



Title	Estimation of microinhomogeneity of conduction impairment by wavelet analysis during early phase of myocardial ischemia in pigs
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**ESTIMATION OF MICROINHOMOGENEITY OF CONDUCTION
IMPAIRMENT BY WAVELET ANALYSIS DURING EARLY
PHASE OF MYOCARDIAL ISCHEMIA IN PIGS**

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Abstract : Ventricular fibrillation (VF) is most frequent in the very early phase in acute coronary occlusion, and is triggered by the re-entrant mechanism in this phase. An inhomogeneous conduction in the ischemic myocardium would be substrates for re-entry. The aim of this study was to examine the relationship between the severity of irregularities of the QRS complex and VF. Eleven pigs were analyzed, and the heart was fixed in the pericardial cradle. Ag-AgCl bipolar electrodes were fixed on the epicardium in ischemic and non-ischemic regions. The proximal portion of the left anterior descending coronary artery was occluded for one hour. Electrocardiograms (ECGs) were continuously recorded on a magnetic tape, and wavelet analysis was performed on signal-averaged ECG (25 beats) every 60 sec after the experiment. The number of local maxima (N) and the duration between the first and the last local maximum (D) were automatically measured. N and D significantly increased in the ischemic area, but not in the non-ischemic area. N and D increased approximately twofold just before the occurrence of VF in 8 fibrillated pigs ($p < 0.01$, each). There were significant positive linear relationships between the rate of increase in N and D to VF and basal heart rate before coronary occlusion ($r = 0.90$, $p < 0.01$ in N, $r = 0.84$, $p < 0.01$ in D at 160 Hz). These results suggest that there would be a threshold inhomogeneous conduction for the occurrence of VF and an increase in heart rate would accelerate the inhomogeneous conduction in acute myocardial ischemia.

Key words : ventricular fibrillation, wavelet analysis, inhomogeneous conduction, acute myocardial ischemia

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INTRODUCTION

Ventricular fibrillation (VF) resulting in sudden cardiac death is most frequent in the very early phase in myocardial ischemia^{1,2)} and has been considered to be triggered by the re-entrant mechanism. The development of ischemia-related reentrant ventricular arrhythmia, particularly VF, depends upon slowed conduction within the ischemic region and its boundaries in the first 15 minutes of the onset of acute no-flow ischemia (Ia phase)³⁻⁷⁾.

Simson *et al.*⁸⁾ reported that 5 to 10 minutes after the onset of no-flow ischemia, subepicardial bipolar electrocardiograms (ECGs) showed delayed and fractionated activity arising from delayed ventricular activation throughout the ischemic region. This indicates that inhomogeneity of slowing of impulse propagation is present in a small myocardial tissue lying between two electrodes which could create micro-reentry circuit. Uniform slow conduction does not by itself produce fractionation theoretically, while is responsible for increased ECG width⁹⁾. Therefore, the degree of fractionation, or irregularities of ECG could be regarded as an index of inhomogeneity of conduction delay. However, the relationship between this and the occurrence of fatal ventricular arrhythmia has not been directly examined.

Wavelet analysis is a recently-introduced time-scale technique that can estimate the frequency content of a signal as a function of time¹⁰⁻¹³⁾. This method has been applied to ECG analysis, for detection of the localization of irregularities in the QRS complex caused by buried fractionated potentials¹⁴⁻¹⁷⁾. The purpose of this study was to clarify the relationship between the degree of inhomogeneity of conduction delay, which was assumed to be quantified by wavelet transform, in the very early phase of myocardial ischemia and the occurrence of VF in open-chest anesthetized pigs.

METHODS

Animal preparation

Fifteen pigs of either male or female, from 25 kg to 30 kg in body weight, were anesthetized with intravenous sodium pentobarbital (25 mg/kg) after sedation by intramuscular administration of ketamine sulfate (12.5 mg/kg). After intubation, anesthesia was maintained by inhaled fluothane (0.5-2%). Polyethylene cannulas were inserted into the right jugular vein for administration of lactate Ringer solution and sodium pentobarbital as necessary, and into the right carotid artery for measurement of blood pressure and blood sampling for blood gas analysis (170 pH/Blood Gas Analyzer, CIBA-CORNING, U.S.A.). ECG of a bipolar limb lead and arterial pressure were continuously monitored throughout the experiment.

The left lateral thoracotomy was performed at the fourth intercostal space. The heart was cradled in the pericardium to expose the anterior surface of the heart.

A proximal segment of the left anterior descending (LAD) coronary artery just above the first large diagonal branch was carefully dissected and isolated. The probe of Doppler flowmeter (T206, Transonic, U.S.A.) was fixed, and a snare occluder was placed around the artery just below the flow probe. Blood flow was continuously monitored throughout the experiment.

