Arrhythmogenic Influence of Intracoronary Thrombosis During Acute Myocardial Ischemia

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Background Patients with acute coronary artery thrombosis often develop primary malignant ventricular arrhythmias (MVA) early after coronary occlusion. In contrast, acute ischemia induced by nonthrombotic balloon occlusion during routine coronary angioplasty rarely elicits such arrhythmias. This study was designed to assess the role of intracoronary thrombosis in arrhythmogenesis during acute ischemia.

Methods and Results We compared the incidence of MVA associated with acute left anterior descending coronary artery (LAD) thrombosis elicited in open-chest anesthetized dogs by electrical injury (n=10) or intracoronary stent (n=9) versus LAD balloon occlusion (n=15). Compared with animals subjected to balloon occlusion, those with thrombotic occlusion had a significantly greater incidence of MVA, defined as nonsustained ventricular tachycardia (total duration > 10 seconds), sustained ventricular tachycardia, or ventricular fibrillation developing within the first 30 minutes of occlusion. In the combined thrombosis groups, MVA developed in 11 of 19 animals (58%) (6 of 10 dogs with electrical injury and 5 of 9 stent animals). In contrast, MVA occurred in only 1 of 15 animals (7%) subjected to balloon occlusion. This striking and significant difference in arrhythmias occurred despite the fact that radioactive microsphere perfusion analysis documented that the extent of left ventricular myocardium rendered ischemic was equal in all groups (percent of left ventricular myocardium with occlusion flow ≤ 50% of baseline: electrical injury, 25.2±5.3%; stent, 27.1±3.6%; balloon, 34.3±11.6%; P=NS). Furthermore, there were no differences between the animals with thrombosis or balloon occlusion with respect to changes in echocardiographic parameters of left ventricular function, aortic pressure, or heart rate after occlusion.

Conclusions These data provide evidence that despite equal magnitudes of jeopardized myocardial mass, acute ischemia induced by thrombotic coronary occlusion results in a greater incidence of MVA than does nonthrombotic balloon occlusion. These findings suggest that the process of intracoronary thrombosis itself exerts arrhythmogenic effects above and beyond the impact of ischemia on myocardium induced by coronary occlusion. (Circulation. 1994;90:139-147.)

Key Words • arrhythmias • ischemia • thrombosis • thrombin

Sudden cardiac death is a public health problem of substantial magnitude, accounting for more than 300,000 fatalities per year in the United States.1-4 Sudden cardiac death most frequently results from malignant ventricular arrhythmias related to the short- and long-term effects of ischemic heart disease.5-16 Such lethal arrhythmias are typically precipitated by acute myocardial ischemia related to coronary thrombosis,6-15 with a peak incidence of arrhythmias immediately following the onset of occlusion and a precipitous decline occurring thereafter.1-4 These primary malignant arrhythmias result from interactions between cardiac electrophysiologic alterations due to acute ischemia as well as structural alterations related to previous infarction and local metabolic changes induced by acute ischemia.16,17

Surprisingly, acute ischemia induced by balloon occlusion during routine percutaneous transluminal coronary angioplasty (PTCA) rarely elicits acute malignant ventricular arrhythmias, even with proximal occlusions subtending substantial myocardial mass.18 Therefore, factors other than the extent of ischemic myocardium must account for the comparatively high incidence of early malignant ventricular arrhythmias associated with spontaneous acute coronary occlusions. It is well established that acute coronary occlusion in humans is most commonly precipitated by the formation of an intracoronary thrombus superimposed on an ulcerated atherosclerotic plaque.9-15,19 Evidence of intracoronary thrombosis is also frequently found at autopsy in patients who died as a result of sudden cardiac death, although its role as the precipitating arrhythmogenic event in such cases is less clear.5-15 Given these observations and the lack of both intracoronary thrombi and malignant arrhythmias in patients undergoing balloon occlusions during routine coronary angioplasty, we hypothesized that acute ischemia induced by thrombotic coronary occlusion results in greater arrhythmogenicity than ischemia of equal magnitude associated with nonthrombotic balloon occlusion. If validated, this concept suggests that products generated in association with intracoronary thrombosis contribute either directly or indirectly to arrhythmogenesis in the ischemic heart. Most previous experimental studies on the electrophysiologic behavior of intact ischemic hearts have used models in which ischemia was induced by nonthrombotic mechanical obstruction of an epicardial coronary artery using balloons, ligatures, or clamps or have used preparations that are buffer perfused in the absence of blood cell...
elements. Accordingly, the present study was designed to compare the incidence of arrhythmias associated with acute myocardial ischemia induced by acute coronary thrombosis versus nonthrombotic balloon occlusion.

