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Update review

ST-segment elevation in the electrocardiogram: a sign of myocardial ischemia

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Abstract

In 1972 Kjekshus et al. published the seminal article 'Distribution of myocardial injury and its relations to epicardial ST-segment changes after coronary occlusion in the dog' in *Cardiovascular Research*. In this article it was shown that the ST-segment elevation occurring *early* after occlusion of the left descending coronary artery was closely related to the depletion of the necrotic cells from creatine kinase and to flow reduction at a *later* stage (24 h). This correlation was especially prominent if the infarction was transmural. Starting from these phenomenological relationships, this article briefly describes and summarizes the experimental research which was carried out in other laboratories after the publication of Kjekshus et al. Special emphasis is laid on the discussion of the main basic mechanisms which underly the clinically observed ST-segment elevation and its evolution after the acute stage of ischemia, i.e. the changes in the transmembrane action potential and the alteration in electrical cell-to-cell coupling. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

In 1972 Kjekshus et al. [1] published an article entitled 'Distribution of myocardial injury and its relation to epicardial ST-segment changes after coronary occlusion in the dog' in *Cardiovascular Research*. This and other related publications [1–5], were aimed at the definition of early markers of infarct size. ST-segment elevation was already used in clinical electrocardiography as a direct indicator of acute ischemia at that time. Nevertheless, the articles published by these authors are considered seminal, because they marked the beginning of a period which brought considerable insight into the electrophysiological alterations in myocardial ischemia and the mechanisms of infarct formation. In Section 2 of this brief review, devoted to the publication by Kjekshus et al., the early work on ST-segment changes as a sign of myocardial ischemia will be discussed. Section 3 will focus on the relation between the alterations of the ST-segment in the electrocardiogram, the underlying early changes in metabolism and extension of necrosis. In Section 4, the cellular electrophysiologic mechanisms leading to the changes of the intracardiac extracellular electric field and the electrocardiogram will be discussed. Finally, further complexities inherent to the interpretation of ST-segment elevation in vivo will be outlined in Section 5.

2. ST-segment elevation as a marker of acute myocardial ischemia

The term ischemic *injury* was originally derived from the observation that mechanical injury to the heart produces changes of the extracellular electrogram closely similar to ischemia. In 1879, Burdon-Sanderson and Page [6] already described the effects of mechanical injury to the surface of the frog heart and noted that, during activity, the injured site was charged positively with respect to the non-injured surface. In the past four decades, many investigators have studied the effects of mechanical or ischemic injury on local extracellular electrograms in the heart. Thus, it was gradually established that ST-elevation described in the surface electrocardiogram corresponded in reality to a combination of a TQ-segment change and a *real* ST-segment change. Samson and Scher [7] provided first evidence that the diastolic baseline depression in the extracellular electrogram was associated with a change in resting membrane potential of ischemic cells, a finding which was confirmed by Prinzmetal et al. [8]. Samson and

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Scher [7] postulated that the real ST-segment elevation was mostly due to shortening of the ischemic action potential, a view that was later partially disputed. At the time of the publication of the work by Maroko, Kjekshus, Sobel, Ross, Braunwald and others, it was generally accepted that ST-segment elevation was an indicator of ischemic injury. However, most of the basic cellular mechanisms underlying the alterations of the ischemic electrocardiogram were as yet inappropriately described, as discussed below.

