Physiological and Pathological Remodeling in Acute Inferior Wall Myocardial Infarction

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ABSTRACT: In acute myocardial ischemic syndrome the electrocardiogram is capable of providing sophisticated information on coronary artery anatomy (the culprit artery, the level of obstruction, the arterial dimension), along with the hemodynamics, molecular biological characteristics and ionic changes that occur in the involved and uninvolved ischemic musculature. In acute myocardial ischemia, during a sudden obstruction of a distal co-dominant right coronary artery the ECG may be able to discriminate between physiological and pathological remodeling, providing predictive information to differentiate low from high risk cases during acute inferior wall infarction.

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KEY WORDS: physiological and pathological cardiac remodeling, acute inferior myocardial infarction (AIMI), sudden obstruction of right coronary artery

The concept of cardiac remodeling, proposed by molecular biologists and electrophysiologists, was initially applied to experimental myocardial infarction by analyzing the structural and metabolic changes that occur in the uninvolved myocardium [1]. Recently, this concept was extended to include hypertrophic remodeling that occurs in response to both functional (altered electrical activation) and morphological stressors. These changes incorporate alterations in electrophysiology along with structural myocardial changes including fibrosis, connexin 43 down-regulation [2], and ionic remodeling. This electrical remodeling is represented by asymptomatic changes in T wave polarity referred to as "T wave" or "cardiac" memory [3]. It is this author's contention that the electrocardiogram provides important information on the coronary anatomy and the hemodynamic, molecular and ionic changes resulting from acute ischemic syndromes [4,5].

My principal aim is to introduce the concept of electrocardiographic remodeling, whereby the ECG reflects the structural, hemodynamic and electrophysiological changes that occur in the uninvolved cardiac muscle. Furthermore, analysis of the ECG should permit differentiation between "physiological" and "pathological" remodeling resulting from sudden obstruction of a coronary artery. I propose that physiological ECG remodeling is indicative of a single isolated obstructed artery with functionally normal uninvolved muscle and that pathological remodeling occurs when one coronary artery is suddenly totally obstructed against a background of preexisting chronic myocardial ischemia but is exacerbated by an acute ischemic event [6,7] of the uninvolved muscle. The former state of physiological remodeling may occur in healthy non-involved myocardium as a reaction to the hemodynamic and metabolic changes that occur with regional ischemic injury. Similar changes occur in the normal heart of a newborn or in the physiological hypertrophy seen in athletes [8,9].

With this approach, physiological and pathological ECG remodeling can occur after sudden obstruction of a distal artery (up to the first marginal) where the right coronary artery is co-dominant (namely, where the RCA and the circumflex artery supply the posterior wall of the left ventricle). For this purpose basic ECG rules need to be established. The first rule states that maximal ST segment elevation and the highest T waves are seen in LIII. The opposite remodeling area is evident in AVL which shows the deepest ST segment and an inverted T wave that is less deep than that of L1 [10]. The second rule states that the ST segment elevation and positive T wave in LII represent the electrical potentials of the posterior wall and is "remodulated" almost always in V2 (the upper septal region), as the ST segment may also be accompanied in some cases by V3 (mid-septal), V4 (lower-septal) and V5 (apical) leads [Figure 1]. ST segment depression with inverted T waves represents the remodeling pattern in the right posterior septum, an area always involved in sudden obstruction of the RCA [11,12]. The ST segment depression and inverted T waves in V1 (the anterior septal potential) indicate that the obstruction is distal to the first right marginal artery [13]. ST segment elevation with positive T waves in LII may also indicate that the RCA is co-dominant, where maximal ST depression with an inverted T wave isolated to V2 is consistent with an electrophysiological remodeling. This pattern can be seen in the other precordial leads [Figure 1].

