Abnormal Sympathetic Innervation of Viable Myocardium and the Substrate of Ventricular Tachycardia After Myocardial Infarction

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Objectives
The aim of this study was to characterize the relationship between impaired sympathetic innervation and arrhythmia with noninvasive biologic imaging in an animal model of post-infarct ventricular tachycardia (VT).

Background
Innervation might be abnormal in the normally perfused borderzone of myocardial infarction, contributing to myocardial catecholamine overexposure and arrhythmogenic risk.

Methods
Myocardial infarction was induced by mid-left anterior descending coronary artery balloon occlusion in 11 pigs. Positron emission tomography (PET) of tissue perfusion and catecholamine uptake and storage was performed with [13N]-ammonia and [11C]-epinephrine 4 to 12 weeks later. Magnetic resonance imaging and invasive electrophysiology (electroanatomic mapping, basket catheter, VT inducibility) were performed within 1 week of PET.

Results
When compared with a normal database of 9 healthy animals, reduced perfusion was observed in 37 ± 7% of the left ventricle (LV). Epinephrine retention was reduced in 44 ± 7% of LV, resulting in a perfusion/innervation mismatch of 7 ± 4% LV. Sustained monomorphic VT was inducible in 7 of 11 animals. These animals showed a larger perfusion/innervation mismatch (10 ± 4% vs. 4 ± 2% LV for animals without VT; p = 0.02). Regionally, the degree of perfusion/innervation mismatch did not correlate with wall thickness or thickening but showed a significant correlation with reduced myocardial voltage (r = 0.93; p = 0.001) and with the site of earliest VT activation (chi-square 13.1; p < 0.001).

Conclusions
Noninvasive mapping of cardiac sympathetic nerve terminals reveals regionally impaired catecholamine uptake and storage in the normally perfused borderzone after experimental myocardial infarction. These areas might be useful to characterize the individual risk for ventricular arrhythmia. (J Am Coll Cardiol 2008;51:2266–75) © 2008 by the American College of Cardiology Foundation

Despite the high success rate of coronary revascularization, life-threatening ventricular arrhythmia remains an important cause of mortality after myocardial infarction (MI) (1,2). Improved characterization of the arrhythmogenic substrate is thus important for optimized identification of individuals at risk and improved therapeutic decision making.

Impairment of sympathetic innervation is thought to be critically involved in ventricular arrhythmogenesis. Overexposure to catecholamines and impaired pre-/post-synaptic balance seem to promote electromechanical instability (3–5). Nuclear imaging with radiolabeled catecholamine analogs allows for noninvasive assessment of the integrity of sympathetic nerve terminals in the myocardium. With this approach, it has been demonstrated that sympathetic nerve terminals are more susceptible to ischemic damage than cardiomyocytes (6,7). After MI, regional impairments of neuronal catecholamine uptake frequently exceed the area of scar (8–12). This pattern moderately correlated with noninvasive electrophysiological abnormalities (11,12). In other studies, an association of impaired innervation with ventricular refractoriness was described (13), and alterations of catecholamine uptake have been observed in patients with arrhythmia but without coronary artery disease (3,4,14).
A direct link between the presence and extent of impaired sympathetic innervation, regional myocardial electrophysiological alterations, and the presence and site of inducible ventricular tachycardia (VT) has not yet been established after MI. In an effort to identify the contribution of impaired sympathetic innervation to the arrhythmogenic substrate, we employed a previously established, well-controlled animal model of MI (15) and performed regional characterization with detailed invasive electrophysiological studies (EPS) and high-end noninvasive biologic and functional imaging.

**Methods**

**Porcine model of MI.** Myocardial infarction was induced in 15 young farm pigs (25 to 35 kg), as previously described (15). Under general anesthesia (induction with ketamine/xylazine/telazol, maintenance with 1.2% to 2.0% isoflurane), balloon occlusion of the mid left anterior descending coronary artery (LAD), immediately distal to the second diagonal branch, was performed for 150 min under fluoroscopic guidance. To prevent fatal arrhythmia, lidocaine was prophylactically given, and ventricular fibrillation was treated by rapid cardioversion. Post-operative treatment included narcotics and nonsteroidal anti-inflammatory drugs (ketorolac tromethamine). One animal died owing to ventricular fibrillation during balloon occlusion, and 3 animals died from sudden death in the follow-up period, without completion of further procedures.