Methods

Experimental Preparations and Protocols

Acute coronary occlusions were induced in the left anterior descending coronary artery (LAD) just distal to the first diagonal branch by angioplasty balloon or intracoronary thrombosis. LAD balloon occlusions (n=19) were induced using standard techniques for PTCA. Thrombotic occlusions were elicited by one of two methods: by electrical injury through direct coronary instrumentation (n=17), resulting in a platelet-rich thrombus most closely analogous to that seen in patients with acute myocardial infarction, or to more precisely mimic conditions obtained with nonthrombotic occlusion induced indirectly by intracoronary balloon, thrombotic occlusions were induced in a separate group by indirect catheter deployment of a copper-coated intracoronary stent (n=16).

In all groups, conditioned dogs (25 to 35 kg) were anesthetized with morphine sulfate (1 mg/kg SC) and nembutal (30 mg/kg IV). The animals were mechanically ventilated with a mixture of room air supplemented with oxygen. Both femoral arteries and veins and the left carotid artery were surgically isolated and cannulated with vascular sheaths (Cordis Corp). A thoracotomy was performed in the first left intercostal space, and the heart was suspended in a pericardial cradle. A left atrial catheter (Cordis Corp) was placed directly through a purse-string suture in the left atrial appendage for injection of microspheres. A high-fidelity micromanometer-tipped catheter (Millar Instruments), zeroed electronically under water in a darkened room, was connected to a direct-writing strip-chart recorder (Gould Medical Instruments) and inserted for measurement of left ventricular or aortic pressure. Transesophageal two-dimensional echocardiograms were obtained in the long-axis view, recorded on videotape, and analyzed off-line with a calibrated microcomputer system (Hewlett-Packard Instruments) as described previously. Arterial blood gases, pH, and hematocrit were monitored hourly, and serum K+ levels were in the normal range (4 mmol/L). Ventilation was adjusted to maintain the partial pressure of oxygen and pH in the physiological range. Core body temperature was monitored and maintained as close as possible to baseline temperature with the aid of a heating blanket (35° to 37°C). All experimental animal protocols were approved by the Washington University Animal Studies Committee.

Thrombosis Induced by Electrical Injury

The LAD was surgically isolated immediately distal to the first large diagonal branch and instrumented according to methods described previously. Briefly, a circumferential Doppler flow probe cuff was positioned on the LAD distal to the first diagonal branch, and an occluder cuff was then placed proximal to the flow probe and adjusted to reduce flow to 90% of baseline. A needle electrode connected to a direct current source was then placed within the lumen of the LAD just proximal to the cuff.

Baseline ECG, hemodynamic, and coronary blood flow measurements were recorded on a direct-writing strip-chart recorder and digitized on-line as well as at a rate of 500 samples per second with a calibrated computer acquisition program (Gould Instruments). Radioactive microspheres for myocardial perfusion analysis were injected using procedures described previously. Two-dimensional echocardiographic recordings (Hewlett-Packard Instruments) were obtained using a transesophageal approach as described previously. To induce coronary thrombosis, electrical current was applied to the intracoronary needle, initially at 200 μA with increments of 50 μA every 30 minutes until documentation of total occlusion assessed by Doppler coronary flow velocity measurements. After the onset of complete coronary occlusion, current was maintained for 10 minutes. Hemodynamic parameters and ECG were recorded throughout the occlusion interval for up to 30 minutes. Microspheres were injected 20 minutes after occlusion, or earlier if the animal developed significant malignant ventricular arrhythmias (defined as runs of ventricular tachycardia ≥10 seconds in duration or the development of ventricular fibrillation). In each instance in which arrhythmias developed before this 20-minute time point, attempts were made to hemodynamically stabilize such animals before microsphere injection using cardioversion. Repeat two-dimensional echocardiography was performed at 30 minutes after coronary occlusion, the animals were killed, and the hearts were excised and prepared for coronary blood flow analysis.