In acute inferior wall infarction, a small Q wave appears in LII, LIII and AVF. This finding is not indicative of necrosis but is caused by the down-regulation of connexin 43 in the

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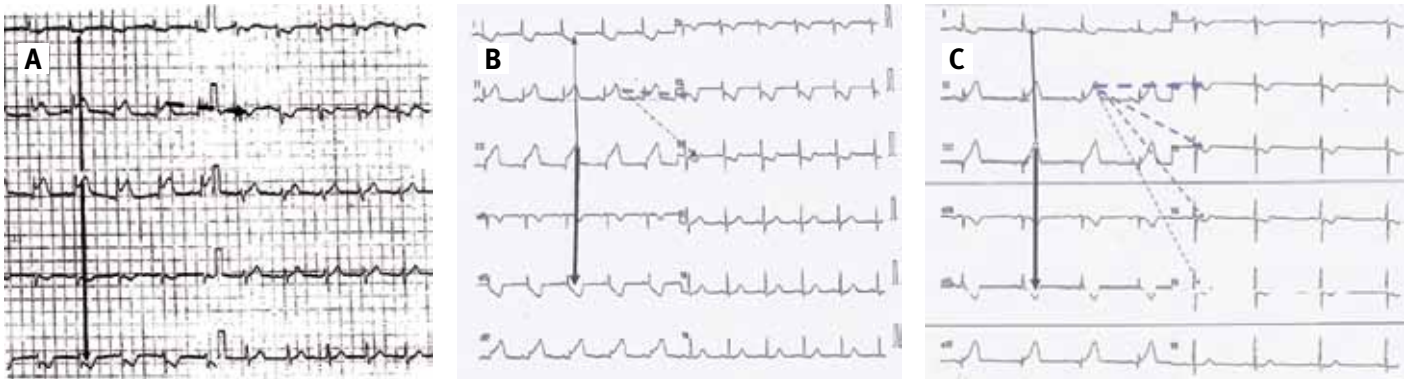
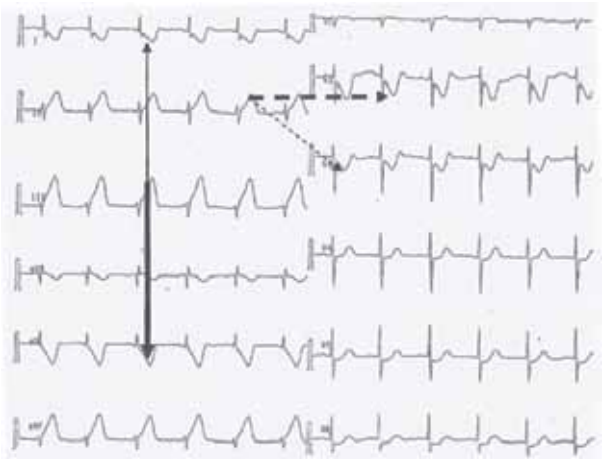
Figure 1. Electrocardiograms of physiological remodeling in acute inferior wall infarction. **[A]** The normal arrow shows the maximal ST segment elevation with the tallest T waves in LIII and the deepest ST segment depression in AVL. This repolarization pattern is shifted to the right and is a unique expression of sudden obstruction of the RCA. ST depression and an inverted T wave are evident in V1, representing a "physiological" remodeling from the ischemic posterior right septum and indicating that the obstruction is distal to the first right marginal artery. The broken arrows indicate that V2 is remodeled from LII which expresses the electrical potential of the posterior cardiac wall. **[B]** The normal arrow shows the typical pattern of a sudden obstruction of the RCA. The changes in V1 are indicative of a distal obstruction. The broken arrows show that V2 and V3 are remodeled from LII. **[C]** The normal arrows show that the ST segment and the T waves are shifted to the right. The broken arrows indicate that V2–V5 are remodeled to LII. Note that the ST depression decreases progressively from V2 through the leads



ischemic posterior papillary muscle, such that the anterior papillary muscle is depolarized earlier [14]. This electrical phenomenon results in a shift of the first vector upwards and to the left, represented in the ECG as small Q waves in the inferior leads. A patient with previous left axis deviation shows no initial Q waves in the inferior leads because the repolarization of both papillary muscles is delayed [Figure 2].

