Intramyocardial Conduction: A Major Determinant of R-wave Amplitude During Acute Myocardial Ischemia

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SUMMARY The relationship of changes in ventricular activation patterns and variations in R-wave amplitude on the surface ECG during the hyperacute phase of myocardial ischemia were studied in nine open-chest dogs. The sum of R-wave amplitude (ΣRWA) changes in surface ECG leads L₅, V₃, and Frank orthogonal leads X, Y and Z were correlated with changes in the conduction time along the specialized conduction system and in intramyocardial conduction times, as well as with hemodynamic and echocardiographically determined left ventricular dimensional changes. The hyperacute phase of myocardial ischemia induced by a one-stage occlusion of the left circumflex coronary artery was marked by a progressive increase in left ventricular end-diastolic diameter and left ventricular end-diastolic pressure as well as a progressive decrease in cardiac output. At the same time, ΣRWA and intramyocardial conduction time followed a synchronous biphasic pattern. In the first 30 seconds after coronary artery ligation, intramyocardial conduction time in the ischemic zone accelerated to a peak of 11.3% above control (p < 0.001). This acceleration of conduction was followed closely by a decrease in ΣRWA to 16.8% below control (p < 0.001). A second phase ensued, characterized by a gradual slowing of intramyocardial conduction time in the ischemic zone to 135.1% above control (p < 0.001) and a synchronous increase in ΣRWA to 53.1% above control (p < 0.001). Conduction time along the specialized conduction system did not change significantly.

Thus, the asynchrony of ischemic ΣRWA alterations with hemodynamic and left ventricular dimensional changes and the similarity of the biphasic responses of ΣRWA to the changes in intramyocardial conduction time in the ischemic area suggest that ventricular activation patterns rather than hemodynamic and intracardiac dimensional changes may play the major role in determining R-wave amplitude responses to acute myocardial ischemia.

INCREASED R-wave amplitude on the surface ECG at peak exercise has been observed frequently in patients with coronary artery disease.¹⁻⁴ Bonoris et al.¹ claimed this sign to be a sensitive and specific marker for the diagnosis of coronary artery disease. Increases in R-wave amplitude may also indicate the extent of ischemia-induced left ventricular dysfunction.²⁻⁴ This suggestion is based on the assumption that R-wave amplitude changes are related, by the Brody effect,⁵ to an increase in left ventricular volume resulting from acute ischemia. However, studies in humans have not consistently corroborated these findings.⁶⁻⁸

We designed a series of experiments using a canine model of acute myocardial ischemia to identify factors that contribute to ischemic R-wave amplitude alterations. In our initial studies we showed that ischemic R-wave amplitude changes could not be explained merely by intracardiac volume changes.⁹ ¹⁰ Other investigators have shown that ventricular activation patterns influence the R-wave amplitude response to volume changes in the normal heart.¹¹⁻¹⁸ The purpose of the present study was to elucidate the role of intramyocardial conduction pattern changes in determining R-wave amplitude variations during acute myocardial ischemia.