Eleven pigs completed the study. Positron emission tomography (PET) was performed at 4 to 12 weeks (6.6 ± 3.2 weeks) after the procedure; magnetic resonance imaging (MRI) and EPS were performed within 1 week of PET. The experimental protocol was approved by the Institutional Animal Care and Use Committee. Animals were maintained in accordance with the guiding principles of the American Physiological Society.

**PET DATA ACQUISITION.** The [11C]-epinephrine was synthesized as previously described (16). The PET imaging was performed with a GE Advance scanner (GE Medical Systems, Milwaukie, Wisconsin), during general anesthesia. After supine positioning, a transmission scan of 10 min was acquired for correction of photon attenuation. To measure myocardial perfusion at rest, a static image of 15 min was acquired 5 min after injection of 400 to 600 MBq of [13N]-ammonia. After a break of 40 min to allow for radioactivity decay, 600 to 800 MBq of [11C]-epinephrine with a specific activity >1 Ci/mmol were injected, and a dynamic imaging sequence (14 frames; 6 × 30, 2 × 60, 2 × 150, 2 × 300, 2 × 600 s) was acquired over 40 min.

**METABOLITE ANALYSIS.** To determine the contribution of [11C]-labeled metabolites to blood activity, venous blood samples were drawn at 1, 5, 10, 20, and 40 min after injection of [11C]-epinephrine. Plasma metabolites were assayed with Sep-Pak cartridges (Waters Corp, Milford, Massachusetts) as previously described (17).

**QUANTITATIVE PET DATA PROCESSING.** Attenuation-corrected transaxial PET images were reconstructed by filtered back-projection. The PET data were analyzed by an observer blinded to electrophysiological results. With volumetric sampling of the [13N]-ammonia perfusion study, myocardial radioactivity was defined in 460 LV sectors and depicted in a polar map (18). Polar maps were normalized to their maximum and used for assessment of regional perfusion. Myocardial segments were transferred to the [11C]-epinephrine images. The initial frame of the sequence was checked to rule out residual activity from the previous [13N]-ammonia injection. Arterial input function was derived from a small circular region of interest in the LV cavity and corrected for the presence of [11C]-labeled epinephrine metabolites. An epinephrine retention index, measured in %/min, was calculated by normalizing myocardial activity at 40 min to the integral under the metabolite-corrected arterial blood time activity curve and was depicted in a parametric polar map for the entire LV.

**GLOBAL POLARMAP ANALYSIS.** Individual polar maps were compared with reference normal databases created from results of 9 healthy age- and weight-matched pigs undergoing the same PET protocol. Myocardial perfusion defect was described as percent area of the polar map depicting relative uptake values below 2.5 SD of the mean of healthy control subjects. Similarly, innervation defect was described as an epinephrine retention index below 2.5 SD of the mean of control subjects (Fig. 1). A global perfusion/innervation mismatch was calculated by subtracting perfusion from innervation defect size. Additionally, global catecholamine storage capacity was described as mean LV epinephrine retention index of the whole polar map.

**REGIONAL POLARMAP ANALYSIS.** A region-of-interest model of 9 myocardial segments was applied, as previously established (19). Segments comprised the apex and basal as well as distal portions of septal, anterior, lateral, and inferior wall. For accurate matching with subsequent tests, septum was defined as the area between anterior and posterior insertion of the right ventricle (RV) on short-axis slices, and the other myocardial walls were defined accordingly (Fig. 2A). For perfusion and innervation polar maps, average SDs from normal values were recorded in each segment. The degree of
perfusion/innervation mismatch was expressed as the difference between SDs from normal subjects for both studies.