Recordings of epicardial ECGs

Two Ag-AgCl bipolar electrodes with 0.3 mm² of surface area and 10 mm apart in each electrode were sutured on the epicardium in the center of the LAD perfusion area which was rendered ischemic, and the perfusion area of left circumflex coronary artery (non-ischemic area). Wilson's central terminal was used as an indifferent electrode. ECG signals were amplified and recorded on thermal recorder (PC216Ax, SONY, Japan) and continuously stored on a magnetic tape (DT-120RA, SONY, Japan) with a frequency range from DC to 10 kHz.

Experimental protocol

After the surgical procedure, all pigs were allowed 20 min for stabilization. After baseline recording of ECGs for 10 min, LAD coronary artery was occluded. After coronary occlusion, we made sure of no flow of LAD coronary artery by flowmeter, and the area of cyanosis. If VF did not occur, LAD coronary artery was reperfused after 1 hr of occlusion, and then sacrificed by intravenous KCl injection. If VF or sustained atrial fibrillation occurred before completion of surgical procedure, we did not try to defibrillate because direct current cardioversion might have induced myocardial damage unrelated to myocardial ischemia.

After the experiment, the heart was isolated and a polyethylene cannula was inserted in the LAD coronary artery at the occlusion site. Then, Evans blue was injected into the LAD coronary artery via the cannula for quantifying the ischemic area. The heart was cut, and total heart weight, left ventricular weight, the weight of left ventricular ischemic area and the ratio of left ventricular ischemic lesion to total left ventricular weight were measured.

These experiments were carried out under the control of the Animal Research Committee in accordance with the Guidelines on Animal Experiments of Fukushima Medical University and the Japanese Government Animal Protection and Management Law (No. 105).

Wavelet analysis

After the experiment, wavelet analysis (See Appendix) was performed on signal-averaged ECG obtained every 60 sec from stored ECG signals on magnetic tape. Analog to digital conversion at 3 kHz of sampling rate, and signal averaging of 25 beats after excluding ventricular premature beat(s) were performed using a personal computer. The resolution was 16 bits. When the root mean square of the differences of all sampling points within the QRS complex between averaged n beats

ECG and $n+1$ th ECG was above 0.2 mV, the $n+1$ th beat was excluded as ventricular premature beat. Wavelet transforms were obtained at 40, 100, 160 and 220 Hz of the central frequency of the analyzing wavelet. In previous study, 100 Hz was the most discriminating frequency for differentiating normal subject and patient with dilated cardiomyopathy¹⁷. Thus, we arbitrarily selected the range of frequency from 40 to 220 Hz for the analysis. Two indices were defined for quantifying the wavelet transform at each frequency: (1) the number of local maxima with amplitude in both ascending and descending limbs above $0.4 \mu\text{V}$; this index represents, the degree of fragmentation of the QRS complex; and (2) the duration from the first to the last local maximum of the wavelet transform; this index indicates how long myocardial activation is present in a myocardial tissue lying between two electrodes.

Statistical analysis

Data were expressed as mean \pm standard deviation. The two-tailed unpaired *t* test was used for comparisons between two groups. Relationships between the rate of increase in the number of local maxima or the duration of wavelet transform, and hemodynamic variables or ischemic area, were analyzed by the linear regression analysis. For comparisons among data derived from wavelet analysis using four frequencies of 40, 100, 160 and 220 Hz or four groups (non-ischemic or ischemic area, and pre- or post-occlusion), one-way analysis of variance was used, followed by Fisher's exact probability test performed as a post hoc test. A level of $P < .05$ was regarded as statistically significant.

RESULTS

Of the 15 pigs entered into the study, two pigs were excluded because they fibrillated during surgical procedure, and two were excluded due to sustained atrial fibrillation at completion of the surgical procedure. Thus, eleven pigs were enrolled for analysis. Eight of 11 pigs fibrillated during coronary occlusion, and 3 pigs did not. One of 3 pigs without fibrillation during coronary occlusion fibrillated 20 sec after reperfusion. We divided them into two groups, i.e., pigs with [VF (+) group, $n=8$] and without VF during occlusion [VF (-) group, $n=3$], and compared these two groups. The time to VF in VF (+) group was from 2.5 to 18 min after coronary occlusion (average 6.7 ± 4.6 min).

Body weight, the weight of left ventricle and the left ventricular ischemic region, and the ratio of left ventricular ischemic region to total left ventricle (%) did not differ between the two groups (Table 1). Since 5 of 8 pigs suffered from VF, 5 to 6 min after coronary occlusion, hemodynamic variables were compared 4 minutes after coronary occlusion. Systolic and mean arterial pressures, heart rate and coronary blood flow were also not significantly different between the two groups 4 minutes after coronary occlusion (Table 2). While arterial pressure was low

Table 1. Comparison of the size of ischemic area between VF (+) and VF (-) group

Group	VF (+)	VF (-)
<i>n</i>	8	3
Body weight (kg)	27±4	27±2
LV weight (g)	79±20	80±5
LV ischemic area (g)	27±7	25±6
Ratio of ischemic area to LV (%)	35±3	33±3