Materials and Methods

Nine healthy adult mongrel dogs, mean weight 17.3 kg (range 11.7–19.4 kg), were anesthetized with i.v. pentobarbital, 30 mg/kg. A midsternotomy was performed and dogs were ventilated with room air by means of a Harvard respirator at a rate of 15 breaths/min. Body temperature was maintained at 37°C throughout each experiment by means of a thermal mattress. The left circumflex coronary artery was isolated approximately 1 cm beyond the bifurcation of the left main coronary artery and proximal to all marginal branches. A 3–0 silk ligature was placed around the artery for subsequent snare occlusion. Left ventricular pressure was measured using a microtip catheter (Millar PC370). Cardiac output was measured by thermodilution using a cardiac output computer (Edwards 9510A) and a triple-lumen Swan-Ganz catheter, with its tip positioned in the pulmonary artery and the injecting lumen in the right atrium. Control cardiac output values were determined by averaging a minimum of three consecutive measurements. Cardiac output was measured at 60-second intervals during the control, ligation and postreper-
fusion periods. Left ventricular dimensions were determined by M-mode and two-dimensional echocardiography in all dogs using a mechanical sector scanner with three rotary elements and a 3.5-MHz transducer (ATL Mark III). During two-dimensional echocardiography the ultrasonographic beam was swept mechanically through an arc of 90°. The transducer was mounted on a rigid bar connected to the operating table and placed in direct contact with the exposed anterior right ventricle as described by Kerber et al. The heart was imaged in the left ventricular long-axis view by directing the echo beam plane between the apex and the base of the heart, and in the short-axis view by directing the echo beam perpendicular to the long axis at the level of the mitral valve. The images were recorded on a Sanyo VTC 7100 videotape recorder and stored on 1/2-inch videotape for subsequent review in real-time, slow-motion or stop-frame format. Left ventricular end-diastolic diameter was measured from the endocardial layer of the septum to the posterior wall at a point synchronous with the peak of the QRS complex on a simultaneously recorded monitor lead. A light-pen microprocessor computer system (Varian Associates) was used to measure changes in ventricular dimensions.

Five surface electrocardiographic leads (L2, V3 and modified Frank orthogonal leads X, Y and Z) were monitored and recorded continuously throughout the experiment. The leads were carefully placed and the dog was restrained in a fixed position to ensure standardized ECG recordings. The ECG leads were placed before the chest was opened. ECG recordings before and after sternotomy did not show significant differences. The surface ECG was recorded at a frequency response of 0.1–200 Hz. R-wave amplitude was measured from the baseline determined by the TP segment (zero level reference) to the peak of the R deflection. This measurement was repeated at 10-second intervals during the control, ligation and reperfusion periods. Each determination represented a mean of 10 consecutive QRS complexes. The sum of R-wave amplitudes (ΣRWA) in all recorded leads at each 10-second interval was then calculated. Further, the spatial vector length was calculated from the R-wave amplitude in leads X, Y and Z according to the formula SVL = √x² + y² + z². Measurements of R-wave amplitudes were scattered throughout the respiratory cycle to negate any respiratory effect on R-wave amplitude.

Two pairs of Teflon-coated, silver-wire bipolar plunge electrodes (36 gauge) insulated except at the tips were placed in the subendocardial and subepicardial layers of both the ischemic and nonischemic normal zones. Electrograms were recorded throughout the experiment with a frequency range of 50–1000 Hz. Endo-epicardial “intramyocardial” conduction time in the ischemic zone was measured from the initial sharp deflection of the ischemic zone endocardial electrogram to the end of the latest sharp deflection of the overlying ischemic zone epicardium (fig. 1). Measurements of intramyocardial conduction in the normal zone were made similarly using endocardial and overlying epicardial normal zone electrograms.

![Figure 1](http://circ.ahajournals.org/) The changes in time of intramyocardial conduction (IMC) as measured from the beginning of the endocardial activation (ENDO) to the end of epicardial activation (EPI) in a representative experiment. As early as 15 seconds after coronary artery ligation (CAL), there is a notable acceleration in IMC followed by a gradual slowing, reaching a plateau of 165 msec 300 seconds after CAL. Immediately after reperfusion (REP), IMC returns toward control levels.
In addition, a multipolar electrode catheter (Elecath 23-7366) was introduced through the right carotid artery and advanced to the noncoronary sinus of Valsalva to record His bundle potentials. Conduction along the specialized conduction system was measured from the initial His potential deflection to the earliest major sharp deflection of the endocardial potential in the normal and ischemic zones. Measurements were continuously recorded on a Hewlett-Packard 4578 photographic recorder throughout the experiment and simultaneously recorded on a Hewlett-Packard eight-channel FM tape recorder (model 3968A instrumentation recorder) for later analysis.