**MRI.** Magnetic resonance imaging was performed with a 1.5-T scanner (Signa, GE Healthcare Technologies, Milwaukee, Wisconsin) and a 4-channel cardiac phased-array coil. An electrocardiography (ECG)-gated cine mode acquisition was used for assessment of ventricular function and geometry (FIESTA, flip angle 50, echo time [TE] 1.0 ms, repetition time [TR] 4.0 ms, field-of-view [FOV] 26 cm, slice thickness 8 mm, 30 frames). Five animals underwent delayed enhancement imaging after intravenous administration of gadolinium-diethyltriaminepentaacetic acid (inversion-recovery fast-gradient-echo pulse sequence, flip angle 20, TE 4.2 ms, TR 7.6 ms, FOV 26 cm, slice thickness 8 mm, contrast dose 0.2 mmol/kg, imaging 10 min after injection). With CINETOOL software (GE Healthcare Technologies), the endocardium and epicardium were manually contoured at end-diastole and -systole in each short-axis level to calculate left ventricular ejection fraction (LVEF), volumes, and mass along with regional wall thickness and thickening and segmental scar percentage in animals undergoing delayed enhancement imaging. For accurate matching with PET, septum was defined as the area between anterior and posterior insertion of the RV, and the other myocardial walls were defined accordingly. The apex, which is not appropriately imaged by short-axis images, was excluded.

**EPS. VT INDUCIBILITY.** After induction of anesthesia and surgical venous access, a quadrupolar electrophysiology catheter was placed in the RV for programmed stimulation as previously described (15); pacing was performed at twice the pacing threshold. Extra stimuli were delivered after 8 drive beats (cycle length 250, 300, 350 ms). The first stimulus (S2) was initially set at 200 to 220 ms after the last pacing stimulus of the drive train (S1). The S2 was then delivered at progressively shorter coupling intervals, scanning in 10-ms steps until the effective refractory period (ERP) was reached. If no arrhythmias were observed, S2 was reset to 30 ms outside ERP. A second stimulus (S3) was added 170 to 200 ms after S2, and scanning in 10-ms decrements was repeated until S2 and S3 were both refractory or equal to 140 ms. If no arrhythmias were induced, a third stimulus (S4) was similarly introduced. After reaching a coupling interval of 140 ms or refactoriness with all extra stimuli, burst pacing was performed by delivering 20 beats at a cycle length of 280 ms. If no arrhythmias were observed, burst cycle length was progressively scanned in 10-ms increments until arrhythmia induction, 2:1 conduction, or a minimum cycle length of 200 ms. If no arrhythmias were observed, the catheter was repositioned in the RV outflow tract and the aforementioned pacing protocols were repeated. The end point was either completion of the protocol to refactoriness or consistent induction of sustained monomorphic VT (at least twice with the same morphology).

**BASKET CATHETER RECORDING.** If VT was induced, a 64 electrode basket catheter was inserted into the LV. Local activation time at any site was defined as time from the onset of the surface QRS to the time the first deflection of the local electrogram crossed the baseline. The site of earliest electrical activation was identified accordingly, and the corresponding anatomical site was identified by fluoroscopic identification of the electrode with the earliest activation time. This anatomical site was assigned to 1 of the 9 myocardial segments.

**ELECTROANATOMICAL MAPPING (EAM).** Electroanatomical mapping was performed with the CARTO system (CARTO XP, Biosense-Webster Inc., Diamond Bar, California). During sinus rhythm, LV and RV endocardium was fully mapped to achieve <15 mm and <20 mm filling. For voltage mapping, bipolar voltage (BV) <0.5 mV was defined as infarct scar, and BV between 0.5 and 1.5 mV was considered infarct border zone, according to previously established criteria (20). Co-registration with PET and MR data was achieved by identification of septum on BV maps and definition of other myocardial walls accordingly (Fig. 2B). Scar and borderzone were expressed as a percent of the entire area assigned to each myocardial segment. If VT was induced and sustained, EAM was performed to obtain propagation mapping for visualization of the earliest activation site (n = 5).

**Statistical analysis.** All data are shown as mean ± SD. A p value <0.05 was considered statistically significant, unless specified otherwise. Pearson’s correlation with Fisher r-to-z was used to describe the relationship between continuous variables. Receiver-operating characteristic (ROC) analysis
was performed with MedCalc Software (Mariakerke, Belgium). All other statistical analysis was carried out with Statview 5.0 (SAS Institute, Inc., Cary, North Carolina).

The Student t test was used for comparison between groups of animals with/without VT inducibility and (assuming independence of segments) for comparison of segments with/without VT inducibility. Assuming independence of segments, 1-way factorial analysis of variance was used for comparison of a continuous imaging variable from EPS, MRI, or PET between 9 segments, and the post hoc Bonferroni-corrected t test was used to assess all possible 2-way comparisons (36 in total), resulting in a corrected p value of 0.0014 for significance. Assuming independence of segments, the chi-square test was used to evaluate the relationship between VT inducibility and the presence/absence of a perfusion/innervation mismatch in segments.