Thrombosis Induced by Intracoronary Stent

Animals subjected to coronary occlusion induced by a stent were initially prepared and instrumented precisely as described in the electrical-injury group. However, no direct coronary artery instrumentation was performed. Instead, after baseline recordings and microsphere injection, intracoronary thrombosis was induced by catheter placement of a stainless steel intracoronary stent (Johnson and Johnson Interventional Systems). To render the stents thrombogenic, they were obtained in an unpolished state; before the procedure, the stents were electroplated with copper and interlaced with fine copper wire woven through the stent interstices. The stents were deployed according to standard interventional techniques. Briefly, the left main coronary artery was engaged with an 11F atherectomy guiding catheter (DVT Instruments) using angiographic guidance with nionic contrast (Omnipaque 350, Winthrop Pharmaceuticals). A steerable 0.014-in guide wire was positioned in the distal LAD, and the stent, mounted on a standard angioplasty balloon catheter (2.5 to 3.0 mm, Advanced Cardiovascular Systems, Inc), was delivered over the indwelling intracoronary guide wire and positioned in the LAD just distal to the first large diagonal branch. The balloon was inflated and deflated, and repeat angiography was performed to confirm optimal stent positioning and deployment. The balloon catheter, guide wire, and guiding catheter were then removed.

The onset of coronary occlusion was monitored by changes in hemodynamics and ECG, as well as by intermittent intracoronary injections of contrast performed every 10 minutes using smaller coronary catheters (6F, Cordis Corp). At the time of each contrast injection, care was taken to minimally engage the left coronary artery and to inject small volumes of nionic contrast. In animals in which the stent alone did not induce coronary occlusion within 30 minutes, a copper coil was positioned within the stent according to previously described techniques. Briefly, the left coronary artery was engaged with an 8F guiding catheter, and a 0.018-in high torque guide wire was steered through the stent and positioned in the distal LAD. The guide catheter was removed, and with the aid of polygon tubing, a copper coil was delivered over the wire into the stent. The wire and tubing were then removed. After development of ECG or hemodynamic evidence of acute occlusion (ST-segment shifts, increases in left atrial or left ventricular filling pressure, decreases in left ventricular systolic pressure or left ventricular dp/dt), confirmatory coronary injections were performed. After coronary occlusion, the animals were monitored precisely as described for animals in which thrombosis was induced by electrical injury.

Nonthrombotic Occlusion by Angioplasty Balloon

Animals subjected to balloon occlusion of the LAD underwent baseline preparation precisely as described for the stent group. Accordingly, one subgroup of balloon occlusion animals (n=15) received pretreatment with aspirin (300 mg) 24 hours
before the procedure and were heparinized (5000-IU bolus and 500-IIU/h infusion) throughout the procedure, whereas a second subgroup (n=4) received heparin but not aspirin. In all animals, the LAD was engaged with an 8F guiding catheter (Advanced Cardiovascular Systems, Inc), and coronary angiography was performed. A 0.014-in high torque floppy guide wire (Advanced Cardiovascular Systems, Inc) was positioned in the distal LAD, and an appropriate-size angioplasty balloon catheter (2.0 to 2.5 mm, Advanced Cardiovascular Systems, Inc) was advanced over the wire, positioned in the artery just beyond the first diagonal branch, and inflated to 4 to 6 atm of pressure. Repeat angiography was performed to ensure optimal balloon positioning and confirm lack of antegrade flow. After the onset of coronary occlusion, the animals were followed in precisely the same manner as the design described for the group in which coronary thrombosis was induced with a stent.

Data Analysis

Hemodynamic indexes that were analyzed included aortic peak systolic and mean diastolic pressures. In five animals in which aortic pressure recordings were unavailable, peak left ventricular systolic pressure was used to estimate peak aortic pressure. Heart rhythms were analyzed from the strip-chart recordings from the entire interval of the observation period (up to 30 minutes) after coronary occlusion. The average heart rate, measured every 5 minutes, was calculated, and the presence of arrhythmias was identified. The total number of premature ventricular complexes (PVCs) was quantitated, as were episodes of couplets and runs of ventricular tachycardia. Malignant ventricular arrhythmias were defined as nonsustained ventricular tachycardia with a total duration >10 seconds and/or the development of sustained ventricular tachycardia or ventricular fibrillation.

