Endocardial Excitation and Conduction During Reperfusion Arrhythmias

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In order to clarify the role of Purkinje fibers in the occurrence of reperfusion arrhythmias, endocardial mapping was performed on perfused canine hearts by attaching 42 close bipolar electrodes to the endocardial surface of the left ventricular septum. Reperfusion with oxygenated Krebs-Ringer solution following 30 min of coronary occlusion induced ventricular tachycardia (VT) in 14 out of 23 preparations. These VT degenerated into ventricular fibrillation (VF) within 1 min after the reperfusion in all but 3 cases. Endocardial mapping revealed that the excitations during VT were always initiated by the Purkinje activities and that myocardial excitations were expanded in a centrifugal manner through Purkinje-muscle junctional area. Furthermore, this excitation pattern was preserved, in the early phase of VT, even though the propagation pattern was distorted. VF was always induced by reperfusion following 30 min of ischemic condition, that is, coronary perfusion with a hyperkalemic ($K = 10$ mM), acidic ($pH = 6.8$) and hypoxic ($PO_2 = 20-40$ mmHg) solution (4/4 cases). Elimination of hyperkalemia from the ischemic condition markedly prevented occurrence of VF (1/6 cases) during reperfusion but it did not affect occurrence of VT (4/6 cases); this implies that hyperkalemia causes the onset of VF but has less effect on the occurrence of VT. It has been separately confirmed by micro-electrode experiment, using the dissected papillary muscle of the canine right ventricle, that abnormal impulse formation during re-oxygenation was triggered in Purkinje fibers around Purkinje-muscle junction.

MANY electrophysiological studies have been performed to investigate the underlying mechanisms of life-threatening ventricular arrhythmias complicated by acute myocardial ischemia. Electrophysiological abnormalities both during acute myocardial ischemia, induced by coronary occlusion, and after coronary reperfusion have been studied extensively through epicardial and transmural observations on multiple monopolar and bipolar electrode recordings¹⁻⁶

Epicardial mappings reveal that delayed and fragmented activities of electrograms, (suggesting the existence of dispersed excitation wave fronts due to inhomogeneous conduction) are inscribed on electrodes attached over the ischemic zone of the ventricles, minutes after coronary occlusion as well as coronary reperfusion. Although the endocardial layers of the ischemic zone are exposed more extensively to ischemia than the epicardial layers,⁷⁻⁹ few experiments have been done on the electrophysiological derangement on the endocardial surface of the ventricles both during exposure to acute ischemia and during recovery from the ischemia by reperfusion, because of technical difficulties in measuring

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Fig.1. Diagrammatic illustration of endocardial mapping of the left ventricular septum.

A: The endocardial surface of the left ventricular septum was obtained by longitudinal incision along the lateral free wall of the left ventricle. The endocardial surface of the preparation was superfused in addition to perfusion through the left coronary artery. Solid circles illustrate recording sites of close bipolar electrodes. St: stimulating electrode; DBE: distant bipolar electrode; AV: aortic valve; MV: mitral valve; CS: coronary sinus; AF: anterior fascicle of left bundle branch; PF: posterior fascicle of left bundle branch; APM: anterior papillary muscle; PPM: posterior papillary muscle.

B: Recording of the endocardial Purkinje fiber and ventricular muscle activities were performed through close bipolar electrodes brought into gentle contact with the beating preparation under their own weight yet are free to move in a direction perpendicular to the preparation. This allows them to be in constant contact with the endocardial surface.

both Purkinje and subendocardial muscle activities in detail.

Recently, the role of endocardial Purkinje fibers in the ventricular arrhythmias during reperfusion has been stressed in several reports.⁴⁻¹⁰ The purpose of this experiment, therefore, is 1) to measure, in detail, the endocardial Purkinje fiber and ventricular muscle conduction during reperfusion arrhythmia through endocardial mapping of the isolated canine left ventricle and of the papillary muscle dissected from the canine right ventricle, and 2) to compare the characteristics of reperfusion arrhythmias with the results obtained when reperfusion was initiated after exposure to ischemic environments involving hypoxia, hyperkalemia, and acidosis.

METHODS

Endocardial mapping of the left ventricle

Fifty one mongrel dogs, weighing from 8 to 15 kg, were anesthetized intravenously with sodium pentobarbiturate (30 mg/kg). Immediately after removal, the canine heart was immersed into a bath and perfused with oxygenated Krebs-Ringer solution at a temperature of $35 \pm 1^\circ\text{C}$ through the left coronary artery. The composition of the Krebs-Ringer solution was (in mM): NaCl, 120.3; KCl, 4.0; CaCl_2 , 1.2; MgSO_4 .