3. ST-segment elevation, changes in ischemic metabolism and infarct size

The main goal of the articles by Maroko, Kjekshus, Sobel, Ross and Braunwald was to define markers of ischemia and early predictors of infarct size. Thus, is was shown that myocardial depletion of creatinephosphokinase (CPK) provided an index of ischemic cell injury and infarct size [3]. In addition, it was demonstrated that the degree of CPK depletion was closely correlated to the extent of myocardial flow reduction after coronary occlusion [3] and to the extent of myocardial necrosis assessed histologically [5]. The results reported in the article by Kjekshus et al. are illustrated and summarized in Fig. 1. In this article, the goal was to correlate the changes in myocardial blood flow and CPK depletion to the changes in the ST-segment of the electrocardiogram. Accordingly, in Fig. 1, extracellular electrograms, recorded with non-polarizable electrodes before and after occlusion of the anterior interventricular coronary artery of a dog heart in situ were compared to the corresponding local levels of CPK taken from the subepi- (‘outer’) and subendocardial

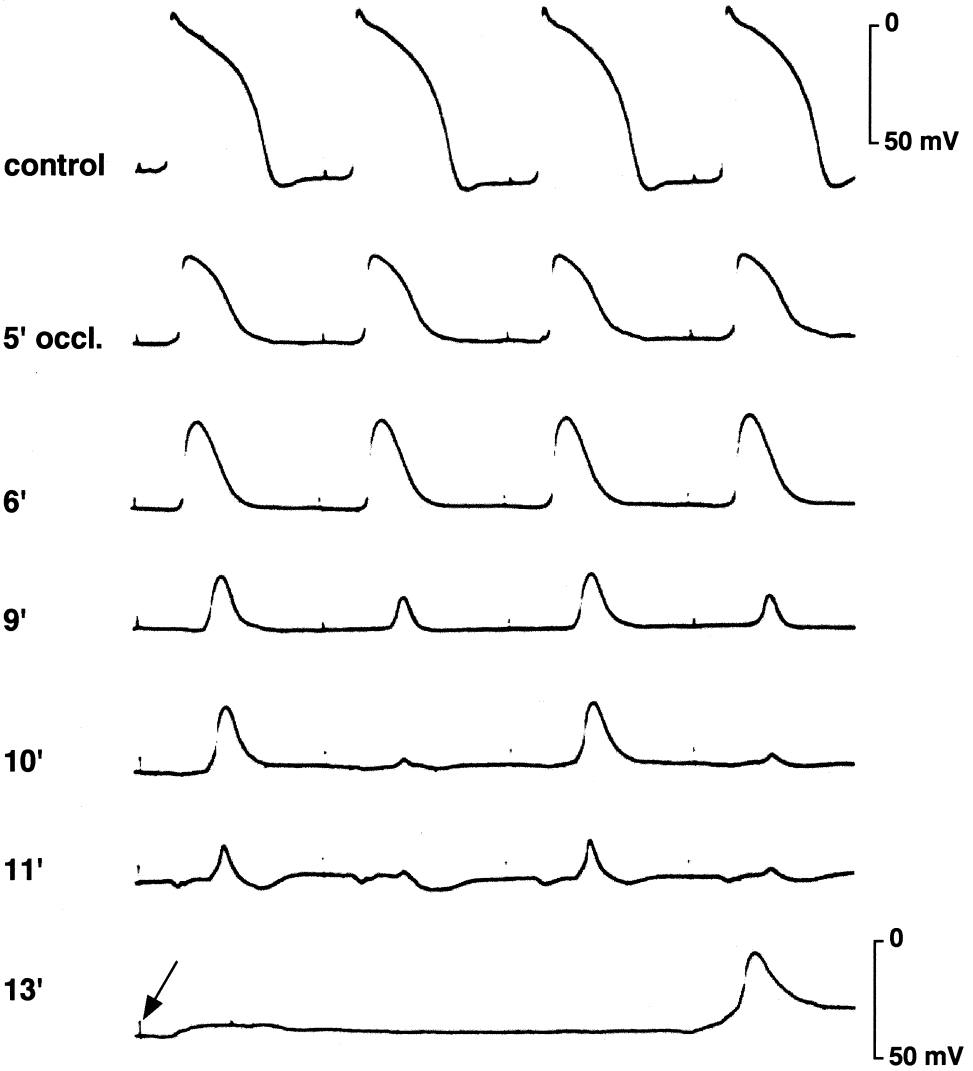

Fig. 1. Epicardial ST-segment changes 15 min after coronary occlusion and CPK activity 24 h later in corresponding subepicardial and subendocardial samples from a representative dog heart. LVP=left ventricular pressure. Locations of numbered sample sites and the occlusive coronary tie are indicated on the central diagram (reproduced from Ref. [1] with permission).

