

Arrhythmogenic Effects of Graded Coronary Blood Flow Reductions Superimposed on Prior Myocardial Infarction in Dogs

Tetsushi Furukawa, MD; Kazuo Moroe, MD; Harry N. Mayrovitz, PhD;
Ronald Sampsel, DVM; Nanako Furukawa, DDS; and Robert J. Myerburg, MD

Background. We studied arrhythmogenesis and its underlying pathophysiology during graded reductions of coronary blood flow, superimposed on prior myocardial infarction to test the hypothesis that spontaneous ventricular fibrillation and induced ventricular tachycardia are dependent on different patterns of coronary flow reduction in hearts with prior myocardial infarction.

Methods and Results. In 10 sham-operated dogs (control group) and 24 dogs with 3-week-old experimental apical myocardial infarction, the left circumflex coronary artery was constricted to produce four grades of flow reduction: 25%, 50%, 75%, and 100%. Among the sham-operated control animals, only one of 10 (10%) developed spontaneous ventricular fibrillation and only two of nine (22%) were inducible into sustained ventricular tachycardia during 100% circumflex coronary artery flow reduction. No spontaneous ventricular fibrillation or inducible ventricular tachycardia occurred with lesser grades (25%, 50%, or 75%) of flow reduction among the control animals. In the myocardial infarction group, five of 24 dogs (21%) were inducible before flow reduction. However, 50% flow reduction in the myocardial infarction group resulted in inducibility of ventricular tachycardia in 12 of 24 dogs (50%); nine of 16 (56%) during 75% flow reduction; and six of 11 (55%) with 100% flow reduction. In addition, none of the dogs in the myocardial infarction group developed spontaneous ventricular fibrillation during 25% or 50% flow reduction, whereas six of 22 (27%) developed ventricular fibrillation during 75% flow reduction and 10 of 21 (48%) during 100% flow reduction. In dogs with spontaneous ventricular fibrillation during flow reduction, the total myocardial mass of the ischemic "risk" zone and infarcted zone was significantly greater than in those without spontaneous ventricular fibrillation ($68 \pm 5\%$ versus $56 \pm 6\%$ [$p < 0.01$]). There was no difference in the total myocardial mass of the ischemic risk zone and infarcted zone between dogs with and without inducible ventricular tachycardia during flow reduction.

Conclusions. In canine model of subacute myocardial infarction, superimposed ischemia increased the likelihood of inducible sustained ventricular tachycardia with lesser grades of coronary flow reduction compared with that necessary to allow spontaneous ventricular fibrillation. The underlying pathophysiology appears to differ between spontaneous ventricular fibrillation and electrically induced sustained ventricular tachycardia. (*Circulation* 1991;84:368-377)

Recurrent ischemia superimposed upon preexisting myocardial infarction (MI) has been identified as a factor predisposing individuals to sudden cardiac death.¹⁻³ Schuster and Bulkley² demonstrated in a population of postinfarction patients that those with a second critically narrowed

coronary artery were highly susceptible to sudden cardiac death. Subsequently, many experimental studies have demonstrated the arrhythmogenicity of acute ischemia superimposed upon convalescent or healed MI.⁴⁻¹⁰ In most of these studies, acute ischemia was produced by complete occlusion of a coro-

From the Research Division, Miami Heart Institute (T.F., K.M., H.N.M., R.S.), Miami Beach, and the Departments of Cellular and Molecular Pharmacology (N.F.) and Medicine, Division of Cardiology (R.J.M.), University of Miami School of Medicine, Miami, Fla.

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Address for correspondence: Tetsushi Furukawa, MD, Division of Cardiology (R-94), Department of Medicine, University of Miami School of Medicine, PO Box 016960, Miami, FL 33101.

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nary artery.⁴⁻⁹ Despite the recognition that many victims of sudden cardiac death have only partial coronary obstruction at necropsy, however, only limited experimental data are available to date on arrhythmogenic effects of partial coronary obstruction superimposed on previous MI.¹¹⁻¹⁷

We therefore used a canine MI model to test the hypothesis that partial coronary flow reduction superimposed on prior MI is arrhythmogenic. Because the partial coronary flow reduction superimposed on preexisting MI increased both spontaneous and electrically inducible ventricular tachyarrhythmias, we studied the differences in the grade of coronary flow reduction, and the electrophysiological and anatomic bases for differences between spontaneous and electrically inducible ventricular tachyarrhythmias.

Methods

Surgical Preparation

Thirty-seven mongrel dogs weighing 15–25 kg were anesthetized intravenously with 20 mg/kg sodium thio-pental and were intubated and ventilated with a Bennet MA-I volume-limited positive-pressure respirator. Surgery was performed using standard sterile techniques, and during the procedure anesthesia was maintained with a mixture of nitrous oxide, halothane, and oxygen. The chest was entered through a left-sided thoracotomy at the fourth intercostal space. The pericardium was incised and the heart exposed. In 10 of the animals (control group), a sham operation was performed. The procedure consisted of a thoracotomy and pericardiotomy. In the other 27 dogs (MI group), an experimental MI was created by ligating the left anterior descending coronary artery just distal to the first diagonal branch and all of the distal branches of the circumflex, left anterior descending, and posterior descending arteries visible on the surface of the left ventricular apex.^{18,19} After surgery was completed, the chest was closed and the endotracheal tube removed. During the recovery period, standard postoperative care, including antibiotics and antipyretics, was administered.