$7\text{H}_2\text{O}$, 1.3; NaHCO_3 , 24.2 and glucose, 5.5. The perfusing solution was oxygenated by bubbling a mixed gas of 95% O_2 and 5% CO_2 , and coronary perfusion was maintained at a constant hydrostatic pressure of 100 cm H_2O .

The left ventricle of the perfused heart was incised longitudinally at the lateral free wall to expose the endocardial surface of the left ventricular septum. After mounting on the bottom of the bath, the endocardial surface of the left ventricular septum was also superfused with the oxygenated Krebs-Ringer solution at a rate of 60 ml per min.

A total of 42 close bipolar electrodes, each of which consisted of a pair of stainless needles (100 micrometers in diameter) that are insulated except for the distal cut ends and separated 0.5 to 0.6 mm from each other, were attached to the preparation to measure the activation sequence over the entire surface of the left ventricular septum, as is shown in Fig. 1.

Electrograms recorded from the 42 electrodes were fed into a micro-computer operated system¹¹ which can handle 96 channel electrocardiographic signals simultaneously. The electrograms, after being amplified at 60 dB through RC bandpass filter with 50 to 300 Hz, were processed at a sampling interval of 1 msec. Some of these electrograms were continually monitored on a 4-

Fig.2. Time course for occurrence of malignant ventricular arrhythmias after reperfusion. VT: Ventricular tachycardia; VF: ventricular fibrillation.

channel storage oscilloscope (Sony-Tektronix 5111A) and photographed with a polaroid camera.

The waveforms of the electrograms recorded from the close bipolar electrodes were composed of the two components: the small but sharp initial deflections which corresponded to the Purkinje fiber (PF) activities, and the large late deflections which correspond to the ventricular muscle (VM) activities. The arrival time of PF or VM activities was defined as the deflection peak for each component. The experiment, confirmed that the excitation sequences of the PF and VM activities, which were obtained when the preparation was stimulated at the proximal end of the left bundle branch, were consistent with these reported previously¹²⁻¹⁴

Mapping of the papillary muscle of the right ventricle

Twenty five canine hearts were used for the study of reoxygenation arrhythmias. The right ventricle was opened along the pulmonary artery and the right anteroseptal papillary muscle (RAP) was excised with attached branches of the specialized conducting system (right bundle branch, RBB) and mounted in a tissue bath. All free-running Purkinje fibers were trimmed away. The

Fig.3. PF and VM activities in reperfusion ventricular tachycardia.

A: Tracings of distant bipolar electrograms involving triplets of non-paced contractions at 26 seconds after reperfusion. B: Close bipolar electrograms of the paced, first and second non-paced beats. C: Diagrammatic illustration of recording sites (solid circles) or electrograms.

preparations were superfused with Krebs-Ringer solution gassed with 95% O₂ + 5% CO₂ at a flow rate of 10 ml/min. The temperature was maintained at 37.0 ± 0.3°C. A pacing stimulus of 2 msec in duration and 1.2 times the diastolic threshold was applied to the preparation at a cycle length of 1 sec. To study both the orthodromic and antidromic conduction pathways of the RAP, one pair of stimulating bipolar electrodes was placed on the proximal RBB and a second pair on the apex of the papillary muscle.

Surface extracellular potentials were obtained by using modified bipolar electrodes, which were made from metal microelectrodes with 5 micro meter of the exposed tip length (Frederick Haer & Co). One electrode was placed on the surface of the papillary muscle and the other 1 mm

Fig.4. Endocardial excitation patterns in the early phase of ventricular fibrillation.
 A: Tracings of distant bipolar electrograms indicating ventricular fibrillation.
 B: Tracings of close bipolar electrograms recorded on the Purkinje-muscle junctional area, suggesting that even in ventricular fibrillation synchronization and rhythmicity of excitation are preserved locally to some extent.
 C: Endocardial excitation patterns of three arbitrary beats. Figures printed on each map indicate arrival times of excitation measured from the beginning of the first beat. # indicates the earliest excitation point for each beat.

above that to eliminate the large field effects of the muscle. The signal from modified bipolar electrodes through the voltage follower was amplified with an appropriate frequency response. This technique yields a low noise monopolar recording of Purkinje fiber, the ventricular muscle potentials, and the excitation sequences of the Purkinje and muscular conductions by mapping about 80 points on the preparation.

