Mechanism of sudden cardiac death in pigs with viable chronically dysfunctional myocardium and ischemic cardiomyopathy

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Fallavollita, James A., Brian J. Riegel, Gen Suzuki, Uma Valeti, and John M. Canty, Jr. Mechanism of sudden cardiac death in pigs with viable chronically dysfunctional myocardium and ischemic cardiomyopathy. Am J Physiol Heart Circ Physiol 289: H2688–H2696, 2005. First published August 5, 2005; doi:10.1152/ajpheart.00653.2005.—Pigs with viable chronically dysfunctional myocardium and ischemic cardiomyopathy are at high risk of sudden cardiac death (SCD). We sought to identify the arrhythmic mechanism of SCD, the relation to changes in left ventricular (LV) function, and inducibility of malignant arrhythmias before SCD. Juvenile pigs (n = 72) were instrumented with chronic stenoses on proximal left anterior descending and circumflex arteries. Survival was only 29% 3 mo after instrumentation, and all deaths were sudden and without prodromal symptoms of heart failure. Triphenyltetrazolium chloride staining demonstrated necrosis in only nine animals averaging 2.3 ± 0.9% of the LV, with no difference between SCD animals and survivors. Implantable loop recorders (n = 13) documented both ventricular fibrillation (n = 6) and bradyasystole (n = 2) as the arrhythmic mechanism of death. Although regional and global function were depressed [anteroseptal wall thickening 1.8 ± 0.2 vs. 4.2 ± 0.2 mm in Sham animals (P < 0.001); fractional shortening 21 ± 2 vs. 31 ± 1% in Sham animals (P < 0.01)], there were no differences between SCD animals and survivors. LV mass increased in animals with ischemic cardiomyopathy and was greater in animals with SCD (4.0 ± 0.2 vs. 3.1 ± 0.1 g/kg in survivors; P < 0.001). Serial programmed ventricular stimulation failed to induce any sustained arrhythmias. We conclude that pigs with viable dysfunctional myocardium and globally reduced LV function have a high rate of SCD with a spectrum of arrhythmias similar to patients with ischemic cardiomyopathy. The risk is independent of necrosis but appears to increase with LV hypertrophy. Like patients with ischemic cardiomyopathy, programmed stimulation is insensitive to predict SCD when viable dysfunctional myocardium is the pathological substrate.

hibernating myocardium; arrhythmias

PATIENTS WITH CHRONIC coronary artery disease and ischemic cardiomyopathy develop left ventricular (LV) dysfunction that is disproportionate to the mass of infarcted myocardium (7, 26). This is due to viable dysfunctional myocardium arising from either repetitive episodes of reversible ischemia (chronically stunned and hibernating myocardium) or remodeling in response to LV dysfunction (11). Viable, chronically dysfunctional myocardium with both normal (chronically stunned myocardium) (17) and reduced (hibernating myocardium) (22) resting perfusion is common in patients with ischemic cardiomyopathy and present in at least half of all patients (2). Although the amount of hibernating myocardium impacts functional improvement and symptoms of heart failure after revascularization, it is also an extremely important determinant of survival. This appears to be independent of LV dysfunction because patients with hibernating myocardium have a higher mortality than patients with irreversible scar (1). Although cause-specific mortality has not been widely studied, small investigations have suggested that the poor prognosis is related to arrhythmic death (16, 35). Although indirect, this is consonant with the profound effect of coronary revascularization on improving survival in the setting of global LV dysfunction, which may largely negate the potential benefit of an implantable cardiac defibrillator (9).

In support of viable dysfunctional myocardium being a pathological substrate increasing the risk of sudden cardiac death (SCD) independently of scar, we recently demonstrated (12) that pigs with hibernating myocardium and normal global LV function develop SCD in the absence of heart failure or significant infarction. Sudden death in this model is due to ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF), with total coronary occlusion and collateral-dependent hibernating myocardium frequently present before sudden death (12). When the volume of viable dysfunctional myocardium was increased by placing chronic stenoses on both the proximal left anterior descending coronary artery (LAD) and left circumflex coronary artery (18), animals developed global LV dysfunction and a hemodynamic picture similar to that of patients with ischemic cardiomyopathy and compensated LV failure. Although this was associated with trivial myocardial necrosis, the development of global LV dysfunction markedly amplified the risk of SCD compared with animals instrumented with a single LAD stenosis (18).

