R-wave Amplitude Variations During Acute Experimental Myocardial Ischemia: An Inadequate Index for Changes in Intracardiac Volume

Daniel David, M.D., Masahito Naito, M.D., Chin C. Chen, M.D., Eric L. Michelson, M.D., Joel Morganroth, M.D., and Mark Schaffenburg

SUMMARY The role of intracardiac volume in controlling electrocardiographic R-wave amplitude changes during acute myocardial ischemia was studied in 24 open-chest dogs. The R-wave amplitude in surface ECG leads 2, V_6, and Frank X, Y and Z leads were correlated with hemodynamic, echocardiographic and angiographic changes in a 5-minute circumflex coronary artery ligation and reperfusion model. After coronary ligation, left ventricular end-diastolic diameter and volume increased progressively above control, reached a peak and plateau at 120-130 seconds after ligation and did not return to control levels until more than 5 minutes after release of the occlusion. In contrast, the R-wave amplitude showed a biphasic response to acute ischemia, reaching a nadir (\(\Delta R = 18.2\%\) below control) at 30 seconds after coronary ligation and only subsequently increased to reach a peak (\(\Delta R = 52\%\) above control) at 150 seconds after ligation. In addition, R-wave amplitude returned immediately to control levels within 10 seconds after reperfusion. In six other dogs, both vena cavae were occluded for a 30-second period, beginning 180 seconds after coronary ligation. Although intracardiac volume decreased markedly, R-wave amplitudes increased even more. Thus, the demonstration of discordance between alterations in intracardiac volume and R-wave amplitude in these studies suggests that factors other than intracardiac volume determine R-wave amplitude changes in the course of acute myocardial ischemia.

THE IMPORTANCE of intracardiac blood volume to the magnitude of scaler ECG potentials was first postulated by Brody.\(^1\) Brody suggested that an increase in intracardiac blood volume decreases tangentially oriented electrical vectors, whereas the radially oriented vectors are increased. The initial QRS vectors that generate the R wave on the surface ECG are radially oriented, so increases in intracardiac volume could thereby result in increases in R-wave amplitude — the Brody effect.\(^1\) These theoretical considerations were later corroborated by a series of experiments in laboratory animals with normal myocardium\(^6\) and in other studies using biophysical and computer models.\(^9,11\)

Clinical studies have shown an increase in R-wave amplitude during maximal exercise in patients with proved coronary artery disease.\(^16,17\) Assuming that the increases in R-wave amplitude in these patients are directly related to ischemia-induced increases in intracardiac volume by the Brody effect, some authors have advocated using R-wave changes as a sensitive and specific indicator of coronary artery disease.\(^12\) Moreover, exercise-induced increases in R-wave amplitude have been suggested as a diagnostic marker to identify patients with ischemia-induced left ventricular dysfunction.\(^13\) However, contradictory results as to the predictive value of exercise-induced R-wave amplitude changes in the diagnosis of coronary artery disease and their relation to left ventricular dysfunction have since been published.\(^15,17\)

The present study was designed to determine, under controlled experimental conditions, the relationship between intracardiac volume changes and surface electrocardiographic R-wave amplitude variations during the immediate phase of acute myocardial ischemia. A canine model of acute coronary ligation was used.

Materials and Methods

Twenty-four mongrel dogs, mean weight 18.4 kg (range 12.5-21 kg), were anesthetized with 30 mg/kg i.v. pentobarbital. A midsternotomy was performed and dogs were ventilated with room air by means of a Harvard respirator at a rate of 15 respiratory cycles/min. Constant body temperature was maintained throughout the experiments. 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 and a 3-0 silk ligature was placed around the artery for subsequent snare occlusion. Left ventricular pressure was measured using a microtip catheter (Millar model PC370). In nine dogs, cardiac output was measured by thermodilution using an Edwards model 9510A cardiac output computer 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 taken as the mean

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of a minimum of three consecutive measurements. More measurements were performed at 60-second intervals during the ligation and postreperfusion periods.

