Determinants of Arrhythmic Death Due to Coronary Spasm: Effect of Preexisting Coronary Artery Stenosis on the Incidence of Reperfusion Arrhythmia

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SUMMARY Coronary spasm can occur in the presence or absence of coronary artery disease. We therefore determined the effect of preexisting coronary stenosis on the incidence of ventricular fibrillation during reperfusion after circumflex coronary artery (CFX) occlusion. Twenty dogs underwent a 30-minute open-chest CFX occlusion. During reperfusion, CFX blood flow was restricted by a partial occluder. In dogs that survived reperfusion, peak CFX flow was 91 ± 44% of baseline (mean ± SD) compared with 163 ± 68% in dogs that died of ventricular fibrillation (p < 0.02). In another 17 dogs, the left anterior descending coronary artery was gradually occluded by an ameroid constrictor. After 17–39 days, the CFX was acutely occluded for 30 minutes and then reperfused. Collateral flow to the CFX, measured by microspheres, was 27.6 ± 28.3 ml/min/100 g in dogs that died of reperfusion ventricular fibrillation, compared with 64.4 ± 27.2 ml/min/100 g in surviving dogs (p < 0.02). Thus, the risk of reperfusion ventricular fibrillation is greater in dogs with normal coronary arteries than in dogs with a flow-limiting partial stenosis of the artery undergoing transient occlusion, or chronic stenosis of a second coronary artery inducing collateralization to the artery subsequently undergoing transient occlusion. These results suggest that the risk of ventricular fibrillation during release of coronary spasm may be greater in patients without than in those with coronary artery disease.

ACUTE OCCLUSION of a previously patent coronary artery is a major cause of sudden death in coronary artery disease. However, ventricular fibrillation (VF) due to reopening of a transiently occluded coronary artery and subsequent reperfusion of ischemic myocardium may also be responsible for sudden death in patients with coronary disease. Reperfusion VF could result from lysis of platelet plugs or thrombi, or from release of coronary artery spasm. Angiographic studies have revealed that spasm occurs in both apparently normal and partially stenosed coronary arteries.

Most animal models of reperfusion, however, are analogous only to release of occlusion in normal arteries. That is, the return of blood flow to the ischemic myocardium is unrestricted. If, however, transient occlusion occurs in an artery already partially stenosed by atherosclerotic disease, the level of blood flow during reperfusion would be reduced by the preexisting stenosis. This situation would be better modeled by coronary artery occlusion followed by partial reperfusion. The incidence of reperfusion VF under such conditions is unknown; nor has the effect of chronic coronary occlusion of arteries other than the one undergoing transient occlusion been studied in relation to the outcome of reperfusion.

Therefore, to determine the effect of preexisting coronary stenosis on arrhythmias during reperfusion, we investigated the incidence of VF during sudden but restricted reperfusion of the circumflex coronary artery (CFX) and during sudden unrestricted reperfusion of the CFX, but in the setting of various degrees of collateral flow stimulated by prior gradual occlusion of the left anterior descending coronary artery (LAD).

Materials and Methods

Foxhounds of either sex that weighed 17–34 kg, ranging in age from 8 months to 4 years, were studied.

Experimental Protocol

Restricted Reperfusion

The dogs were anesthetized with i.v. sodium pentobarbital; the initial dose was 26.5 mg/kg and additional doses (5 mg/kg) were given as needed. The dogs

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were intubated and ventilated mechanically using a Harvard pump with a mixture of room air and oxygen. The rate was adjusted to maintain arterial blood pH and oxygen saturation. Lead 2 of the ECG was continuously monitored and the dog's temperature was measured with a 24-gauge Yellow Springs intra-myocardial probe and maintained at 36–38°C using a warming blanket as needed. The femoral artery was cannulated to monitor pressure.

Thoracotomy was performed in the fifth left intercostal space, and the heart was suspended in a pericardial cradle. The CFX was dissected free proximal to the first obtuse marginal branch and an electromagnetic flow probe (Carolina Medical Electronics) was attached. A partial occluder that would restrict CFX blood flow but not completely occlude the artery was fashioned for each dog. The partial occluders were plastic cylinders 2.5 mm long with an internal diameter of 1.8, 2.0 or 2.2 mm. The internal diameter was modified as needed by passing ligatures of 2-0 silk around the cylinder. We thus obtained a range of flows during reperfusion. The heart was paced (Medtronic Model 5800) by leads sutured to the left atrial appendage.

