Hibernating Myocardium
Chronically Adapted to Ischemia but Vulnerable to Sudden Death
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Abstract—The inability to reproduce spontaneous ventricular fibrillation in an animal model of chronic coronary artery disease has limited advances in understanding mechanisms of sudden cardiac death (SCD). Swine with hibernating myocardium arising from a chronic left anterior descending coronary artery (LAD) occlusion have a high rate of SCD that parallels the poor clinical survival of medically treated patients with hibernating myocardium. Kaplan-Meier analysis (n=426) demonstrated a cumulative mortality of 49% after 5 months that was almost entirely attributable to spontaneous SCD. Using implantable loop recorders, ventricular fibrillation was documented as the arrhythmic mechanism of death in all animals (n=10) and was usually preceded by ventricular tachycardia (n=8). Physiological studies before SCD (n=7) demonstrated total LAD occlusion and collateral-dependent myocardium (n=5), excluding acute occlusion as a major trigger of arrhythmia. The physiological substrate of hibernating myocardium was present before SCD, with reductions in LAD perfusion (SCD 0.79±0.13 versus 0.80±0.08 mL/min per g) and wall thickening (SCD 28±3% versus 22±3%) that were similar to survivors (n=14). Triphenyltetrazolium chloride infarcts among animals with SCD were infrequent (4 of 32) and small, averaging 4.6% of LV mass. Histology (n=4) showed postmortem changes but no acute inflammation nor contraction band necrosis. These data support the notion that hibernating myocardium is a pathophysiological substrate at high risk of SCD. This is independent of changes in functional stenosis severity, acute myocardial necrosis, or fibrotic scar. Thus, regional adaptations that promote myocyte survival in the setting of chronic repetitive ischemia result in a substrate with enhanced vulnerability to lethal arrhythmias and SCD. (Circ Res. 2004;94:1142-1149.)

Key Words: hibernating myocardium • sudden cardiac death • ventricular fibrillation

Sudden cardiac death (SCD) arising from lethal ventricular arrhythmias continues to represent a substantial clinical problem in the management of patients with chronic coronary artery disease.1 When SCD is the initial manifestation of heart disease, pathological findings demonstrate multivessel disease, yet acute plaque rupture and myocardial infarction are both absent in almost one of four patients without prior cardiovascular symptoms.2,3 This implies that acute or chronic infarction is not a requisite substrate for the development of lethal arrhythmias in many patients. An additional corroboration of these observations is the low frequency of myocardial infarction demonstrated in individuals who are successfully resuscitated with aborted SCD.4

Although structural scar in the setting of advanced LV dysfunction is associated with an increased risk of arrhythmic death, the presence of jeopardized but viable myocardium may be an equally important risk factor. Viable chronically dysfunctional myocardium is common in patients with ischemic cardiomyopathy (40% to 60% of patients).5 Although it can reflect stunning or remote zone remodeling when resting blood flow is normal, regions of hibernating myocardium with reduced resting blood flow seem to identify a subgroup of patients at particularly high risk of SCD.6 In support of this, we have observed a similarly increased mortality that was almost always sudden in a swine model of hibernating myocardium.7 Studies in this model have demonstrated that chronic repetitive ischemia leads to regional cellular remodeling in the absence of infarction that could promote arrhythmogenesis. These changes include regional myocyte hypertrophy,8 altered SR calcium uptake,9 increased interstitial connective tissue,10 and inhomogeneity in sympathetic innervation,11 all of which have individually been associated with arrhythmogenesis. Although the precise mechanisms accounting for the increased mortality when hibernating myocardium is present are unknown, revascularization has a profound and positive impact on survival.12

Based on these observations, we hypothesized that the regional remodeling and adaptive responses that maintain
myocyte viability in hibernating myocardium result in a substrate that is vulnerable to sudden death. This results from ventricular arrhythmias that develop in the absence of acute or healed infarction. As a first step to test this in the swine model of hibernating myocardium, we characterized the terminal rhythm responsible for spontaneous SCD, determined whether physiological features of hibernating myocardium were present before an event, and identified whether pathological evidence of acute infarction was present in animals succumbing to SCD. The results demonstrate that SCD in hibernating myocardium arises from spontaneous ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF) in the setting of chronic left anterior descending coronary artery (LAD) occlusion and collateral-dependent myocardium. The infrequency of pathological evidence of infarction indicates that the regional adaptive responses that maintain viability in the setting of chronic repetitive ischemia results in increased electrical instability.