During the early postoperative period, three of the MI animals had unwitnessed deaths, reducing this group to 24 animals. None of the 10 sham-operated animals died during the postoperative period.

Electrophysiologic Studies Before and During Graded Coronary Blood Flow Reductions

Open-chest studies were carried out 3 weeks after the original surgery. The animals were anesthetized with intravenous urethane (625 mg/kg) and α -chloralose (125 mg/kg). Throughout each experiment, supplementary anesthetic was given as needed to maintain a constant level of anesthesia. A thermal mattress was used to maintain a physiological body temperature. The animals were intubated and ventilated with a Bennet MA-I respirator. Saline-filled polyethylene catheters were placed in the right femoral artery to monitor arterial blood pressure and obtain blood samples for blood gas measurements.

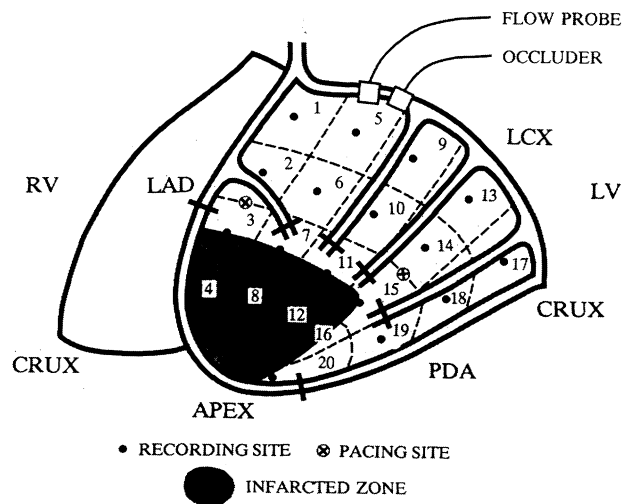


FIGURE 1. Predetermined recording and pacing electrode sites and their spatial relation to the infarcted zone. LV, left ventricle; RV, right ventricle; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PDA, posterior descending coronary artery.

Catheters in the right femoral vein were used to infuse anesthetics and normal saline to replace spontaneous fluid losses. Intravenous bolus injections of 300 IU/kg heparin sodium, followed by continuous infusion of 20 IU/kg/hr, was given to anticoagulate animals. Throughout each experiment, ventilation was adjusted to maintain PO_2 between 85 and 100 mm Hg and pH between 7.35 and 7.45. Intravenous sodium bicarbonate was administered as needed to maintain pH.

The chest was opened through a left thoracotomy in the fifth intercostal space and the heart was suspended in a pericardial cradle. The left circumflex coronary artery was dissected, and a flow probe (model MT-4025, Micron Instruments) and inflatable cuff vascular occluder (model VO-3, Rhodes Medical Instruments) were placed around the artery just proximal to the origin of obtuse marginal branch. Blood flow in the left circumflex coronary artery was measured with an electromagnetic flow meter (Micron Instruments, model RC1000). Pairs of Teflon-coated, 0.005-inch (0.013 cm)-diameter stainless steel plunge electrodes, with the wires bared 0.5–1 mm from the tip, were inserted through 23-gauge needles. For recording bipolar endocardial electrograms, 20 pairs of plunge electrodes were inserted from 20 evenly spaced epicardial sites (Figure 1) of the left ventricular free wall and anchored to the endocardium. These epicardial insertion sites were the same for every dog, with 1.5–2.2 cm between the adjacent electrode pairs, which depended on the size of the heart. One pair of plunge electrodes was also anchored to the right ventricular free wall to record right ventricular endocardial electrogram. For recording bipolar subepicardial electrograms, 20 pairs of plunge electrodes were inserted from the same 20 epicardial sites as for endocardial recording elec-

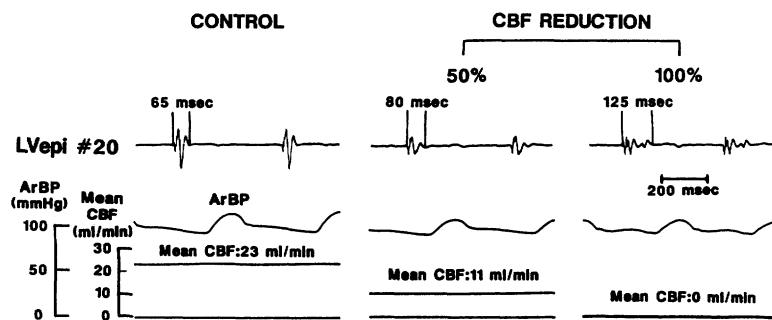


FIGURE 2. Representative tracings of the subepicardial bipolar electrogram demonstrating the prolongation of electrogram duration during coronary blood flow reduction. The duration of the bipolar electrogram was increased from control value of 65 msec to 80 msec during 50% coronary blood flow reduction and to 120 msec during 100% flow reduction. ArBP, arterial blood flow; CBF, coronary blood flow; LVEpi, left ventricular subepicardium.

trodes and were anchored to the subepicardial myocardium. For pacing the heart, two pairs of plunge electrodes were inserted from the left ventricular free wall (one in the anterior and another in the posterior free wall) within 1 cm of the epicardial infarction border line and were anchored to the midmyocardium.²⁰ No attempt was made to control the orientation of the 0.5 to 1-mm-long bared ends of plunge electrodes, which hooked onto endocardial surface, midmyocardium, or subepicardial myocardium. Thus, the interpolar distance of a bipolar plunge electrode could vary from 0.5 mm to 2.5 mm. The proximal terminal of the plunge electrodes was connected to a distribution box which in turn was linked to an oscilloscopic photographic recorder (model DR-16, Electronics for Medicine). Throughout each experiment, a lead II electrocardiogram, the local electrograms, circumflex coronary artery blood flow, and arterial pressure were continuously monitored. The electrograms were obtained at filter settings of 30–500 Hz. All records were obtained at a paper speed of 100 mm/sec.