Experimental Protocol

Acute myocardial ischemia was induced by a one-stage complete occlusion of the left circumflex coronary artery for 5 minutes using a ligature snare. The 5-minute ligation time was chosen to avoid the first phase of malignant ventricular arrhythmias, which have a peak incidence at about 7 minutes. Ligation was followed by abrupt reperfusion and a 30-minute recovery period during which all variables were monitored. Five other dogs that developed severe ventricular arrhythmias during ligation or reperfusion were excluded from this study.

Statistical Analysis

The data were analyzed at baseline and at 10-second intervals during coronary artery ligation and during the first minute after reperfusion. Proportional changes from control were analyzed. Therefore, to determine significant changes from control over time, the data were transformed by taking natural logarithms, which facilitated the use of standard statistical methods. We assumed an approximately normal distribution for each transformed variable. This was verified by construction of probability plots. For each variable, the statistical significance of changes between baseline and each of the subsequent times was tested using paired t tests. For each change, the sample mean difference on the logarithmic scale and the 95% confidence interval (derived from the t test) for this difference were calculated from the transformed data. A maximal likelihood estimate (i.e., point estimate) and 95% confidence intervals for the proportional change were obtained by taking the appropriate function (fc) of the corresponding quantities (x) calculated from the transformed data (fcx = e^x - 1). Data are therefore expressed as point estimates plus 95% confidence intervals rather than as mean ± SD.

Results

Coronary Artery Ligation

Left ventricular end-diastolic cross-sectional dimensions progressively increased to reach a peak and plateau of 32.6% above control (p < 0.001) 150–180 seconds after coronary ligation (table 1) (figs. 2 and 3). Left ventricular end-diastolic pressure increased to reach a peak and plateau of 672.9% above control (p < 0.001) 150–180 seconds after ligation (table 1). Cardiac output declined steadily during ligation, reaching a nadir of 24.0% below control (p < 0.001) 180 seconds after ligation (table 1). The sum of the R-wave amplitudes (ΣRWA) on surface electrocardiographic leads L₃, V₅, X, Y and Z showed a biphasic pattern during the first 150 seconds after coronary artery ligation (figs. 2 and 3). As early as 10 seconds after coronary ligation, ΣRWA decreased 10.1% from the control value (p < 0.01). This decrease in ΣRWA was most marked 30 seconds after ligation (16.8%, p < 0.001) (fig. 2, table 1). Thereafter, ΣRWA increased continuously and returned to preligation amplitudes by approximately 80 seconds after ligation, and reached a peak of 52.6% above control (p < 0.001) 180 seconds after ligation and did not change significantly during the rest of the 5-minute ligation period (table 1). The calculated spatial vector length (SVL) showed similar results (table 1).

Intramyocardial conduction time in the ischemic zone after ligation showed a distinct biphasic pattern with a time course similar to that for changes in ΣRWA (table 1, figs. 1 and 3). By 15 seconds after ligation, endo-epicardial conduction time was shortened from a mean preligation control value of

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**Figure 2.** The time course of changes in the mean sum of R-wave amplitude (ΣRWA) and its relation to mean changes in echocardiographically determined left ventricular end-diastolic diameter (LVEDD) in nine dogs are shown. In the initial phase after coronary artery ligation (CAL), LVEDD shows a progressive monophasic increase, whereas ΣRWA shows a biphasic response. Conduction initially accelerates and only after 30–40 seconds begins to slow, reaching maximal slowing approximately 20 seconds after peak LVEDD. After reperfusion (REP), ΣRWA returns rapidly to control levels, whereas LVEDD shows a protracted course of normalization.
TABLE 1. Time Course of Electrical and Mechanical Events During Acute Short Coronary Occlusion and Reperfusion