We performed the present study to determine whether the physiological substrate and mechanism of SCD in animals with global LV dysfunction from two-vessel coronary disease were similar to or differed from those with hibernating myocardium and normal LV dysfunction from a single LAD stenosis. We used Reveal Plus implantable loop recorders to identify the spectrum of arrhythmic mechanisms of SCD. Serial echocardiography was used to identify whether LV dysfunction preceded SCD and to determine whether regional or global dysfunction differed in animals with SCD compared with survivors. Finally, a chronically implantable right ventricular (RV) pacing lead was used to perform serial programmed electrical stimulation to identify whether inducible tachyarrhythmias were present before SCD.

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METHODS

**Coronary artery instrumentation.** All experimental procedures and protocols conformed to guidelines for the care and use of animals in research and were approved by the University at Buffalo Institutional Animal Care and Use Committee. Juvenile farm-bred pigs were fasted, premedicated with a Telazol (tiletamine 50 mg/ml and zolazepam 50 mg/ml)-xylazine (100 mg/ml) mixture (0.022 ml/kg im.), and given prophylactic antibiotics (cefazolin 0.5 mg iv and gentamicin 40 mg iv). Pigs were intubated, and sedation was maintained with isoflurane (1–2%) and oxygen (balance). Through a thoracotomy (fourth left intercostal space), the proximal LAD and left circumflex coronary artery were exposed with a limited pericardiotomy, leaving the rest of the pericardium intact. Fixed-diameter Delrin stenoses (1.5-mm inner diameter) were secured around both arteries. The wound was closed, and the pneumothorax was evacuated. A single postoperative dose of antibiotics was repeated, and an intercostal wound was closed, and the pneumothorax was evacuated. A single (1.5-mm inner diameter) were secured around both arteries. The wound was closed, and the pneumothorax was evacuated. A single postoperative dose of antibiotics was repeated, and an intercostal

corner nerve block (marcaine) and analgesics (butoprofen 2.2 mg/kg im and banamine 1.0–2.5 mg/kg im) were given postoperatively to alleviate pain. Survival analysis was performed on a total of 72 pigs, which included 17 animals used to characterize hemodynamics, flow, and function in survivors in a previous publication (18). Myocardial necrosis was assessed by triphenyltetrazolium chloride (TTC) staining and quantified as a percentage of LV mass (12). Point counting was used to quantify coagulate tissue staining of trichrome-stained histological sections (n = 17 animals) (22).

**Implantable loop recorder.** Implantable loop recorders (Reveal Plus model 9526; Medtronic) were used to establish the cardiac rhythm responsible for sudden death (n = 13). The recorders were placed in a subcutaneous pocket along the upper thoracic spine as previously described (12). Implantation was performed at the time of coronary artery instrumentation in eight animals, and in five animals a second surgical procedure was performed 28 ± 5 days later. The loop recorder was programmed to activate as follows: no. of subject-activated events = 0, no. of autoactivated events = 3, storage mode = 42 min, consecutive beats required to record an event = 16, bradycardia detection <30 beats/min (bpm), and asystole duration >3.0 s. The tachycardia detection rate was initially set at >230 bpm. Because the maximal heart rate decreased with age, it was lowered to 180 bpm 1 mo after initial coronary instrumentation. Gain and sensitivity settings were manually adjusted for optimal detection of the QRS complex without triggering on the T wave. Loop recorders were interrogated every 2 wk after implantation (after sedation with Telazol-xylazine) and after sudden death to document arrhythmias.