In each experiment, the left circumflex coronary artery was constricted to achieve each of four preselected levels of reduction in mean coronary blood flow: 25%, 50%, 75%, and 100% reductions. The variation of coronary blood flow during each grade of flow reduction was less than $\pm 5\%$ during the 20 minutes required for data acquisition. In an effort to avoid bias due to the sequence of grades of myocardial ischemia, the order of the four grades of coronary blood flow reduction was randomized for each experiment. Bipolar electrograms were recorded from all recording sites prior to and 10 minutes after establishing each grade of coronary artery blood flow reduction. Representative tracings of the subepicardial bipolar electrogram are demonstrated in Figure 2 as an example of the measurement of the duration of the electrogram. After induction of myocardial ischemia, the bipolar electrogram showed a progressive diminution in amplitude, and the terminal portion often fragmented into low and irregular spikes, sometimes making accurate distinction between the terminal portion of the depolarization waves and repolarization waves difficult. As indicated in Figure 2, the onset of local bipolar electrogram was defined as the earliest electrical activity that deviated from a stable baseline, and the end of the electrogram was

defined as the point of return to baseline.²¹ After the electrograms had been recorded, programmed ventricular stimulation was carried out from two ventricular pacing sites using programmable stimulator (model 5325, Medtronic). Rectangular pulses 1 msec in duration and twice diastolic threshold were used for pacing. From each of the pacing sites, single and double extrastimuli were delivered after 8 beat trains of ventricular drive pacing at cycle lengths of 350 msec and 300 msec. For each extrastimulus, diastole was scanned at 10 msec decrements to the point of ventricular refractoriness. Upon completion of the study for each of the graded blood flow reduction steps, the coronary artery constriction was released and 40 minutes was permitted for recovery prior to repeating the protocol with the subsequent grade of blood flow reduction. Coronary artery constriction was released slowly over approximately 3 minutes, so that no sustained form of reperfusion arrhythmia was observed. Within approximately 10 minutes after release of coronary artery constriction, blood flow in the left circumflex coronary artery, arterial blood pressure, and the amplitude and duration of bipolar electrograms at every endocardial and subepicardial recording site had returned to the control values.

When sustained monomorphic ventricular tachycardia (VT) was induced, electrograms were recorded from all 41 recording sites. The onset of local bipolar electrogram was defined as the earliest electrical activity that deviated from a stable baseline at each recording site.²¹ The onset of the QRS complex in lead II of the electrogram was used as the zero reference. The earliest recorded activation site was defined as the "observed breakthrough of activation" of the VT.²¹ Upon completion of mapping, burst ventricular pacing was used in an effort to terminate the VT. When the VT could not be terminated by pacing or it degenerated into polymorphic VT or ventricular fibrillation (VF), an epicardial direct current shock of 10 J was applied and if necessary a second shock of 20 J was delivered. In cases in which the two shocks did not terminate the induced or spontaneous ventricular tachyarrhythmia, the protocol was not advanced and the experiment was terminated. In those instances in which an induced VT was successfully terminated by pacing or DC shock, re-

producibility of initiation of the VT by programmed stimulation was assessed.

The response to programmed ventricular stimulation was defined as VT when the last stimulated beat was followed by at least five consecutive ventricular complexes. Sustained monomorphic VT was defined as VT with a cycle length of greater than 120 msec lasting for 30 seconds or longer without any spontaneous change in rate or surface electrocardiographic QRS complex configuration. Sustained polymorphic VT was defined as VT with a mean cycle length of greater than 120 msec lasting for 30 seconds or longer with beat-to-beat changes in rate and/or surface electrocardiographic QRS complex configuration. VF was defined as a ventricular tachyarrhythmia that did not manifest a uniform surface electrocardiographic configuration with clearly identifiable, discrete QRS complexes, during which the mean cycle length was less than 120 msec. When there was immediate VF or degeneration to VF within 3 seconds of initiation, the VF was considered to be the primary arrhythmia; when an organized ventricular arrhythmia degenerated to VF 3 seconds or longer after initiation, VT was considered to be primary, with subsequent degeneration to VF. When VT degenerates to VF within 30 seconds after initiation, it is impossible to determine whether VT was sustained or nonsustained. In the present experiment, VT was defined as sustained when it continued for 15 seconds or longer before degenerating to VF; when VT degenerated to VF within 15 seconds after initiation, it was defined as nonsustained. Cycle length was determined using the local bipolar electrograms recorded with the epicardial electrodes not being used for cardiac stimulation.