The extent of ischemic left ventricular myocardium was assessed by echocardiographic measurement of the extent of regional wall motion abnormalities, analyzed off-line according to methods described previously. Briefly, left ventricular regional wall motion scores were assessed qualitatively in the long-axis view at baseline and during coronary occlusion. The left ventricle was divided visually into regions, and a qualitative motion score was determined for each segment (normal, 1; hypokinetic, 2; akinetic, 3; dyskinetic, 4). A total motion score for the entire left ventricle was then calculated as the sum of all the segment scores for a given heart.

The extent of ischemic myocardium was also assessed through analysis of regional myocardial perfusion determined by radiolabeled microsphere analyses performed according to standard procedures. Briefly, hearts were fixed in formalin, the left ventricle was cut into four transverse slices, and the slices were divided into equal radial segments (ranging from 4 to 12 segments, depending on the slice layer). The segments were then subdivided into three sections from epicardium to endocardium and processed for microsphere analysis, with flows expressed as milliliters per minute per gram. The magnitude of reduction in flow within individual sections after occlusion was calculated with respect to changes in absolute flows measured within each individual section. Occlusion flows were then expressed as percent change from baseline within each section (designated as 100%). Because of regional heterogeneity of flows at baseline within individual hearts, reductions in flow within individual sections during coronary occlusion were also expressed relative to the mean baseline flow in the entire left ventricle in each animal, calculated as the sum of the absolute baseline flows in all sections divided by the total number of sections. Section flows calculated by both methods were then categorized according to percent severity of reduction versus baseline (0% to 10%, 11% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%). The extent of left ventricular myocardium in each flow-reduction category was then calculated as the sum of the weights of the sections within each category divided by the total left ventricular weight. The percent of left ventricular mass with flow <50% of baseline was similarly calculated as the sum of the weights of sections with occlusion flows <50% of baseline divided by the total left ventricular weight. Because of animal-to-animal differences in absolute baseline flows, the extent of ischemic risk area was also calculated relative to a normalized mean baseline section flow calculated for all animals in the entire study (1.5 mL·min⁻¹·g⁻¹); with this calculated baseline value as a normalized reference, significant ischemia in individual sections was defined as flow ≤0.6 mL·min⁻¹·g⁻¹. Using this approach, the percent of ischemic left ventricular myocardium was then calculated as the sum of the weights of sections with flow ≤0.6 mL·min⁻¹·g⁻¹ divided by the total left ventricular weight.

Statistical Analysis

Values are given as mean±SEM, and the incidence of malignant arrhythmias was analyzed by χ² using a 2×2 contingency with Yates' correction factor. ANOVA was used to assess blood flow data, hemodynamic and echocardiographic data among the three groups, and the significance of differences in hemodynamic and echocardiographic parameters before and after coronary occlusion within each group. A value of P<.05 was considered significant.

Results

Thrombotic Coronary Occlusion

Thrombosis by Electrical Injury

Thrombotic occlusion by electrical injury was attempted in 17 animals. However, 7 of these animals were excluded from analysis, including 4 animals in which coronary occlusion failed to develop despite current levels up to 550 μA and 3 other animals in which occlusion microsphere data could not be obtained because of the sudden onset of refractory ventricular fibrillation. During the control interval, the remaining 10 animals were in normal sinus rhythm, and all hemodynamic, echocardiographic, and coronary flow measurements were normal (Fig 1). After initiation of intracoronary current, complete coronary occlusion was induced at a mean time interval of 115±15 minutes (range, 54 to 197 minutes), as determined by Doppler flow. Cyclic flow variations developed before the onset of complete coronary occlusion in 2 animals. After onset of complete occlusion, no episodes of spontaneous reperfusion occurred, as documented by Doppler coronary flow probe monitoring. Overall for the group, occlusion did not result in significant changes in peak aortic pressure (from 138±3 to 135±4 mm Hg, P=NS) or heart rate (from 140±7 to 151±7 beats per minute, P=NS) (Fig 2). After thrombotic occlusion, PVCs developed in 8 of 10 of the animals (80%) with an average of 5.3 PVCs per minute; malignant ventricular tachycardia developed in 6 of 10 animals (60%). Two animals developed ventricular fibrillation; in 1 animal, ventricular fibrillation developed after ventricular tachycardia, and in 1 animal, ventricular fibrillation occurred without prior ventricular tachycardia. Compared with animals subjected to balloon occlusion, the incidence of malignant arrhythmias was significantly greater with thrombotic occlusion induced by electrical injury (Fig 3).

