Decrease in the High Frequency QRS Components Depending on the Local Conduction Delay

Tetsu Watanabe, MD; Michiyasu Yamaki, MD; Hidetada Tachibana, MD; Isao Kubota, MD; Hitonobu Tomoike, MD

The high frequency components contained in the QRS complex (HF-QRS) are a powerful indicator for the risk of sudden cardiac death. However, it is controversial whether conduction delay increases or decreases the HF-QRS. In 21 anesthetized, open-chest dogs, the right atrium was constantly paced. A cannula was inserted into the left anterior descending artery and flecainide, lidocaine or disopyramide was infused to slow the local conduction. Sixty unipolar electrograms were recorded from the entire ventricular surface and were signal-averaged. Data were filtered (30–250 Hz) by using fast-Fourier transform. The HF-QRS was calculated by integrating the filtered QRS signal. Activation time (AT; dV/dt minimum) was delayed and the HF-QRS was reduced in the area perfused by flecainide, lidocaine or disopyramide. The percent increase in AT closely correlated the percentage decrease in the HF-QRS; the correlation coefficients were 0.75, 0.83 and 0.76 for flecainide, lidocaine and disopyramide infusion, respectively, (p<0.001). Decrease in the HF-QRS linearly correlated with the local conduction delay. This study proved that conduction delay decreases the HF-QRS, and that the HF-QRS is a potent indicator of disturbed local conduction. (Jpn Circ J 1998; 62: 844–848)

Key Words: Flecainide; Fast-Fourier transform; Lidocaine; Signal averaging

Methods

Instrumentation

Twenty-one adult mongrel dogs (weight, 12–33 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv) and received supplemental doses as needed. Dogs were ventilated by a respirator with room air supplemented with oxygen (3–5 L/min). The thorax was opened at the fifth intercostal space, then the pericardium was opened and a pericardial cradle was made to support the heart in the appropriate position. The sinus node was crushed, and the right atrium was paced at a cycle length of 400 msec using a model SEN-7203 stimulator (Nihon Koden, Tokyo, Japan). After an intravenous bolus administration of heparin (10,000 IU), a 24-gauge plastic cannula was inserted into the left anterior descending artery (LAD) at the distal site of the second diagonal branch. The cannula was kept open by continuous infusion of saline at 1 ml/min. A globe-shaped electrode array was placed on a ventricular surface for simultaneous monitoring of electrograms from 60 epicardial sites. Each unipolar electrode consisted of fine silver wire (0.2-mm diameter) sutured to the sock. The electrode array was 6 rows (1–6) and 10 columns (A–J). All recording electrodes were referenced to the Wilson’s central terminal, and multichannel electrograms were digitized every millisecond using a multiplexed data processing system (CD-G015, Chunichi Denshi, Nagoya, Japan). After an electrocardiogram lead II and blood pressure were recorded simultaneously throughout the study on a model 2G66 recorder (NEC San-ei, Tokyo, Japan).

Experimental Protocol

Flecainide (low dose: 10 μg/kg per min; high dose: 100 μg/kg per min, n=7), lidocaine (low dose: 0.12 mg/kg per min; high dose: 0.6 mg/kg per min, n=7) or disopyramide (low dose: 20 μg/kg per min; high dose: 200 μg/kg per
Fig 1. Representative maps of activation times at control, and during low-dose and high-dose infusion of flecainide. (*)The site of ‘the earliest activation’. Arrows indicate the epicardial electrograms at the center of perfused region: lead ‘D2’ and non-perfused region: lead ‘H2’.