Postmortem Studies

After completion of the study, the animals were killed by the intravenous administration of 1 g KCl, and the heart was immediately excised. Using a dual perfusion method, the masses of infarcted zone and ischemic "risk" zone were quantified.²² The left main coronary artery orifice was sutured closed, and an incision was made at the site of previous circumflex coronary artery occlusion. Catheters were positioned both distal and proximal to the incision, and the artery was ligated at both places. Evans blue dye (0.5%) was infused into the proximal segment and triphenyltetrazolium chloride (1.5%) into the distal segment of the artery for a period of 10 minutes at a pressure of 100 mm Hg. The free wall of the right ventricle was removed and the left ventricle cut into 0.5 cm-thick transverse slices from apex to base. The areas of infarcted zone and ischemic-risk-zone were outlined by planimetry in each slice, and their masses were calculated and expressed as percentage of total left ventricular mass.²³ Locations of bipolar plunge electrodes and their spatial relation to the infarcted zone and the ischemic risk zone were also determined using two methods. In 11 dogs, radiofrequency energy (450 Hz) of approximately 100 J (10 W×10

sec) was delivered through the plunge electrodes to the myocardial sites at which the bipolar plunge electrodes were placed to produce local electrocautery using an electrosurgical generator (model SSE2L, Volleyleb).²⁴ In the remaining 23 dogs, the hearts were stained and cut into slices with the plunge electrodes remaining in situ. When the site of electrode was within 1 cm of the border zone between normal myocardium and the infarcted zone, it was arbitrarily classified as a border zone between normal myocardium and infarcted zone. When the site was within 1 cm of the border between the ischemic risk zone and the infarcted zone, it was classified as a border zone between the ischemic risk zone and the infarcted zone. At all other sites, it was classified into one of the normal myocardium, the ischemic-risk-zone, or the infarcted zone.

Statistical Analysis

Continuous data are presented as mean±standard deviation, and their statistical significance was evaluated using Student's unpaired *t* test. Statistical significance of binomial responses (incidence of VF, inducibility of VT, and degeneration of VT into VF) between the normal group and the MI group was evaluated with the χ^2 test with Yates' correction. Because binomial responses at different grades of coronary blood flow reduction within a group were not independent of each other, their statistical significance was evaluated with the Cochran *Q* test for more than one related sample.²⁵ Statistical significance of the difference between the increases in the incidence of spontaneous VF and the inducibility of VT from the control state to the certain grade of coronary flow reduction was also evaluated with the Cochran *Q* test (see "Appendix").²⁵ Differences with $p < 0.05$ were considered significant.

Results

Spontaneous Ventricular Fibrillation

All 10 sham-operated dogs (control group) underwent each of the four grades of flow reduction in the left circumflex coronary artery in random order. Of the 24 MI dogs, 23 dogs underwent 25% reduction in coronary blood flow, 24 underwent 50% reduction, 22 underwent 75% reduction, and 21 underwent 100% reduction. The small decreases in the number of animals studied at 25%, 75%, and 100% flow reductions were due to an irreversible arrhythmia terminating the experimental protocol before completing all four grades of flow reduction.

In the control group, none of the dogs developed spontaneous VF during 25%, 50%, or 75% coronary blood flow reduction, and only one of the 10 (10%) developed spontaneous VF during 100% reduction (Table 1). In the MI group, none of the dogs developed spontaneous VF during 25% or 50% coronary blood flow reduction. Six of the 22 (27%) developed VF during 75% reduction, and 10 of the 21 (48%) developed VF during 100% reduction (Table 1).

TABLE 1. Incidence of Spontaneous Ventricular Fibrillation

	CBF reduction									
	0%		25%		50%		75%		100%	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Control group	0/10	(0)	0/10	(0)	0/10	(0)	0/10	(0)	1/10	(10)
<i>p</i> vs. 0% CBF reduction*			NS		NS		NS		NS	
MI group	0/24	(0)	0/23	(0)	0/24	(0)	6/22	(21)	10/21	(48)
<i>p</i> vs. 0% CBF reduction*			NS		NS		<i>p</i> <0.05		<i>p</i> <0.01	
<i>p</i> Between groups†	NS		NS		NS		NS		NS	

CBF, coronary blood flow; NS, not significant; MI, myocardial infarction.

**p* obtained by comparing the incidence of spontaneous ventricular fibrillation between the control state and each grade of coronary blood flow reduction in each group.

†*p* obtained by comparing the incidence of spontaneous ventricular fibrillation between control group and MI group before or during the same grade of coronary blood flow reduction.

During 75% flow reduction, five of the six episodes of VF were preceded by premature ventricular complexes (PVCs). Five of the 16 dogs that did not develop VF had developed PVCs and/or nonsustained VT. The average time from the onset of coronary constriction to the onset of PVCs was 3.3 ± 2.6 minutes and to the onset of VF was 4.6 ± 3.9 minutes. Thus, the onset of spontaneous VF was preceded by the onset of PVCs and appeared to be promoted by intermittently occurring PVCs. During 100% flow reduction, eight of the 10 VF episodes were preceded by PVCs. Four of the 11 dogs that did not develop VF had developed PVCs and/or nonsustained VT. The average time from the onset of coronary constriction to the onset of PVCs was 3.1 ± 2.7 minutes and to the onset of VF was 4.0 ± 3.8 minutes. Within the MI group, no animals developed spontaneous VF with 50% or less coronary flow reduction, but the incidence of spontaneous VF during 75% and 100% flow reduction reached statistical significance (*p*<0.05 for 75% and *p*<0.01 for 100%; Table 1).