('inner') muscle layers. From this article, a close correlation between the ST-segment changes recorded *early* (15 min after coronary occlusion), the later sign of cell necrosis (CPK content after *24 h*), and the remaining cononary blood flow, became evident. Moreover, there was a consistent gradient between the more severe subendocardial CPK depletion and the subepicardial CPK depletion and the correlation between epicardial ST-segment changes was closer to the changes in CPK in the subepicardium than in the subendocardium. These transmural gradients among electrical, metabolic and flow changes after coronary occlusion appeared later to be specific for the dog heart. In dog hearts, a variable collateral circulation interferes with the flow reduction from the primarily occluded vessel [9]. In the pig heart, collateral flow is absent and an ischemic border zone in which coronary flow changes from normal to very low extends over only a few mm [10]. The border zone itself is composed of interdigitating healthy and necrotic tissue with a sharp separation between necrotic and surviving tissue [10]. The gradual change in the average concentration of ischemic metabolites and creatine phospohate across this border zone is therefore due the changing ratio of necrotic to surviving cells. Similarly to the observations by Kjekshus et al., the experiments in porcine hearts confirmed that the correlation between ST-segment changes during early ischemia with the later indicators of necrosis is only valid if the alterations of the ST-segment are measured before the first 15–20 min of acute ischemia. At later stages, the metabolites continue to change while the alterations in the ST-segments become reduced [11] because of cell-to-cell uncoupling (see below).

4. Cellular electrophysiologic and ionic changes explaining ST-segment elevation

Recording transmembrane action potentials from the surface of whole, arterially-perfused heart made it possible to establish the basic relationship between changes in the extracellular unipolar electrograms and the cellular electrical changes. In a seminal paper Downar et al. [12] showed that regional ischemia was associated with rapid changes in the transmembrane action potentials. A rapid loss of membrane polarization during the resting phase (shift of the resting potential to more positive values) was followed by a loss of amplitude, a shortening and a decrease in upstroke velocity of the transmembrane action potential, until the ischemic tissue became totally inexcitable after about 10 min of ischemia (Fig. 2). In addition to the characterization of the basic changes in the action potential, this work showed major cellular electrophysiologic features of the acutely ischemic tissue, which later became relevant for our understanding of the malign ventricular arrythmias: (1) electrical alternans, which was described as a harbinger of ventricular tachycardia and fibrillation, and (2) the prolonged recovery of the action potential upstroke, termed post-repolarization refractoriness, a phenomenon due to time-dependent recovery of Na^{+} and Ca^{++} channels from inactivation [13]. This initial study on the changes in the transmembrane action potential of ischemic tissue stimulated a number of further experimental investigations aimed at: (1) a more close definition of the nature of the cellular electrical changes; or (2) the relationship between the extracellular and transmembrane potentials. To separate the real ST-segment change from the

