JACC Vol. 20, No. 5
November 1, 1992:1270–6

Prediction of Immediate Ventricular Arrhythmias After Coronary Artery Ligation

SHLOMO A. BEN-HAIM, MD, DSc,*† BRUNO BECKER, MD,‡ DAVID D. GUTTERMAN, MD,§ YEOUDA EDOUTE, MD, PhD,* ELIESER KAPLINSKY, MD,‖ YORAM PALTI, MD, PhD*

Haifa, Kfar Saba and Tel Aviv, Israel, and Iowa City, Iowa

Objectives. Our aim was to test the hypothesis that increased beat to beat morphologic variations in the body surface electrocardiogram (ECG) are associated with fragmented diastolic electrical activity that appears after coronary artery ligation and to correlate the appearance of spontaneous ventricular fibrillation after coronary ligation with the magnitude of the ECG beat to beat variability.

Background. Unstable and variably delayed electrical activation precedes the development of ventricular fibrillation in dogs with acute ischemia. Detection of these highly variable low amplitude signals from the body surface is currently impossible. We have developed a system designed to measure the degree of beat to beat variability of the ECG.

Methods. With high fidelity electrocardiography, subtle beat to beat ECG morphologic variations were detected in epicardial and body surface electrograms and quantified as the variance of the ECG voltage at specific points of the cardiac cycle. The ratio of the variance at the QRS offset to that of the QRS onset (beat to beat variability index) was then calculated.

Results. Ventricular fibrillation developed in 12 of 27 dogs after left anterior descending coronary artery ligation. In 7 of the 12 dogs it occurred immediately (<15 min) after ligation; in the other 5 it developed late (>15 min) after ligation. Dogs with subsequently immediate ventricular fibrillation had a significantly higher beat to beat variability index than that of dogs with late or no ventricular fibrillation both before coronary ligation (4.7 ± 1.4 vs. 1.1 ± 0.2 and 0.8 ± 0.1, respectively, $p < 0.001$) and after ligation (6.4 ± 2.6, 1.0 ± 0.6 and 1.2 ± 0.6, respectively, $p < 0.001$). In dogs that developed ventricular fibrillation immediately after coronary ligation, the arrhythmia was preceded by fragmented diastolic electrical activity on the epicardial electrogram and a simultaneous increase in the beat to beat morphologic variability of the terminal portion of the body surface ECG QRS complex.

Conclusions. Beat to beat QRS offset morphologic variations appear to be increased before and further increased after coronary artery ligation in dogs that develop ventricular fibrillation immediately after ligation. Increased beat to beat variability index may be associated with the presence of electrophysiologic instability and can predict early ventricular fibrillation.

(J Am Coll Cardiol 1992;20:1270–6)

Direct recording of electrical potentials from normal and ischemic myocardium has yielded an enormous amount of information regarding the mechanism of ventricular arrhythmias associated with acute myocardial ischemia and its long-term course. However, these data are unavailable in clinical practice, as the subtle and complex changes in electrical activity from the ischemic myocardium cannot be recorded on the surface electrocardiogram (ECG). The advent of signal-averaging techniques (averaging many complexes) makes it possible to detect repetitive, fixed and reproducible activity on the surface ECG beyond the QRS complex. The presence of a stable and reproducible delayed activity beyond the QRS complex has been found to be of predictive value for detecting ventricular arrhythmias (1–4).

Most cases of ventricular fibrillation and sudden cardiac death, however, are associated with acute changes in the electrophysiologic properties of the myocardium, including unstable and variably delayed activation. Many investigators (5–7) have demonstrated that this delayed activation appears and increases before the development of malignant ventricular arrhythmias and ventricular fibrillation. Beat to beat variability could not be detected by surface recordings because of its extremely low amplitude and because current signal-averaging techniques factor it out. The ability to detect the appearance of dynamic and changing electrical activity beyond the QRS complex is of clinical significance for two reasons. 1) Such changes have been shown in experimental models to precede and predict the occurrence of ventricular tachycardia and fibrillation during the hyper-

From †the Cardiovascular Research Group, Rappaport Family Institute for Research in the Medical Sciences and the Departments of Physiology and Biophysics, Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; ‡the Department of Cardiology, Meir Hospital, Kfar Saba, Israel; §The College of Medicine, University of Iowa, Iowa City, Iowa; and ‖the Heart Institute, Chaim Sheba Medical Center, Tel-Hashomer, Tel Aviv, Israel. This study was supported in part by Grant 12321 from the Israel Academy of Sciences and Humanities and by a grant from the W. and S. Wein Research Fund, Israel.