Thrombosis by electrical injury reduced coronary blood flow to <0.6 mL·min⁻¹·g⁻¹ in 23.4±2.4% of the left ventricular myocardium (Fig 4). With respect to percent flow reduction within individual sections calculated relative to individual sectional baseline flows, acute occlusion reduced flow to ≤25% in 12.1±2.3% of
the left ventricle and ≤50% in 25.2±5.3% of the left ventricular mass (Fig 5). Calculated relative to mean sectional baseline flow, coronary occlusion reduced flow in individual sections to ≤25% in 15.1±1.9% of the left ventricular mass and ≤50% in 28.4±4.5% of the left ventricle (Fig 5). Occlusion resulted in significant regional wall motion abnormalities in all animals (wall motion score from 6±0 to 14±1.4, \( P=.001 \)).

**Thrombosis by Intracoronary Stent**

Thrombotic coronary occlusion induced by intracoronary stent was attempted in 16 animals, of which 7 were excluded from analysis. In 3 animals, technical considerations precluded delivery of the stent to the LAD target site; 1 animal developed unexplained profound respiratory acidosis; 1 animal had no risk area by microsphere analysis; in 1 animal, ventricular tachycardia and fibrillation developed, precluding microsphere analysis for blood flow; and ventricular tachycardia developed in 1 animal in association with angiographic monitoring injection before ischemia. During the control interval, the remaining 9 animals were in normal sinus rhythm, and all hemodynamic and echocardiographic measurements were normal. Stent deployment induced complete coronary occlusion in 6 of 9 animals within 30 minutes (mean, 17±3 minutes; range, 9 to 30 minutes) as judged by angiography. In the remaining 3 animals, a copper coil was positioned within the coronary stent, resulting in complete occlusion within the subsequent 20-minute period. Overall for the group, occlusion did not result in significant changes in peak aortic pressure (from 147±10 to 145±8 mm Hg, \( P=NS \)) or heart rate (from 134±8 to 128±13 beats per minute, \( P=NS \)) (Fig 2).

During coronary occlusion, PVCs developed in 7 of 9 animals (78%) (average, 5.8 PVCs per minute). Malignant ventricular arrhythmias developed in 5 of 9 animals (56%), characterized by ventricular tachycardia in four instances and de novo ventricular fibrillation in an additional animal. Significant differences were observed in the incidence of malignant arrhythmias compared with animals subjected to balloon occlusion (\( P<.05 \)) (Fig 3). Flow during coronary occlusion was reduced to <0.6 mL/min·g⁻¹ and 25.5±4.3% of the left ventricular myocardium (Fig 4). Relative to individual section baseline flows, acute occlusion reduced flow to ≤25% in 14.5±3.5% of the left ventricle and ≤50% in 27.1±3.6% of the left ventricular mass (Fig 5). Coronary blood flow during occlusion in individual sections, calculated relative to mean left ventricular baseline flow, was reduced...
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myocardium with flow <0.6 mL·min⁻¹·g⁻¹. There were no significant differences in the mean ischemic risk area (denoted by closed squares, mean±SEM) between the groups. Extent of ischemic risk alone did not predict the development of VT/VF in the two thrombosis groups.

Fig 2. Plots of changes over time in heart rate (top) and peak aortic systolic pressure (bottom) in animals occluded by balloons and in animals with coronary thrombosis induced by either electrical injury or an intracoronary stent. From baseline to 30 minutes after occlusion, there were no significant differences between the groups, with respect to differences in these parameters at any specific time point or changes over time.

to ≤25% in 15.7±3.0% of the left ventricle and ≤50% in 31.6±5.2% of the left ventricular mass (Fig 5). Coronary occlusion resulted in significant regional wall motion abnormalities in all animals (wall motion score, 6±0 to 12.9±0.2, P<.001). There were no differences among the two coronary thrombosis groups with respect to incidence, type or time of onset of arrhythmias, extent of ischemic myocardium, or magnitude of echocardiographic or hemodynamic changes.