To support the assumption of independence of myocardial segments, a correlation analysis was performed with the most important PET variable, the mismatch between perfusion and innervation abnormality. Values in the distal anterior wall segment (the predominant site of VT inducibility) did not correlate significantly with corresponding values from any of the 8 other segments. Additionally, there is biological support for the independence of segments from a prior publication using a similar animal model (21), where multiple different VT morphologies were observed between and within animals, supporting that the segment showing VT inducibility can be treated as an independent entity.

**Results**

**Electrophysiological characterization.** During EPS, sustained monomorphic VT was inducible in 7 of 11 animals. Eight sites of earliest VT activation were identified in the 7 animals. All VTs were reproducibly induced by triple extrastimuli pacing, and a subgroup showed entrainment during overdrive pacing, suggesting a re-entry mechanism. Four were terminated by burst pacing; the remaining 4 needed cardioversion to be terminated. On 12-lead surface ECG, the QRS configuration of the VT showed a superior axis and right bundle branch block pattern in 7 (Fig. 3) and a superior axis and left bundle branch block pattern in 1 VT. According to endocardial mapping, the earliest activation site and thus the regional VT exit site was frequently located in the distal anterior wall segment (Figs. 3 and 4A). Time between infarction and imaging was not different between inducible and noninducible animals (48 ± 24 days vs. 43 ± 23 days; p = 0.80).

The EAM localized very low voltage areas (<0.5 mV) corresponding to scar predominantly in the distal septal
wall, whereas the borderzone with mildly reduced voltage of 0.5 to 1.5 mV was localized in the distal anterior wall (matching the earliest activation site of VT) but also to a lesser degree in the distal septal wall and apex (Fig. 4A).

LV function and geometry. The LVEF was 33 ± 4% at MRI and not significantly different between animals with and without VT inducibility (p = 0.08) (Table 1). No differences between groups were detected for end-diastolic volume (p = 0.35), end-systolic volume (p = 0.20), and LV mass (p = 0.75).

Regional end-diastolic wall thickness and wall thickening were lowest in the distal septum, although differences were small. Wall thickness was otherwise homogeneous, whereas wall thickening showed a gradient between basal and distal segments (Fig. 4B). In the 5 animals undergoing delayed enhancement imaging, infarct location coregistered with PET defects and reduced CARTO voltage. On a segmental basis, presence and transmural extent of infarct correlated significantly with PET perfusion reduction (r = 0.69; p < 0.001), epinephrine reduction (r = 0.77; p < 0.001), and reduced voltage (r = 0.78; p < 0.001) but not with perfusion/innervation mismatch (r = −0.06; p = 0.71).

Myocardial perfusion and sympathetic innervation. On a per-animal level, PET perfusion defect size was 37 ± 7% of LV and innervation defect size was 44 ± 7% of LV, resulting in a mismatch of 7 ± 4% of LV. Absolute defects for perfusion (Table 1) (p = 0.32) and innervation (p = 0.82) were not different in animals with and without VT inducibility, but the extent of perfusion/innervation mismatch (p = 0.019) (Fig. 5) was significantly different. Receiver-operating characteristic analysis revealed an area under the curve of 0.95 (95% confidence interval 0.64 to 0.98) for the perfusion/innervation mismatch to identify inducible VT, which was higher than that of any other global parameter (Table 1).

On a segmental level, regional analysis showed that myocardial perfusion deviated most significantly from normal subjects in the distal septum and apex, whereas segmental epinephrine retention index deviated significantly in distal septum, apex, and distal anterior wall. This resulted in the largest perfusion/innervation mismatch in the distal anterior wall, the segment where VT most frequently originated and where areas of mildly reduced voltage suggestive of the infarct borderzone were identified by voltage mapping (Fig. 4C). Figure 6 shows representative imaging results in an animal with VT inducibility.

Segmental analysis and correlations. Table 2 summarizes results in the 8 segments that were identified as sites of earliest activation of VT. These segments showed a significantly higher degree of perfusion/innervation mismatch and a higher percentage of mildly reduced voltage of 0.5 to 1.5 mV. Additionally, the earliest site of VT activation was significantly associated with presence of a segmental perfusion/innervation mismatch, if a 1.5-SD reduction of innervation below perfusion was chosen as the threshold to classify a segment as mismatch (chi-square 13.1; p < 0.001).
Finally, correlation analysis was performed for mean values in the 9 myocardial segments. Abnormality of segmental innervation correlated significantly with reduced segmental voltage, giving further support to the electrophysiological implications of impaired innervation (Fig. 7).