When the dog's temperature, blood pressure and blood gases were stable, the partial occluder was placed around the CFX distal to the flow probe. The CFX was then completely occluded for 30 minutes with a bulldog clamp placed between the flow probe and the partial occluder. Completeness of the occlusion was shown by the flow probe. After 15 minutes of occlusion, at the end of the period of high susceptibility to VF, a pacing at 200 beats/min was begun. Four dogs developed VF during coronary artery occlusion and were excluded. At the end of the 30-minute occlusion, the bulldog clamp was abruptly removed. The partial occluder was left in place on the CFX. The ECG, systemic blood pressure and CFX reperfusion blood flow were monitored for 10 minutes. Dogs that did not develop VF during this period were considered survivors. They were then sacrificed.

**Chronic LAD Stenosis**

To study the effect of chronic stenosis of a coronary artery other than the artery subjected to sudden occlusion and reperfusion, dogs were anesthetized with inhaled nitrous oxide, 0.5%, and halothane, 0.5%. A left thoracotomy was performed under sterile conditions and the heart was suspended in a pericardial cradle. An ameroid constrictor\(^9\) of appropriate diameter (1.2–1.6 mm) was placed around the LAD between the first and second major branches. The chest was then closed and the dog returned to the kennel.

Seventeen to 39 days later, the dogs were anesthetized and thoracotomy was performed as in the first protocol. A flow probe was placed on the CFX proximal to the obtuse marginal branch. Catheters were placed in the left atrium for injecting microspheres and in the femoral artery for withdrawing reference blood samples and monitoring pressure and blood gases. Pacin and monitoring of the ECG and temperature were performed as in the first protocol.

Regional myocardial blood flow was determined using radioactively labeled microspheres. Approximately 4 million tracer microspheres, 15 ± 3 \( \mu \) in diameter, labeled with cerium-141, strontium-85 or scandium-46 (3M Co.) and suspended in 3 ml of saline, were injected into the left atrium over approximately 30 seconds. For each flow determination, withdrawal of an arterial reference sample was begun 10–15 seconds before microsphere injection and continued for at least 90 seconds after completion of injection using a Harvard infusion/withdrawal pump at 7.64 ml/min.

When the dog's temperature, blood pressure and blood gases were stable, microspheres were injected to determine baseline myocardial blood flow. The CFX was then occluded with a bulldog clamp. Ten minutes after occlusion, a second bolus of microspheres labeled with a second nuclide was injected to determine collateral flow. Fifteen minutes after occlusion, pacing was begun at 200 beats/min. Eight dogs died of VF during occlusion and were excluded. Thirty minutes after occlusion, the bulldog clamp was abruptly removed. Reperfusion was observed for 10 minutes. Dogs that did not develop VF during this period were considered survivors.

The dogs were then sacrificed by excising the hearts. Each heart was cut in slices 1 cm thick (in planes parallel to the ativoventricular groove) and each slice was weighed.

To determine myocardial blood flow, normal zone tissue samples were taken from myocardium adjacent to the LAD, proximal to the ameroid constrictor. Reperfusion zone samples were taken from tissue bounded by the obtuse marginal and second branches of the CFX, at or basal to the horizontal plane of the ameroid constrictor. Two full-thickness samples that weighed about 2 g were cut from each zone. Each sample was bisected into endocardial and epicardial portions, which were placed into scintillation vials and weighed. The radioactivity of these myocardial samples and of the blood reference samples was measured in a Packard Auto-gamma Spectrometer (model 5220) using windows appropriate for the three radionuclides. Myocardial blood flow values were determined from the reference and myocardial sample counts, using simultaneous equations to correct for overlap. The two samples within each zone were averaged. Endocardial, epicardial and transmural blood flow values in ml/min·100 g\(^{-1}\) were determined for each dog.