Manuscript received October 22, 1991; revised manuscript received May 4, 1992, accepted May 14, 1992.

*Present address and address for correspondence: Shlomo A. Ben-Haim, MD, DSc, Cardiovascular Division, Department of Internal Medicine, University of Iowa, College of Medicine, Iowa City, Iowa.

0735-1097/92/$5.00

acute phase of myocardial infarction (5,6) (and therefore easily detectable by signal averaging); and 2) in the chronic infarct model, the stable and reproducible changes become unstable and dynamic and vary from beat to beat before the development of arrhythmias (8).

A system was thus designed to measure the degree of beat to beat variability in amplitude of the electrical activity during the cardiac cycle from surface ECG leads. Special emphasis was directed toward the post-QRS period (ST segment). This experimental study was designed to correlate electrical beat to beat variability as it is detected in the QRS complex with dynamic changes in the local activation in the ischemic zone after coronary artery ligation. Thus, we investigated whether surface lead variability would detect the variably delayed and fragmented activity characteristic of the ischemic myocardium.

Methods

Animal preparation. Twenty-seven male or female adult mongrel dogs (18 to 25 kg) were studied. The study conforms to the Position of the American Heart Association on Research Animal Use adopted November 11, 1989 by the American Heart Association.

The dogs were anesthetized with sodium pentobarbital (30 mg/kg body weight, intravenously); supplemental doses (30 mg) were administered as dictated by the presence of corneal reflex or pressor response to surgical incision. Animals were intubated and ventilated on a large-animal respirator (Harvard Apparatus) to maintain a partial pressure of oxygen (Po_2) of 80 to 110 mm Hg and a partial pressure of carbon dioxide (Pco_2) of 35 to 45 mm Hg. Cannulas were placed in the right femoral artery and vein for measuring arterial pressure and administration of fluid.

The pericardium was incised through a left fifth intercostal space incision and sutured to the chest wall, forming a pericardial cradle. The proximal left anterior descending coronary artery was surgically isolated to allow placement of a vascular snare. A test occlusion for 15 s was performed to outline the epicardial zone of ischemia (cyanosis). A pair of silver-silver chloride electrodes was placed in the ischemic epicardium of the left ventricular wall and in the nonischemic epicardium over the right ventricle 5 mm apart.

Body surface electrocardiograms. Body surface ECGs were recorded with the use of needle electrodes introduced into the subcutaneous areas of the two lateral aspects of the chest wall. The ECG signals were fed into a specially designed differential amplifier (gain 1,000 to 50,000, band pass 3 to 600 Hz) with an internal noise level <0.5 μV. Baseline ECG recordings were obtained 5 min before coronary artery ligation. Then the ECG was recorded for 60 s every 2 min for the 2-h period of ligation. All signals were recorded on-line with the use of a 12-bit analog to digital converter (increments of 0.5 μV) at a sampling rate of 1 kHz.

Signal-averaging technique. The following cross-correlation technique was used to properly align consecutive complexes for determination of the signal average and variance. A user-defined fiducial point (peak of the R wave) on a representative ECG complex was used as the center of a template, 61 ms long, for cross-correlation and error function algorithms. A local maximal correlation and minimal error were searched for as an index of the correct relative temporal position in the subsequent beats. This alignment procedure was carried out on a band-passed ECG (with the use of a noncausal filter, IIR, 4 to 40 Hz) it improved its performance. Once identified, a 512-ms-wide window was set, with the peak of the QRS complex at 149 ms from its beginning. Voltages from 40 consecutive temporally fitted windows were then averaged in the time domain as

$$A_i = 1/N \sum_{j=1}^{j=N} S_{ij}, \quad [1]$$

where the time domain variance (σ_i) was calculated as

$$\sigma_i = 1/N \sum_{j=1}^{j=N} (S_{ij} - A_i)^2, \quad [2]$$

where j denotes the beat index (1 . . . N), i denotes the temporal position within the ECG complex (1 . . . 512), and S and A are the raw ECG voltages and the time domain average respectively.