Inducible Sustained Ventricular Tachycardia

In the control group, the stimulation protocol was completed in all of the 10 dogs during 25%, 50%, and 75% coronary blood flow reductions, and in nine of the 10 during 100% flow reduction. In one dog, the stimulation protocol could not be completed during 100% flow reduction because of spontaneous VF. In the MI group, the stimulation protocol was completed in all 23 dogs during 25% flow reduction, in all 24 during 50% flow reduction, in 16 of the 22 during 75% flow reduction, and in 11 of the 21 during 100% flow reduction. In six dogs during 75% flow reduction and 10 dogs during 100% flow reduction, the stimulation protocol could not be completed because of spontaneous VF.

Among the control dogs, sustained VT was not inducible during 25%, 50%, or 75% reductions in circumflex coronary flow. Sustained VT was inducible in two of nine dogs (22%) during 100% flow reduction, and both were polymorphic (Table 2). In the MI group, sustained monomorphic VT with cycle lengths ranging from 170 to 260 msec was induced in

five of 24 dogs (21%) before coronary blood flow reduction. Sustained VT was inducible in five of the 23 (22%) during 25% flow reduction (all monomorphic), in 12 of the 24 (50%) during 50% flow reduction (nine monomorphic and three polymorphic), in nine of the 16 (56%) during 75% flow reduction (six monomorphic and three polymorphic), and in six of the 11 (55%) during 100% flow reduction (three monomorphic and three polymorphic) (Table 2). During 50% and 75% coronary flow reduction, the probability of inducing sustained VT was significantly higher in the MI group than in the control group (Table 2). Further, within the MI group, the probability of inducing sustained VT during 50%, 75%, and 100% flow reduction was significantly greater than the probability before flow reduction (Table 2). When analysis was applied only to sustained monomorphic VT, the probability of inducing sustained monomorphic VT during 50% flow reduction was significantly higher than the probability before flow reduction (Table 2).

In the MI group, during 50% coronary blood flow reduction, the inducibility of sustained VT was increased from five of 24 (21%) in the control state to 12 of 24 (50%), whereas none of the 24 dogs developed spontaneous VF in the control state or during 50% flow reduction. During 50% flow reduction, the frequency of inducibility of sustained VT compared with the control state was significantly greater than the increased incidence of spontaneous VF (*p*<0.05). However, during 75% or 100% flow reduction, the frequency of inducibility of sustained VT and incidence of spontaneous VF compared with controls were not significantly different.

Among the animals induced into sustained VT in the MI group, spontaneous degeneration into VF occurred in none of the five (0%) VT inductions before coronary blood flow reduction, and none of the five (0%) inductions during 25% flow reduction. However, nine of the 12 (75%) animals induced into VT during 50% flow reduction, nine of the nine (100%) during 75% flow reduction, and six of the six (100%) during 100% flow reduction did degenerate into VF (Table 3). Figure 3 illustrates sustained monomorphic VT induced before coronary blood

TABLE 2. Inducibility of Sustained Ventricular Tachycardia

	CBF reduction				
	0%	25%	50%	75%	100%
	n (%)	n (%)	n (%)	n (%)	n (%)
Sustained VT					
Control group	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	2/9 (22)
<i>p</i> vs. 0% CBF reduction*		NS	NS	NS	NS
MI group	5/24 (21)	5/23 (22)	12/24 (50)	9/16 (56)	6/11 (55)
<i>p</i> vs. 0% CBF reduction*		NS	<i>p</i> <0.01	<i>p</i> <0.05	<i>p</i> <0.05
<i>p</i> between groups†	NS	NS	<i>p</i> <0.05	<i>p</i> <0.05	NS
Sustained monomorphic VT					
Control group	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/9 (0)
<i>p</i> vs. 0% CBF reduction*		NS	NS	NS	NS
MI group	5/24 (21)	5/23 (22)	9/24 (38)	6/16 (38)	3/11 (27)
<i>p</i> vs. 0% CBF reduction*		NS	<i>p</i> <0.05	NS	NS
<i>p</i> between groups†	NS	NS	<i>p</i> <0.05	NS	NS

CBF, coronary blood flow; VT, ventricular tachycardia; NS, not significant; MI, myocardial infarction.

**p* obtained by comparing the inducibility of VT between prior to flow reduction and during each grade of blood flow reduction in each group.

†*p* obtained by comparing the inducibility of VT between control group and MI group prior to flow reduction or during the same grade of flow reduction.

flow reduction and during 50% flow reduction, both of which had identical morphology and cycle length. Sustained monomorphic VT induced during 50% flow reduction spontaneously degenerated into VF (Panel B), whereas VT induced prior to flow reduction did not (Panel A). The incidence of spontaneous degeneration of VT into VF was significantly higher during 50% and 75% flow reduction than before flow reduction (Table 3). When analysis was applied only to sustained monomorphic VT, the incidence of spontaneous degeneration of VT into VF was also significantly higher during 50% flow reduction than before coronary flow reduction (Table 3).