To measure the size of any infarct that might result from the ameroid constrictor, the slices of heart were incubated in 2,3,5 triphenyltetrazolium chloride (Fisher), which stains normal tissue red and leaves infarcted tissue white.\(^11\) The apical and basai surfaces of the slices were photographed. The slice diced for regional blood flow determination was represented by photographs of the facing surfaces of adjacent slices. The pictures of the slices were projected and the stained infarct zone was traced. The areas of the normal and infarct zones were measured using a video-analyzer (Telefactor Corp.).\(^12 e 13\) To determine the
weight of infarcted tissue in each slice, the weight of the entire slice was multiplied by the mean of the fractions of the apical and basal surfaces lying in the infarct zone. Summing the weights of the infarct zones of the slices yielded the total weight of the infarcted tissue for each dog. The percent infarct of the left ventricle was calculated as (infarct weight/weight of LV) \times 100. Infarct size was measured in 16 of the 17 dogs that completed the study.

We did not try to determine if ameroid constriction completely occluded the LAD; our purpose was to induce collateral vessel development, which requires only an 80% stenosis.\textsuperscript{14}

The acceleration in flow during onset of reperfusion was calculated as \( \Delta t = \Delta F/\Delta t \), where \( F = \text{CFX blood flow} \) and \( t = \text{time in seconds} \). Occlusion flow, \( F(O) \), is zero, and we selected \( \Delta t = 1 \) second. Thus, the acceleration in the first second of reperfusion, \( A(1) = [F(1) - F(O)]/\Delta t \), becomes simply the CFX flow at 1 second, \( F(1) \).

Statistical analyses were performed using the t test and Fisher’s exact test. Values are reported as the mean ± SD.

### Results

#### Reperfusion Restricted by Partial CFX Stenosis

Eleven of 20 dogs developed VF during reperfusion (VF group) and nine dogs survived. There were no significant differences between the VF group and the survivors in heart rate at baseline, mean arterial pressure at baseline, or mean arterial pressure recorded after 29 minutes of occlusion (just before reperfusion) (table 1).

CFX blood flow at baseline was similar in the VF group (44.5 ± 16.3 ml/min) and in the survivors (39.4 ± 13.1 ml/min, NS). However, peak CFX flow during reperfusion was significantly higher in the VF group (72.0 ± 39.0 ml/min) than in survivors (38.4 ± 27.1 ml/min, \( p < 0.05 \)). Peak CFX flow during reperfusion, calculated as a percentage of baseline flow, was 162.5 ± 67.7% in the VF group. This also was significantly higher (\( p < 0.02 \)) than that of survivors (91.1 ± 43.6%) (fig. 1). All dogs whose reperfusion flow exceeded 160% of baseline flow died of VF.

Five of the surviving dogs had ventricular tachycardia (VT), defined as a sequence of three or more premature ventricular complexes that reverted spontaneously to sinus rhythm. The mean peak reperfusion blood flow in these five dogs (56.0 ± 23.8 ml/min) was higher than the peak flow in the survivors with premature ventricular complexes only or no arrhythmia (16.4 ± 6.0 ml/min, \( p < 0.01 \)). However, considerable overlap of individual values among dogs with VF and survivors with VT was evident (fig. 1). The time of onset of VF, or of VT in survivors, ranged from 8–126 seconds after the onset of reperfusion. VT began much later in survivors (74.8 ± 32.7 seconds after the onset of reperfusion) than in dogs in which VT deteriorated to VF (29.7 ± 19.8 seconds, \( p < 0.02 \)).

The acceleration in CFX flow at the onset of reperfusion, when the increase in CFX flow was most rapid, was also examined as a potential factor contributing to survival after reperfusion. The acceleration of CFX flow after 1 second of reperfusion, however, was similar in the VF group (31.9 ± 15.3 ml/min\(^2\)) and in survivors (35.0 ± 25.9 ml/min\(^2\)).

#### Effect of Chronic LAD Stenosis on Arrhythmia After Release of CFX Occlusion

Seventeen dogs completed the study; eight dogs survived and nine dogs died of VF during reperfusion (VF group). Hemodynamic data are listed in table 2. The survivors and the VF group had similar heart rate and mean arterial pressure at baseline, after 10 minutes of occlusion (at the time of collateral flow determina-
TABLE 2. Hemodynamic Measurements — Chronic Left Anterior Descending Coronary Artery Stenosis