A relative variance signal (σ_{ri}) was defined as

$$\sigma_{ri} = \sigma_i \Big/ \sum_{j=1}^{j=512} \sigma_j. \quad [3]$$

We defined two 50-ms-long windows of interest. The first was placed at the QRS onset (starting 75 ms before the R wave) and the other at the QRS offset (starting 25 ms after the peak of the R wave). Using this definition we defined beat to beat variability index (BTBVI) as the ratio between the variance of the amplitudes of the QRS offset and that of the QRS onset. (This metric is useful chiefly because it is normalized for ambient noise.) Specifically, we calculated

$$BTBVI = \sum_{i=175}^{i=225} \sigma_i \Big/ \sum_{i=25}^{i=75} \sigma_i, \quad [4]$$

where i denotes the temporal position in ms within the processed ECG window and i = 150 ms represents the peak of the R wave.

Statistical analysis. Results are presented as mean value ± SD. Statistical significance for comparisons among the three recording sites as well as among the three groups was determined by using analysis of variance for repeated measures and Tukey's test for contrast determination.

Results

After left anterior descending coronary artery ligation, 12 of the 27 study dogs developed ventricular fibrillation. Of

JACC Vol. 20, No. 5
November 1, 1992:1270-6

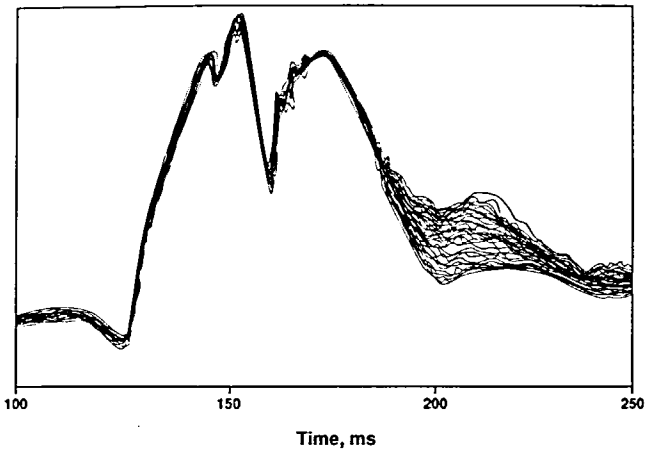


Figure 1. Overlay of 30 consecutive body surface electrocardiographic beats after ligation of left anterior descending coronary artery and before the development of immediate ventricular fibrillation. Note the increased morphologic variability (thickness of curve) at the terminal part of the QRS complex (180 to 230 ms). In dogs with immediate ventricular fibrillation, the development of epicardial diastolic fragmentation coincided with the increased morphologic variability of the terminal part of the QRS complex.

these, 7 developed the arrhythmia within 15 min of ligation (immediate ventricular fibrillation group), whereas 5 developed it 15 to 30 min after ligation (late ventricular fibrillation group). The 15 dogs that did not develop ventricular fibrillation after coronary artery ligation were classified in the no ventricular fibrillation group. In all dogs a clear demarcation of the ischemic region appeared during coronary artery occlusion.

After coronary artery ligation, continuous diastolic electrical activity (fragmented electrogram) developed in the ischemic epicardial recordings of the dogs with immediate ventricular fibrillation. This event coincided with the appearance of a highly variable terminal body surface QRS configuration, as shown graphically in Figure 1 after overlaying 30 consecutive QRS complexes.

The relative variance signal, calculated from 40 consecutive beats, was altered after coronary artery ligation. The most prominent alteration, a marked increase in the relative variance during the terminal QRS segment, was noted in the dogs with immediate ventricular fibrillation (Fig. 2). This phenomenon was evident at all recording sites (body surface and both right and left ventricular epicardium). Nevertheless, the left ventricular epicardial tracing, which was also the tracing recorded from an ischemic epicardium, showed the most prominent alterations.