Fig 2. The HF-QRS area maps at control, and during low-dose and high-dose infusion of flecainide in the same each experiment as indicated in Fig 1. Arrows indicate filtered QRS complexes at the center of the perfused region: lead ‘D2’ and non-perfused region: lead ‘H2’.
function, previously reported by Abboud et al.\textsuperscript{17} \(G(w)\) in a frequency domain. \(H(w)\), was computed to produce a filtered wave frequency series \(\tilde{F}(w)\). A product of \(\tilde{F}(w)\) with a transfer function subjected to a 1,024-point FFT analysis to produce a \(1,024\) points. A time series \(f(t)\) representing the ECG complex (FFT), ECG data were padded with zeros for a total \(1024\) but not filtered ECG wave forms. \(1024\) level. The RMS values were computed from the averaged flat portion of the PR segment was defined as the zero level. The RMS values were computed from the averaged (but not filtered) ECG wave forms. For analysis with the fast-Fourier transform algorithm (FFT), ECG data were padded with zeros for a total \(1024\) points. A time series \(f(t)\) representing the ECG complex was subjected to a 1,024-point FFT analysis to produce a frequency series \(F(w)\). A product of \(F(w)\) with a transfer function, \(H(w)\), was computed to produce a filtered wave \(G(w)\) in a frequency domain.

\[
G(w) = \frac{F(w)H(w)}{(1/1+\alpha WL/w^n)^m (1-1/1+\alpha WH/w^m)}
\]

with \(WL\) and \(WH\) being the low and high cut-off frequency of the filter. The frequency range we used was \(30–250\) Hz, designated as the ‘high frequency component’. Parameters \(m\) and \(n\) determine the decay slope of the filter. In this study, parameter \(m\)–\(n\) was \(4–100\), respectively. A filtered wave form \(g(t)\) was produced by transformation (inverse FFT) of \(G(w)\) to the time domain. The high frequency QRS components was calculated by integrating the electrogram during the QRS interval,\textsuperscript{16} which we called ‘HF-QRS’. Epicardial activation of each electrogram was defined as the minimum derivative of the QRS signal.\textsuperscript{18} The earliest activation measured on the cardiac surface was assigned to time zero and the activation time (AT) was determined from time zero to each activation, and an isochronal map was constructed.\textsuperscript{14} Changes in AT and the HF-QRS for each sodium channel blocker were measured at the center of the perfused region.

Statistical Analysis

Quantitative data are reported as mean±SE. Statistical analysis was performed with the Wilcoxon signed-ranks test. A confidence level of 95% was considered statistically significant.

Results

Effects of Sodium Channel Blockers on AT and the HF-QRS Area

The 21 dogs were divided into 3 groups: 7 were given flecainide, 7 lidocaine, 7 disopyramide. Fig 1 illustrates the cardiac surface distribution of the ATs before (control) and after flecainide infusion (low and high dose of flecainide) in a representative experiment with an asterisk indicating the site of ‘the earliest activation’. The delay in ATs was not apparent on the maps at control or during low-dose infusion of flecainide. However, a marked delay in ATs was seen in the perfused area during high-dose infusion. The configuration of the electrogram showed a widened QRS complex and an increased R wave in the perfused area.

Fig 2 shows the HF-QRS maps before and after low and high-dose infusion of flecainide. With high-dose flecainide, a decrease in the HF-QRS was clearly observed in the perfused area. This region corresponded to the area showing conduction delays in the AT map (Fig 1). In Fig 2, it can also be seen that the amplitude of the high frequency components of the QRS complex markedly decreased with high-dose flecainide infusion.

Fig 3A shows changes in the ATs for each sodium channel blocker at the center of the perfused region. ATs were significantly delayed by a high-dose infusion of each sodium channel blocker. Low-dose lidocaine and each high-dose sodium channel blocker significantly reduced the HF-QRS. AT, activation time; HF-QRS, high frequency QRS component; \(*p<0.05\ vs\ control, \ †p<0.05\ vs\ low\ dose.\)
Conduction Delay and High Frequency QRS Components

Fig 4. Correlation between AT and the HF-QRS at control, and during low-dose and high-dose infusion of flecainide, lidocaine or disopyramide. Correlation coefficients: flecainide, $r=0.75$, $p<0.001$; lidocaine, $r=0.83$, $p<0.001$; disopyramide, $r=0.76$, $p<0.001$.

disopyramide, a low dose significantly delayed ATs ($p<0.05$ vs control). High-dose sodium channel blockers significantly reduced the HF-QRS in the perfused region (Fig 3B). Infusions of low-dose lidocaine also reduced the HF-QRS ($p<0.05$ vs control).