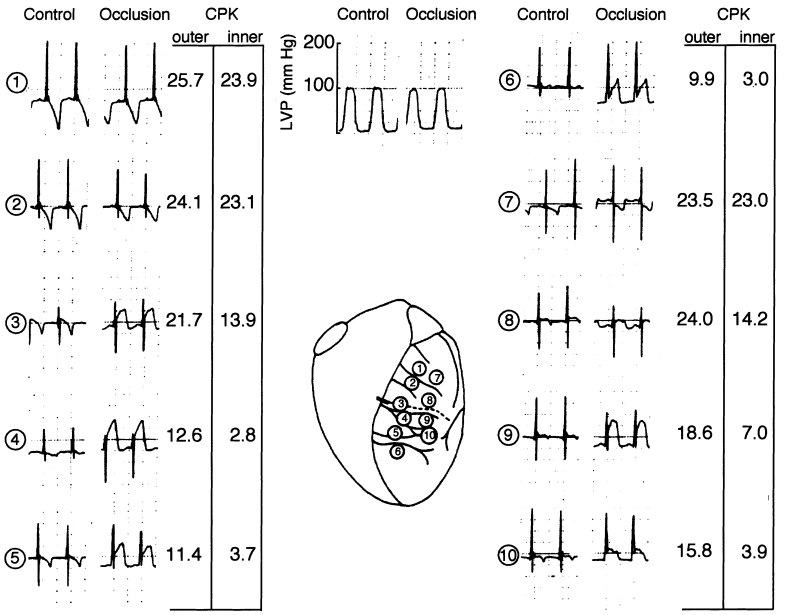

Fig. 2. Transmembrane action potentials recorded from the subepicardium of the left ventricle of an in situ pig heart before and after occlusion of the left anterior descending coronary artery (modified from Ref. [12] with permission).

TQ-segment change, DC electrograms, recorded by non-polarizable electrodes, were recorded from multiple intramural and epicardial sites in whole hearts [11]. As shown in Fig. 3A and B, regional ischemia produced a marked shift of both the ST-segment and the TQ-segment. In the case of the porcine heart, where ischemic zones are transmural, the changes were relatively homogenous throughout the ventricular wall. Therefore, the gradient in extracellular potential during the ST- and the TQ-segment could be attributed to flow of injury current between the extra- and intracellular compartments of normal and ischemic tissue. The ischemic injury current was estimated to be of a strength which theoretically could exert a stimulatory effect [14]. Since a stimulatory effect of diastolic current flow can only occur at sites where current is flowing in an outward direction (from the intracellular to the extracellular compartment), a special arrhythmogenic role was attributed to injury current in the situation of electrical alterans [14].

The work on the cellular electrophysiological basis of ST-segment elevation and TQ-segment depression also revealed a further important alteration of electrical behavior associated with ischemia, namely the electrical uncoupling of cardiac cells [11]. In the work of Kjekshus et al., ST-segment elevation was postulated as a valid marker of myocardial ischemia only in the minutes immediately following coronary occlusion. Assessment of real ST-segment elevation and TQ-segment depression revealed that both became maximal after approximately 10–15 min of coronary occlusion and declined afterwards until they almost vanished in the center of the ischemic zone after 2 h of maintained coronary occlusion [11]. This general