The dogs with no or late ventricular fibrillation had a different pattern of alteration in beat to beat variability. After coronary artery ligation, the relative variance signal of the late and no ventricular fibrillation groups did not increase in the region of the terminal QRS complex (Fig. 3 and 4). An inconsistent elevation was noted of the relative variance signal recorded from the left ventricular epicardium after coronary artery ligation.

Beat to beat variability before coronary artery ligation (Table 1). Quantifying the alterations noted in the Figures 2, 3 and 4, we calculated the beat to beat variability index for each dog, both before and after coronary artery ligation. The variability index before coronary artery ligation was higher at each recording site in dogs with immediate ventricular fibrillation than in dogs with late or no ventricular fibrillation. The baseline index did not differ significantly between dogs in the latter two groups.

Beat to beat variability after coronary artery ligation (Tables 2 and 3). After coronary artery ligation, the most prominent alteration was the increased beat to beat variability index in the dogs with immediate ventricular fibrillation. The differences between the beat to beat variability index in these dogs and that in the dogs with no or late ventricular fibrillation increased after coronary artery ligation. The

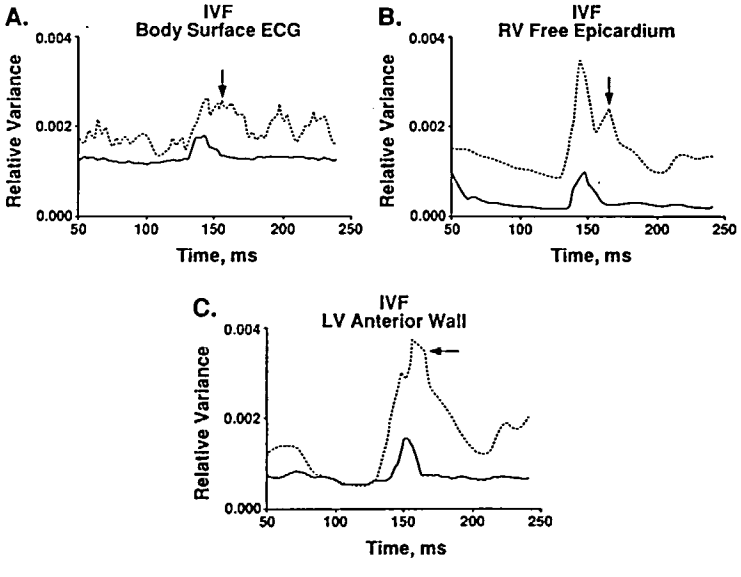


Figure 2. Relative variance signals, calculated from 40 consecutive beats of the electrocardiogram (ECG) recorded before (**solid line**) and after (**dotted line**) ligation of the left anterior descending coronary artery in a dog that developed immediate ventricular fibrillation (IVF). **A**, Signal derived from the body surface ECG. **B**, Signal derived from the right ventricular (RV) epicardial tracing. **C**, Signal derived from the ischemic anterior left ventricular (LV) epicardium. Coronary artery ligation altered the relative variance signal; the most prominent alteration was an increased relative variance of the terminal portion of the QRS complex that was greatest in the recording taken from the ischemic left ventricular epicardium.