Materials and Methods

All experimental procedures and protocols conformed to institutional guidelines for the care and use of animals in research. Details of the surgical preparation have been presented elsewhere. Briefly, juvenile farm-bred pigs (nominal weight, ~10 kg; Bippert Farms, Alden, NY) were fasted and premedicated with a Telazol (tiletamine 50 mg/mL and zolazepam 50 mg/mL) and xylazine (100 mg/mL) mixture (0.022 mL/kg IM) and given prophylactic antibiotics (cefazolin 500 mg and gentamicin 40 mg IV). They were intubated, and a surgical plane of anesthesia was maintained with isoflurane (1% to 2%) and oxygen (balance). Through a thoracotomy (fourth left intercostal space) and a 1- to 2-cm limited pericardiotomy, a 2.5-mm-diameter Delrin stenosis was secured around the proximal intercostal space and a 1- to 2-cm limited pericardiotomy, a 1.5-mm-diameter Delrin stenosis was secured around the proximal LAD. The chest was closed, and the pericardium was evaded. A dose of cefazolin was repeated, and an intercostal nerve block (bupivacaine) and analgesics (butorphanol 0.1 to 0.2 mg/kg IM and flunixin 1 to 2 mg/kg IM) were given postoperatively to alleviate pain. Pigs were in their normal state of health within 48 hours. They were fed ad libitum and were usually housed in groups.

Survival Analysis of Swine With Hibernating Myocardium

To evaluate the timing and frequency of sudden death in swine with a chronic LAD stenosis, a Kaplan-Meier analysis was performed on all similarly instrumented animals studied in our laboratory since 1994 (n=426). Sudden death was defined as witnessed or unwitnessed death occurring without clinical signs of illness. Animals were censored at the time of pharmacological treatment or intervention. Animals that were euthanized electively for symptoms of acute heart failure (n=8, 0.5%) were not included as sudden deaths. Similarly housed sham-instrumented controls (n=36), in which the LAD was dissected or instrumented with a nonstenotic LAD occluder, were used for comparison.

Spontaneous Arrhythmias by Holter and Implantable Loop Recorder

A series of animals with hibernating myocardium (n=12) underwent serial Holter monitoring beginning 1 week after instrumentation (baseline study) and repeated at approximately 1-month intervals (total of 44 recordings). Preordial electrocardiographic leads were attached to a tape-driven recorder (Del Mar Model 459), which was secured in a nylon jacket. Recordings were analyzed for ST-segment changes, ventricular arrhythmias, mean heart rate, and indices of heart rate variability. A representative QT interval was measured during sinus rhythm in the early morning hours and corrected for heart rate using Fredericia’s formula [QTc=QT/(RR)^1/3]. Three animals developed SCD between 2 and 3 months after instrumentation, but none occurred during the recording periods.

To determine the arrhythmia at the time of spontaneous SCD, additional animals (n=44) received an implantable autoactivated loop recorder (REVEAL Plus Model 9526; Medtronic Inc.). Loop recorders were placed 38±7 days after instrumentation, because SCD before 1 month was infrequent. Under anesthesia, a 2-cm incision was made along the left upper thoracic spine (at approximately the T4 level), and the recorder was inserted into a subcutaneous pocket. Gain and sensitivity settings were manually adjusted for optimal detection of the QRS without triggering on the T wave. The recorder was programmed to trigger for asystole >3.0 seconds or >16 consecutive beats of bradycardia (<30 bpm) or tachycardia. Because sinus rates in swine exceed 200 bpm during exercise, we initially programmed the upper rate to 220 bpm but decreased this to 180 bpm in follow-up studies. Up to 40 minutes were stored with 13 autoactivated events (1 minute of data stored before and after triggering) and 1 manually activated event (14 minutes). Animals were monitored for an average of 88±6 days.