Values are means±SD, LV; left ventricle VF; ventricular fibrillation

Table 2. Comparison of hemodynamic variables between VF (+) and VF (-) group

Group	Preocclusion	4 min of occlusion
Heart rate (beat/min)		
VF (+)	91±15	96±15
VF (-)	111±11	116±11
Systolic arterial pressure (mmHg)		
VF (+)	77±15	71±8
VF (-)	78±4	71±3
Mean arterial pressure (mmHg)		
VF (+)	67±13	60±9
VF (-)	62±5	59±5
Diastolic arterial pressure (mmHg)		
VF (+)	62±14	54±9
VF (-)	54±5	53±4
Coronary flow (ml/min)		
VF (+)	20±7	0
VF (-)	19±6	0

before coronary occlusion in the present study, coronary blood flow normalized by myocardial weight was within the normal range (70 ± 30 ml/100 g). We intentionally did not perform any cardiotoxic or vasoconstrictor treatment except fluid supplement, because of the possible effect of these drugs on the myocardial conduction. Arterial pressure tended to decrease, and although the heart rate tended to increase after coronary occlusion, it was not statistically significant (Table 2).

Changes of wavelet transform after coronary occlusion

Representative changes of the QRS complexes and wavelet transforms at 160 Hz of central frequency of the analyzing wavelet obtained from a pig in VF (+) group are shown in Figure 1. The QRS complex and its wavelet transform remained essentially unchanged after coronary artery occlusion in the non-ischemic area. On the contrary, the number of local maxima and the duration of wavelet

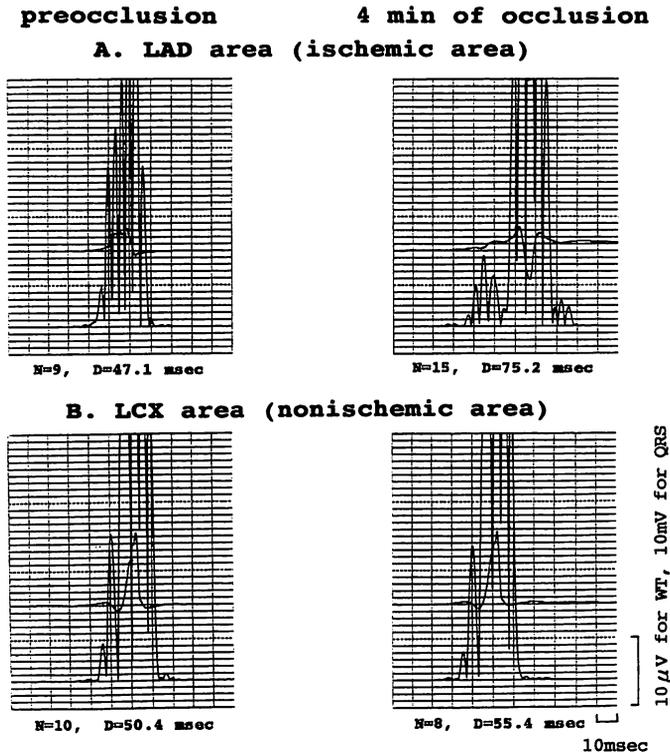


Figure 1. Representative changes of QRS complexes and wavelet transforms at 160 Hz of central frequency of the analyzing wavelet from pre-occlusion to before ventricular fibrillation (4 min of occlusion) in a pig which fibrillated at 5 min in LAD coronary artery (A, upper panel) and LCX coronary artery (B, lower panel). N=number of local maxima of wavelet transform (WT). D=duration from the first to the last local maximum of the wavelet transform.

transform significantly increased in the ischemic area 4 min after coronary occlusion, in accordance with the significant change in QRS waveform and increase in the duration of QRS complex.

Figure 2 compares the average number of local maxima and duration of wavelet transforms for all four frequencies at baseline before occlusion and at 5 min of ischemia in 8 of 11 pigs which did not suffer from VF until 5 min. The higher the frequency was, the greater the number of local maxima and the shorter the duration of wavelet transforms were, both at baseline and at 5 min of ischemia, although differences among 40, 100, 160 and 220 Hz did not reach statistical significance at baseline and at 5 min of ischemia in non-ischemic region. At 5 min of ischemia, the number of local maxima significantly increased at 100, 160 and 220 Hz, and the durations increased in all four frequencies in the ischemic area, compared to baseline values before occlusion, as well as values obtained from non-ischemic area after coronary occlusion. These results suggest that inhomogenous conduction plays a role in ischemia-induced VF.