In the MI group, the site of observed breakthrough of activation of VT was determined in five sustained monomorphic VTs induced before coronary blood flow reduction and in 13 monomorphic VTs induced only during coronary blood flow reduction. The precise activation sequence of polymorphic VT could not be determined with our mapping technique. All

VTs induced without coronary blood flow reduction had the observed breakthrough of activation in the border zone of the infarcted myocardium: four of five (80%) in the endocardium and one of five (20%) in the subepicardium. All VTs induced only during coronary blood flow reduction had the observed breakthrough of activation within the ischemic risk zone: 10 of 13 (77%) in the subepicardium and 3 of 13 (23%) in the endocardium.

Ischemia-Induced Prolongation of Electrogram Duration

The prolongation of the electrogram duration in the epicardial border zone between the ischemic-risk-zone and the infarcted zone were compared between dogs with and without spontaneous and induced ventricular tachyarrhythmias (Table 4). Because spontaneous VF usually developed within a few minutes after coronary artery constriction in dogs with spontaneous VF, the electrograms recorded

TABLE 3. Degeneration of Ventricular Tachycardia Into Ventricular Fibrillation in Myocardial Infarction Group

	CBF reduction				
	0%	25%	50%	75%	100%
	n (%)	n (%)	n (%)	n (%)	n (%)
Sustained VT					
Degeneration to VF	0/5 (0)	0/5 (0)	9/12 (75)	9/9 (100)	6/6 (100)
<i>p</i> vs. 0% CBF reduction*		NS	<i>p</i> <0.05	<i>p</i> <0.01	NS
Sustained monomorphic VT					
Degeneration to VF	0/5 (0)	0/5 (0)	6/9 (67)	6/6 (100)	3/3 (100)
<i>p</i> vs. 0% CBF reduction		NS	<i>p</i> <0.05	NS	NS

CBF, coronary blood flow; VT, ventricular tachycardia; VF, ventricular fibrillation; NS, not significant.

**p* obtained by comparing the incidence of spontaneous degeneration of VT into VF between prior to flow reduction and during each grade of blood flow reduction.

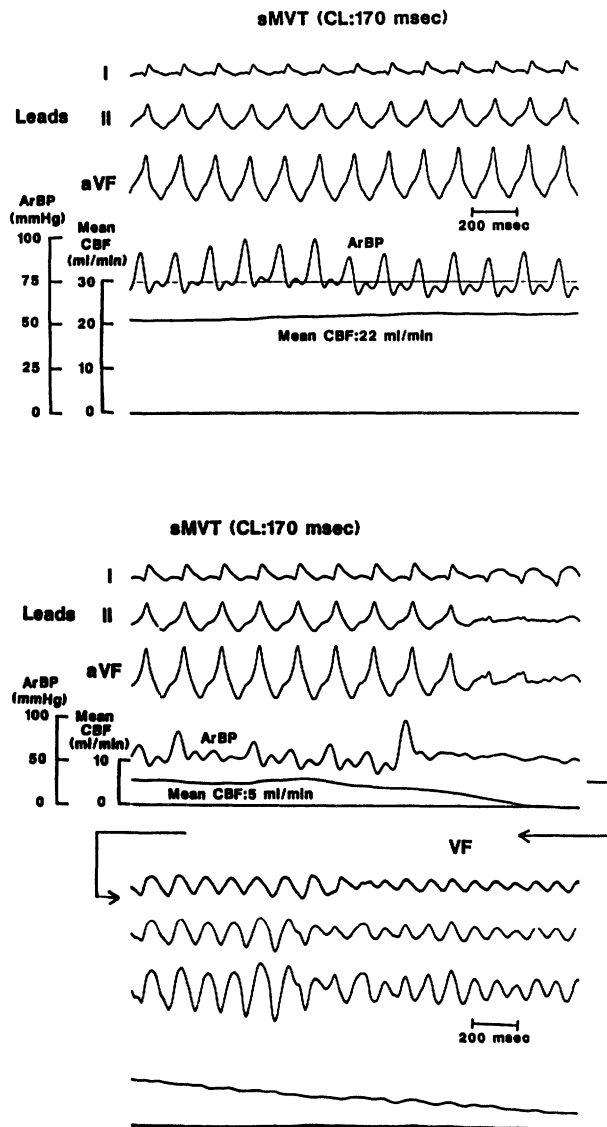


FIGURE 3. Panel A: Sustained monomorphic ventricular tachycardia (VT) induced prior to coronary flow reduction. During VT the mean coronary blood flow was 22 ml/min and VT did not degenerate into ventricular fibrillation. Panel B: Sustained monomorphic VT induced in the same dog during 50% reduction in coronary blood flow. VT had a morphology and cycle length (170 msec) identical to those of induced VT before coronary flow reduction. During VT the mean coronary blood flow was 5 ml/min, and VT spontaneously degenerated into VF. sMVT, sustained monomorphic VT; CL, cycle length; ArBP, arterial blood pressure; CBF, coronary blood flow.

immediately before development of VF were used for comparison. The prolongation of the electrogram duration was greater in dogs with inducible sustained VT during ischemia than those without (Table 4). In contrast, there was no difference in the prolongation of electrogram duration in the epicardial border zone between the ischemic-risk-zone and the infarcted zone between dogs with and without spontaneous VF (Table 4).