**Transthoracic echocardiography.** Regional and global LV function was serially evaluated with transthoracic echocardiograms performed at ~1 wk (n = 14), 1 mo (n = 15), and 2 mo (n = 19) after initial instrumentation. Echocardiographic parameters in animals that developed arrhythmic death were compared with those that survived to a terminal study. The results in animals instrumented with two coronary stenoses were compared with eight sham-instrumented animals that underwent thoracotomy and dissection of the LAD and circumflex artery without placement of a stenosis. Echocardiograms were performed with a 2.5-MHz (GE Vingmed System V; GE Medical Systems) or a 2.25-MHz (Ultramark 9; ATL Ultrasound) phased-array transducer (described previously [18, 31]). Sedated animals (Telazol-xylazine) were studied on their left side through a right parasternal window. Standard M mode was used to obtain wall thickness measurements of the anteroseptum and posterior walls from a midventricular short-axis view. As recommended by the American Society of Echocardiography, end diastole was defined as the onset of the QRS complex and end systole was the point of minimum chamber diameter (36). Regional function was assessed with myocardial wall thickening (ΔW/T, end-systolic thickness − end-diastolic thickness). Fractional shortening, an assessment of global function, was defined as [(100−(LV end-diastolic dimension) − (LV end-systolic dimension))/(LV end-diastolic dimension)]. LV ejection fraction was quantified from the estimated LV volumes (18) and defined as 100−[(LV end-diastolic volume) − (LV end-systolic volume)]/(LV end-diastolic volume). LV mass was calculated as recommended by the American Society of Echocardiography [LV mass in g = 0.81(0.14 (LV end-diastolic dimension + posterior wall + anteroseptal wall)]−1 (LV end-diastolic dimension)]+0.61 [23] and reported relative to body weight (g/kg).

**Serial programmed ventricular stimulation from RV apex.** Because previous studies documented a low risk of sudden death within the first month after coronary stenosis placement (18), programmed stimulation was delayed to allow sufficient growth that would facilitate placement of a chronic RV pacing lead for serial studies. Nine pigs were studied starting 35 ± 2 days after initial instrumentation. Fasted animals were premedicated with Telazol-xylazine and given a dose of cefazolin (1.0 g iv) and gentamicin (60 mg iv). Pigs were prophylactically intubated (and provided with oxygen at 3 l/min), and sedation was maintained with propofol (5–10 mg·kg·h−1) infusion. With sterile technique, a 6-cm midline neck incision was made and the right external jugular vein was identified. A single 6-F active fixation pacemaker lead was inserted through the jugular vein, advanced under fluoroscopy to the RV apex, and secured in a stable position. The lead was connected to the ventricular port of a dual-chamber Medtronic pacemaker (atrial port closed with a sterile plug). Excess pacing lead was coiled in the right atrium.

Programmed ventricular stimulation was delivered at approximately three times threshold voltage (programmer model 9790; Medtronic). After an eight-beat train at a basic cycle length of 400 ms, a single extrastimulus was introduced late in diastole (starting at 300 ms after the preceding beat) and decremented in 15-ms steps to a lower limit of 200 ms (programmer limit). Subsequently, double and then triple extrastimuli were introduced with S2 (or S2 and S3) delivered at 200 ms (or 15 ms above the refractory period) and S1 (or S4) initially at 300 ms and then decremented by 15-ms steps to a lower limit of 200 ms. If no sustained ventricular arrhythmias were induced, we evaluated burst pacing with the S1 train decremented by 15-ms steps to a lower limit of 200 ms. On completion of the programmed stimulation protocol, the pulse generator was secured in the subcutaneous tissue, the incision was closed, and a dressing was applied. Additional doses of cefazolin and gentamicin were administered after completion of the study. Programmed stimulation was repeated transcutaneously every 2 wk until animals died or were terminated (2.6 ± 0.6 studies per animal, range 1–6).

**Survival and statistical analyses.** Kaplan-Meier survival analysis was used to determine the frequency and temporal occurrence of sudden death. This analysis was conducted using all similarly instrumented animals studied in our laboratory since 1998 (n = 72), including those animals in which physiological studies were previously reported (18). Animals that were terminated or died in conjunction with a study were censored at that point and were not included as sudden deaths. The eight sham-instrumented animals served as controls.

The reported values are means ± SE. ANOVA was used to compare echocardiographic parameters between groups (Sudden Death, Survivor, and Sham) at each time point. The Holm-Sidak test was used for all pairwise post hoc comparisons. Kaplan-Meier survival curves were compared with the log-rank test. Significance for all statistics was defined as P < 0.05.

RESULTS

**Survival analysis of animals chronically instrumented with LAD and circumflex artery stenoses.** A total of 72 animals underwent surgical implantation of stenoses on the proximal LAD and circumflex artery, and 8 control animals had a similar surgical procedure with dissection of both arteries but without placement of stenoses. One animal developed clinical signs of

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congestive heart failure and was electively terminated. Figure 1 shows the Kaplan-Meier survival curve for all animals. There were only three deaths within the first week of surgery (4.2%), but beginning 3 wk after instrumentation sudden death occurred at a rate of 30% per month. A total of 40 animals had spontaneous sudden death, with cumulative survival of 83% at 1 mo, 56% at 2 mo, and 29% 3 mo after instrumentation. Sudden death was occasionally witnessed in association with feeding, transfer between cages, or sedation for procedures. There were no deaths in sham-instrumented controls, in which the coronary arteries were dissected free but not instrumented with a stenosis ($P < 0.01$).