Left ventricular dimensions were determined using M-mode and two-dimensional echocardiography in all dogs using a commercially available three-rotary-element sector scanner (Advanced Technology Laboratories Mark III) with a 3.5-MHz transducer. During two-dimensional echocardiographic imaging the ultrasonographic beam was swept mechanically through an arc of 90°. The transducer was attached to a rigid bar connected to the surgical table and placed in direct contact with the exposed anterior right ventricular surface using methods previously described. The transducer was placed with special care to avoid pressure on the heart. Depth markers were set at 5 or 7 cm. The images were displayed in real time at a rate of 56 or 44 frames/sec. Two views of the heart were obtained, the long-axis view by directing the echo beam plane between the apex and the base of the heart, and the short-axis view by directing the echo beam perpendicular to the long axis at the level of the base of the mitral valve. The images were stored on one-half-inch video tape, which could be reviewed in real-time, slow-motion or frame-by-frame presentations. The left ventricular diastolic diameter was measured from the endocardial layer of the septum to the posterior wall at a point synchronous with the QRS complex of a simultaneously recorded monitor lead.

A light-pen microprocessor computer system (Varian Associates) was used to measure changes in ventricular dimensions. Left ventricular volume was measured in six dogs by means of cineangiography of the left ventricle. Five to 10 ml of contrast medium (Renografin 76) with 37% iodine were hand-injected in the various phases of the experimental protocol and the angiograms were recorded by a General Electric angiographic x-ray apparatus. Left ventricular dimensions were then calculated by planimetry (Tektronic model 31). Calculations were computed according to the method described by Dodge et al. and converted with modification for the anteroposterior view, using the equation

\[ VA = \frac{\pi}{6} Da^2 L \]

where \( V \) = volume, \( D \) = minor axis, \( L \) = major axis, and \( a \) = anteroposterior position. Surface electrocardiographic leads 2, \( V_6 \), and Frank orthogonal leads X, Y and Z were monitored and recorded continuously throughout the experiments. Care was taken with lead placement, and animal limbs were restrained in fixed positions to avoid distortion of the ECG. The ECG pattern before and after thoracotomy did not show any major differences. Under these conditions, the McFee lead system and the Frank orthogonal system show very little differences. The Frank orthogonal system was therefore chosen to facilitate correlations with human studies. The surface ECG was recorded at a frequency range of 0.1–200 Hz. R-wave amplitude was measured using the TP segment as the baseline (0 level reference) to the peak of the R-wave deflection. R-wave amplitude was measured at 10-second intervals during the control, ligation and postreperfusion periods. Each measurement represented a mean of 10 consecutive QRS complexes. These measurements were scattered randomly throughout the respiratory cycle to cancel the effects of respiration on R-wave amplitude, although these effects were shown to be minimal in our lead system. All parameters were continuously recorded on a Hewlett-Packard photographic recorder model 4578 throughout the experiment and simultaneously recorded on a Hewlett-Packard eight-channel FM tape recorder (model 3968A instrumentation recorder) for later reproduction.

**Experimental Protocol**

In 18 dogs (group 1), 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 earliest phase of malignant ventricular arrhythmias, which peak in frequency at approximately 7 minutes. The ligation was followed by abrupt coronary arterial reperfusion and a 30-minute recovery period, during which all variables were monitored.

A short period of right ventricular inflow obstruction (simultaneous clamping of the inferior and superior venae cavae) was induced transiently for 30 seconds in six dogs (group 2) at 180 seconds into the ligation period of the left circumflex artery. Post-inflow occlusion data were analyzed separately in these six dogs.

Thirteen other dogs developed severe ventricular arrhythmias before completing the protocol, precluding serial measurements, so they were not included in data analysis.

**Statistical Analysis**

Data were analyzed at baseline, at 10-second intervals after coronary artery ligation and a postreperfusion period of 60 seconds.

To compare proportional changes with the control state over time, the data were transformed by taking natural logarithms, which facilitated the use of standard statistical methods. The distribution of each transformed variable could be approximated by a normal distribution as determined by a probability plot. For each of the variables, 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 was calculated from the transformed data. A maximum likelihood estimate (i.e., point estimate) and 95% confidence intervals for the proportional change were obtained by taking the appropriate function of the corresponding quan-
Results

The sequential electrocardiographic changes in QRS amplitude in a representative experiment (of group 1) are demonstrated in figure 1. Immediately after the occlusion of the left circumflex coronary artery, a reproducible pattern of left ventricular dimensional, hemodynamic and electrocardiographic changes occurred in 15 of the 18 dogs (83%) in group 1. Beginning with the first beats after coronary occlusion, left ventricular end-diastolic dimensions progressively increased. By 30 seconds after ligation, ventricular end-diastolic diameter and volume increased by point estimates of 22.2% (p < 0.001) and 23.9% (p < 0.001) above control, respectively. Left ventricular end-diastolic diameter and volume continued to increase and peaked at approximately 120–130 seconds after ligation, to point estimates of 36.9% (p < 0.001) and 50.8% (p < 0.001) above control, respectively (table 1). Neither left ventricular end-diastolic dimension nor left ventricular end-diastolic volume changed further during the remainder of the 5-minute ligation period (fig. 2).