**Discussion**

In summary, our data show that impairment of myocardial catecholamine uptake and storage exceeds the reduction of tissue perfusion after experimental MI. This dysinnervation of normally perfused viable myocardium occurs in the infarct borderzone, is more extensive if sustained VT is inducible, and correlates regionally with reduced voltage and the earliest endocardial activation site of VT. These results suggest a contribution of impaired sympathetic innervation to the substrate of post-infarct VT.

Using several different radiolabeled catecholamine analogs, previous studies have suggested that sympathetic nerve terminals are more susceptible to ischemic damage than cardiomyocytes. Significant impairments of innervation have been observed after short periods of experimental ischemia (7), and abnormally reduced catecholamine uptake has been observed in hibernating viable myocardium of pigs (22) and in patients with extensive coronary artery disease but without evidence of MI (23). After MI, several studies reported innervation impairments exceeding the extent of scar (8–12), and regional correlation between innervation defect and the ischemic area at risk before revascularization has been described (10). Few of these studies reported some association of impaired innervation with noninvasive electrophysiological parameters such as frequency of ventricular arrhythmia (11), heart rate variability (24), and depolarization and repolarization (12). The present study is the first to substantiate the link between abnormal innervation of viable myocardium after MI and ventricular arrhythmia by a detailed regional correlation between impaired myocardial catecholamine handling, invasive electrophysiology, and the site of inducible VT.

Sympathetic innervation is believed to play a key role in ventricular arrhythmogenesis (25). Impairment of catecholamine reuptake contributes to reduced clearance of neurotransmitter from the synaptic cleft and thus to myocardial

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**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Voltage &lt;0.5mV (% of segment)</th>
<th>Voltage 0.5-1.5mV (% of segment)</th>
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<tbody>
<tr>
<td>A EPS</td>
<td></td>
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<tr>
<td>B MRI</td>
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<tr>
<td>C PET</td>
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**Figure 4** Regional Results of EPS, MRI, and PET

Regional results of EPS (A), MRI (B), and PET (C) in the 9 myocardial segments described in Figure 2. Shown are mean ± SD of all animals, except for site of ventricular tachycardia (VT) inducibility, which is shown as an absolute number. For each variable except site of VT, values in segments were compared with each other with analysis of variance, assuming independency of segments. Symbols indicate that the respective segment, highlighted in orange, differed significantly from a large number of other segments (*p<0.0014 vs 8 other segments, †p<0.0014 vs 7 other segments, ‡p<0.0014 vs 6 other segments).
Table 1  Individual and Grouped Results From EPS, PET, and MRI

<table>
<thead>
<tr>
<th>Animal #</th>
<th>EPS VT Inducibility</th>
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<th>MRI</th>
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<tr>
<td></td>
<td></td>
<td>Perfusion Defect (%LV)</td>
<td>Innervation Defect (%LV)</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
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<tr>
<td>11</td>
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</table>

All (n = 11) — 37 ± 7 44 ± 7 16 ± 1 7 ± 4 33 ± 4 84 ± 23 57 ± 16 66 ± 13
VT yes (n = 7) — 35 ± 5 45 ± 6 16 ± 1 10 ± 4* 34 ± 3 79 ± 20 52 ± 12 67 ± 14
VT no (n = 4) — 40 ± 10 44 ± 9 16 ± 1 4 ± 2 30 ± 4 93 ± 27 65 ± 20 64 ± 13
AUC for VT, mean (95% CI) — 0.64 (0.31–0.89) 0.55 (0.24–0.84) 0.57 (0.26–0.85) 0.95 (0.64–0.98) 0.79 (0.45–0.96) 0.61 (0.28–0.87) 0.68 (0.35–0.91) 0.62 (0.28–0.88)

Summed data are shown as mean ± SD. *p = 0.02 versus VT no.