TABLE 4. Comparison of Ischemia-Induced Prolongation of Electrogram Duration Between Dogs With and Without Arrhythmias in Myocardial Infarction Group

	% Change in electrogram duration in IRZ-IFZ during each grade of CBF reduction		
	50% reduction	75% reduction	100% reduction
Spontaneous VF during ischemia*			
Yes	...	52±11%	138±60%
No	...	44±8%	129±48%
Yes vs. no†	...	NS	NS
Inducible sustained VT during ischemia‡			
Yes	37±8%	65±11%	169±96%
No	17±4%	40±9%	104±24%
Yes vs. no†	p<0.05	p<0.01	p<0.05

IRZ-IFZ, border zone between ischemic-risk-zone and infarcted zone; CBF, coronary blood flow; VF, ventricular fibrillation; NS, not significant; VT, ventricular tachycardia.

*During 50% coronary blood flow reduction, none of the dogs had developed spontaneous VF.

†p obtained by comparing the value between dogs with and without each type of arrhythmia during the same grade of blood flow reduction.

‡Dogs with inducible sustained VT before flow reduction were excluded.

Pathological Findings

The mass of the infarcted zone and the total mass of the infarcted and ischemic risk zones were compared between dogs with and without spontaneous or inducible ventricular tachyarrhythmias to elucidate the relation between pathological changes and arrhythmia developments (Table 5). Dogs with spontaneous VF during coronary blood flow reduction had

TABLE 5. Comparison of Area of Infarcted Zone and/or Ischemic Risk Zone Between Dogs With and Without Arrhythmias in Myocardial Infarction Group

	Area of IFZ*	Area of IFZ & IRZ*
Inducible sustained VT before CBF reduction		
Yes	18±5%	...
No	10±5%	...
Yes vs. no†	p<0.01	...
Spontaneous VF during CBF reduction		
Yes	14±6%	68±9%
No	10±4%	58±8%
Yes vs. no‡	NS	p<0.01
Inducible sustained VT during CBF reduction†		
Yes	12±5%	63±9%
No	8±3%	59±11%
Yes vs. no‡	NS	NS

IFZ, infarcted zone; IRZ, ischemic-risk-zone; CBF, coronary blood flow; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Areas of IFZ and IFZ & IRZ are expressed as percentage of total left ventricular mass. See text for details.

†Dogs with inducible sustained VT before flow reduction were excluded.

‡p obtained by comparing the value between dogs with and without each type of arrhythmia.

a significantly greater total mass of the infarcted and the ischemic risk zones than those without ($68 \pm 9\%$ versus $58 \pm 8\%$, $p < 0.01$). There was no significant difference in the mass of the infarcted zone or the total mass of the infarcted and ischemic risk zones between dogs with and without inducible sustained VT during ischemia.

Discussion

Acute coronary ischemia superimposed on previous MI has been of increasing interest in studies of the pathophysiology of sudden cardiac death.¹⁻³ Several experimental models designed to study acute coronary occlusion superimposed on convalescent or healed MI have demonstrated an enhanced arrhythmogenicity of hearts with prior MIs.⁴⁻⁹ Despite the recognition that many victims of sudden cardiac death have only partial coronary obstruction at necropsy,¹¹⁻¹⁷ however, only limited experimental data are available to date on arrhythmogenic effects of partial coronary obstruction superimposed on previous MI.¹⁰ Therefore, the present study was designed to study arrhythmogenic effects of graded coronary blood flow reduction superimposed on pre-existing MI. The results show increases in both the incidence of spontaneous VF and the probability of inducing sustained VT with partial reduction in coronary artery blood flow in dogs with prior MI. Increasing inducibility of sustained VT required a less degree of reduction in coronary blood flow than was required to induce incidence of spontaneous VF.

Before discussing the relevance of the data in the present study, some characteristics and limitations of our experimental method should be addressed. The unique feature of our experimental design was the superimposition of acute ischemia by reducing blood flow in circumflex coronary artery to four different preselected levels. This method was designed to simulate the pathophysiological condition of partial reduction of regional coronary blood flow occurring in patients with advanced coronary lesions. However, there are several apparent limitations. Most important, we did not directly measure regional myocardial blood flow. The extent and severity of actual local ischemia during blood flow reduction in circumflex coronary artery would be addressed more accurately by actual measurement of local perfusion using microspheres. Repeated occlusions of circumflex coronary artery also might possibly create irreversible injury. The size of ischemic risk area might also change from one occlusion to the next, because the actual size of ischemic zone is likely to depend on the patency of the collaterals. In order to minimize the influences of these factors, we randomized the order of four levels of coronary flow reduction in each animal. Further, to minimize the possible irreversible injury, ischemic periods were limited to 20 minutes, and the animals were systemically anticoagulated. Nevertheless, the possible creation of small amounts of irreversible injury and the change of the patency of the collaterals can not be completely excluded. Fi-

nally, it was not possible to complete programmed ventricular stimulation at higher grades of coronary blood flow reductions for many animals that succumbed to ischemic VF; programmed ventricular stimulation could not be completed in one third of post-MI dogs at 75% flow reduction and in half of dogs at 100% flow reduction. This necessary loss of data on inducibility of VT by programmed ventricular stimulation may limit our comparisons between the effect of acute ischemia on spontaneous VF and inducibility of VT.