<table>
<thead>
<tr>
<th></th>
<th>VF</th>
<th>Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>101.1 ± 12.9</td>
<td>114.4 ± 21.1</td>
</tr>
<tr>
<td>Occlusion (10 min)</td>
<td>91.7 ± 15.8</td>
<td>108.1 ± 18.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>163.3 ± 35.0</td>
<td>177.5 ± 20.5</td>
</tr>
<tr>
<td>Occlusion (10 min)</td>
<td>163.3 ± 24.0</td>
<td>171.3 ± 20.3</td>
</tr>
<tr>
<td>CFX blood flow (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54.4 ± 22.4</td>
<td>50.7 ± 22.1</td>
</tr>
<tr>
<td>Peak reperfusion</td>
<td>168.7 ± 140.0</td>
<td>163.6 ± 107.5</td>
</tr>
<tr>
<td>1 sec reperfusion</td>
<td>96.4 ± 76.5</td>
<td>79.2 ± 34.6</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Abbreviations: CFX = circumflex coronary artery; VF = ventricular fibrillation.

tion), and after 29 minutes of occlusion (just before reperfusion). There was no significant difference between the two groups in CFX blood flow at baseline and at peak reperfusion, or in acceleration in CFX flow in the first second of reperfusion. In every dog, peak CFX flow during reperfusion was at least 150% of baseline flow.

Baseline transmural myocardial flow measured in the CFX bed before CFX occlusion was 116.5 ± 33.3 ml/min·100 g⁻¹ in the VF group and 124 ± 24.2 ml/min·100 g⁻¹ in survivors (NS). Collateral flow to the CFX bed (determined after CFX occlusion) was significantly higher (p < 0.02) in survivors (64.4 ± 27.2 ml/min·100 g⁻¹, 60% of normal zone flow) than in the VF group (27.6 ± 28.3 ml/min·100 g⁻¹, 27% of normal zone) (fig. 2). Seven of eight dogs with collateral flow greater than 50% of normal zone flow survived reperfusion. Only one of nine dogs with collateral flow below this level survived (p = 0.006, fig. 3).

Collateral flow to the epicardial layer of the reperfusion zone at 10 minutes after occlusion was 72.3 ± 20.9 ml/min·100 g⁻¹ in survivors, significantly higher (p < 0.005) than epicardial flow in the VF group, 31.6 ± 25.2 ml/min·100 g⁻¹. Endocardial flow was also higher in survivors than in the VF group (56.7 ± 40.5 vs 23.5 ± 32.3 ml/min·100 g⁻¹ respectively), though not significantly so. The endocardial/epicardial ratio was similar in the VF and survivor groups (0.65 ± 0.35 vs 0.75 ± 0.47, respectively, NS).

Three of the eight survivors developed VT. There were no significant differences in any of the blood flow or collateral flow measurements between these three dogs and the five survivors with only premature ventricular complexes or no arrhythmia.

Seven dogs had no visible infarct distal to the ameroid constrictor on the LAD. Of the 10 visible infarcts, five were transmural; three of these were in the VF group and two were in the survivors. The mean infarct size in the VF group was 4.6 ± 5.0% of the left ventricle, compared with 4.9 ± 8.6% of the left ventricle in survivors.

Discussion

Increased attention has focused recently on the role of transient ischemic events, caused by platelet aggregates or coronary spasm, as a mechanism of acute myocardial infarction or sudden death. Implicit in this concept is the role of reperfusion of ischemic myocardium as a mechanism that might alter the effects of the transient period of ischemia per se. Although VF during reperfusion of ischemic myocardium after temporary coronary artery occlusion has been studied as a model of sudden death, all previous studies have used animal models in which the coronary arteries were normal. Because most victims of sudden death, however, have some degree of coronary atherosclerosis, we explored the effect of preexisting coronary artery stenosis on the development of reperfusion arrhythmias.

In the first study, a flow-limiting stenosis was produced, upon which a 30-min complete occlusion was superimposed, followed by reperfusion. The peak flow...
during reperfusion was reduced by the flow-limiting stenosis. Under these circumstances we found a significant inverse relation between survival during reperfusion and peak rate at which blood flow returned to the ischemic myocardium. VF developed in all six dogs whose peak reperfusion flows exceeded 160% of baseline flow, but occurred in only five of 14 dogs (36%) whose flow was less than this value. Further, among reperfusion survivors the severity of transient arrhythmias also correlated inversely with reflow rate; dogs that manifested VT had higher reflow rates than dogs without VT. There was, however, considerable overlap in peak reperfusion flow rate between surviving dogs that suffered transient VT and dogs that died of VF. This suggests that other factors beside peak flow rate determine reperfusion fate. Examination of acceleration in circumflex flow at the onset of reperfusion failed to show any difference between VF dogs and survivors.