Concomitant with these changes in left ventricular dimensions and volume was a parallel gradual increase in left ventricular end-diastolic pressure (p < 0.001) and a reduction in cardiac output (p < 0.001) (table 1). However, during the first 75 seconds after ligation, while left ventricular end-diastolic volume and left ventricular end-diastolic dimensions were increasing continuously, R-wave amplitude on surface electrocardiographic leads 2, V5, X and Y showed a biphasic pattern, with an initial decrease and then an increase. As soon as 10 seconds after ligation, the R-wave amplitude in each of these leads was decreased significantly (p < 0.01–0.001) from control values. This decrease in R-wave amplitude was most marked 30 seconds after ligation (fig. 1, table 1). Thereafter, R-wave amplitudes began to increase, and returned to preligation amplitudes by approximately 80 seconds after ligation. R-wave amplitudes continued to increase, overshooting preligation values.

Figure 1. An electrocardiographic trend recording of a representative experiment. All five ECG leads are recorded simultaneously at a speed of 5 mm/min. CAL = time of circumflex coronary artery ligation; REP = time of reperfusion. Note the marked initial decrease in R-wave amplitude in all leads except Z, followed by a marked increase and then a plateau phase. After reperfusion, R-wave amplitude returned to preligation control level.
TABLE 1.  R-wave Amplitude, Hemodynamic and Dimensional Changes in Group 1 Dogs

<table>
<thead>
<tr>
<th>Time (sec)</th>
<th>RV₁ (n = 15)</th>
<th>RL₂ (n = 15)</th>
<th>RX (n = 15)</th>
<th>RY (n = 15)</th>
<th>RZ (n = 15)</th>
<th>ΣR (n = 15)</th>
<th>LVEDP (n = 15)</th>
<th>CO (n = 9)</th>
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Results are expressed in percent change from control. The p values are calculated based on a point estimate and 95% confidence level.

* p < 0.001.
† p < 0.01.

Abbreviations: CAL = coronary artery ligation; REP = coronary reperfusion; RV₁, RL₂, RX, RY, RZ = R-wave amplitude in these five measured ECG leads; ΣR = sum of R-wave amplitude of all five ECG leads; LVEDP = left ventricular end-diastolic pressure; CO = cardiac output; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume.

Figure 2.  The mean sum of R-wave amplitude (Σ-RWA) changes in 15 dogs after coronary artery ligation (CAL) of the circumflex coronary artery and after reperfusion (REP) are plotted against mean changes in echocardiographically measured left ventricular end-diastolic diameter (LVEDD) and angiographically measured volume (LVEDV). Results are expressed as percent change from control. Note the initial decrease in RWA, reaching a nadir at 30 seconds after CAL but then increasing. Both LVEDD and LVEDV progressively increased after CAL and reached their peak and plateau phase earlier than the RWA. After REP, RWA rapidly returned to control levels, whereas LVEDD and LVEDV showed a much slower restitution time course.
(p < 0.001), and reached a peak at 160–180 seconds after ligation. These increases in R-wave amplitudes were sustained throughout the remainder of the 5-minute ligation period (fig. 2).

In the six group 2 animals, vena caval inflow obstruction was performed 180 seconds after ligation. Each dog showed markedly reduced left ventricular end-diastolic dimensions and left ventricular end-diastolic volume to levels approaching preligation control values (table 2, fig. 3). This abrupt reduction in left ventricular dimensions occurred as early as 10 seconds after inflow obstruction. However, despite this reduction in left ventricular volume, R-wave amplitude showed a further significant (p < 0.01) increase. After release of the vena cavae, both left ventricular dimensions and R-wave amplitude returned within seconds to their preinflow occlusion peak values (fig. 3).