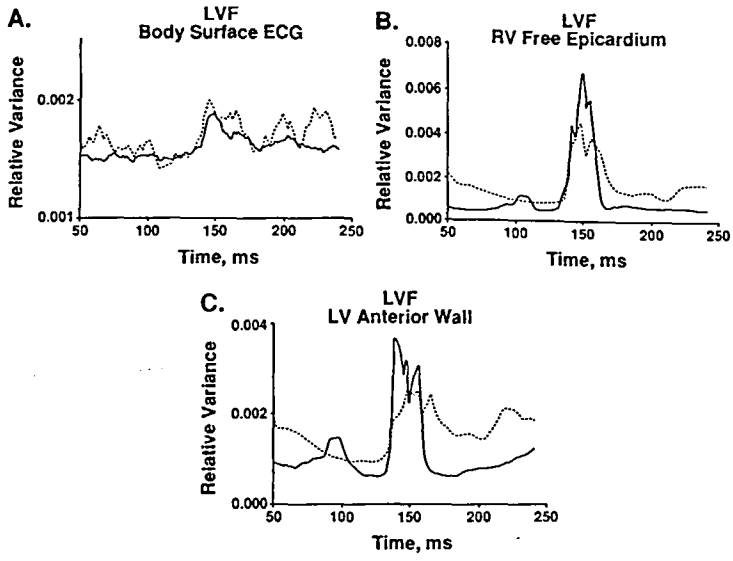


Figure 3. Relative variance signals, calculated from 40 consecutive beats of the electrocardiogram (ECG) recorded before (**solid line**) and after (**dotted line**) ligation of the left anterior descending coronary artery in a dog with late ventricular fibrillation (LVF). **A,** Signal derived from the body surface ECG. **B,** Signal derived from the right ventricular (RV) epicardial tracing. **C,** Signal derived from the ischemic anterior left ventricular (LV) epicardium. Although coronary artery ligation altered the relative variance signal, there were no prominent or consistent changes; in particular, no increased relative variance of the terminal portion of the QRS complex was noted.

increase in the index in the group with immediate ventricular fibrillation was statistically significant at the right ventricular free epicardium and body surface recordings.

Coronary occlusion increased the beat to beat variability index significantly only in the group with immediate ventricular fibrillation (Table 3). It did not alter the index in the groups with no or late ventricular fibrillation.

The beat to beat variability index enabled discrimination of the groups with immediate ventricular fibrillation from those with no or late ventricular fibrillation both before and after coronary artery ligation (Fig. 5 and 6).

Discussion

The major finding of this study is that beat to beat variation in the amplitudes of the terminal part of the QRS complex relative to that of the early QRS complex is increased significantly before and after coronary occlusion that causes ventricular fibrillation.

We used a simple technique to assess time domain stability of the ECG configuration. The beat to beat variability of the QRS configuration is affected by several factors including myogenic noise, electronic noise of the signal acquisition equipment, and that of external electromagnetic sources. These contributions to the beat to beat variability are expected to be equally present throughout the ECG signal. Nevertheless, dynamic alterations of the QRS configuration synchronized with the heartbeat (e.g., the repolarization and depolarization processes) will increase the variance signal only in specific regions of that ECG. Therefore, when reading the normalized variance signal, we can gain information about the relative steadiness of different regions within the ECG with respect to the QRS complex.

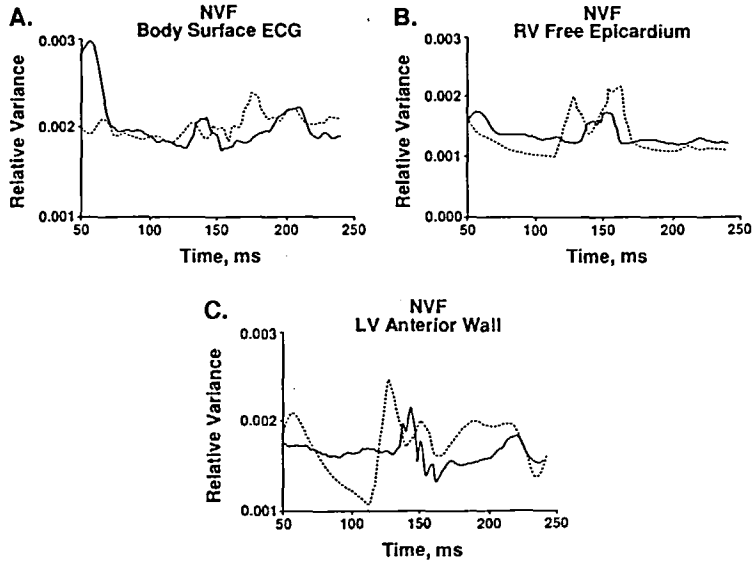


Figure 4. Relative variance signals, calculated from 40 consecutive beats of the electrocardiogram (ECG) recorded before (**solid line**) and after (**dotted line**) ligation of the left anterior descending coronary artery in a dog that did not develop ventricular fibrillation (NVF). **A,** Signal derived from the body surface electrogram. **B,** Signal derived from the right ventricular (RV) epicardial tracing. **C,** Signal derived from the ischemic anterior left ventricular (LV) epicardium. No consistent alterations could be detected.