**Mechanism of sudden death in two-vessel model of hibernating myocardium.** Eight of the thirteen animals with an implanted loop recorder developed spontaneous sudden death an average of 52 ± 7 days after instrumentation (range 25–82 days). All deaths occurred during the day, between the hours of 7 AM and 7 PM. All recorded rhythms associated with sudden death are shown in Fig. 2. VT occurred in six animals. Because the Reveal Plus rejects rates >300 bpm as artifact (Medtronic, personal communication), loop recorders frequently triggered when low-amplitude VF developed. Therefore, the transition to VF was only recorded in four animals. In three of these four animals, VF was preceded by VT at 340–450 bpm (mean 403 ± 33 bpm). The fourth animal had a junctional tachycardia with a very closely coupled ventricular ectopic beat triggering VF. The other two rhythms associated with sudden death were bradyasystole.

**Progression of myocardial dysfunction in relation to SCD in pigs with ischemic cardiomyopathy.** Echocardiographic measurements at each evaluation are shown in Table 1. There were no differences in age or animal weight between groups at any time point. Spontaneous sudden death ($n = 13$) occurred 35 ± 7 days after the 1-mo echocardiogram and 5 ± 1 days after the 2-mo echocardiogram. In the Survivor group ($n = 11$), elective termination was performed 59 ± 26 days after the 1-mo echocardiogram and 12 ± 9 days after the 2-mo echocardiogram.

Serial changes in regional function over time are illustrated in Fig. 3. All three groups of animals had similar anteroseptal wall thickening ($\Delta$WT) immediately after surgery (1 wk). Wall thickening initially increased with growth of the animals, with no significant differences among groups 1 mo after instrumentation. However, after 2 mo anteroseptal dysfunction was evident in the chronically instrumented animals (1.8 ± 0.2 vs. 4.2 ± 0.2 mm in Sham group; $P < 0.001$). There were no significant differences in regional wall thickening between the animals that later developed SCD compared with those that survived ($P = 0.45$ at 2 mo). Wall thickening in the posterior region supplied by the nonstenotic right coronary artery remained similar among groups over time.
Changes in global LV function (Fig. 4) paralleled the results of anteroseptal wall thickening distal to the chronic stenoses. Both LV fractional shortening and estimated ejection fraction were similar among the groups of animals at 1 wk and 1 mo after instrumentation. However, after 2 mo global function was reduced in both groups of instrumented animals compared with the Sham controls. Fractional shortening in the instrumented animals averaged 21 ± 2% vs. 31 ± 1% in Sham animals (P = 0.01), and the average ejection fraction was 42 ± 3% vs. 59 ± 2% in Sham animals (P = 0.01). There were no significant differences in fractional shortening (P = 0.59) or ejection fraction (P = 0.53) between those that died suddenly and those that survived.

There were less consistent trends in LV dimensions and estimated LV volumes. At the 1-wk and 1-mo studies, there were no differences in end-diastolic or end-systolic dimensions (Table 1) or estimated end-diastolic or end-systolic volume indexes (Fig. 5) between groups. The chronically instrumented groups tended to have larger ventricular dimensions and indexed volumes at the 2-mo study; however, only the end-systolic parameters [end-systolic dimension (P = 0.04), Table 1; estimated end-systolic volume index (P = 0.04), Fig. 5] of the Sudden Death group were significantly increased compared with the Sham controls. There were no significant differences between survivors and animals developing SCD.

Serial changes in LV mass estimated by echocardiography and normalized to body weight are shown in Fig. 6. There were...
no differences among the three groups at 1 wk after initial surgery \( (P = 0.93) \). By 1 mo, there was a trend toward LV hypertrophy among animals with two-vessel stenoses compared with controls, but the difference was not statistically significant \( (P = 0.17) \). After 2 mo, however, LV hypertrophy was evident in both groups of instrumented animals compared with Sham controls \( (P < 0.05 \text{ for each comparison}) \), and LV mass in the Sudden Death group was greater than that in the Survivor group \( (P = 0.04) \).