Despite these limitations, the present study did demonstrate that the incidence of spontaneous VF, inducibility of VT, and degeneration of VT to VF were increased by partial or total coronary artery occlusion superimposed on prior MI. Several studies have previously shown that total coronary artery occlusion in the presence of preexisting MI increased the incidence of spontaneous VF.^{4,6-8} Kabell et al¹⁰ also have shown that the incidence of spontaneous VF increased with superimposition of partial coronary artery occlusion. Our data indicate that at least 75% flow reduction at the proximal portion of circumflex coronary artery may be necessary to increase the incidence of spontaneous VF.

An expanding body of clinical data has demonstrated that VT induced in the laboratory can be used to guide treatment for the majority of survivors of out-of-hospital cardiac arrest.²⁶⁻³⁰ Despite several clinical studies that have suggested that acute ischemia increased the inducibility of VT,³¹⁻³³ the influence of acute ischemia on VT inducibility has not been systematically studied. Our present data show that acute ischemia superimposed on prior MI significantly increased VT inducibility. Interestingly, the probability of inducing sustained VT increased with less grades of coronary flow reduction than those required to increase the incidence of spontaneous VF. The probability of inducing sustained VT increased with 50% flow reduction at the proximal portion of circumflex coronary artery. Again, the exact severity of acute regional ischemia required to increase spontaneous or inducible ventricular tachyarrhythmias was unclear and should be measured with microspheres.

Acute ischemia superimposed on infarction also increased the incidence of spontaneous degeneration of induced VT into VF. However, this should be concluded with some cautions, because not all the VTs induced during coronary flow reduction had the same morphology as, or morphology similar to, the VTs induced before coronary flow reduction. During 50% coronary flow reduction, sustained monomorphic VT was induced in the same five dogs with inducible VT in the control state; these five sustained VTs induced during 50% flow reduction had morphology and cycle length identical or similar to that in VTs in the control state. All five VTs were stable and did not degenerate into VF without additional ischemia, whereas four of the five degenerated into VF spontaneously during 50% coronary flow reduction.

This observation appeared to support the hypothesis that additional superimposed ischemia increases incidence of spontaneous degeneration of VT into VF. These observations appear to agree with a previous hypothesis³⁴⁻³⁶ that tachycardia-induced ischemia in areas of myocardium with jeopardized coronary flow is a possible mechanism for degeneration of VT into VF. A possible clinical implication is that in patients with a prior MI who develop VT, the VT may be stable in those without a second critical coronary obstruction, whereas the VT could more easily degenerate into VF in those with second critical coronary obstruction.

The mechanisms involved in the generation of spontaneous VF, compared with electrically induced VT, may be different during acute ischemia in the presence of preexisting MI. The incidence of spontaneous VF during ischemia was related to the cumulative myocardial mass exposed to the combination of acute ischemia and chronic infarction. In contrast to spontaneous VF, the probability of inducing VT only during additional ischemia appeared to have no relation to the cumulative myocardial mass that was exposed to acute and chronic abnormalities. Finally, all the VTs induced only during additional superimposed ischemia had the observed breakthrough of activation in border between the infarcted zone and the ischemic risk zone, and ischemia-induced prolongation of local electrograms at the infarcted border zone was greater in dogs with inducible VT during additional ischemia than those without. These findings may suggest that, in some cases, the potential structural basis for arrhythmia created by the previous MI needs additional electrophysiological modification by superimposed ischemia to successfully initiate arrhythmias. Further studies are necessary to make conclusive comment on this hypothesis.

In summary, partial reduction in coronary blood flow in hearts with prior MI increases both the incidence of spontaneous VF and the probability of inducing sustained VT. Spontaneous VF and induced VT develop on different patterns of coronary flow reduction. The probability of inducing sustained VT appears to increase with less degree of ischemia superimposed on prior MI. These data provide information that helps to explain the pathophysiological mechanisms responsible for the increased risk of sudden cardiac death in post-MI patients with residual ischemia. Evaluation of the severity and the location of the residual ischemia may improve the strategies of treatment of patients with prior MI who are at a high risk of sudden cardiac death.

Appendix

Statistical significance of the difference between increase in probability of having spontaneous VF during certain grades of coronary blood flow reduction from the control state and that of inducing sustained VT was evaluated with the Cochran *Q* test.¹⁸ The *Q* value for the difference in increase of spontaneous VF and induced VT (Q_{diff}) was obtained by the following equation:

$$Q_{\text{diff}} = Q_{\text{all}} - Q_{\text{VF}} - Q_{\text{VT}}$$

where $Q_{\text{all}} = Q$ value for four sample groups (group 1, spontaneous VF in the control state; group 2, spontaneous VF during the certain grade of coronary flow reduction; group 3, inducible VT in the control state; group 4, inducible VT during the certain grade of coronary flow reduction); $Q_{\text{VF}} = Q$ value between spontaneous VF in the control state (group 1) and during coronary flow reduction (group 2); $Q_{\text{VT}} = Q$ value between inducible VT in the control state (group 3) and during coronary flow reduction (group 4). The *Q* value is known to be distributed as χ^2 with degree of freedom (df) = *k* - 1, where *k* is the number of sample group. Thus, the Q_{diff} is distributed as χ^2 with $df_{\text{diff}} = df_{\text{all}} - df_{\text{VF}} - df_{\text{VT}}$.

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KEY WORDS • acute ischemia • myocardial infarction • ventricular tachycardia • ventricular fibrillation

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T Furukawa, K Moroe, H N Mayrovitz, R Sampson, N Furukawa and R J Myerburg

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