Transmembrane potentials of Purkinje fiber and muscle cell on Purkinje-muscle junctional area were recorded through standard glass microelectrodes filled with 3M KCl and having a resistance ranging 10 to 20 megohms.

After an initial equilibration period of 2 hours, control electrical activities were recorded under pacing. To detect the origin of spontaneous beats during experiments, extracellular potentials were monitored on the oscilloscope (Tektronix 5111A) and stored by the open reel taperecorder (Sony Magnescale 614A) from the following 4 points: proximal RBB, distal RBB, Purkinje-muscle junctional area, and papillary muscle. The preparations were perfused for 30 min with a glucose-free Krebs-Ringer solution, that was

gassed with 95% N₂ + 5% CO₂, resulting in final PO₂ of 20–30 mmHg in a tissue bath. Reoxygenated Krebs-Ringer solution and arrhythmias due to reoxygenation were analyzed every ten minutes.

RESULT

Occurrence of ventricular arrhythmias was examined on the preparations which were reperfused with the oxygenated Krebs-Ringer solution after 30 min of cessation of coronary flow. Figure 2 shows the time course of the occurrence of ventricular tachycardia (VT) and fibrillation (VF) after reperfusion. In fourteen out of 23 cases, ventricular tachycardia which satisfies a criterion of three or more consecutive premature contractions occurred after reperfusion, and they degenerated into VF within one min except for 3 cases. To investigate what mechanisms may underlie such reperfusion arrhythmias, modes of excitation propagation over the endocardial surface of preparations were examined during VT and its transition into VF.

Figure 3A illustrates tracings of the electrograms recorded from the distant bipolar elec-

Fig.5. Effects of predisposing ischemic condition before reperfusion on occurrence of malignant ventricular arrhythmia.

Top row: Occurrence of VT and VF during reperfusion following 30 min of real ischemia. Data is the same as shown in Fig. 2.

Second to bottom row: Occurrence of VT and VF during reperfusion of oxygenated solution following 30 min of perfusion with solution listed in the left side of each row.

trodes, which can survey the electrical phenomena over the whole preparation. Triplets of non-paced ventricular contractions appear between the paced beats. Figure 3B illustrates a part of the tracings of the close bipolar electrograms simultaneously recorded from the Purkinje-muscular junctional area. It is clearly shown that the Purkinje activities always precede the deflections due to ventricular muscle excitation both in the first and in the second non-paced beats as well as the paced beats. Furthermore, no widening or fragmentation which suggests re-entry mechanisms was observed on recording of all the electrograms, indicating that these ventricular arrhythmias may be caused by abnormal impulse formation of the Purkinje fibers. Such excitation patterns that suggest abnormal impulse formation of the Purkinje fibers were preserved even in the early phase of transition from VT into VF.

Figure 4 is an example of sequential changes in the endocardial excitation pattern during transition from VT into VF. Although fibrillatory wave forms are inscribed on tracings of the distant bipolar electrodes, local activities of the ventricular muscles still inscribe sharp deflections with every beat and also maintain some rhythmicity (Fig. 4), suggesting that in the early phase of VF synchronous excitation may proceed locally even though modes of the propagation sequence

differed from beat to beat. In fact, examination of the patterns of excitation propagation on the endocardial surface of the preparations disclosed that the ventricular muscle excitation for each beat was always initiated around the Purkinje-muscle junctional area and, as a whole, propagated over the septum in a centrifugal manner despite manifesting localized conduction disturbances, as shown in Fig. 4.

It has been reported that among abnormalities observed in the extracellular environment during ischemia, factors of hypoxia, acidosis and hyperkalemia predominantly affect abnormalities of impulse formation and excitation conduction in the cardiac tissue.¹⁵⁻²⁹ To observe effects of these extracellular environmental factors on reperfusion ventricular arrhythmias, occurrence of reperfusion arrhythmias was examined on the preparations which, in place of the predisposing real ischemia induced by coronary occlusion, had been perfused for 30 min with the following three kinds of modified Krebs-Ringer solution: 1) hypoxic ($PO_2 = 20-40$ mmHg), acidic ($pH = 6.8$) and hyperkalemic ($K = 10$ mM) solution; 2) hypoxic and acidic and normo-kalemic (4 mM) solution; 3) only hypoxic solution.