**Serial programmed RV stimulation.** Spontaneous sudden death occurred in five of the nine pigs undergoing serial programmed stimulation 63 ± 7 days after initial instrumentation (range 40–82 days). Despite the fact that ventricular tachyarrhythmias were the mechanism of sudden death in the majority of animals in this study, sustained VT was not induced during RV apical programmed stimulation \( (n = 21) \). The only induced arrhythmia was a single six-beat run of VT in an animal 82 days after initial instrumentation.

**Postmortem evaluation of animals with sudden death vs. survivors.** The direct measurement of LV mass at postmortem \( (n = 49) \) confirmed the presence of hypertrophy in the animals that experienced sudden death (Fig. 7). LV mass-to-body weight ratios in the Sudden Death animals were 30% greater than in Survivor animals \( (P < 0.001) \) and 52% greater than in Sham controls \( (P < 0.001) \). The LV mass-to-body weight ratio was also significantly greater among Survivor than Sham controls \( (P = 0.04) \). Myocardial necrosis was present by TTC staining in nine animals (4 animals with sudden death and 5 survivors), with an average infarct volume of 2.3 ± 0.9% of LV mass. Areas of negative staining were typically associated with gross fibrosis consistent with chronic infarction. There were no significant differences in the frequency or extent of necrosis between the Sudden Death and Survivor groups. As we previously reported \( (18, 22) \), connective tissue staining was increased in regions subtended by a chronic coronary stenosis (Fig. 8), but because of the variability among animals the regional differences did not achieve statistical significance \( (ANOVA: P = 0.14) \). The values for regional connective tissue staining were nearly identical in the animals that experienced sudden death compared with survivors \( (P = 0.99) \).

**DISCUSSION**

There are several new and important findings from our studies. First, increasing the area at risk of developing viable dysfunctional myocardium with critical stenoses on the LAD and circumflex coronary artery increases the frequency of arrhythmic death in the absence of significant myocardial necrosis. In contrast to pigs with a single LAD stenosis, where SCD was uniformly due to VF \( (12) \), bradyasystolic events appear to account for ~25% of arrhythmic events with VT/VF.
Sudden death. In animals with a single LAD stenosis with also show some differences in the arrhythmic mechanism of mic cardiomyopathy for placement of an implantable defibril-
mic cardiomyopathy where more than half of arrhythmic deaths occur in patients that are not inducible (3, 15). Finally, regional and global dysfunction preceded the development of SCD, yet this was not associated with advanced heart failure. Although the degree of regional and global LV dysfunction in animals developing SCD was similar to that in animals that survived, there was greater LV hypertrophy. Collectively, these findings lend further support to the hypothesis that viable dysfunctional myocardium increases the risk of sudden death independently of infarcted myocardium (1, 16, 35) and the risk of SCD is amplified by reductions in global ejection fraction in the absence of advanced heart failure.

**Sudden death in pigs compared with patients with ischemic cardiomyopathy.** We previously reported (12) that sudden death occurs in the absence of infarction in pigs with a single LAD stenosis. In these studies, hibernating myocardium was associated with preserved LV function and coronary occlusion with collateral-dependent myocardium frequently preceded SCD. As shown in Fig. 9, the rate of sudden death in pigs increased significantly with the addition of a second chronic stenosis ($P < 0.01$). Although this could be due to the increase in the mass of myocardium at risk of ischemia from $\sim 45\%$ to $\sim 75\%$ of the LV (43, 44), these observations are also consistent with the well-established inverse relation between arrhythmic death and ejection fraction. The importance of this relation is underscored by the fact that ejection fraction is currently the major clinical variable used to risk-stratify patients with ischemic cardiomyopathy.

These two porcine models of chronic ischemic heart disease also show some differences in the arrhythmic mechanism of sudden death. In animals with a single LAD stenosis with normal LV function, spontaneous sudden death ($n = 10$) was always associated with VF and, when recorded, preceded by VT (12). In contrast, two of the eight animals with ischemic cardiomyopathy had terminal bradyasystole. This distribution of arrhythmias is similar to the experience in patients with ischemic cardiomyopathy. Although there are very limited data, the available evidence suggests that the majority are due to VT degenerating into VF but a substantial minority are due to bradyarrhythmias (24).