**Correlation Between AT and the HF-QRS**

The relation between the degree of increased AT and decreased HF-QRS is shown in Fig 4. The percentage increase in AT (%AT) closely correlated with the percentage decrease in the HF-QRS (%HF-QRS); correlation coefficients for flecainide, lidocaine and disopyramide infusion were 0.75 ($p<0.001$), 0.83 ($p<0.001$) and 0.76 ($p<0.001$), respectively.

**Discussion**

The conduction delay was locally evoked by the intracoronary administration of a sodium channel blocker. The results showed that decreased levels of the HF-QRS are well correlated with the degree of delayed AT.

**Relation of the HF-QRS to Local Delay in Ventricular Conduction**

Local conduction delay has been presumed as the origin of the high frequency component during QRS complex from studies on acute or chronic myocardial ischemia. However, whether the conduction delay increases or decreases, the HF-QRS has been controversial and can not be solved only by studies on myocardial ischemia, because myocardial ischemia produces various electrophysiological changes, accompanying a decrease in conduction velocities. Cellular electrophysiology suggests the following probable changes in ischemic myocardium: (1) a depolarization of the resting membrane potential; (2) diminishing the upstroke velocity, amplitude, and duration of action potential; (3) an accumulation of K+ in the extracellular space, which also inhibits the Na+/K+ pump; and (4) acidification (increase H+) in both intracellular and extracellular compartments. To avoid these effects, a condition, other than ischemia, that creates slow conduc-

tion in themyocardium has been required. Thus, the present study used sodium channel blockers in order to produce local conduction disturbances without ischemia. The results strongly suggest that conduction delay decreases the HF-QRS.

The mechanism of the attenuation of the high frequency components due to slowed ventricular conduction is still unclear. A study by Abboud et al. simulated the phenomenon on a 3 dimensional heart model; slowing of the conduction velocity produced a decreased amplitude of the high frequency component in the QRS complex in the model heart. They suggested that slowed conduction may decrease the number of terminal branches in the activation process. This causes synchronized activation in a large amount of myocardium, which shifts high-frequency activation to a lower frequency.

In the present study, we used 3 different types of sodium channel blockers to minimize their different effects on the myocardium, because heterogeneity in sodium channel blockers has been noticed recently (eg, different binding kinetics and affinities) depending on the channel state (open or closed). The results showed similar effects among the sodium channel blockers in the relation between the HF-QRS and the conduction delay, which indicated that differences in the subclass of sodium channel blockers did not interfere with the relation.

**Clinical Implication: Relation to Clinical Observation**

Prolongation of QRS duration has been recognized in exercise-induced myocardial ischemia. It reflects delayed conduction, and is thought to be an indicator of multiple diseased vessels and exercise-induced wall motion abnormalities in patients with coronary artery disease. However, the sensitivity of this parameter for detecting delayed conduction is not high. We previously reported a method for detecting local activation using a multiple unipolar lead system which allowed us to evaluate the degree of conduction delay quantitatively, from body or cardiac surface electrodes. The constructed activation sequence clearly detected the abnormality of local activation in myocardial ischemia infarction or ventricular hypertrophy which indicated that the local conduction delay could predict the severity of exercise-induced myocardial ischemia 24,25 or the severity of hypertrophy. However, to obtain this information, a complicated system is required. The present study may provide an alternative method for detecting local activation by use of a limited-numbered lead system.

The reduction of the HF-QRS is possibly correlated with arrhythmogenicity. We previously reported a relationship between arrhythmogenicity and a reduction of the high frequency QRS components in patients with chronic myocardial infarction. Because the conduction delay is one of the most important factors for the re-entrant circuit, the HF-QRS may be a potent indicator of the risk for cardiovascular events. However, further examination will be needed to confirm the clinical significance of the HF-QRS.

**Acknowledgments**

This study was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Culture and Sports, Japan (08670756, 08457200) and a grant from Suzuken Memorial Foundation.