Table 1. Beat to beat Variability Index Measured in Three Groups Before Ligation of the Left Anterior Descending Coronary Artery

Beat to Beat Variability Index	No VF (n = 15)	Late VF (n = 5)	Immediate VF (n = 7)
Body surface ECG	0.7 ± 0.2	0.7 ± 0.2	0.9 ± 0.2*
RV free epicardium	1.0 ± 0.2	1.0 ± 0.1	1.2 ± 0.2*
LV anterior epicardium	1.1 ± 0.2	0.8 ± 0.1*	4.7 ± 1.4†

*$p < 0.05$, †$p < 0.001$ comparing each value with its corresponding value in the no ventricular fibrillation group. Data are presented as mean value ± SD. ECG = electrocardiogram; LV = left ventricular; RV = right ventricular; VF = ventricular fibrillation.

Table 3. Statistical Differences Between Beat to Beat Variability Index Before and After Ligation of the Left Anterior Descending Coronary Artery

Beat to Beat Variability Index	No VF	Late VF	Immediate VF
Body surface	NS	NS	$p < 0.05$
RV free epicardium	NS	NS	$p < 0.001$
LV anterior epicardium	NS	NS	NS

Statistical significance was calculated between each value and its corresponding value using analysis of variance for repeated measures. Abbreviations as in Table 1.

Beat to beat variability and fragmented diastolic activity. Our results show that continuous electrical activity (fragmented electrograms) present in epicardial recordings during the electrical diastole, similar to those recorded by Kaplinsky et al. (5), are associated with a highly variable terminal QRS configuration in both epicardial and body surface recordings. This highly variable terminal QRS configuration can be further examined in terms of beat to beat variability index. Our results showed that, coincidental with the appearance of the epicardial fragmented activity, increased beat to beat relative variability appeared in the terminal portion of the QRS complex and extended into the ST-T segments. On this basis we suggest that the appearance of fragmented electrical activity in the epicardial recordings is associated with increased beat to beat relative variability of the terminal portion of the QRS complex and the ST-T segments. Thus, the development of an increased beat to beat variability index may be associated with the presence of epicardial fragmented activity, which would be indicative of forthcoming ventricular arrhythmia. Nevertheless, the increased beat to beat variability documented before ligation in the group with immediate ventricular fibrillation was not associated with diastolic fragmentation of the epicardial ECG. Therefore, the relation between beat to beat variability and diastolic fragmentation may be more complex; either the beat to beat index is a more sensitive index or the two measures reflect independent electrophysiologic properties of the myocardium. In the latter case, both methods could provide complementary information regarding the potential for ischemic arrhythmias.

The phenomenon of fragmented diastolic electrical activity, also known as "diastolic bridging," is related to slow, nonhomogeneous conduction of subepicardial activation (8). Therefore, one may postulate that our results are caused by nonhomogeneous conduction of subepicardial activation in dogs that develop ventricular fibrillation early after coronary artery occlusion. However, other mechanisms may also contribute to the appearance of a highly variable terminal QRS configuration such as a time-varying depolarization process or altered autonomic neural input to the heart.

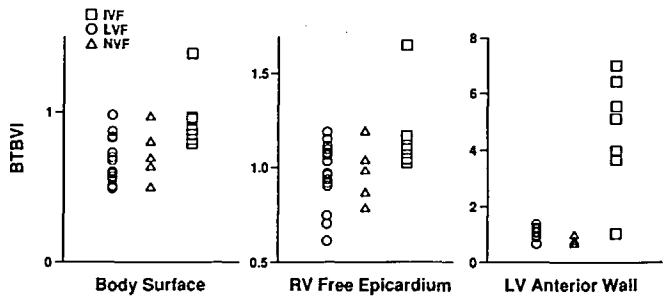
Beat to beat variability and development of immediate ventricular fibrillation. The increased beat to beat morphologic variability of the terminal part of the QRS complex was present only in dogs that developed immediate ventricular fibrillation after left anterior descending coronary artery occlusion. This finding is compatible with the bimodal distribution of ventricular arrhythmias occurring during the 1st 30 min after experimental complete coronary artery occlusion. The first phase (1a ["immediate ventricular arrhyth-