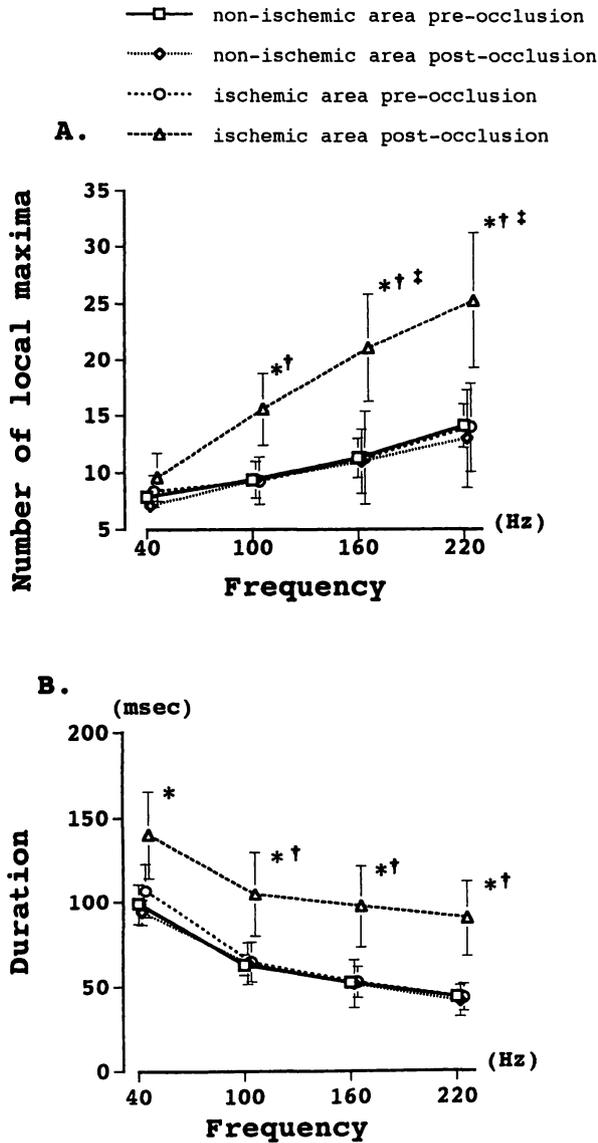


Figure 2. Comparisons of the number of local maxima (A) and the duration of wavelet transform (B.) at four frequencies analyzed, and in four groups, i.e., before and 5 min after occlusion in ischemic and nonischemic areas. The number of local maxima significantly increased, and the duration of wavelet transform significantly decreased as the frequency increased after coronary occlusion in ischemic area. *, $p < 0.01$ vs other 3 groups; †, $p < 0.01$ vs values at 40 Hz in ischemic area after coronary occlusion; ‡, $p < 0.01$ vs values at 100 Hz in ischemic area after coronary occlusion.

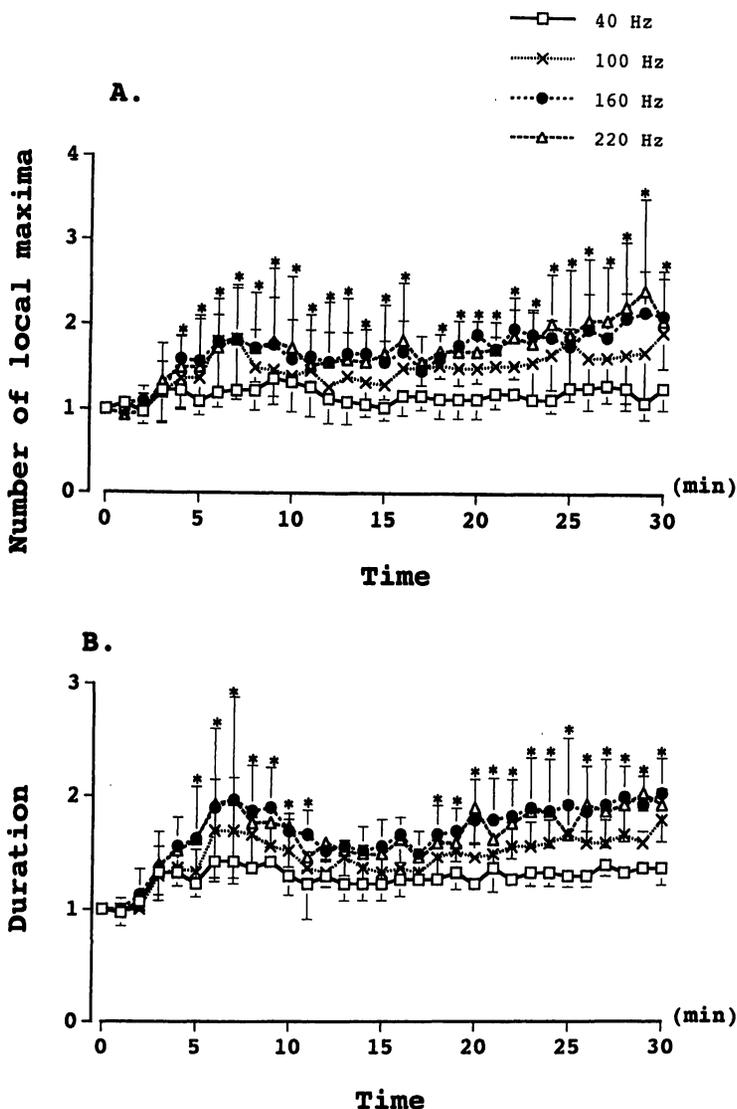


Figure 3. Time courses of the rates of changes in the number of local maxima (A) and the duration of wavelet transform (B) in all four frequencies 30 min after coronary occlusion in 3 pigs without ventricular fibrillation. *, $p < 0.05$ vs before coronary occlusion at 160 Hz.