At 5 minutes after coronary artery ligation, reperfusion was accomplished by abrupt release of snare ligatures. After coronary artery reperfusion, reduction in R-wave amplitude was observed in each dog (table 1, fig. 2). The R-wave amplitude in each ECG lead returned to within 90% of its preligation value as early as 10 seconds after reperfusion and approximated preligation levels after 40–60 seconds of reperfusion.

In contrast to the rapid normalization of R-wave amplitudes, hemodynamic and left ventricular chamber dimensional changes returned much more slowly over a 5-minute period toward preligation values (not shown).

Three of the 24 dogs, inexplicably, showed no significant R-wave changes, although each had changes in hemodynamics and left ventricular chamber dimensions similar to those observed in the 15 dogs with typical electrocardiographic changes.

Discussion

This study demonstrates that a characteristic sequence of electrocardiographic, left ventricular dimensional and hemodynamic changes occur during acute experimental canine circumflex coronary artery ligation. Our results warrant a renewed consideration of the role of left ventricular volume in determining R-wave amplitude changes (the Brody effect) during acute myocardial ischemia.

A number of clinical studies have supported the Brody effect hypothesis in patients with coronary artery disease. Bonoris et al.13,14 in evaluating exercise stress testing and angiographic data in patients with coronary artery disease, postulated that an increase in R-wave amplitude during exercise was dependent upon an increase in intracardiac volume during the ischemic period. They suggested, therefore, that an increase in R-wave amplitude during exercise testing was a reliable marker for the diagnosis of coronary artery disease,13 and furthermore, was an indication of more severe left ventricular dysfunction.13 Other investigators have reported similar findings.14, 28–28

However, the Brody effect hypothesis has been challenged in other studies. Simoons18 reviewed a series of patients and reported that although R-wave amplitude augmentation during exercise was more frequent in patients with coronary artery disease, this finding was statistically less sensitive and specific than ST-segment changes for the diagnosis of coronary artery disease. He suggested factors other than intracardiac volume to explain the increase in R-wave amplitude, including abnormal myocardial conduction patterns related to previous myocardial damage, regional impairment of left ventricular contraction, and altered depolarization and repolarization patterns.19 Wagner et al.19 reported that although increases in R-wave amplitude often occur in patients with coronary artery disease, this sign is unreliable as a predictor of the presence or absence of the severity of coronary artery disease. Battler et al., using radionuclide cardiac imaging techniques during exercise testing of patients17 and intramyocardial sonomicrometry in an animal model,18 also reported an inconsistent correlation between R-wave amplitude variations and intracardiac volume changes.

Studies attempting to identify the "Brody effect" in clinical settings other than coronary artery disease

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<th>Procedure</th>
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<th>RL2 (n = 6)</th>
<th>RX (n = 6)</th>
<th>RY (n = 6)</th>
<th>LVEDD (n = 6)</th>
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Results are expressed in percent change from control. The p values are calculated based on a point estimate and 95% confidence level.

*p < 0.001.

Abbreviations: CAL = coronary artery ligation; VCO = vena caval occlusion; VCR = vena caval release; REP = reperfusion; RV2, RL2, Rx, Ry, Rz = R-wave amplitude in these five ECG leads; LVEDD = left ventricular end-diastolic diameter; LVCA = left ventricular end-diastolic cross-sectional area.

Group 2 dogs were those that underwent vena caval occlusion and release during the period of coronary artery ligation.
have also provided controversial results. Ishikawa et al.29 studied patients with cardiomegaly and congestive heart failure of various etiologies and found that a reduction in cardiac size due to therapy resulted in a net increase in R-wave amplitude. These observations, which were also contrary to the Brody effect hypothesis, further suggested that other factors might be involved. Manoach et al.30 studied the same problem in a canine model and observed that administration of digitalis resulted in an increase in R-wave amplitude. They suggested, therefore, that reduction in myocardial stretching might be an additional factor controlling R-wave amplitude.

