse velocity remain relatively constant during the first 2 min after interruption of myocardial perfusion. Afterwards, a rapid decrease takes place to about 50–60% of the initial value, i.e. to about 25 cm/s for longitudinal and to about 10–15 cm/s for transverse propagation[21]. At this stage there is a rapid, beat to beat transition from this still relatively rapid conduction to complete inexcitability. At epicardial measuring sites at least, very slow impulse transmission at velocities below 10 cm/s was observed only occasionally in the transverse and never in the longitudinal direction.

The rapid transition from propagation to inexcitability is characteristic for the acute stage of ischemia and explains most of the conduction pattern shown on figure 1. It is closely associated with the formation of the unidirectional conduction blocks, as shown on figure 2. On the left hand of figure 2 conduction block is shown 6 min after the induction of ischemia. Stimuli applied at intervals of 450 ms in the center of an epicardial multiterminal recording electrode produce excitation and propagation only towards the lower left corner of the electrode. The tissue on the upper right part of the electrode which was unexcitable at the time of stimulation is excited with delay by circulating excitation. This recording shows the basic features underlying the intraischemic conduction block: a) A local inhomogeneity and b) a time dependence of local excitability. This time dependence is also shown on figure 2B, which depicts the conduction map of the subsequent beat. In contrast to beat A which was obtained during regular pacing at an interval of 450 ms, beat B was elicited after increasing the interval abruptly to 900 ms. This *prolongation of the local recovery time* is followed by immediate restoration of regular spread as is evident from the elliptic shape of the isochrone lines of beat B. The abrupt transition from a state of inexcitability to conduction is exemplified by the tissue at the lower left hand part of the map. This area blocks the impulse in beat A and conducts the impulse at a (longitudinal) velocity of 26 cm/s during beat B. Once a unidirectional block is established (e.g. by a premature stimulus) a blocked area will, by virtue of not being excited, have a longer recovery than a neighboring zone of conducting tissue. During a subsequent beat, the original zone of block may therefore have regained excitability at a time when the (originally conducting) neighboring zone is still refractory. Such a process will produce the beat to beat shifts of conducting and blocked tissue which characterize the irregular conduction pattern during the arrhythmias (fig. 1).

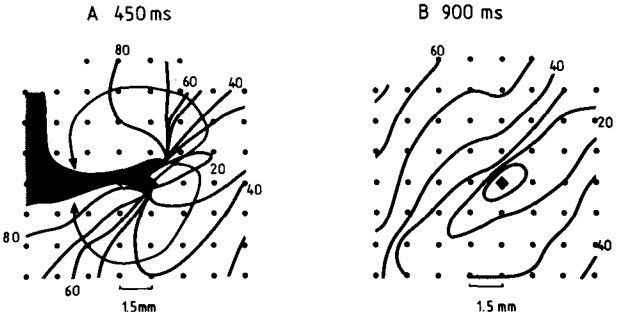

Figure 2. Epicardial activation, represented by isochronic maps, 6 min after induction of ischemia in an isolated perfused pig heart. Isochrones are shown in increments of 20 ms. They were constructed from 60 simultaneously recorded epicardial electrograms. The electrode terminals, arranged in a square lattice, covered in area of 1 cm^{-2}. In beat A, stimulation of the center of the area produces propagation on the left. The wavefront circulates around the center and excites the shadowed area, which originally was blocked with a delay of 100 ms. The recovery time of the tissue was increased during the next beat B by increasing the stimulus interval to 900 ms. This produces almost normal spread with a velocity of 26 cm/s in longitudinal direction. The longitudinal axis of the elliptic isochrones corresponds to the longitudinal fiber direction. (Reproduced with permission by the American Heart Association)[21].

The time-dependent conduction is explained by prolonged recovery of the ischemic action potential, i.e. by an effect of ischemia on ionic channels in the membrane (see next paragraph). The mechanisms underlying the local inhomogeneity of excitability and conduction is less evident. Most likely, it is related to the microscopic fiber architecture (branching of fibers) which sets the condition for unidirectional propagation when the margin of safety for propagation becomes low in electrically depressed tissue (for discussion see Cranefield[8] or Kléber et al.[21]).