Figure 2. Lack of Q/r acute inferior wall infarction due a sudden obstruction of a co-dominant RCA of a previous ECG with left anterior hemiblock. The ECG shows that the frontal axis is shifted to the left. This axis suggests that the posterior papillary muscle is depolarized earlier than the anterior one (see initial R waves shifted to the right and down in DII, DIII, AVF). The obstructed artery is a co-dominant RCA because the higher ST segment and T waves are in DIII. The lack of the initial Q/R in this ECG suggests that the posterior papillary muscle is depolarized earlier than the anterior one, despite the down-regulation of connexin 43 in this acute ischemia area. The ST depression and inverted T waves in V2 and V3 follow the rule of physiological remodeling of the ischemic posterior wall expressed in DII



MOLECULAR AND ELECTROPHYSIOLOGICAL BIOLOGY OF THE ISCHEMIC AREA

The high peaked T waves in LII, LIII and AVF indicate that the epicardium is well protected from the ischemic insult. It was previously shown by Lucas and Antelevitch [15] that at rest the epicardial action potential is shorter than the endocardial AP. This electrophysiological phenomenon results in positive T waves in the precordial leads. During acute myocardial ischemia, the epicardial AP becomes even shorter, such that tall peaked T waves are seen in the ischemic region as there is no change in the endocardial AP. Since administration of a potassium blocker (4-aminopyridin) does not result in any change in AP during ischemia, this implies an important role for potassium in shortening the epicardial AP. This role for potassium manifests during oxygen, sugar and fatty acid deprivation, causing ATP to lose phosphorus atoms and stimulating ATP-dependent receptors during ischemia [16]. These receptors have an extremely low basal physiological activity [17], which is enhanced by increased availability of adenosine during acute ischemia. This effect is exacerbated by a reduction in calcium concentration inside the cell during the acute ischemic event, weakening contraction of the sarcomere and thereby reducing oxygen demand [18,19]. Although this is the molecular basis of the tall peaked T waves registered by the electrodes over the ischemic area, these higher T waves convey protection to the

ischemic epicardium. This molecular-electrical phenomenon (a complex adenosine K^+ adenotriphosphate-dependent channel action potential) also results in hyperpolarization of the muscularis media of the microcirculation, inducing local vasodilatation in the epicardial ischemic layer and shifting blood flow from the healthy surrounding myocardium to the ischemic area. This provides additional epicardial ischemic protection [20].

MOLECULAR AND ELECTROPHYSIOLOGICAL BASIS OF ST SEGMENT ELEVATION

The ST segment of the electrocardiogram expresses phase II of the AP. During an acute ischemic event, due to a sudden obstruction of an epicardial artery, calcium enters the sarcolemma along with hydrogen [21]. This phenomenon reduces the intracellular pH and creates an injury vector from the healthy towards the ischemic muscle as expressed by ST elevation. It is likely that these metabolic changes create a significant calcium gradient between healthy and ischemic myocardium that influences the ST segment [22,23].

ELECTROPHYSIOLOGICAL REMODELING IN THE PRECORDIAL LEADS OF THE ECG

The endocardium of the anterior wall reacts to the high intracavitary pressure created by inferior wall infarction. This mechanical pressure activates two well-described tension receptors including potassium-dependent receptors encoded in TREK and a second non-specific receptor [24], reducing the endocardial phase II of the AP. This effectively circumvents hypercontractility of the endocardial layer, resulting in significant endocardial protection [15,16,19]. This electrophysiological phenomenon creates an injury vector from the epicardium to the endocardium, which is expressed by ST depression in the precordial leads. Similarly, the amplitude of the sub-endocardial AP is reduced by stimulating the potassium-dependent tension receptors. The high concentration of potassium induces a shortening of the AP [15,24], resulting in a tall peaked endocardial T wave that appears as a deep inverted T wave in the precordial leads. This phenomenon is referred to as mechanical-electrical feedback.

CRITICAL CHRONIC OBSTRUCTION OF THE LAD ARTERY IN AMII

In 1988 our group described the ECG pattern of ST segment depression as tall peaked positive T waves due to a sudden subtotal obstruction of the left anterior descending artery [25]. Since physiological remodeling is characterized by ST segment depression with an inverted T wave, acute inferior myocardial infarction with precordial ST depression and a positive T wave in the precordial leads would suggest a concomitant critical obstruction of the LAD [Figure 3A]. The molecular cause of the positive T wave is identical to that involved in the biology of epicardial ischemia.