The mechanisms leading to bradyasystolic arrest are likely complex but similar to the diversity of mechanisms reported in dogs with acute ischemia in a two-vessel coronary artery disease model (25). It is unlikely that the development of bradyasystole reflects advanced heart failure based on clinical observations immediately preceding the event. It is also unlikely that this arises as a terminal event following a large infarction because pathological evidence of significant infarct (unpublished observations). A plausible explanation is that the mechanism of death when the circumflex artery is the “culprit vessel” may be bradyasystole and may differ from VT/VF, which arises when the LAD is involved. This may reflect regional differences in ischemia, size of the area at risk of ischemia, or the relation between risk region and collateral flow.

**Regional and global myocardial dysfunction precedes development of sudden death.** The serial echocardiographic evaluation of animals that subsequently developed lethal arrhythmias clearly shows that regional and global LV dysfunction was present before sudden death. This suggests that recurrent ischemia led to regional myocyte apoptosis (20, 28) and subsequent cellular remodeling and hypertrophy (19), which was a vulnerable substrate. This contrasts with the development of acute coronary occlusion and transmural myocardial infarction, which would have been associated with normal myocardial function before the event. It is also consistent with
the observation in animals with a single LAD stenosis that the development of hibernating myocardium with total coronary occlusion and collateral-dependent myocardium was present before sudden death (12). Nevertheless, it is important to emphasize that any comparison between the Sudden Death and Survivor groups is limited by the undefined duration of survival after elective termination of some of the animals. The shape of the survival curve (Figs. 1 and 9) does not suggest any lessening of the risk of sudden death over time, and thus it is impossible to definitively identify a time at which the animals are no longer at risk of spontaneous sudden death. Nevertheless, we found no significant differences in regional or global LV function during the development of hibernating myocardium and ischemic cardiomyopathy between animals destined to die compared with survivors.

Although systolic function was similar among instrumented animals, we found a higher LV mass among the animals that developed SCD. This is consistent with a large body of clinical data showing that LV hypertrophy is a poor prognostic sign in patients with established heart disease. It is also compatible with the observation that LV hypertrophy is a frequent pathological finding among victims of spontaneous sudden death as an initial manifestation of heart disease (10, 45). In this model, the development of hypertrophy is unrelated to increases in afterload. Rather, compensatory hypertrophy appears to develop secondary to global LV dysfunction and the reduction in ejection fraction. Although not statistically significant, the trend toward larger LV dimensions and volumes in animals developing SCD lends support to the clinical association between the risk of sudden death and levels of B-type natriuretic peptide (8, 41). Further studies evaluating serial biomarker levels in pigs will be required to address this hypothesis directly.

Inability of serial programmed stimulation to predict sudden death. Programmed ventricular stimulation has been used to stratify patients with depressed LV function and myocardial scar to assess subsequent risk of SCD. Although this is a risk factor for SCD when the ejection fraction is depressed, over half of the arrhythmic deaths arise in the subset of patients that are not inducible. The programmed ventricular stimulation protocol used in our study was limited by a single RV apical site and the restrictive programming capabilities of a pacemaker generator. Nevertheless, we were unable to induce sustained VT or VF in any of the animals. Although the protocol was similar to that used in humans, it is possible that induction of VT requires more aggressive pacing protocols in the pig; and additional studies evaluating shorter cycle lengths, greater repetitive ventricular stimuli, or multiple pacing sites including the LV will be required.

Despite these limitations the absence of inducibility is consistent with the lack of significant myocardial necrosis in this model and suggests that other mechanisms may be operative in inducing VT/VF. These may be particularly relevant to the subset of patients considered candidates for primary prevention of SCD with an implantable defibrillator. For example, a recent substudy of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) demonstrated that the 2-year incidence of VT/VF was the same in patients with inducible VT/VF (31%, P = not significant) as in patients who were noninducible (27%) (15). In fact, because 64% of the patients were not inducible, most VT/VF events occurred in the noninducible group. Interestingly, defibrillator therapy for VF was more common in patients who were noninducible (8.1 vs. 2.2%, P = 0.08) (15). Dynamic alterations in cardiac action potential duration (APD) restitution rather than reentry associated with scar could be responsible for the development of VT/VF under these circumstances (14). In support of this, we recently demonstrated (4) an increase in the slope of the APD restitution curve in pigs with hibernating myocardium and a single LAD stenosis. These changes were limited to hibernating myocardium and resulted in inhomogeneity in APD restitution throughout the LV, which may lead to a particularly vulnerable substrate. Further studies will be needed to evaluate the spatial distribution of APD restitution as a substrate for SCD in this model.