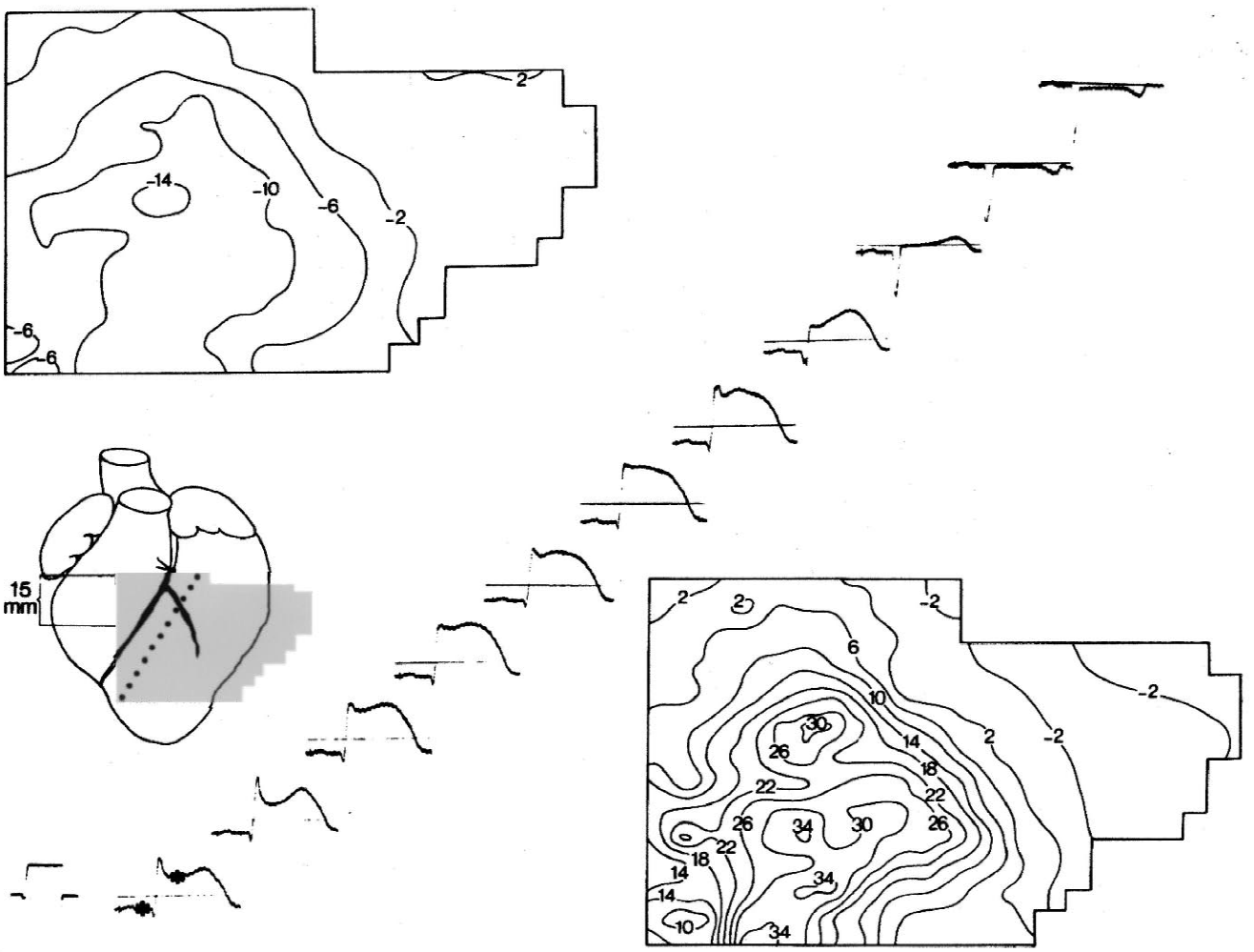

Fig. 3. Epicardial potential distribution in diastole (top) and systole (bottom) after 15–25 min of occlusion of the left anterior descending artery. Asterisks on the lowest electrogram indicate the moments during the cycle at which the potentials were measured. Signals were recorded from the shadowed area under the anterior aspect of the heart shown in the inset, at sites 3 mm apart. The extracellular complexes shown were recorded from sites along the line of steep potential gradients indicated. Square wave pulse indicates a 30 mV calibration. Isopotential lines in both maps represent 4 mV steps (modified from Ref. [11] with permission).

decrease of injury current was best explained by an increase of resistance within the current loop, the obvious candidates for this change being the gap junctions. Uncoupling in ischemia was also suggested by direct measurements of alterations in tissue resistance in whole hearts [15].