Table 2. Beat to beat Variability Index Measured in Three Groups After Ligation of the Left Anterior Descending Coronary Artery

Beat to Beat Variability Index	No VF (n = 15)	Late VF (n = 5)	Immediate VF (n = 7)
Body surface	0.8 ± 0.2	0.8 ± 0.3	1.5 ± 0.3*
RV free epicardium	0.9 ± 0.5	1.1 ± 0.2	2.7 ± 0.7*
LV anterior epicardium	1.2 ± 0.6	1.0 ± 0.6	6.4 ± 2.6*

*$p < 0.001$ comparing each value with its corresponding value in the no ventricular fibrillation group. Values are presented as mean values ± SD. Abbreviations as in Table 1.

Figure 5. Distribution of beat to beat variability index (BTBVI) among dogs before occlusion of the left anterior descending coronary artery, as derived from the body surface, right ventricular (RV) free epicardium and left ventricular (LV) anterior epicardium. **Squares** = immediate ventricular fibrillation (IVF); **triangles** = late ventricular fibrillation (LVF); **circles** = no ventricular fibrillation (NVF).



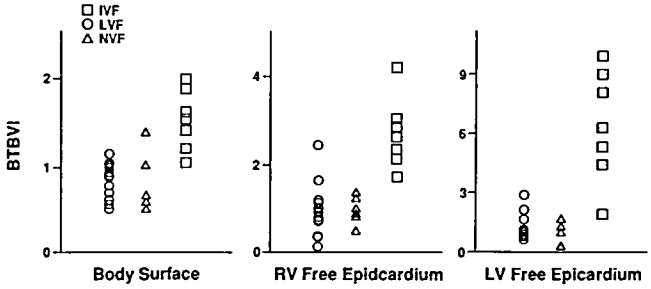


Figure 6. Distribution of beat to beat variability index (BTBVI) among dogs after occlusion of the left anterior descending coronary artery, as derived from the body surface, right ventricular (RV) free epicardium and left ventricular (LV) anterior epicardium. **Squares** = immediate ventricular fibrillation (IVF); **triangles** = late ventricular fibrillation (LVF); **circles** = no ventricular fibrillation (NVF).

mias"]) usually occurs 2 to 15 min after occlusion. The second phase (1B, ["delayed ventricular arrhythmias"]) occurs 15 to 30 min after occlusion (5,9). It seems that two different mechanisms are responsible for the generation of these arrhythmias. Phase 1a arrhythmias occur as a consequence of slow conduction and delayed activation of subepicardial muscle, whereas phase 1b arrhythmias may be related to the release of endogenous catecholamines, which has been shown to occur at 15 to 20 min of ischemia (10,11). Indeed, our analysis shows that after coronary artery ligation, dogs with late or no ventricular fibrillation did not show any significant alteration in beat to beat configuration.

Ventricular arrhythmias in the immediate phase after coronary occlusion are probably caused by reentry. Mapping experiments (6) have demonstrated that circular movement reentry occurs in acutely ischemic myocardium, often changing the position and dimension of the reentrant circuits as well as the revolution time of the impulse from beat to beat. Furthermore, dispersion in refractory periods, which has been found to increase after coronary artery ligation, is thought to facilitate the establishment of unidirectional block, one of the prerequisites for reentry (12). Our results stress the important role of electrical instability of the myocardium as a cause of immediate ventricular fibrillation and localize this process of instability to the terminal QRS complex in the ischemic myocardium.

Beat to beat variability before coronary artery ligation. Dogs with immediate ventricular fibrillation after coronary artery ligation had an increased beat to beat variability index in the baseline recording before ligation. This sign of electrical instability was present at all three recording sites in this group. This observation suggests that this group may have a different electrical substrate or that an unnoted perturbation might have been introduced during the preparation of the experimental model, such as depth of the anesthesia, coronary artery dissection or interruption of the autonomic fibers lying in close proximity to the artery. We cannot exclude the potential contribution of these mechanisms in the increased beat to beat variability at baseline that further increased after coronary artery occlusion.