AIMI WITH SEVERE THREE-VESSEL DISEASE OR LEFT MAIN CORONARY ARTERY OBSTRUCTION

We previously described the ECG characteristics of acute circumferential sub-endocardial ischemia represented by a distal obstruction. The finding of maximal ST depression and the deepest T waves in V4 and V5 suggest acute circumferential sub-endocardial ischemia, due to either triple-vessel disease or critical chronic obstruction of the left main coronary artery. Note the differences between the patterns in Figures 1C and 3B. In the first case (Figure 1C) the ST segment and the inverted T waves progressively decrease across the chest leads, whereas in the second case (Figure 3B) there is a progressive increase in ST depression and inverted T waves. This latter pattern represents the most severe emergency case of acute inferior wall infarction [20]

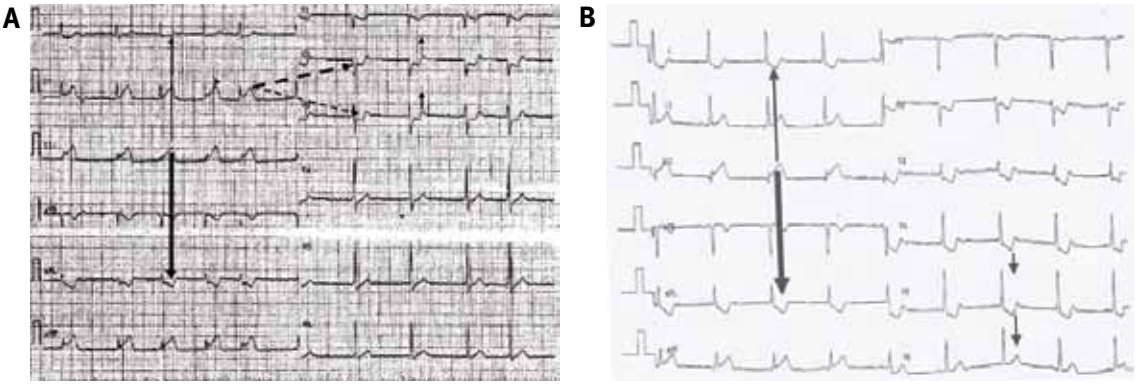


Figure 3. ECGs of pathological remodeling in acute inferior wall infarction. **[A]** Typical pattern in the limb leads from sudden obstruction of the RCA. Changes in V1 indicate that the obstruction is distal to the first marginal arterial branch. V2 and V3 show similar ST depression to that noted in Figure 1B; however, the peak of the T waves is positive, indicating that the anterior cardiac wall has regional sub-endocardial ischemia, most likely due to a critical chronic LAD obstruction. The small arrows show the direction of the T waves. **[B]** The normal arrows indicate the typical pattern of a sudden obstruction of the RCA. The changes in V1 indicate

maximal ST segment depression with inverted T waves in V4 and V5 and a pulse rate of < 90 beats per minute. These effects are either due to sudden obstruction of the left main coronary artery or they may occur with severe triple-vessel coronary artery disease. In this respect, it is important to differentiate ST depression with an inverted T wave maximally detected in V2 and V3 as part of physiological remodeling (as described) from similar changes maximally detected in V4 and V5, which are indicative of pathological remodeling in the presence of chronic myocardial ischemia. As a result, those patients presenting with sudden obstruction of a distal RCA and maximal ST depression with inverted T waves in V4 and V5 without sinus tachycardia are at very high risk [12].

SUMMARY

The ECG provides highly sophisticated data during sudden obstruction of a distal co-dominant RCA in AIMI. It may well be that the ECG is a unique non-invasive method for differentiating between physiological and pathological remodeling (as described). These remodeling concepts were proposed by the molecular and electrophysiological experimental cardiac laboratories; I suggest that the ECG has the capacity to translate this cellular information in ischemic syndromes into clinical practice.

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"Too many pieces of music finish too long after the end"

Igor Stravinsky (1882-1971), Russian, and later French and American composer, pianist and conductor. A musical revolutionary who pushed the boundaries of musical design, Stravinsky's compositional career was notable for its stylistic diversity. He first achieved international fame with three ballets commissioned by the impresario Sergei Diaghilev and first performed in Paris by Diaghilev's Ballets Russes: *The Firebird* (1910), *Petrushka* (1911) and *The Rite of Spring* (1913)

"Courage is what it takes to stand up and speak; courage is also what it takes to sit down and listen"

Winston Churchill (1874-1965), British politician, best known for his leadership of the Britain during the Second World War