Our study, using a canine model of acute myocardial ischemia, documented that coronary artery ligation resulted in an almost instantaneous deterioration of function of the ischemic myocardium with a concomitant, continuous and progressive increase in left ventricular dimensions, plateauing at 120–130 seconds after ligation. The associated R-wave amplitude changes demonstrated four distinctive phases: (1) an early decrease with a nadir at 30 seconds after ligation, when left ventricular dimensions were increasing; (2) a continuous increase in R-wave amplitude to the level of preligation values shortly before the peak increase in left ventricular dimensions; (3) a further increase in R-wave amplitude during the plateau phase of peak left ventricular dimensions; and (4) a rapid decrease of amplitude to control values immediately after reperfusion, when left ventricular dimensions were returning more slowly toward baseline values (fig. 2). Moreover, in the six dogs undergoing cardiac inflow obstruction at the time of maximal ischemic increase in R-wave amplitude, a marked decrease in left ventricular dimensions was not accompanied by the expected decrease in R-wave amplitude. Instead, R-wave amplitude significantly increased during this short period (fig. 3). These discordant observations cannot be explained by the Brody effect.

The clinical observations cited above and our experimental findings indicate that in the diseased heart, factors other than cardiac volume changes could have
an important influence on R-wave amplitude changes. Further work is required to determine the influence of other factors, including: (1) the loss of electromotive forces in the ischemic area; (2) ischemic wall motion changes; (3) wall thinning during acute ischemia; (4) increased stretch imposed on dyskinetic ischemic myocardial segments; and (5) changing patterns of intra- and transmural conduction. Recently published provocative experimental work has suggested a role for each of these factors. 31-38

Thus, R-wave amplitude changes occur with a distinct time course during acute myocardial ischemia in the dog. The discordance of R-wave response and volume changes during acute ischemia excludes intracardiac volume as the sole determinant of R-wave amplitude. The present study brings into focus the inherent difficulties of using R-wave changes to identify either ischemia or left ventricular dysfunction in the clinical setting.

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The Transition to Ventricular Fibrillation Induced by Reperfusion After Acute Ischemia in the Dog: A Period of Organized Epicardial Activation

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SUMMARY Ventricular fibrillation was induced in eight of 10 open-chest dogs by reperfusion after a 15-minute occlusion of the proximal circumflex coronary artery. Simultaneous recordings were made from 27 epicardial electrodes spaced over both ventricles. Analysis of the initial 1.5–2.5 seconds of the transition from sinus rhythm or ventricular tachycardia to fibrillation revealed that ventricular activation occurred in an orderly, rapidly repeating sequence in all hearts. Each activation front arose near the border of the ischemic-reperfused region and passed across the nonischemic portion of the ventricles to the opposite side of the heart as a single, organized wavefront. As the arrhythmia progressed, the time between the appearance of successive activation fronts on the epicardium decreased. Concurrently, the time for each activation front to traverse the ventricles increased. The simultaneous increase in rate of appearance and decrease in conduction velocity for each successive cycle resulted in overlapping cycles in which a new activation front arose from the ischemic-reperfused region before the previous front terminated over the right ventricle. The overlap between successive activation fronts increased as the arrhythmia continued. Thus, ventricular activation during the transition to ventricular fibrillation arose near the border of the ischemic-reperfused region and was organized as it passed across the nonischemic tissue, but the body surface ECG appeared disorganized because of variable spacing between successive, coexistent activation fronts.

VENTRICULAR FIBRILLATION has been defined as chaotic, asynchronous, fractionated activity of the ventricles.1 The nature of the initiation of fibrillation and the manner in which ventricular activation during this phase progresses to chaotic fractional activity are not known. During the last 120 years, several mechanisms for the initiation of fibrillation have been proposed.2 Proposed mechanisms involving automatic foci include a single focus giving rise to rapidly repeating impulses, and multiple foci firing at different rates throughout the ventricles. Proposed mechanisms involving reentry include a single, large circus pathway involving both ventricles; a single, small reentrant pathway that enlarges as the arrhythmia progresses, giving rise to subsidiary reentrant pathways until all of the ventricular muscle is involved; and multiple, disorganized, constantly changing, small reentrant pathways involving all of the ventricular muscle from the onset of the arrhythmia.2

To investigate the mechanisms of initiation, ventricular fibrillation has been studied by visual inspection, cinematography, electrocardiography, recording from a few intracellular electrodes or epicardial electrodes, recording from many epicardial electrodes in a small grid, and by determining the dispersion of refractory periods and the fibrillation threshold.1, 3–7 Although all of these techniques have supplied important information, the sequence of global activation during the onset of ventricular fibrillation is unknown. For an unstable arrhythmia, such as fibrillation, knowledge of the global activation sequence requires simultaneous recordings from numerous sites distributed over both

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