Figure 5 illustrates predisposing effects of each solution on occurrence of VF and VT during reperfusion, comparing them with incidence of reperfusion arrhythmias obtained by combining

Fig. 6. Abnormal impulse formation from Purkinje fiber during re-oxygenation.

A: Block diagram of the preparation, the dissected papillary muscle of the canine right ventricle. Prox, Dist, PMJ and M indicate lead points for surface extracellular potentials shown in this figure. RBB: right bundle branch, Prox: proximal portion of RBB, Dist: distal portion of RBB, PMJ: Purkinje-muscle junctional area, M: Ventricular muscle. AP indicates the recording site for membrane action potential.

B: Control. Membrane action potential (AP) fires spontaneously at a cycle length of 2 seconds. Activation of the preparation is initiated at the Purkinje activity (P), and then proceeds to ventricular muscle (M) through PMJ via distal RBB.

C: During re-oxygenation. Repetitive firings with various coupling intervals ranging from 1.3 to 0.54 sec are found during re-oxygenation. Surface recordings show that impulse formation occurs at PMJ in such repetitions.

data shown in Fig. 2 into a total, that is, the data obtained during reperfusion after 30 min of predisposing ischemia. On the all preparations which had been perfused for 30 min with a hypoxic, acidic and hyperkalemin solution, ventricular fibrillation always was induced by reperfusion, as shown in the second row of Fig. 5. When the factor of hyperkalemia was eliminated from the predisposing perfusate, incidence of ventricular reperfusion arrhythmia remained still as high as that observed in the real ischemic group. However, occurrence of VF was reduced significantly in proportion to increase in frequency of VT, suggesting that degeneration from VT into VF was markedly prevented by elimination of hyperkalemic factor, as shown in the third row of Fig. 5. Furthermore, reperfusion after predisposing perfusion with the hypoxic, normo-acidic and normo-kalemin solution infrequently induced VT, non of which degenerated into VT.

To confirm induction of abnormal impulse formation in Purkinje-muscle junctional area by reperfusion, mapping of membrane action potentials were performed on the papillary muscle dissected from the canine right ventricle.

Thirteen preparations which showed normal automaticity originating from proximal RBB at

a cycle length ranging from 1 to 5 sec under normoxia, were studied for reoxygenation arrhythmia (Fig. 6A). During hypoxia no abnormal impulse formation was observed in 13 cases under pacing. In 4 of 13 cases, reoxygenation arrhythmias were observed; 2 cases with single abnormal impulse formation and another 2 cases with repetitive formations. Analysis of the abnormal impulse formation was performed in these 4 cases. Figure 6C (right) show an example of repetitive formations during reoxygenation. Control recording of Purkinje action potential before hypoxia (Fig. 6B) showed a constant automaticity whose cycle length was 2 sec and, which was originating from proximal RBB. The repetitive impulse formation was observed both in the early and late periods (1–5 and 10–15 min) of reoxygenation. The extracellular potential recordings revealed that each abnormal beat had the same pattern as that of the normal beat in Purkinje muscle activations. Thus, Purkinje spike, which always preceded muscle activity, suggests that the focus of abnormal beats was the terminal Purkinje fibers in Purkinje-muscle junctional area. This result was consistently reproducible in the remaining three cases with the abnormal impulse formations.

DISCUSSION

Malignant ventricular arrhythmias are frequently associated with ventricular reperfusion following 20 to 30 min of acute ischemia induced by ligation of the coronary artery of *in situ* canine or rat hearts. Thus, the mortality of the reperfusion arrhythmias due to ventricular fibrillation is as high as 25 to 56 percent, which is comparable to that which occurs during acute ischemia induced by coronary occlusion. The incidence of the ventricular fibrillation (48 percent) during reperfusion in this experiment is consistent with the mortality reported from *in situ* experiments on reperfusion arrhythmia.³⁰⁻³⁵

The ventricular arrhythmias induced during reperfusion have the following characteristics: 1) they are induced almost within one min of reperfusion and tend to continue for a short duration; 2) they frequently exhibit rapid unifocal ORS patterns with many runs of ventricular tachycardia; and 3) they are easily suppressed by rapid pacing. Several authors^{6,34-35} have therefore assumed that enhancement of the idioventricular rhythm is the main cause of such reperfusion arrhythmias, and that the abnormal impulse formation in the Purkinje fibers, which were observed on the excised and superfused Purkinje fiber preparations, are closely related to the mechanisms of the enhanced idioventricular rhythm during reperfusion. However, this assumption has not been proven because of difficulties in measuring the endocardial Purkinje activities in detail.