A closer definition of the two basic processes determining the electrocardiographic changes in ischemia: (1) the change in the transmembrane action potential; and (2) the change in electrical cell-to-cell coupling became possible with the development of more sophisticated techniques to determine changes in ion activity in the extra- and intracellular spaces and cell-to-cell resistance. In the work of Harris [16] it was demonstrated that ischemic cardiac tissue loses K ions from its intracellular space, a change which was associated with arrhythmogenesis. The introduction of ion-sensitive electrodes into whole hearts [17,18] made it possible to directly monitor extracellular $[H^+]$, $[K^+]$, and $[Na^+]$ in the ischemic region and to correlate these values with the changes in the transmembrane action potential. Very similar to ST-segment elevation, TQ-segment depression and the associated changes in transmembrane potential, $[K^+]$ increased rapidly in the ischemic zone towards a plateau level, and showed a secondary increase after 15–20 min. The change in resting potential followed the change in extracellular $[K^+]$ closely and estimates of the change in $[K^+]$ equilibrium potential suggested a total balance between the depolarized resting potential and the distribution of $[K^+]$ ions [19]. The mechanisms governing the change in resting potential and the cellular loss of potassium became a matter of a long lasting controversy among several groups partially offering divergent experimental findings and/or interpretations. The main issue was related to the fact that the changes in resting potential and the changes in extracellular $[K^+]$, $[K+]_o$, can be mutually interactive, i.e. an increase in $[K+]_o$ can explain the change in membrane potential, and inversely, the change in membrane potential can explain the loss of intracellular $[K^+]$. The observation that hypoxic and ischemic cells lose potassium [20] and that action potential shortening during hypoxia is largely due to opening of ATP-sensitive K^+ channels [21,22] was taken as argument favoring the opening of $[K^+]$ channels as the primary mechanism [23]. As a second hypothesis, it was argued that an increase of $[K^+]_o$ was simply reflecting an inhibition of energy-dependent K^+/Na^+ pumping. This hypothesis was at least partially corroborated by the fact that the K^+/Na^+ pump was shown in early ischemia to react to a Na^+ load [19,24] and that the methods to determine intracellular Na^+ in ischemia showed controversial results. A third hypothesis related the cellular K^+ loss to anaerobic glycolysis, intracellular and metabolic acidification. It was postulated that K^+ might redistribute consequent to an electrogenic anion movement (e.g. lactate), a theory that appears to explain the loss of K^+ from skeletal muscle during fatigue and strenuous, anaerobic exercise [19]. Further hypotheses included shifts of ion concentrations associated with osmotic swelling [25]. A major difficulty with the definition of the mechanism of cellular K^+ loss during ischemia relates to the fact that K^+ accumulates in the narrow intercellular clefts. Consequently, the large change in $[K^+]_o$ reflects a very minor imbalance of the unidirectional transmembrane fluxes [26]. In contrast to the mechanisms responsible for the shift in resting membrane potential, the changes in the transmembrane action potential seem to be relatively well understood. Thus, the positive shift in membrane potential and increased $[K^+]_o$ lead to a progressive inactivation of Na^+ channels with a decrease in upstroke velocity and amplitude of the action potential. Comparison of the different components of ischemia, acidification, elevated $[K^+]_o$ and hypoxia has shown that acidification and hypoxia each add to the effect of elevated $[K^+]_o$ to alter the action potential [27], whereby the ATP-sensitive K^+ current may play an additional role [28].

A striking feature of the electrical changes in myocardial ischemia is the dissociation between the very early changes in the transmembrane action potentials and the more delayed electrical cell-to-cell uncoupling. As aforementioned, it is only this dissociation which allows for the flow of injury current and the generation of the early ST-segment changes in the electrocardiogram to occur: the changes in transmembrane potential build up the driving force for injury current flow, the current flow itself requires low resistance pathways between the ischemic and non-ischemic region, i.e. intact cell-to-cell coupling. Cable analysis in a specially developed arterially-perfused rabbit papillary muscle has shown that electrical cell-to-cell uncoupling develops rapidly after about 12–15 min after coronary occlusion and is completed after about 30–40 min [29]. This rapid onset can be modified by preconditioning [30], acidification [31] and by measures affecting energy metabolism [32]. Its exact mechanism is not fully clarified, because a number of changes, all known per se to affect gap junction resistance in vivo, occur almost simultaneously with ischemic cell-to-cell uncoupling: acidification [33,34], increase in intracellular $[Ca^{++}]$, [33,34] and accumulation of lipid metabolites [35]. The observation that the increase in intracellular $[Ca^{++}]$ slightly precedes the onset of ischemic cell-to-cell uncoupling [36] has led to the hypothesis that $[Ca^{++}]$ would be the initiator of electrical uncoupling and that all other aforementioned changes occur as a consequence of the rapidly developing energy imbalance and the breakdown of ionic homeostasis. Several observations indicate that the decrease in the cytosolic thermodynamic driving force, the so-called free energy change of ATP-hydrolysis [37], leads to a depletion of $[Ca^{++}]$ from sarcoplasmic reticulum as the primary event of these afterwards self-perpetuating ionic and metabolic changes [38].