The role of the changes of action potential in conduction slowing

The action potential upstroke of a normal cardiac cell varies with heart rate only during the short relative refractory period, i.e. when a cell is excited during the phase of repolarization of the preceeding beat[41]. The recovery of the rapid Na^+ inward current from inactivation during this period is completed almost instantaneously. The degree of recovery depends on the level of membrane potential during repolarization, i.e. it is voltage-dependent, not time-dependent[12]. In whole hearts this will not influence the spread of normal excitation because the interval between subsequent beats is longer than the duration of the action potential even at very fast heart rates, and therefore, action potential upstroke characteristics and conduction will not change with rate.

In acute, reversible myocardial ischemia which is associated with a depolarization of the cell[19], the reduction in action potential amplitude and upstroke velocity and the prolonged recovery from inactivation have a crucial influence on the velocity of propagation. The nature of both the ischemic depolarization and the depression of the action potential have only partially been clarified, however.

Ischemic depolarization is related to a cellular loss and an extracellular accumulation of K^+ ions[14, 15]. Potassium accumulation starts 15 s after interruption of coronary flow; it increases extracellular K^+ concentration to levels of 12–15 mM after 7–10 min and is rapidly reversible within the first 15 min of ischemia. The associated shift of resting membrane potential is about 30 mV[19]. The main cause of the K^+ imbalance is an increase of the passive (unidirectional) K^+ efflux[32, 38], whereas the inhibition of the active K^+ influx (Na^+/K^+ pump) appears to be small[5, 19, 43] during the reversible phase. Despite many attempts, the mechanism of increased K^+ efflux has not yet been completely clarified. An increased conductance to potassium ions[39] cannot explain the phenomenon completely[20]. One hypothesis, which links the increased K^+ efflux to lactate transport[20], is supported by the observation that extracellular K^+ accumulation in myocardial ischemia is pH- and CO_2-dependent[23]. In compact ventricular myocardium, anaerobic glycolysis and lactacidosis produce a secondary increase of CO_2 (300 mm Hg after 10–15 min)[6]. The cellular potassium loss occurs only in these compact tissue masses which form an obstacle for CO_2 diffusion (personal observation) and it can be reversed by artificially lowering the partial CO_2 pressure[23]. The system responsible for transport (or extrusion) of lactic acid appears to be CO_2 and/or pH dependent as well (skeletal muscle[27]; heart[9]). At normal pH, lactate anions and protons are extruded in equimolar amounts, whereas lactate transport exceeds H^+ extrusion at low pH[27, 28] and K^+ efflux develops[20]. It appears therefore that early ischemic depolarization is a consequence of intracellular metabolic acidosis rather than of inhibition of energy-dependent transport processes.

It is well known that action potentials generated in tissue depolarized by electrical current or elevated extracellular $[K^+]$ are of small amplitude and have a low upstroke velocity. This is because the membrane channels responsible for producing the initial portion of the action potential are partially inactivated[12, 41]. Moreover, the recovery from inactivation of both the fast Na^+ and the slower Ca^{++} channels becomes markedly prolonged[12]. In depolarized ischemic tissue, the absolute refractory period may exceed the duration of the action potential ('post-repolarization refractoriness'), and the relative refractory period can last for several hundred milliseconds[10]. This increases the chance that a propagating wavefront will encounter completely or partially inexcitable tissue at normal or slightly elevated heart rates. An example of this is shown on figure 3 which depicts transmembrane action potentials (upper traces) and extracellular electrograms (lower traces) from an epicardial ischemic zone in a Langendorff-perfused pig heart stimulated at different cycle lengths. Regular pacing of the heart at an interval of 450 ms produces an action potential of reduced amplitude and duration in a one-to-one fashion. Delayed activation (probably reflecting a low velocity of propagation in the ischemic zone) is indicated by the negative T-wave in the extracellular electrogram. Decreasing the stimulation interval shortens the recovery time and is followed by intraischemic block (3:2 block at 430 ms, 2:1 block at 410 ms and high degree block at 400 ms).