A detailed examination of the endocardial excitation sequence of this experiment showed that during reperfusion tachycardia, which turned into ventricular fibrillation within a few seconds, the endocardial excitation patterns were still compatible with those from the unifocal impulse formation originated by the endocardial Purkinje fibers. The abnormal impulse formation due to triggered activities or enhanced automaticity has been observed experimentally on the Purkinje fibers dissected from the infarcting tissues of the one-day-old infarcting dog hearts,³⁶⁻³⁷ or exposed to abnormal extracellular environments which may induce intra-cellular calcium overload.³⁹⁻⁴¹

Several reports have studied the relationship between reperfusion arrhythmic and triggered activity. Ferrier et al⁴² observed repetitive firing of the Purkinje fibers on isolated canine ventricular tissue which were perfused with the oxy-

genated solution after 30 min of ischemic condition. They concluded that such abnormal impulse formation was due to abnormal automaticity which appeared in association with a transient reduction of the maximum diastolic potential (MDP) of the subendocardial Purkinje fibers after reperfusion. In this experiment, triggered activities were also observed on the Purkinje fibers near the PM junction one to 10 min after reperfusion but they did not appear to be associated with a marked depolarization of MDP up to -60 to -50 mV. This inconsistency may be attributed to differences in predisposing ischemic conditions and in isolation of ventricular tissue.

In a recent *in vitro* experiment measuring the intra-cellular calcium ion in the ventricular muscle with use of aequorin, a calcium sensitive dye⁴³ a transient but very extensive increase in the intra-cellular calcium ion was observed during re-oxygenation. Therefore, it is conceivable that the abnormal impulse formation, caused by a transient increase in the intra-cellular calcium ion, may be one of the most important mechanisms for ventricular arrhythmias including ventricular premature contractions and almost all of the ventricular tachycardias during reperfusion.

Ventricular fibrillation during reperfusion can not be explained only by the above stated mechanism, because multiple re-entry circuits of excitation are supposed to exist in the ventricles spatially and temporarily in a random manner.⁴⁴ The basic mechanisms to induce such random re-entry may be explained only by the augmented heterogeneity of the myocardial electrophysiological properties, especially both the excitation refractoriness and conductivity.³¹⁻³² Reperfusion of the acute ischemic ventricular tissue with the oxygenated blood improves the electrophysiological properties of ischemic myocardial cells almost to control levels within one min³⁴; however during the improvement in this brief periods an extensive heterogeneity of the electrical properties may develop in the reperfusion area. This heterogeneity may be maximized upon the short coupled ventricular contractions that originate from the abnormal impulse formation from the Purkinje fibers, contributing to development of ventricular fibrillation.

Such assumption may be verified by the results illustrated in Fig. 5. Namely, hyperkalemia, which may be a main factor causing augmentation of heterogeneity in excitation refractoriness and conduction during reperfusion as well as acute ischemia, enhanced markedly development

of VF from VT, although it affected little on occurrence of ventricular arrhythmias due to abnormal impulse formation.

Clinical significance of reperfusion arrhythmias

The clinical importance of reperfusion ventricular arrhythmias is a matter of controversy⁴⁵⁻⁴⁶. Clinical settings in which reperfusion ventricular arrhythmias are supposed to occur are: 1) relief of coronary artery spasm in spastic angina, 2) thrombolysis or angioplasty for the obstructed coronary artery, and 3) development of new collaterals or bypass graft surgery. Malignant ventricular arrhythmias leading to ventricular fibrillation are frequently associated with variant form angina,⁴⁵ but ventricular arrhythmias with intra-coronary thrombolysis for acute myocardial infarction usually have characteristics of accelerated idioventricular rhythms, providing a useful indicator of the success of recanalization.⁴⁶ Why reperfusion arrhythmias occurring in patients who have had successful coronary thrombolysis are not so malignant as in variant form angina has not been clarified.

It is speculated that the extensive electrophysiological inhomogeneity that produced experimentally or in sudden relief of coronary spasm may not develop during reperfusion with coronary thrombolysis, where hours of preceding ischemia may elapse before reperfusion, and recanalization may gradually proceed in association with thrombolytic reaction.

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