Physiological Substrate Preceding SCD

Studies of myocardial function and perfusion were performed 3 months after instrumentation to compare the physiological substrate in animals that subsequently developed SCD (n=7) to those that survived (n=14). Animals were sedated with Telazol/xylazine followed by propofol (5 to 10 mg/kg per hr IV). A 6F introducer was placed into the brachial artery, through which a 5F Millar catheter was inserted into the left ventricle for pressure measurement and microsphere injection. Aortic pressure and a reference withdrawal sample for microsphere flow analysis were obtained from the side port of the introducer. In these animals, hemodynamics and perfusion were assessed at rest and during pharmacological vasodilation with adenosine (0.9 mg/kg per min IV) using phenylephrine (200 to 1000 mg/min IV) to prevent adenosine-induced hypotension. Regional wall thickening and global LV function were assessed using 2D echocardiography (GE System 5).

Postmortem Pathological Analysis (n=32)

A subgroup of swine with witnessed SCD underwent postmortem pathological analysis. Hearts were harvested as soon as possible after SCD (time to sampling, ~2 hours). The LV was sectioned into concentric rings that were stained with triphenyltetrazolium chloride (TTC) to exclude acute or healed myocardial infarction. In four animals, electron and light microscopy was used to identify evidence of infarction, as previously described. To evaluate the role of postmortem changes, the findings in hibernating and remote regions were compared with sham hearts fixed immediately (n=4). Data represent the mean±SEM. Differences in parameters over time were assessed using ANOVA. Flow and echocardiographic measurements in hibernating versus normally perfused myocardium were compared with paired t tests. Differences between animals with SCD and survivors were compared by unpaired t tests. The P<0.05 level was considered significant.

Results

Survival curves of swine with hibernating myocardium attributable to a chronic LAD stenosis are compared with sham-instrumented controls in Figure 1. A total of 161 animals developed sudden death. The onset of sudden death was coincident with the development of a physiologically significant stenosis and dysfunctional myocardium. Early postoperative mortality (<7 days) was 1.9%. Cumulative mortality from SCD increased with the development of hibernating myocardium, averaging 28% after 3 months and 49% after 5 months of instrumentation. There was no mortality in sham-instrumented swine.
Arrhythmic Mechanism of SCD

Monitored sudden death events occurred an average of 90±13 days after instrumentation (identified by arrows on Figure 1). Figure 2 shows an example of an arrhythmia associated with SCD in a pig where the prodromal rhythm was recorded. All 10 pigs developed VF, with no evidence of bradyarrhythmias. Loop recorders triggered when low-amplitude VF developed, because the Reveal Plus recorder rejects rates >300 bpm as artifact (Medtronic Inc, personal communication). As a result, there were variable periods of prodromal rhythm available for analysis. In 8 animals VT preceded VF, in 1 animal sinus rhythm degenerated directly to VF, and in 1 animal only VF was recorded. The initial VT rate averaged 445±28 bpm and usually accelerated before the development of VF. When the transition from sinus rhythm was recorded (n=7), there was evidence of sympathetic activation vis-à-vis sinus tachycardia (220±25 bpm). There were no episodes of nonsustained VT before SCD, and no ST segment depression or elevation was evident on the recordings.

Serial Holter Monitoring

The results from Holter recordings are summarized in Figure 3. Average heart rate decreased with growth from 136±6 to 95±3 bpm over a 3-month period (P<0.001). There were no alterations in heart rate variability over time, nor were there time-dependent changes in the corrected QT interval. Although ventricular ectopic activity was rare (38±25 complexes per recording; range, 0 to 1074), 5 of 12 animals exhibited at least one episode of nonsustained VT (8±6 runs per recording; range, 0 to 260). There were no significant bradyarrhythmias. ST segment deviation of >1 mm occurred in 5 animals. Transient ST-segment elevation was more common within the first month of instrumentation, and after 1 month, only ST depression occurred.