The decrease of amplitude and rate of rise of the ischemic action potential is not due to the extracellular K^+ accumulation and the depolarization alone. Other factors such as acidosis and, possibly, unknown ischemic metabolites induced a further decrease of the depolarizing currents at a given resting membrane potential[24, 30]. In fact, this was already suggested by the elegant measurements of recovery curves with suction electrodes by Schütz in 1936[33]. Astonishingly, little is known about any effects that extra- or intracellular pH changes might have on the kinetics or the single channel conductances of the Na^+ or Ca^{++} channels. The consequence of this extra-depression by acidosis (or by additional factors) for conduction slowing is shown in figure 4. This figure compares conduction velocity measurements during normoxic perfusion of hearts at different levels of elevated $[K^+]_o$ (effect of K^+ alone) with the relationship between conduction velocity and $[K^+]_o$ during ischemia. Elevation of extracellular potassium alone produces a marked slowing of propagation only above 7 mM and a block above

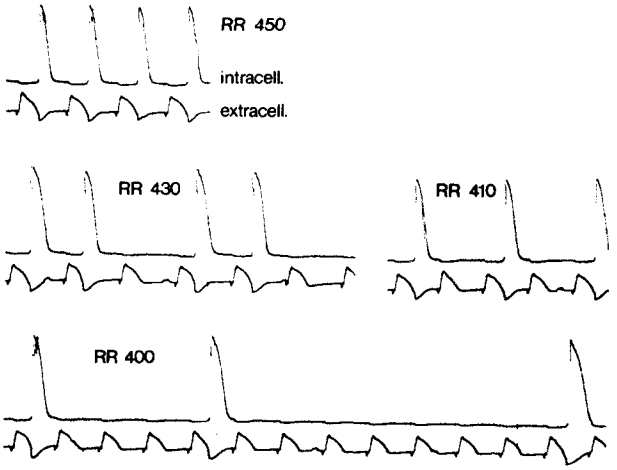

Figure 3. Action potentials (upper traces) and extracellular electrograms (lower traces) from an ischemic region of an isolated perfused pig heart are shown at different interstimulus or R-R intervals which are given in milliseconds. The delayed activation of the ischemic zone is indicated by the negative T-wave on the ventricular complex of the extracellular electrogram. At an RR interval of 450 ms, every stimulus produces an excitation of the ischemic region. The gradual decrease of the RR-interval from 450 ms to 400 ms produces an increasing degree of intraischemic conduction block. Note absence of negative T-wave on the electrogram during the blocked beats.

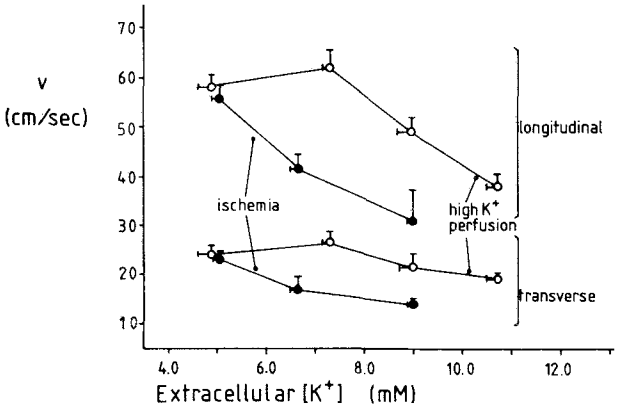

Figure 4. Velocities of conduction in direction of the longitudinal and transverse fiber axis are plotted versus interstitial potassium concentration measured with an ion-sensitive electrode. Open symbols represent the measurements during perfusion of the isolated pig heart with a solution containing elevated [K^+], filled symbols represent the measurements made during ischemia. At a given potassium concentration conduction slowing is more expressed during ischemia than during perfusion with elevated [K^+] (Reproduced with permission by the American Heart Association)[21].

12 mM. In ischemia slowing occurs already at low potassium levels and the tissue gets inexcitable above 10 mM.