Figure 3 shows the time courses of the rates of changes in the number of local maxima and the duration of wavelet transform every 1 min at all four frequencies until 30 min after coronary occlusion in the ischemic area of VF (-) group. Both the number of local maxima and the duration of wavelet transform started to increase 4-5 min after coronary occlusion and peaked around 7 min, followed by slight recoveries. These indices gradually increased again after approximately 15 min. Both of these indices did not change throughout the experiment in nonis-

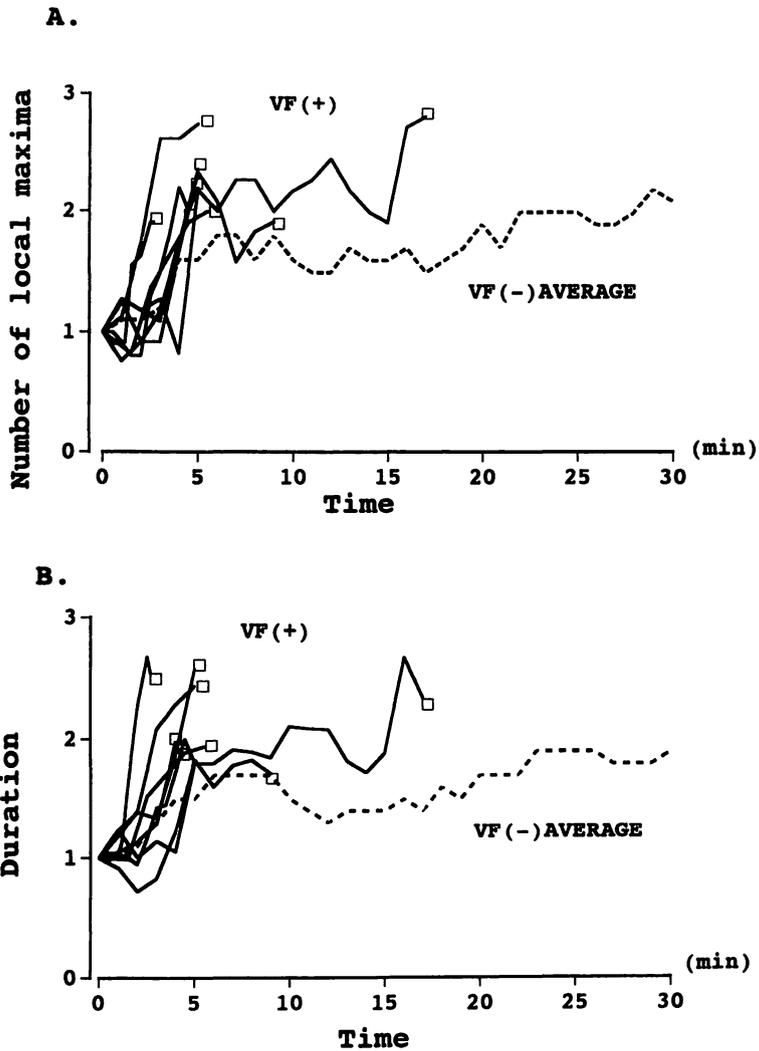


Figure 4. Individual changes of 8 pigs with and average changes of 3 pigs without ventricular fibrillation during coronary occlusion (mean \pm standard error) in the number of local maxima (A) and the duration of wavelet transform (B) compared to preocclusion values. \square = occurrence of ventricular fibrillation.

chemic area.

Comparisons of indices of wavelet transform between VF (+) and VF (-) group

Figure 4 represents each individual change of VF (+) group and average changes of VF (-) group regarding the number of local maxima (upper panel) and the duration of wavelet transform (lower panel) at 160 Hz. Both indices reached the maximal values just before or at the occurrence of VF in 7 of 8 pigs in VF (+) group. All 3 pigs with the maximum values of the rate of changes in both