Diurnal Variation in Sudden Death

Figure 4 summarizes the diurnal variation in monitored SCD events from animals with implantable loop recorders. This was compared with the diurnal variation in heart rate and nonsustained VT recorded by Holter monitoring. Because of the low frequency, the events have been averaged in 4-hour intervals beginning at midnight. All sudden deaths occurred between 4:30 AM and 8:11 PM, with the highest frequency between 12 noon and 4 PM. This corresponded to the diurnal variation in sympathetic tone as reflected by mean heart rate, which peaked at a similar time. Nonsustained VT was infrequent at night and increased during the day, with a peak frequency somewhat later than that of sudden death and heart rate.

Sinus Rhythm

Figure 2. Arrhythmic mechanism of SCD in a pig with hibernating myocardium. Each animal with monitored SCD developed VF. Selected panels from the Reveal Plus loop recorder demonstrate sinus rhythm recorded 1 day before SCD. The next morning, VT followed a brief episode of sinus tachycardia and degenerated into VF. Physiological study performed before SCD demonstrated total LAD occlusion with collateral-dependent hibernating myocardium and no myocardial necrosis. Eight of 10 animals had VT before VF, and in 1, sinus tachycardia degenerated into VF. In the remaining animal, only VF was recorded.

Ventricular Tachycardia

Ventricular Fibrillation
Pathophysiological Substrate of Hibernating Myocardium Before SCD

Seven animals had undergone a physiological study 2 to 42 days before SCD (study performed at 96±10 days and SCD occurrence at 115±10 days). Resting function and hemodynamics from swine with SCD are compared with survivors studied at a similar time point (98±2 days, n=14) in Figure 5. In 5 of the 7 animals that subsequently developed SCD (with VT/VF documented by loop recorder in 3), the LAD was occluded at the antemortem study and supplied by collaterals arising from the circumflex and right coronary arteries. Ventriculography demonstrated anterior hypokinesis in each animal before SCD, and regional dysfunction was confirmed by measurements of reduced LAD wall thickening (28±3% versus 81±6% in remote regions, P<0.001). Regional function was no different than in those that survived, and there was no evidence of global LV dysfunction in animals with SCD (Figure 5). Left ventricular mass was similar in the two groups of animals (224±15 g in animals with SCD versus 222±15 g, P=NS). Heart rate and systolic pressure were comparable in the two groups, but LV end-diastolic pressure was lower in SCD animals (20±4 versus 27±2 mm Hg, P<0.05).

Measurements of the transmural distribution of myocardial perfusion at rest and during adenosine vasodilation are shown in Figure 6. Resting subendocardial flow was reduced in the
LAD region of animals with SCD (LAD 0.79±0.11 versus 1.19±0.08 mL/min per g; P<0.05) and survivors (LAD 0.80±0.08 versus 1.22±0.09 mL/min per g; P<0.001). Absolute flows at rest and during adenosine vasodilation, as well as transmural distribution, were not different in animals with SCD versus those that survived. Subendocardial flow reserve was exhausted in both groups, with a trend to develop a transmural steal during adenosine. Although one animal had TTC evidence of necrosis, the measurements of flow, function, and hemodynamics were not significantly different if this animal was excluded. Collectively, these data suggest that the impairment in flow and function in animals with hibernating myocardium is not more severe in animals that subsequently developed SCD.

Pathological Findings in Animals With SCD

The myocardium was normal, with no TTC evidence of infarction in 28 of 32 swine. In the remaining four animals, evidence of small healed infarctions was present, averaging 4.6±1.6% of LV mass. Representative light microscopy from an animal with SCD versus sham control is shown in Figure 7. Light microscopy of subendocardial samples showed glycogen depletion in both LAD and remote regions of animals with SCD, reflecting the time delay in sampling. Nevertheless, there was no evidence of contraction band or coagulation necrosis indicative of recent infarction. Electron microscopy of swine with SCD showed postmortem ischemic changes, and blinded quantitative analysis of swine with SCD.
demonstrated that the percentage of myocytes with mitochondrial swelling (LAD 88±5% versus 90±2% in normal remote myocardium), mitochondrial autolysis (LAD 8.5±4.2% versus 7.0±2.4% in normal remote myocardium), and nuclear matrix extraction (LAD 83±6% versus 82±4% in normal remote myocardium) were similar in LAD and normally perfused remote regions. Likewise, occasional sarcotlemmal disruption and Jennings granules were seen, but there were no regional differences in animals with SCD. No abnormalities were observed in sham-instrumented animals in which the heart was immediately excised and sampled. Thus, the similarity of the changes in normally perfused and hibernating LAD regions from animals with SCD is consistent with postmortem changes arising from acute global ischemia before sampling.