Nonthrombotic Balloon Occlusion of the Coronary Artery

At baseline, all 19 animals were in normal sinus rhythm, and all hemodynamic and echocardiographic measurements were normal. Four animals in this group were excluded from analysis: 2 were excluded before balloon occlusion, including 1 animal with proximal arterial dissection and another with unexplained hypotension and metabolic acidosis; in 2 other animals, the balloon could not be positioned effectively beyond the proximal aspect of the LAD. In the remaining 15 animals, balloon inflation induced prompt and complete LAD occlusion beyond the first diagonal branch as judged by angiography. Overall for the group, occlusion did not result in significant changes from baseline with respect to peak aortic pressure (from 141±6 to 123±8 mm Hg, P=NS) or heart rate (from 141±5 to 137±4 beats per minute, P=NS) (Fig 2). Although 87% of animals subjected to balloon occlusion developed occasional PVCs (average, 1.3 PVCs per minute), nonsustained ventricular tachycardia developed in only 5 animals (33%), and the total duration of ventricular tachycardia was very short in 4 animals (0.8, 1.0, 1.6, and 5.4 seconds). Malignant ventricular arrhythmias developed within 30 minutes of acute occlusion in only 1 animal (7%) (Fig 3). Compared with the animals with coronary thrombosis, animals subjected to balloon occlusion had a significantly lower incidence of malignant ventricular arrhythmias (1 of 15 [7%] compared with 11 of 19 [58%] in the combined thrombosis groups, P<.01). Although the incidence of PVCs cannot be directly related to malignant arrhythmias, there also was a striking difference in the total number of PVCs over the 30-minute ischemic observation period between the thrombosis groups (electrical injury, 159±73 PVCs; stent, 175±72 PVCs) and the balloon occlusion group (39±18 PVCs, P<.01).

Coronary blood flow during balloon occlusion was reduced to <0.6 mL · min⁻¹ · g⁻¹ in 23.1±3.4% of the total left ventricular myocardium (Fig 4). Acute occlusion flow in individual sections, relative to baseline within each section, was reduced to ≤25% in 12.2±4.0% of the left ventricle and ≤50% in 34.3±11.6% of the left ventricular mass (Fig 5). Flow during occlusion in individual sections, calculated relative to mean sectional baseline, was reduced to ≤25% in 13.7±4.2% of the left ventricle and ≤50% in 40.7±11.1% of the left ventricular
mass (Fig 5). Occlusion resulted in significant regional wall motion abnormalities in all animals (wall motion score, 6±0 to 12.5±0.4, P<.001). Animals subjected to nonthrombotic balloon occlusions received pretreatment with heparin with or without aspirin, whereas animals undergoing thrombotic occlusions received neither agent. This design was intended to mimic conditions in patients with acute myocardial infarction at high risk for lethal arrhythmias as well as in those undergoing balloon angioplasty who rarely develop arrhythmias. For animals given aspirin and heparin compared with those given heparin alone, from baseline to occlusion there were no differences with respect to arrhythmias or changes in hemodynamic and echocardiographic parameters. There were no differences between the thrombosis groups (both singly and combined) and animals with balloon occlusion with respect to ischemic myocardium by microsphere perfusion analysis (Fig 5) or in changes in echocardiographic or hemodynamic parameters (Fig 2).

It is important to consider whether the animals excluded from the analysis for technical reasons or lack of microsphere data to assess regional myocardial flow would have influenced the results. Of the 7 animals excluded from the electrical injury group, in 4 ischemia could not be induced; in 3 others, ischemia was induced, but development of hemodynamically unstable ventricular tachycardia or fibrillation precluded microsphere administration. Likewise, in the stent thrombosis group, 5 animals were excluded due to technical considerations that precluded induction of ischemia, and in 1 other the ischemic risk area was trivial; 1 other animal that developed ventricular fibrillation, precluding microsphere injection, was similarly excluded. Finally, in the balloon group, none of the animals in which ischemia was induced were excluded. Thus, inclusion of all animals in which ischemia was induced would have enhanced the differences between the thrombosis groups compared with the group with balloon occlusion.

**Discussion**

The present study demonstrates that despite equal magnitudes of jeopardized myocardium, acute ischemia induced by thrombotic coronary occlusion results in a greater incidence of malignant ventricular arrhythmias than does nonthrombotic balloon occlusion. These findings suggest that the process of intracoronary thrombosis itself exerts arrhythmogenic properties above and beyond the effects of ischemia on myocardium induced by coronary occlusion per se. These results may have implications for the management of patients with coronary artery disease in general and acute myocardial ischemia and infarction in particular.