Relation to other large-animal models of SCD. Advances in understanding substrate factors in SCD have partly been hampered by the inability to model human disease experimentally. Although considerable insight has been gained regarding mechanisms of arrhythmias arising during acute ischemia, there are very few animal models exhibiting a high rate of SCD and documentation of the arrhythmic mechanism responsible for SCD has been limited. For example, models of inherited arrhythmias exist in dogs and include the German shepherd model of polymorphic VT (32) and the boxer model of arrhythmogenic RV dysplasia (6). Although spontaneous sustained VT has been recorded in these animals, the arrhythmic mechanism responsible for SCD has not been documented and spontaneous SCD only occurs in a minority of the dogs. Healed myocardial infarction results in a low rate of SCD in dogs, but the incidence of VF can be increased by transient transmural ischemia during the intense sympathetic activation of peak exercise (37). Tachycardia-induced heart failure models have demonstrated substantial cellular and molecular remodeling in association with spontaneous VT (34, 39). Nevertheless, the few documented rhythms at the time of death indicate brady-systole occurring in the setting of advanced biventricular failure rather than VT degenerating into VF (27). Finally, chronic atrioventricular block and RV pacing leads to hypertrophy and cellular remodeling with a 10–15% rate of spontaneous SCD (42). It can be increased in the setting of myocardial infarction and stimulation of sympathetic nerve sprouting with nerve growth factor (13) or subthreshold electrical stimulation of the stellate ganglion (40).

The present model of ischemic cardiomyopathy differs from these models in several respects. First, sudden death has an incidence of ~70%, is entirely arrhythmic, and occurs in the absence of advanced heart failure. Second, the arrhythmic events occur spontaneously and, as in humans, appear to be related to transient sympathetic activation. Finally, they occur in the absence of healed infarction or an inherited genetic predisposition to SCD. Although the specific physiological triggers and substrate factors responsible for SCD remain to be established, the model is characterized by LV hypertrophy, chronic coronary artery disease, and LV dysfunction, which are the pathological factors identified in patients with SCD. Other pathological substrates include cellular hypertrophy (28), altered calcium handling (19), inhomogeneity in myocardial repolarization (4), and a critical reduction in flow reserve (21, 22) that would result in subendocardial ischemia during sympathetic activation.
Methodological limitations. Postmortem coronary angiography was not performed in the animals after sudden death, and TTC staining may be insensitive for detecting acute myocardial infarction because it relies on the loss of dehydrogenase activity (38). Therefore, we are unable to exclude acute coronary occlusion as a potential mechanism of sudden death. However, two lines of evidence suggest that this was not the major mechanism of sudden death in this model. First, serial echocardiography clearly showed that regional and global LV dysfunction was present before sudden death, and the degree of dysfunction was similar to that in animals that survived. Coronary angiography in nine of these surviving animals showed severe stenoses of both the LAD and circumflex coronary artery, with complete occlusion and collateral-dependent myocardium associated with 6 of the 18 instrumented vessels (18). Second, in a chronic single-vessel model of hibernating myocardium we previously documented (12) complete coronary occlusion and collateral-dependent myocardium before sudden death in five of seven animals. Therefore, in a similar chronic stenosis model, a majority of the episodes of sudden death could not be due to acute vessel occlusion. Additional studies will be required to clarify the role of acute ischemia in this model with telemetric physiological monitoring and the physiological investigation of animals resuscitated from sudden death.

Clinical implications. The clinical relevance of our model is underscored by the chronic nature of ischemic heart disease and documentation of the spectrum of arrhythmic mechanisms of sudden death similar to those described in patients with cardiomyopathy (24). Thus our model may offer potential insights into SCD in patients with ischemic heart disease. Similar to clinical studies, we found that LV mass was greater among animals destined to die (10, 45), but LV function and programmed ventricular stimulation were poor predictors (3, 15, 41). Perhaps most importantly, our findings support the hypothesis that viable myocardium in the setting of ischemic cardiomyopathy is associated with a worse prognosis and an increased risk of sudden death (1, 16, 35). Whether this is due to the risk of developing new acute coronary syndromes, inhomogeneity in APD restitution properties (4), or heterogeneity in sympathetic nerve function (29, 30) will require further study.

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