**Discussion**

There are several important new findings from our study. First, swine with a chronic LAD stenosis experience a moderately high frequency of sudden death that coincides with the development of viable, chronically dysfunctional myocardium. This arises from spontaneous VF that is usually preceded by VT. Antemortem studies in a subgroup of animals confirmed physiological findings of hibernating myocardium before SCD. Pathological evidence of infarction was rare, and the demonstration of a total LAD occlusion before SCD excluded stenosis progression as a major trigger of lethal ventricular arrhythmias. Collectively, these findings support the notion that the regional cellular remodeling and inhomogeneity in sympathetic innervation characteristic of hibernating myocardium leads to a substrate that enhances the vulnerability to lethal arrhythmias and spontaneous sudden death.

**Arrhythmic Mechanism and Pathophysiological Substrate of SCD in Hibernating Myocardium**

Our results demonstrate that swine with hibernating myocardium develop spontaneous VT that degenerates into VF. Because we were unable to record an event during Holter monitoring, the detailed electrophysiological sequence of events before SCD could not be ascertained. VT was demonstrated in 8 of 10 animals in which a prodromal rhythm was recorded before VF. Although VT cycle lengths in swine are shorter than those found in patients with structural scar, the rates we recorded were within a range reported for inducible VT in pigs with chronic infarction.17 Recordings of the transition from sinus rhythm were limited, but sinus tachycardia (average rate, 220 bpm) was documented in several animals. Although this indicates moderate sympathetic activation, the heart rates were below the maximal heart rate in exercising swine, which approaches 260 bpm.18

Non sustained VT was infrequent, but not surprising, because this is usually associated with depressed LV function and healed infarction, which were with rare exception absent in this model of hibernating myocardium. Based on this, our findings are germane to the large patient population that develops SCD as an initial manifestation of coronary heart disease as opposed to those with advanced LV dysfunction, heart failure, and myocardial scar.1 Almost one in four patients having SCD as their initial manifestation of heart disease have advanced multivessel coronary disease, stable plaque, and no evidence of acute or healed infarction.3 Although severe coronary disease and plaque instability are found in half of the patients, acute myocardial infarction and total thrombotic coronary occlusion are relatively uncommon, which is supported by the low incidence of cardiac enzyme elevation found in patients resuscitated from SCD.4

Although we do not have continuous analysis of the hemodynamic variables preceding SCD, the antemortem physiological studies confirm several important features. First, the fact that the LAD was totally occluded and collateral dependent in 5 of 7 animals excludes progression of the stenosis as a trigger for SCD in most animals. The physiological studies also demonstrate that the reductions in resting flow, adenosine flow reserve, and resting function were no different in animals that subsequently developed SCD compared with survivors studied at a similar time point. Although we cannot exclude the possibility that coronary flow reserve decreased after these studies, we have demonstrated that collateral flow in this model is stable between 3 and 5 months after instrumentation.7 In addition, we have previously demonstrated that swine with hibernating myocardium are protected against subendocardial ischemia during submaximal stress elicited by β-adrenergic stimulation.19 Although the frequency of VF in nontransmural ischemia is extremely low in normal swine (unpublished observations), subendocardial ischemia could still be a trigger immediately before SCD if sympathetic activity was excessive and myocardial demand increased to a level beyond which the adapted heart could compensate.