The vast majority of episodes of sudden cardiac death result from malignant ventricular arrhythmias developing in patients with underlying coronary artery disease and acute myocardial ischemia.1-15 Intracoronary thrombosis is a process common to both acute myocardial ischemia and sudden cardiac death. Acute transmural myocardial infarction is typically precipitated by occlusive coronary thrombus forming at the site of an ulcerated atherosclerotic plaque.9-15 Intracoronary thrombosis is similarly evident at postmortem examination in a majority of cases of sudden cardiac death.9-15 These observations, taken together with the absence of malignant ventricular arrhythmias during acute ischemia induced by nonthrombotic balloon occlusion associated with routine PTCA, suggest that the presence or absence of intracoronary thrombosis and attendant local activation of the coagulation system within the heart contributes to arrhythmogenesis. However, not all patients with acute transmural myocardial infarction develop primary malignant ventricular arrhythmias; this event occurs in approximately 20% of such cases.1-5 Furthermore, patients with unstable ischemic syndromes other than transmural infarction (ie, nontransmural infarction, unstable angina) have a much lower incidence of sudden cardiac death, despite the fact that a substantial portion of these patients have intracoronary thrombi.11-15 Clearly, arrhythmogenesis during acute myocardial ischemia is a complex, multifactorial process.

Observations from the present study document that the process of intracoronary thrombosis, whether resulting from platelet-rich clots induced by electrical
injury or mixed platelet-fibrin thrombi elicited by intracoronary stent, exerts critical arrhythmogenic effects during acute ischemia. The mass of ischemic myocardium is known to be the critical substrate for and an important determinant of arrhythmogenesis.14,17,22

Acute ischemic compromise of extensive myocardial mass invariably results in malignant arrhythmias, even with nonthrombotic occlusions,16,20-31 both due to the direct effects of ischemia, as well as the resultant hemodynamic responses and consequent expansion of the ischemic region related to decreased coronary perfusion pressure. Accordingly, the present study was designed to render a substantial proportion of myocardial mass ischemic without inducing hemodynamic compromise and to carefully match the extent of ischemic left ventricular mass in all animals. Based on microscopic determinations of myocardial perfusion and echocardiographic analysis of regional wall motion, the dramatic difference in malignant arrhythmias occurred despite nearly identical extent and severity of ischemic myocardial mass in the groups. Furthermore, thrombotic occlusion resulted in arrhythmias in some animals with relatively modest magnitudes of ischemic mass, whereas others with more extensive involvement were arrhythmia free. There were no significant differences between thrombotic and balloon occlusion animals with respect to other easily identifiable functional factors, including changes in heart rate or aortic perfusion pressure, or the magnitude of regional and global left ventricular dysfunction.

Previous experimental studies have delineated many of the pathophysiological factors contributing to and mechanisms underlying the genesis of malignant ventricular arrhythmias associated with acute myocardial ischemia.16,17,20-31 However, most prior experimental preparations designed to evaluate the incidence of and mechanisms underlying arrhythmogenesis associated with acute ischemia have used nonthrombotic coronary occlusions induced by clamps, balloons, and ligatures and therefore failed to take into account the process of intracoronary thrombosis, the underlying pathophysiological event in patients with acute transmural ischemia who develop malignant arrhythmias. Although nonthrombotic occlusions have been shown to induce malignant ventricular arrhythmias in experimental preparations, in most such studies, these occlusions were proximal and resulted in extensive ischemic myocardium, which likely explains the greater incidence of arrhythmias in these models compared with that induced by the more distal balloon occlusions used in the present study. However, even ischemia induced by nonthrombotic coronary occlusion, in the absence of heparin, likely elicits at least partial activation of the coagulation system. Such an effect could also contribute to the arrhythmogenesis observed in these previous studies. This conclusion is supported by data obtained from patients with vasospastic angina in whom fibrinopeptide A levels increase markedly, reflecting thrombin-induced conversion of fibrinogen to fibrin.36 The fact that the incidence of vasospastic angina in these patients was not altered by heparin but that the increase in fibrinopeptide A was prevented further suggests that ischemia can elicit activation of the coagulation system. This concept is also consistent with the striking lack of malignant arrhythmias in patients subjected to nonthrombotic coronary occlu-

sions during routine coronary angioplasty in whom heparin is routinely administered. Taken together with the present findings, these observations suggest that the process of intracoronary thrombosis contributes to arrhythmogenesis.