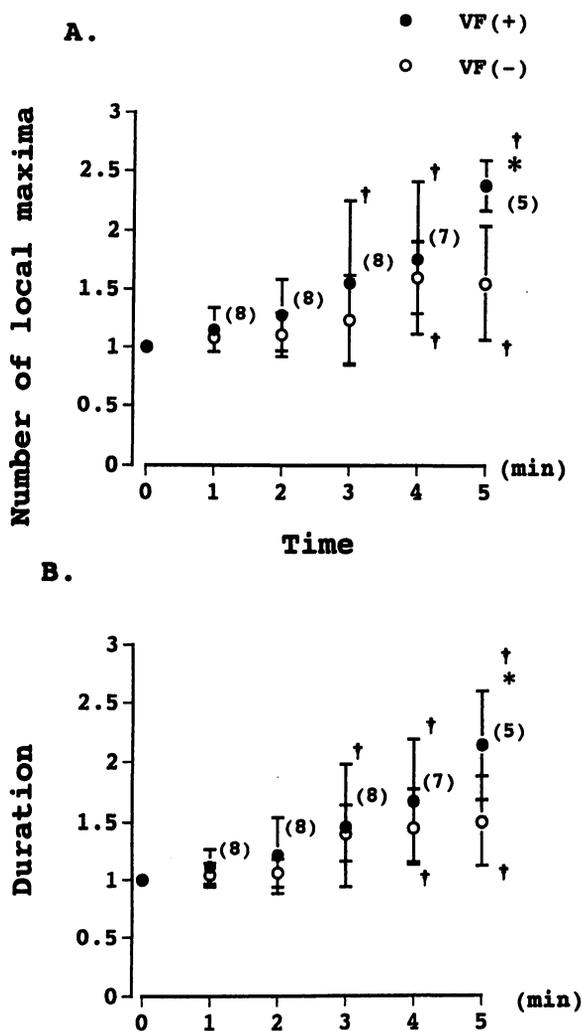


Figure 5. Comparisons of the number of local maxima (A) and the duration of wavelet transform (B) 5 min after coronary occlusion between VF (+) group and VF (-) group. Data represent the rates of changes compared with pre-occlusion values. The number in parentheses indicates the number of pigs showing VF (+). *, $p < 0.01$ vs VF (-) group; †, $p < 0.01$ vs before coronary occlusion.

indices above 2.5 developed VF, and there was a tendency for the rate of increases in both indices to be greater in VF (+) group compared with VF (-) group, especially in the early phase after coronary occlusion. Thus, the number of peaks and the duration of the wavelet transform between the two groups were compared in a time-dependent manner as shown in Figure 5. Both indices significantly increased at 3 min of ischemia in VF (+) group, while at 4 min in VF (-) group. Both indices in VF (+) group tended to be greater from 2 to 4 min than those in

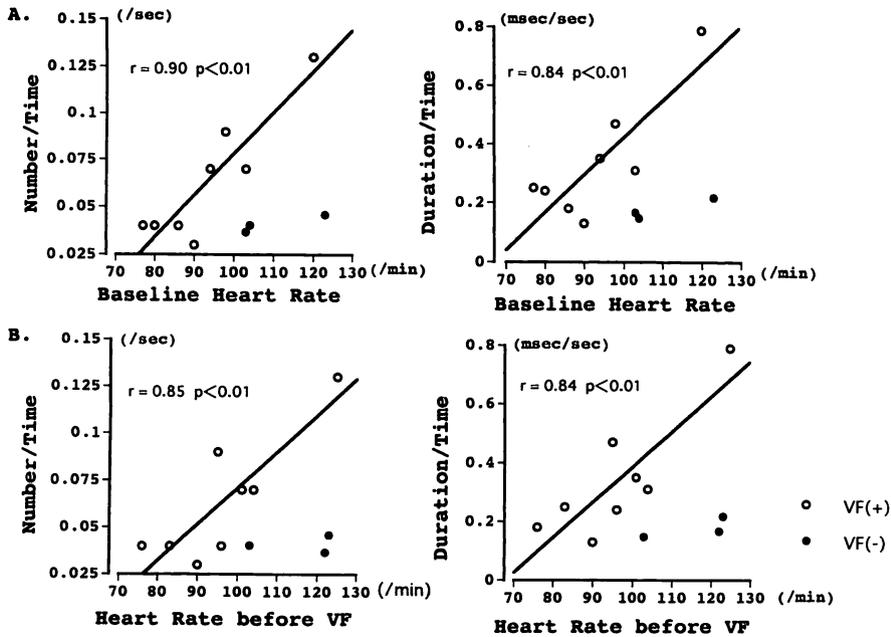


Figure 6. Relationships between the rates of increases in the number of local maxima and the duration of wavelet transform and heart rate before coronary occlusion (A) and just before VF (B).

VF (-) group, and a significant difference was observed at 5 min, compared with VF (-) group. However, when compared with each maximal ratio of the two indices attained in VF (+) and VF (-) groups, there were no significant differences in the number of local maxima [the ratio of maximal value to baseline value in VF (+) and VF (-); 2.4 ± 0.3 at 6.6 ± 5.1 min and 2.4 ± 0.3 at 9.0 ± 2.0 min, respectively; N.S.] and the duration of wavelet transform [the ratio of maximal value to baseline value in VF (+) and VF (-); 2.4 ± 0.3 at 6.3 ± 5.3 min and 2.2 ± 0.4 at 9.0 ± 2.0 min, respectively; N.S.].

Relationship between indices of wavelet transform and hemodynamic variables or ischemic area in VF (+) group

The rate of increases in the number of local maxima and the duration of wavelet transform were approximated by the ratio of both indices to time from coronary occlusion to just before VF. When these values were compared to various variables, significant linear relationships were found only with heart rate, i.e., to basal heart rate ($r=0.90$, $p<0.01$, and $r=0.84$, $p<0.01$, in the rate of increases in the number of local maxima and the duration of wavelet transform, respectively: Figure 6A.) and heart rate just before VF ($r=0.85$, $p<0.01$, and $r=0.84$, $p<0.01$, in the rate of increases in the number of local maxima and the duration of wavelet transform, respectively: Figure 6B). There were no significant relationships

between those two indices of wavelet transform and mean blood pressure, the weight of left ventricular ischemic area and the ratio of left ventricular ischemic lesion to total left ventricular weight.