<table>
<thead>
<tr>
<th>CAL time (sec)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΣRWA</td>
<td>-10.1†</td>
<td>-15.3†</td>
<td>-16.8*</td>
<td>-13.4†</td>
<td>-8.8†</td>
</tr>
<tr>
<td></td>
<td>(-13.8 to -6.3)</td>
<td>(-20.4 to -9.8)</td>
<td>(-20.8 to -10.6)</td>
<td>(-18.7 to -7.8)</td>
<td>(-14.9 to -2.4)</td>
</tr>
<tr>
<td>SVL</td>
<td>-10.5†</td>
<td>-15.6†</td>
<td>-16.8*</td>
<td>-14.9†</td>
<td>-10.8†</td>
</tr>
<tr>
<td></td>
<td>(15.8 to -4.8)</td>
<td>(-23.3 to -7.2)</td>
<td>(-24.0 to -8.8)</td>
<td>(-21.8 to -7.3)</td>
<td>(-18.4 to -2.5)</td>
</tr>
<tr>
<td>TMCz</td>
<td>-9.8</td>
<td>-11.3*</td>
<td>-7.9</td>
<td>3.4</td>
<td>9.5*</td>
</tr>
<tr>
<td></td>
<td>(-12.4 to -5.7)</td>
<td>(-14.5 to -7.2)</td>
<td>(-10.8 to -2.3)</td>
<td>(-5.7 to 0.4)</td>
<td>(4.3 to 14.2)</td>
</tr>
<tr>
<td>LVEDP</td>
<td>11.5*</td>
<td>24.4*</td>
<td>24.4*</td>
<td>78.1*</td>
<td>215.1*</td>
</tr>
<tr>
<td></td>
<td>(-7.2 to 34.0)</td>
<td>(-0.9 to 56.1)</td>
<td>(-0.9 to 56.1)</td>
<td>(26.1 to 151.5)</td>
<td>(119.0 to 353.3)</td>
</tr>
<tr>
<td>LVEDD</td>
<td>11.1*</td>
<td>18.2*</td>
<td>22.4*</td>
<td>24.6*</td>
<td>27.6*</td>
</tr>
<tr>
<td></td>
<td>(8.7 to 13.4)</td>
<td>(14.7 to 21.9)</td>
<td>(18.0 to 26.9)</td>
<td>(19.4 to 30.0)</td>
<td>(22.6 to 32.7)</td>
</tr>
<tr>
<td>CO</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Results are expressed as percentage change from control along with the 95% confidence interval.

*p < 0.001.
†p < 0.01.

Abbreviations: CAL = coronary artery ligation; CO = cardiac output; LVEDD = left ventricular end-diastolic diameter; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; REP = reperfusion; ΣRWA = sum of R-wave amplitude of all five ECG leads; TMCz = transmyocardial conduction time in the ischemic zone; SVL = spatial vector length.

60.6 msec to a nadir of 52.5 msec (-13.4%, p < 0.001). By 30 seconds after ligation, conduction time was prolonged to 56.2 msec (-7.9%, p < 0.01 from control) and by 45 seconds returned toward the baseline value of 59.3 msec (NS). Thereafter, conduction time continued to prolong gradually, reaching a peak of 116.5 msec (135.1%, p < 0.001) 180 seconds after ligation (table 1, figs. 1 and 3). Mean intramyocardial

**Figure 3.** The time course of the percent change from control in the mean sum of R-wave amplitude variations (ΣRWA) and in mean intramyocardial conduction time (IMC) during acute myocardial ischemia in nine dogs. Note the synchronous biphasic pattern in both variables after coronary artery ligation (CAL). The initial acceleration in IMC is followed by a decrease in ΣRWA, whereas the later slowing of conduction is followed by an increase in ΣRWA. Both IMC and ΣRWA return almost synchronously to approximately control levels immediately after reperfusion (REP).
TABLE 1. (Continued)