The precise electrophysiological mechanisms underlying the malignant arrhythmias observed in the experimental thrombosis group are beyond the scope of the present study. However, several potential mechanisms likely contribute. Coronary thrombosis is a complex and dynamic process determined by interactions involving the thrombogenic endothelial surface, circulating clotting factors and platelets, systemic and local vasoactive substances, and inflammatory mediators.37 These multiple moieties not only interact in complex ways with structural factors within the ischemic myocardium but also are further influenced by the effects of activation of local and systemic neurohormonal systems, the presence or absence of residual antegrade or collateral perfusion, and endothelial cells themselves, which play an important role in synthesis and catabolism of many of these substances. Although multiple factors derived from the thrombus or induced during thrombotic occlusion could be arrhythmogenic, thrombin is particularly likely to play a role. Thrombin exerts a multiplicity of effects in myocytes, vascular smooth muscle cells, platelets, and endothelial cells. Potential actions of thrombin include phosphoinositide hydrolysis, calcium mobilization, mitogenesis, inhibition of adenylate cyclase, stimulation of platelet aggregation, and release of arachidonic acid.38-44 Specifically with respect to the heart, thrombin has been shown to elicit direct electrophysiological effects on myocytes, including increased automaticity, lengthening of repolarization, and increased incidence of afterdepolarizations,38,39 each of which could contribute to arrhythmogenesis, particularly during ischemia. Thrombin could be arrhythmogenic via at least four different pathways: (1) direct stimulation by thrombin of phospholipase (PL) C in cardiac myocytes;40 (2) thrombin stimulation of PLD in platelets, leading to release of phosphatidic acid, which can directly stimulate PLC in cardiac myocytes;41 (3) thrombin stimulation of PLA2 in endothelial cells, leading to release of lysophosphatidyl choline (LPC) into the vasculature and thereby eliciting electrophysiological alterations in distal ischemic myocytes;42 and (4) thrombin-induced accumulation of LPC in ischemic ventricular myocytes.47

Clinical Implications

The present experimental findings implicating intracoronary thrombosis in arrhythmogenesis provide the basis for explanation, at least in part, of the striking differences in the incidence of lethal arrhythmias in patients with spontaneous coronary thrombosis versus those undergoing balloon occlusions. Although conspicuous by its absence during balloon occlusion, evidence of intracoronary thrombosis is characteristically present not only in patients presenting with acute myocardial infarction but also at autopsy in victims of sudden cardiac death with documented coronary artery disease. Postmortem analyses of the hearts of sudden death victims typically demonstrate platelet aggregates in the myocardium distal to ulcerated thrombosed coronary plaque, which presumably are the embolic source of
such aggregates. Platelets, and products such as arachidonic acid and thromboxane A2 that reflect the intense platelet activation induced during intracoronary thrombosis, have been implicated in arrhythmogenesis in patients with ischemic heart disease. Furthermore, thrombin concentrations have been documented as high as 9 U/mL adjacent to intracoronary thrombi. In addition, elevated serum and coronary venous effluent levels of fibrinopeptide A, a polypeptide released by the action of thrombin on fibrinogen and therefore a marker for thrombin activity, have been documented early after the onset of acute myocardial infarction and reflect sustained thrombin activity during early ischemia. Thus, thrombin produced during intracoronary thrombosis could come into contact with ischemic endothelial cells, both locally at the site of clot production and potentially at the level of ischemic myocytes downstream in the more distal ischemic myocardial bed and regions of the ischemic border zone, a site we have shown is critical for initiation of nonreentrant mechanisms in the ischemic heart.

These data provide evidence that, and suggest mechanisms by which, ischemic myocardium is exposed to both primary clot components as well as byproducts generated in association with intracoronary thrombosis that may contribute to arrhythmogenesis. In aggregate, these observations, taken together with previous experimental findings from our laboratory and others regarding the potential direct and indirect electrophysiologic effects of products generated during intracoronary thrombosis, suggest that therapeutic interventions designed to block the formation of and/or inhibit the adverse electrophysiologic effects of such products could reduce the incidence of malignant arrhythmias and thereby modify the incidence of sudden cardiac death in patients with ischemic heart disease.

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References


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