DISCUSSION

Wavelet analysis was applied for time-frequency analysis of the QRS complex obtained from epicardial bipolar ECG in order to estimate the microinhomogeneity of conduction disturbance in the ischemic zone. The main result of this study was that there might be a threshold of inhomogeneity of conduction delay in the ischemic area for the development of VF in the very early phase of no-flow ischemia, and an increase in heart rate in the pre-occlusion stage would accelerate such an inhomogeneity, resulting in increased incidence of VF.

The duration of the QRS complex obtained from bipolar ECG can be considered as a conduction time of excitation wavefront between the electrodes. Therefore, the prolongation of QRS duration indicates delayed conduction in the myocardium lying between two electrodes. However, uniform slow conduction would not produce fractionation⁹. The fractionation of the QRS complex would be produced by inhomogeneous slowed conduction and/or disruption of excitation wavefront due to regional conduction block.

In the very early phase of no-flow ischemia, changes of transmembrane action potential reportedly do not develop at the same speed throughout the ischemic zone, resulting in inhomogeneous delayed conduction. And membrane excitability is lost at a certain level of depolarization due to ischemia, consequently leading to propagation to block¹⁸. This would not only offer the ideal setting for reentry but also produce fractionation of the QRS complex⁹. Large unstable circus movements maintain the rapid ventricular rhythm during ventricular tachycardia and split up into multiple wavelets characteristics or VF¹⁹. Therefore, regional fractionation would reflect substrates for VF in myocardial ischemia.

Wavelet analysis is a time-scale technique that estimates the frequency content of a signal as a function of time¹⁰⁻¹³. This method has been applied to the analysis of the body surface signal-averaged ECG, including the localization of irregularities in the QRS complex caused by buried fractionated potentials generated by the slowly activated tissues¹⁴⁻¹⁷. Compared with other time-frequency analyses such as short-time Fourier transform and Wigner distribution, wavelet analysis has better simultaneous time-frequency resolution and less oscillatory cross-terms¹¹. Thus, wavelet analysis provides a fruitful alternative to standard techniques for the detection of fractional potentials buried in signal averaged high-resolution ECGs.

Wavelet analysis detected a certain degree of irregularities in the QRS complex even in normal bipolar epicardial ECG, probably due to microinhomogeneities even in a normal ventricular propagation as a functional consequence of the normal cardiac fiber architecture²⁰. Interestingly, in this study, both the number of peaks

and the duration of wavelet transform tended to increase at about 2 minutes and reached a maximum after 5–10 minutes of ischemia, then decreased, followed by gradual increase after 15 minutes without VF. These findings may indicate a biphasic change of conduction disturbance in the early phase of myocardial ischemia. Ventricular arrhythmia occurs in two distinct early periods of myocardial ischemia. The first period, called phase Ia, occurs between 2 and 10 minutes after coronary occlusion; the second period, phase Ib, occurs approximately 12 to 30 minutes after occlusion⁴. The previous experimental evidence suggests that Ia arrhythmia is predominantly caused by reentry due to inhomogeneous delayed conduction^{3–7}, and Ib arrhythmia is linked to the release of endogenous catecholamines which induce abnormal automaticity²¹, as well as the slow and inhomogeneous conduction caused by electrical cell to cell uncoupling²². Thus, it is probable that biphasic changes of both the number of peaks and the duration of wavelet transform would reflect inhomogeneous conduction delay due to the changes in transmembrane action potential immediately following coronary occlusion, i.e., Ia phase, and due to the changes superimposed by cell-to-cell uncoupling in Ib phase.

Many factors in acute ischemia determine the incidence of VF; the size of the ischemic area²³, preconditioning^{24,25}, an increase in heart rate³, and the role of the autonomic nervous system²⁶. In this study, the size of the ischemic area was designed to be the same, and the ratios of the ischemic zone to the total left ventricle were within a narrow range. As shown in Figure 6, the basal heart rate in the pre-ischemic stage and the heart rate just before VF significantly correlated with the rates of increase in both the number of peaks and the duration of wavelet transform in pigs with VF. Harper *et al.*²⁶ reported that conduction velocity decreased more rapidly at the more rapid heart rates. However, the reduction in conduction velocity occurring prior to the onset of regional conduction block was similar regardless of heart rates during no-flow ischemia in the pig heart²⁶. Taking into account their results, the increase in heart rate may more rapidly exacerbate myocardial ischemia, and subsequently, conduction delay. As the cause of increased heart rate, a decrease in parasympathetic tone and/or increase in sympathetic tone may also have a role in our experimental model. Although the precise mechanism of VF induction at higher heart rates is unknown, it has been shown that the most effective beta adrenergic blocking agents in reducing the incidence of sudden death in postinfarction patients are those that greatly reduce heart rate²⁷. Our results suggest that the decrease in heart rate attenuates the rapid increase in inhomogeneous slowed conduction and prevents the development of VF at least in Ia phase.