The question of whether depressed ischemic action potentials are initiated by the Ca^{++} inward currents (so-called 'slow responses'[8] or by the Na^+ inward current (so-called 'depressed fast responses') can only be answered indirectly. The information currently available indicates that the typical behavior of propagation in ischemia, consisting of an abrupt transition from relatively rapid propagation (50–60% of normal) to inexcitability, is related to action potentials generated by depressed Na^+ inward current. Slow Ca^{++}-mediated responses elicited in whole hearts by a perfusate containing 20 mM [K^+] and adrenaline conduct the impulse at velocities (> 10 cm/s in longitudinal direction[21]) which are significantly lower than those measured during ischemia. Moreover, the acutely ischemic cells become inexcitable at resting potentials of about 60 mV[18, 21]. This level is more negative than the threshold of activation of the slow inward current. Calcium-mediated responses may play a role at later stages of ischemia, or in cardiac arrhythmias associated with a different pathophysiological disturbance, however.

Changes of passive electrical properties in ischemia

Weidmann has shown that the electrical properties of heart muscle (in the direction of the longitudinal fiber axis) can be modelled by a uniform electrical cable[42]. In such a model, the amount of depolarizing local current running ahead of a propagating wavefront is mainly determined by the amount of ionic current generated by the excited tissue and by the resistive elements within the circuit of the local currents. In excised heart tissue soaked in a tissue bath (which acts as an infinite volume conductor), the extracellular resistance can be neglected, and the resistances of the gap junctions and the cytoplasm (together with membrane resistance) determine the flow of electrotonic current. The same situation probably holds for propagation in the superficial endocardial tissue layers in whole hearts which are in contact with the cavitary blood. In the large tissue mass of the ventricles, the resistance of the extracellular space enters into consideration. In compact ventricular tissue, the extracellular space makes up 20–25% of the tissue volume[31, 37]. The resistances of the extra- and intracellular spaces are of the same order of magnitude despite the relatively low value of the specific resistance of the extracellular tissue[22]. Therefore, changes in extra- and intracellular resistance have to be considered as equally important for modulating impulse propagation in ischemia.

The earliest sign of uncoupling at gap junctions in ischemia as assessed by morphometric methods can be observed approximately 20 min after the interruption of coronary flow[26]. This corresponds to the onset of irreversible ischemic damage[20]. Information on changes of electrical intracellular resistance during the first minutes following coronary occlusion, which could contribute to conduction slowing during the early arrhythmogenic phase, is not available as yet. Measurements have been made only in hypoxia and showed a 1.7-fold increase in intracellular resistance after 30 min of hypoxic superfusion[44]. Indirect evidence suggests that the coupling between myocardial cells is not significantly affected during this early arrhythmogenic phase. Thus, a marked increase of free intracellular Ca^{++}, which is the most important modulator of coupling resistance, is unlikely during this period. This is indicated from measurements of intracellular Na^+ activity[19], normal resting tension[43], and estimates of resting Ca^{++} from aequorin light emission[2].

The resistance of the extracellular space may be affected by interruption of myocardial perfusion in various ways. A first rapid increase of extracellular resistance (30–40%) is related to the decrease of perfusion pressure and intravascular volume after perfusional arrest[22]. It leads to a small but significant decrease of conduction velocity (16%). The mechanical counterpart, which consists of a partial loss of active tension, has been termed the 'garden-house' effect, or loss of hydraulic stiffness[40]. Both the electrical and the mechanical changes are caused by the hemodynamic alteration and not by ischemic metabolism. Whether, and to what extent, ischemic metabolism affects extracellular resistance remains to be shown. An increase of extracellular resistance may be expected from the swelling of the ischemic cells[36] and the concomitant diminution of the extracellular space.

Conclusions

The slowing of conduction and the formation of conduction blocks in early reversible ischemia are mainly caused by the partial inactivation and the slow recovery of membrane currents generating the action potential. The changes of passive electrical properties (increase of extracellular resistance and cellular uncoupling) are likely to play a minor role.

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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-