<table>
<thead>
<tr>
<th></th>
<th>CAL time (sec)</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>300</th>
</tr>
</thead>
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<tr>
<td>ΣRWA</td>
<td></td>
<td>-5.5</td>
<td>-12.3 to 1.9</td>
<td>-0.5 to 20.9</td>
<td>32†</td>
<td>-14.8 to 1.5</td>
<td>-18.0 to 1.5</td>
</tr>
<tr>
<td>SVL</td>
<td></td>
<td>-7.0</td>
<td>-14.8 to 1.5</td>
<td>-14.8 to 1.5</td>
<td>31.9*</td>
<td>-14.8 to 1.5</td>
<td>-14.8 to 1.5</td>
</tr>
<tr>
<td>TMCa</td>
<td></td>
<td>17.4*</td>
<td>13.1 to 20.3</td>
<td>13.1 to 20.3</td>
<td>69.1*</td>
<td>13.1 to 20.3</td>
<td>13.1 to 20.3</td>
</tr>
<tr>
<td>LVEDP</td>
<td></td>
<td>343.6*</td>
<td>185.5 to 589.3</td>
<td>185.5 to 589.3</td>
<td>641.4*</td>
<td>185.5 to 589.3</td>
<td>185.5 to 589.3</td>
</tr>
<tr>
<td>LVEDD</td>
<td></td>
<td>27.9*</td>
<td>311.2 to 821.5</td>
<td>311.2 to 821.5</td>
<td>32.6*</td>
<td>311.2 to 821.5</td>
<td>311.2 to 821.5</td>
</tr>
<tr>
<td>CO</td>
<td></td>
<td>-20.2*</td>
<td>22.8 to 33.3</td>
<td>22.8 to 33.3</td>
<td>32.6*</td>
<td>22.8 to 33.3</td>
<td>22.8 to 33.3</td>
</tr>
</tbody>
</table>

Conduction time in the nonischemic myocardium during the control period was 61.3 ± 5 msec. This value did not show any significant change from control throughout the coronary occlusion and reperfusion period.

The mean conduction time along the specialized conduction system during the control period was 23 ± 5 msec and was similar for both normal and ischemic zones before coronary artery ligation. This value did not vary significantly from control for either normal or ischemic zone throughout the coronary ligation and reperfusion periods.

Reperfusion

After coronary artery reperfusion, an immediate reduction in ΣRWA was observed consistently (table 1, figs. 2 and 3). The ΣRWA returned to 9.6% (p < 0.01) above predilation values as early as 20 seconds after reperfusion. The endo-epicardial conduction time in the ischemic zone also decreased with the same rapid time course of recovery (table 1, figs. 1 and 3). In contrast to the rapid normalization of ΣRWA and intramyocardial conduction times, hemodynamic variables and left ventricular dimensional changes returned more slowly toward predilation values over a 5-minute period.

Discussion

The results of this study confirm the discordance between R-wave amplitude variations and intracardiac volume changes during the acute phase of myocardial ischemia reported previously.8,9 A progressive monophasic increase in left ventricular end-diastolic dimensions and a decrease in hemodynamic variables during acute myocardial ischemia are accompanied by a distinctive biphasic alteration in R-wave amplitude. The 2RWA decreased immediately and reached a nadir 30 seconds after coronary artery ligation (table 1, figs. 2 and 3). Subsequently, ΣRWA increased significantly, peaking 20–30 seconds after the maximal increase in left ventricular dimensions. These findings and our previous work8,9 challenge the hypothesis that the Brody effect is the major determinant of R-wave amplitude changes during acute myocardial ischemia. Therefore, other factors, including changes in myocardial conduction patterns, may have a role.

The possible effect of ventricular activation patterns on the QRS response to volume changes in the normal heart has been noted in various species. Changes in conduction patterns along the specialized conduction system have been found to have an effect on the R-wave response to volume changes. Manoach et al.11 showed that volume depletion in poikilotherm animals (turtles and frogs), which do not have a specialized conduction system, resulted in an increase in R-wave amplitude, whereas in homeotherm animals, which have a specialized conduction system, volume depletion resulted in a decrease in R-wave amplitude. The latter, but not the former, was consistent with the Brody effect.9 In related studies using chick embryos, Manoach et al.15, 14 pointed out that the time of development of the specialized conduction system marked the transition point from a discordant to a concordant response of R-wave amplitude to volume changes.