**Relation to Previous Animal Models of Sudden Death**

Investigation into the mechanisms responsible for sudden death in chronic coronary artery disease has been limited by the inability to reproduce spontaneous VF in a chronic animal model with a high enough frequency to elucidate the cellular and physiological substrate that leads to arrhythmogenesis.20 Dogs with inheritable arrhythmias exhibit similarities with many human diseases where ventricular arrhythmias arise from alterations in ion channels responsible for depolarization and repolarization.21 Although these have importantly extended our understanding of predisposition to sudden death, the contribution of these mechanisms in coronary artery disease remains unclear. Previous studies of VF associated with ischemic heart disease have largely been limited to evaluating the response to transmural ischemia in the acute and subacute phases of an experimental myocardial infarction. In contrast to the high rate of spontaneous and inducible VT in chronic infarct models, there is a relatively low rate of VF, suggesting that more than myocardial scar or sympathetic denervation is required to produce sudden death.20 Cao et al22 have experimentally amplified the frequency of spontaneous VF after infarction in dogs. By superimposing AV block to produce myocyte cellular remodeling,23 with the infusion of nerve growth factor into the stellate ganglion, the frequency of spontaneous VF in the chronic phase of infarction could be increased to 44%. Their observations have led to the nerve...
sprouting hypothesis of SCD and support the notion that structural, cellular, and neural remodeling are all required to produce a substrate at high risk of spontaneous arrhythmogenesis.

Our results extend these observations to a model of chronic coronary artery disease where all of the SCD was spontaneous and with rare exception occurred in the absence of acute or healed infarction. Importantly, the diurnal variation of SCD is similar to that observed in humans and seems to be modulated by sympathetic tone. This link may result from inhomogeneity in myocardial repolarization during sympathetic activation, because regional reductions in presynaptic norepinephrine uptake are found in hibernating myocardium.3,25 Although infarction is absent in this model, there is an increase in interstitial connective tissue similar to that occurring in hypertrophy and chronic coronary disease that could result in fractionated conduction.7,25

Regional inhomogeneity in the cellular mechanisms responsible for myocyte depolarization and repolarization could also play a role in predisposing hibernating myocardium to VF. We have previously demonstrated that regional myocyte apoptosis in hibernating myocardium leads to cellular hypertrophy that compensates for regional myocyte loss.8 This and regional alterations in at least some of the proteins responsible for sarcoplasmatic reticulum calcium uptake could lead to an increased susceptibility to arrhythmias.9 Biopsy samples from patients with hibernating myocardium have demonstrated remodeling of connexins,26 local cytokine activation,27 and global reversion of some myocytes to a fetal phenotype15,25 that may also contribute to the increased susceptibility to arrhythmogenesis. Thus, hibernating myocardium has diverse structural, neural, and cellular remodeling of pathways that have been individually associated with arrhythmogenesis, and additional studies will be required to identify the specific cellular and electrophysiological mechanisms responsible for SCD in this model.

Limitations
Although we have demonstrated that SCD associated with hibernating myocardium can occur well after the development of a total coronary occlusion, we cannot exclude the possibility that progression of the stenosis contributes to SCD in some animals. In previous studies, we found the frequency of total coronary occlusion to be somewhat less at 2 months (44%) and absent in animals studied at 1 month.16 Regional myocardial function was already depressed at these time points, but it is possible that sudden progression of the stenosis could have resulted in acute ischemia and contributed to SCD in some animals. The evaluation of this possibility will require telemetry to monitor the physiological substrate on a more dynamic basis.

Finally, Holter monitoring was not performed on control animals. Zhao et al28 reported developmental reductions in heart rate in swine that were similar to those we observed at the initial studies and developmental increases in corrected QT interval that were related to the maturation of the cardiac autonomic nervous system. Although the constancy of corrected QT interval that we observed suggests that this did not contribute to SCD in our model, additional studies will be required to determine whether there are differences in repolarization compared with age-matched uninstrumented swine.

Clinical Implications
Our data demonstrate that the regional adaptive responses that result from chronic repetitive ischemia lead to a substrate that is electrically unstable and vulnerable to SCD. This may explain the high short-term mortality of medically treated patients with hibernating myocardium. Because viable dysfunctional myocardium is common in patients with ischemic cardiomyopathy,12,29 amelioration of electrical instability with revascularization could also explain the limited impact of an implantable defibrillator on survival in patients with depressed LV function undergoing coronary bypass surgery.30 It is also conceivable that hibernating myocardium may contribute to the risk of SCD in the large number of patients with depressed LV function that are not inducible at electrophysiological testing.31 Based on these observations, additional clinical studies are needed to identify the impact of viable dysfunctional myocardium as a pathophysiological substrate of SCD in patients with ischemic cardiomyopathy.32

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