Our studies agree with and extend the work of earlier investigators. In 1955, Sewell et al.\(^5\) prevented reperfusion VF by releasing the occluding ligature “intermittently,” and reoccluding the coronary artery briefly if arrhythmias occurred. Petropoulos et al.\(^18\) occluded the circumflex coronary artery while cannulating it and found that VF occurred frequently when subsequent reperfusion was begun at 25 ml/min but not at 4 ml/min. Unfortunately, his report did not mention the duration of the coronary occlusion, an important variable in determining the risk of reperfusion VF.\(^\text{6, 17}\)

Since the cause of reperfusion VF is not known, the mechanism of the protection afforded by reduced reperfusion rate is speculative. One hypothesis relates reperfusion arrhythmias to acute washout of metabolites accumulated during ischemia into normal myocardium.\(^18\) However, VF has also been observed during reoxygenation after global hypoxia.\(^19\)

Others have shown abnormal ion fluxes and defective cell volume regulation in reperfused cells.\(^20-22\)

Reperfusion causes morphologic changes similar to those of temporary perfusion of isolated rat heart with anoxic or calcium-free solutions followed by reoxygenation or calcium repletion.\(^23\) The pathologic process common to reperfusion-induced abnormalities appears to be damage to the cell membrane caused by the period of deprivation, resulting in decreased ability to regulate permeability.\(^24, 25\) The salutary effect of restricting reperfusion may derive from limiting the availability of ions that might further damage the cell.

The mass of myocardium exposed to ischemia may also influence the incidence of reperfusion VF. We have found (unpublished data) that reperfusion VF does not occur when the size of the risk region (the territory supplied by the temporarily occluded CFX) is less than 20% of the left ventricle. To extend this latter observation, in the second part of this investigation we produced chronic stenosis of the LAD to induce formation of collateral vessels, and then studied the effect of this intervention on arrhythmia incidence during reperfusion of the myocardium supplied by the CFX. Dogs that survived reperfusion had significantly higher collateral blood flows to the CFX bed during CFX occlusion (through collaterals formed in response to chronic occlusion of the LAD) than did dogs that died of VF during reperfusion. Only one of eight dogs (11%) died that had collateral flow of at least 50% of normal, compared with eight of nine dogs (78%) with collateral flows less than this value. These results agree with an earlier finding that reperfusion VF does not occur in dogs with high postocclusive retrograde pressure.\(^19\)

Similarly, ischemia is not observed until coronary blood flow is reduced by more than 50%,\(^24-27\) and infarction does not occur when collateral flow exceeds 50% of normal flow.\(^28, 29\) Thus, there appears to be an ischemia threshold below which permanent coronary artery occlusion will not cause infarction and reperfusion will not produce VF.

In conclusion, survival after experimental reperfusion correlates with restriction of reperfusion flow and with the magnitude of collateral flow. Application of these results to the clinical situation must be made cautiously. The relative contributions of occlusion and reperfusion VF to the incidence of sudden death is unknown. In this study, 12 of 49 dogs died during occlusion, and 20 of the remaining 37 dogs died during reperfusion. The risk of reperfusion VF also depends upon the duration of the transient occlusion.\(^6, 17\) Clinically, occlusion may be brief, as often

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**Figure 3.** Transmural collateral blood flow in the circumflex bed (reperfusion zone), expressed as a percentage of baseline flow. Data for dogs that died of reperfusion ventricular fibrillation (VF) and dogs that survived reperfusion are shown. Horizontal bars designate means.
occurs with typical episodes of coronary spasm, or may be prolonged, as in some episodes of spasm or in reperfusion after coronary thrombolysis with streptokinase. Nonetheless, the implications of our results are intriguing. They suggest that significant coronary artery disease, by limiting reflow, may protect against the development of VF that occurs after transient coronary occlusion. Chronic occlusive coronary artery disease may also reduce the risk of reperfusion VF by inducing collateral development and thereby diminishing the intensity of ischemia during transient occlusion.

Acknowledgment

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