Intramyocardial conduction abnormalities in the setting of acute myocardial ischemia are relatively common. Studying the surface ECG phenomenon of perinfarction block, Conrad et al.15, 18 showed that a delay in the conduction time between the endocardium and epicardium within the ischemic zone occurred 2–3 minutes after coronary ligation, but did not notice the initial acceleration in conduction occurring in the first 30 seconds after coronary ligation. These intramyocardial impulse conduction abnormalities were considered to be related to the increase in unipolar epicardial potential in the ischemic zone 2–3 minutes after coronary artery ligation. Other investigators in subsequent studies demonstrated a biphasic transmyocardial conduction pattern in the very early phases of acute myocardial ischemia.14, 16 During the first minute after coronary ligation, conduction accelerated, followed by a prolonged slowing of conduction.

Recent experimental data suggest a pathophysiologic mechanism for biphasic changes in intramyocardial conduction velocity. This biphasic conduction pattern may be related to a progressive increase in the extracellular potassium concentration in the ischemic myocardium. Thus, minor elevations (2.5–4.0 mM) in interstitial potassium concentration can cause an
acceleration in conduction velocity, whereas higher potassium concentrations (4.0–9.0 mM) tend to slow transmyocardial conduction.26-30

In the present study, we found no significant changes in longitudinal conduction time along the specialized conduction system. However, intramyocardial conduction time, estimated from the activation time from endocardium to epicardium in the ischemic zone, demonstrated marked changes in a reproducible biphasic pattern during the initial phase of acute myocardial ischemia. Intramyocardial conduction time was the only one of several variables that showed a biphasic pattern similar to the changes in R-wave amplitude. However, these observations do not preclude an important role for other factors, such as changes in electromotive forces or the stretching and thinning of the myocardium, which have also been claimed to influence the R-wave amplitude response to volume changes and ischemia.31-33

Thus, the similarity and synchronicity of intramyocardial conduction changes and R-wave amplitude variations during acute myocardial ischemia indicate that myocardial activation patterns may be a major determinant of R-wave amplitude alterations during acute myocardial ischemia. These findings may help to explain the contradictory reports concerning the clinical applications of R-wave amplitude alterations to the diagnosis of coronary artery disease and left ventricular dysfunction in patients.

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2-D ECHO IN RV INFARCTION

D'Arcy and Nanda

SUMMARY Real-time, two-dimensional echocardiographic studies were performed in 10 patients with acute myocardial infarction who had clinical features suggestive of right ventricular involvement. All patients showed right ventricular wall motion abnormalities. In the four-chamber view, seven patients showed akinesis of the entire right ventricular diaphragmatic wall and three showed akinesis of segments of the diaphragmatic wall. Segmental dyssynergy areas involving the right ventricular free wall were identified in four patients. One patient showed a large right ventricular apical aneurysm. Other echocardiographic features included enlargement of the right ventricle in eight cases, paradoxical ventricular septal motion in seven cases, tricuspid incompetence in eight cases, dilatation of the stomach in four cases and localized pericardial effusion in two cases. Right ventricular infarction was confirmed by radionuclide methods in seven patients, at surgery in one patient and at autopsy in two patients.

RIGHT VENTRICULAR INFARCTION may frequently complicate left ventricular infarction and represents an important clinical syndrome whose recognition may have vital therapeutic implications. Isolated infarction of the right ventricle is uncommon, occurring in only 2.2% of Wartman and Hellerstein's 160 autopsied patients. Right ventricular infarction more often occurs as an extension of left ventricular infarction and involvement of the right ventricle may exist as many as one-third of the patients with inferior myocardial infarction.

We describe the real-time, two-dimensional echocardiographic features noted in 10 patients with clinical features of right ventricular myocardial infarction.

Methods As part of ongoing clinical and echocardiographic studies in the coronary care unit, 10 patients with clinical features of right ventricular infarction were studied by real time, two-dimensional echocardiography. The diagnosis of acute myocardial infarction was based on a history of characteristic chest pain, electrocardiographic evidence of myocardial injury with subsequent evolutionary changes and positive creatine kinase isoenzyme assay. Patient characteristics are presented in table 1.

Right ventricular infarction was proved at autopsy in two patients, at surgery for repair of a ruptured ven-
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