Beat to beat variability index was increased in data obtained before ligation at all recording sites. However, recordings of left ventricular epicardium resulted in the most significant differences between the immediate, late and no ventricular fibrillation groups. The differences in the magnitude of beat to beat variability index among sites may have been related to the myocardial mass sampled and to contamination of the epicardial electrogram with other sources of electrical noise when measured from the body surface.

Our findings are compatible with those of previous reports (13–15) describing a correlation between QRS beat to beat morphologic variability and the vulnerability to development of ventricular fibrillation in a programmed stimulation study.

Clinical significance. Beat to beat ECG morphologic variability is an important tool for analyzing dynamic electrophysiologic events, and its application to body surface ECG recordings of humans may be promising, because it could provide, noninvasively, valuable information in predicting development of lethal arrhythmias associated with acute ischemia.

We thank Ruth Singer for editing the manuscript, Linda Bang for secretarial assistance and Michael Kienzle, MD for expert comments.

References

1. Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. Circulation 1981;64:235–42.
2. Rozanski JJ, Mortana D, Myerburg RJ, Castellanos A. Body surface detection of delayed depolarization in patients with recurrent ventricular tachycardia and left ventricular aneurysm. Circulation 1981;63:1172–8.
3. Breithardt G, Becker R, Seipel L, Abendroth RR, Ostermeye J. Noninvasive detection of late potential in man: a new marker for ventricular tachycardia. Eur Heart J 1981;2:1–11.
4. Kanovsky MS, Falcone RA, Dresden CA, Josephson ME, Simson MB. Identification of patients with ventricular tachycardia after myocardial infarction: signal-averaged electrogram, Holter monitoring and cardiac catheterization. Circulation 1984;70:264–70.
5. Kaplinsky E, Ogawa S, Balke CW, Dreifus LS. Two periods of early ventricular arrhythmias in the canine acute infarction model. Circulation 1979;60:397–403.
6. Janse MJ, van Capelle FJL, Morsink H. et al. Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts: evidence for two different arrhythmogenic mechanisms. Circ Res 1980; 47:151–65.
7. Pogwizd SM, Corr PB. Reentrant and nonreentrant mechanisms contribute to arrhythmogenesis during early myocardial ischemia: results using three-dimensional mapping. Circ Res 1987;61:352–71.
8. Boineau JP, Cox JL. Slow ventricular activation in acute myocardial infarction: a source of reentrant premature ventricular contraction. Circulation 1973;48:703–13.
9. Kabell G, Scherlag BJ, Hope RR, Lazzara R. Regional myocardial blood flow and ventricular arrhythmias following one-stage and two-stage coronary artery occlusion in anesthetized dogs. Am Heart J 1982;104: 537–45.
10. Carlsson L. Mechanism of local noradrenaline release in acute myocardial ischemia. Acta Physiol Scand 1987;559(suppl 129):7–85.
11. Schoemig A, Dart AM, Dietz R, Mayer E, Kuebler W. Release of

endogenous catecholamines in the ischemic myocardium of the cat. Part A: locally mediated release. Circ Res 1984;55:689–701.

12. Kuo CS, Munakata K, Reddy P, Surawicz B. Characteristics and possible mechanisms of ventricular arrhythmias dependent on the dispersion of action potential duration. Circulation 1983;67:1356–67.
13. Adam DR, Smith JM, Akselrod S, Nyberg S, Powell AO, Cohen RJ. Fluctuations in T-wave morphology and susceptibility to ventricular fibrillation. J Electrocardiol 1984;17:209–18.
14. Ring ME, Fenster PE. Exercise-induced ST segment alternans. Am Heart J 1986;111:1009–11.
15. Smith JM, Clancy EA, Valeri CR, Ruskin JN, Cohen RJ. Electrical alternans and cardiac electrical instability. Circulation 1988;77:110–21.