A further level of complexity describing the determinants of ischemic ST-elevation in the electrocardiogram,

relates to the observation that in whole heart, even in fully developed (no flow) ischemia, the electrical changes are heterogeneous. The distribution of the ST- and TQ segment isopotential lines in Fig. 3 shows: (1) a continuous decrease from the center of the ischemic zone towards the ischemic border; and (2) locally irregular isopotential lines indicating electrical heterogeneity [11]. These gradients were carefully studied and compared to changes in extracellular K^+ and H^+ in intact porcine hearts [39–41]. Interestingly, gradients were found to be present in fully ischemic tissue, i.e. in absence of local oxygen (Fig. 4). Since these gradients developed rapidly over several millimeters, diffusion of K^+ and H^+ from the ischemic to the non-ischemic myocardium could not fully account for the electrical heterogeneity. A further diffusible and volatile substance which may explain this heterogeneity over a relatively large scale is carbondioxide, which accumulates to >300 mmHg in the center of the ischemic zone. In an isolated ischemic rabbit papillary muscle, it was demonstrated that carbon dioxide accumulation and diffusion exerted a major effect on the cellular loss and the concomitant accumulation of extracellular K^+ and that diffusion of carbon dioxide may explain the centrifugal decrease in extracellular K^+ and H^+ in the ischemic region [42].

5. ST-segment elevation: a quantitative marker of regional ischemia?

The mechanisms underlying acute ST-segment changes in the electrocardiogram, as briefly discussed in the above sections, indicate a high level of complexity. Furthermore, there is a certain degree of uncertainty in the interpretation of experimental findings which is mainly related to methodological difficulties in assessing cellular and molecular mechanisms in whole heart tissue with occluded vessels. Albeit complex, the mechanisms described above were investigated in relatively simple and partially reductionistic experimental models. There are a variety of further variables which may be important to the explanation of ischemic ST-segment elevation. Firstly, clinical ischemia may often be related to a limited but not fully interrupted blood supply to the heart. The discrepancy between the sharply demarcated necrotic zone in porcine infarcts and the presence of electrically conducting tissue in human infarcts suggests that the flow pattern in human infarct zones might be complex. Low flow ischemia cannot be considered as pathophysiologically equivalent to total, no-flow ischemia. For example, important ionic changes such as extracellular potassium accumulation are only observed at coronary flow <30% of normal [43]. Furthermore,