Finally, there are several limitations in the present study. First, frequencies only from 40 to 220 Hz were analyzed in this study. However, higher frequencies might contain more valuable information concerning microinhomogeneity of conduction disturbance. Thus, analysis of frequencies more than 220 Hz is considered to be useful. Second, wavelet analysis of ECG was performed only in the central

ischemic region in this study. However, there are regional differences in the ischemic region, including the ischemic border zone. Mapping of the ischemic area is preferable for elucidating this issue. Third, direct evidence of a linkage between inhomogenous conduction delay and the increases in the number of local maxima and/or the duration of wavelet transform is lacking. However, it seems quite difficult to directly assess spatial propagation of excitation without injuring the myocardium. Fourth, to clarify the mechanism of the correlation of the rate of increase in the number of local maxima or in the duration of wavelet transform with heart rate as previously discussed, further experiments including the contribution of the autonomic nervous system to increase the inhomogenous conduction delay will be needed in future study.

In terms of clinical implications, the present study may provide a better understanding for time-frequency analysis of the QRS complex of body surface ECG, when such analysis is applied for the prediction of fatal ventricular arrhythmia or sudden cardiac death in acute myocardial ischemia.

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APPENDIX

In general, the wavelet transform is defined as follows:

$$S(a, b) = (1/\sqrt{a}) \int F(t) g\{(t-b)/a\} dt \quad (1)$$

where $F(t)$ is the electrocardiographic signal, a is the scale (>0), and b is the time. By using $1/a$ instead of $1/\sqrt{a}$, we can obtain a linear scale of the wavelet transform.

$$S(a, b) = (1/a) \int F(t) g\{(t-b)/a\} dt \quad (1')$$

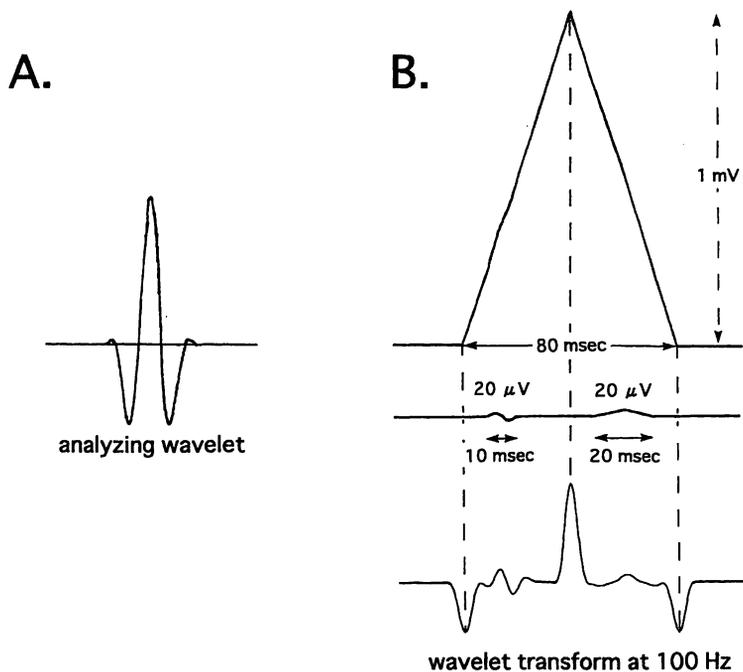
An analyzing wavelet is used for the expansion and synthesis of the signal. The analyzing wavelet used in this study is formed by multiplying cosine waves using a Hanning window function, as shown in Figure A. That is,

$$g(t) = (1/2)\cos 2\pi ft(1 + \cos \pi ft) \quad (2)$$

The $1/a$ in equation (1') is f in equation (2). From the above discussion, we obtain a pertinent wavelet transform, as follows:

$$S(f, z) = (f/2) \int F(t) \cos 2\pi F(t-z)[1 + \cos \pi F(t-z)] dt$$

In the preliminary study using a test signal, wavelet analysis definitely detected fine transient signals hidden in the QRS complex, as shown in Figure B. In the actual analysis in this study, the amplitude was expressed as an absolute value to simplify evaluation of the wavelet transform.



Appendix Figure. A, analyzing wavelet used in this study. The test signal (B) is composed of a large triangular wave with an amplitude of 1 mV and a duration of 80 msec (which simulates the QRS complex), a sine wave with an amplitude of 20 μV and a duration of 20 msec on the descending limb of the large triangular wave. A small sine wave and a triangular wave simulate pathological fractionated potential within the QRS complex (middle panel). While only fine fluctuations are recognized on the ascending and descending limbs of the large triangular wave, the wavelet transform at 100 Hz (lower panel) definitely detects those small signals at the same temporal phase. Three peaks are also recognized on the wavelet transform at three points of discontinuity, corresponding to the large triangular wave.