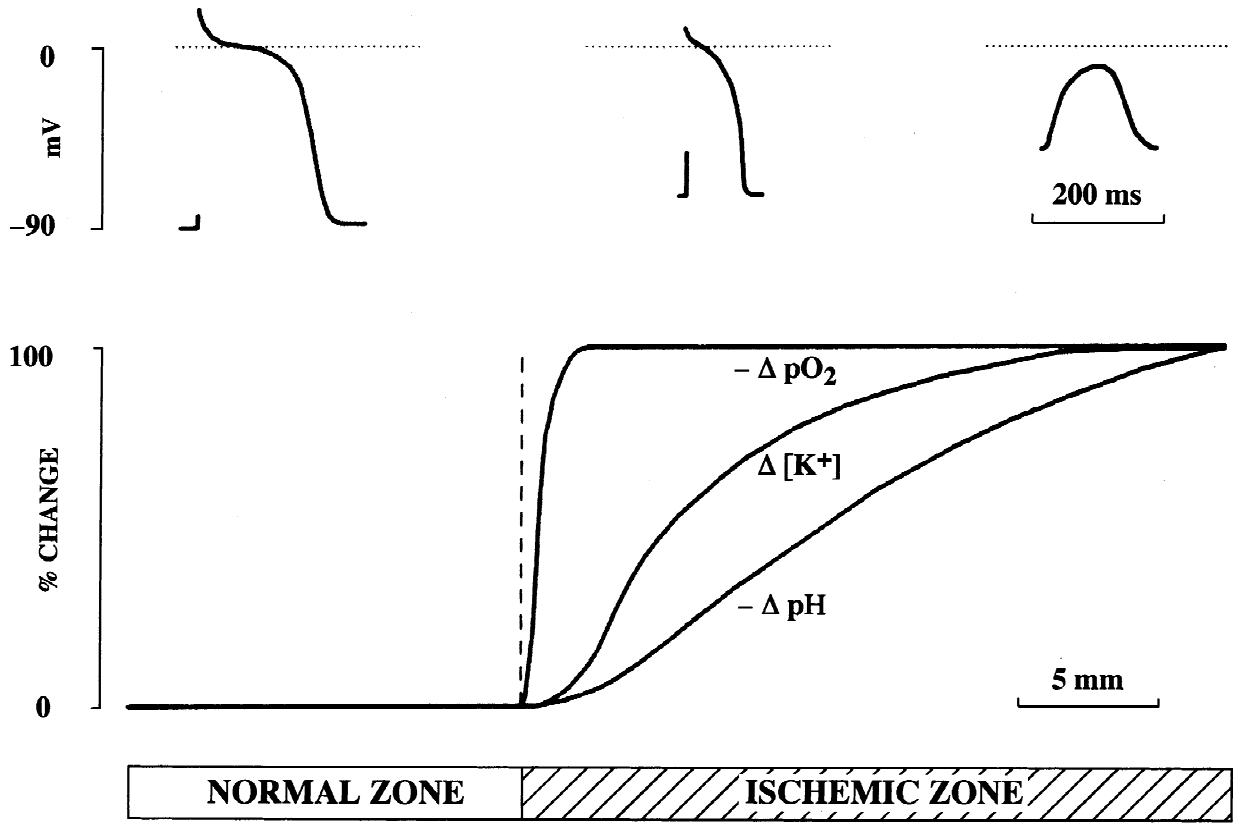

Fig. 4. Lower panel: Diagrammatic representation of the changes in $[K^+]_o$, pH and PO_2 in the ischermic zone from the center to the border. Upper panel: Schematic depiction of action potentials typical for the various ischemic zones shown on lower panel. Reproduced from Ref. [39] with permission.

anoxic perfusion is associated with a considerably larger cellular K^+ loss than no flow ischemia [44]. Thus, relatively small changes in flow reduction are likely to have an impact on the ionic and the associated electrical changes. Secondly, clinical ST-segment elevation after myocardial infarction often persists after the acute phase of ischemia, especially in the case of ventricular aneurysm. Persistent ischemic damage in the border zone of myocardial infarction, combined with a low electrical impedance of scar tissue in the center of the infarction may partially explain this phenomenon [45,46]. As a third factor affecting ST-segment elevation, the influence of the autonomous nervous system should be mentioned. Increased sympathetic tone affects the amount of ST-segment elevation observed early in ischemia [47], and metabolism-related depletion of noradrenaline stores in ischemic myocardium importantly contributes to the electrophysiologic changes observed after coronary occlusion [48,49]. In summary, the work by Kjekshus et al. has demonstrated an important relationship between ST-segment elevation in acute myocardial ischemia and the extent of later necrosis and coronary flow reduction. However, ST-segment elevation as a quantitative marker of acute ischemia should be used with caution, because of the multiple variables contributing to this electrocardiographic change.

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