AUC = area under receiver-operating characteristic curve; CI = confidence interval; EDV = end-diastolic volume; EPI = [11C]-epinephrine; EPS = electrophysiological studies; ESV = end-systolic volume; LV = left ventricle; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET = positron emission tomography; VT = ventricular tachycardia.
catecholamine overexposure. The resulting pre-/post-synaptic imbalance is thought to contribute to electromechanical instability and thus arrhythmogenesis. This is supported by the observation of impaired innervation in the absence of coronary artery disease in a variety of arrhythmogenic diseases such as idiopathic ventricular fibrillation (4), RV outflow tract tachycardia (3), and Brugada syndrome (26). In these studies, however, as in other studies after MI, no regional correlation between innervation status and the origin of arrhythmia was performed.

To get the most accurate information about the pathobiological interrelationship between arrhythmia and impaired sympathetic innervation, we chose the tracer $[^{11}C]$-epinephrine as a radiolabeled natural catecholamine and PET as the currently most powerful noninvasive biologic imaging technique. Advantages of this approach over the more frequently used conventional scintigraphy with $[^{123}I]$-metaiodobenzylguanidine, which might show low uptake in reduced ejection fraction (6,22), are higher spatial resolution, improved regional myocardial assessment, and the more physiological tracer characteristics. Epinephrine reflects neuronal uptake, metabolism, and storage and has thus been considered a more physiological tracer than the more popular PET compound $[^{11}C]$-hydroxyephedrine (HED), which primarily traces uptake-1 capacity (17). This physiological behavior at the same time represents a challenge because of enzymatic metabolism by monoaminooxidases, which is why metabolite correction needs to be performed. Although our high-end approach yields conclusive results, future studies might focus on the reproducibility of our findings with other catecholaminergic tracers to simplify neuronal imaging strategies for a broader-scale clinical setting.

It is also important to recognize the biological/functional nature of the nuclear imaging signal. Although some prior histologic studies reported focally increased density of nerves in the peri-infarct area and postulated nerve sprouting and hyperinnervation as a mechanism contributing to VT (27), these morphologic results are not conflicting with the functional
results of the present study. Higher density of nerves at 1 site might be associated with lower density at several other sites, and the sum of all microscopic changes might still be a macroscopic reduction of catecholamine uptake and storage capacity identified by PET; in addition, even if histologic density of nerves is increased, their functionality might still be abnormal and the overall regional potential for catecholamine uptake and storage might be reduced.

There is clinical interest in using noninvasive catecholaminergic imaging to identify individuals at high risk for life-threatening arrhythmia and to assist in localization of the regional substrate of ventricular arrhythmia for targeted therapy. The problem associated with implantable cardioverter-defibrillator (ICD) implantation is that some patients with sudden cardiac death do not have a high-risk profile and therefore are missed by currently applied criteria (e.g., low LVEF). Conversely, some so-called high-risk patients are not really at high risk, and their ICDs never fire. The quest for better selection of candidates for ICDs (28,29), together with the increasing interest in targeted ablation (30,31) or molecular therapy (15), emphasize the need for noninvasive diagnostic tests to risk-stratify individuals for ventricular arrhythmias. The present study supports a relationship between regionally impaired sympathetic innervation and VT inducibility and thus provides a mechanistic foundation for future clinical trials to assess the use of noninvasive innervation imaging in the work-up of patients for post-infarct VT risk. Previous observations, along with the sudden death of a small fraction of our animals, suggest that our pig model not only shows inducible VT at programmed stimulation but also develops spontaneous arrhythmia. Death of our animals, however, occurred without completion of imaging procedures. Some clinical data support the usefulness of VT inducibility to predict spontaneous VT (28), but the topic of discussion is currently controversial. Whether innervation imaging can predict not only inducible but also spontaneous ventricular arrhythmia in the clinical setting needs to be investigated in prospective clinical trials. Our results not only support but also encourage such clinical studies.

**Study limitations.** Some limitations of this study need to be considered. First, our results show an association between impaired innervation of the viable infarct borderzone and VT inducibility, but do not establish a cause/effect relationship. This, however, has been shown in a prior study (13), where myocardial regions with reduced innervation on PET showed a longer effective refractory period. It is also indirectly supported by retrospective clinical observations of scintigraphically impaired innervation as an independent predictor of cardiac death (32,33). Second, although other tomographic imaging techniques such as computed tomography or MRI can be integrated with electroanatomical mapping with software-based approaches (31), such methodology is not yet available for PET. We thus had to limit our regional analysis to 9 myocardial segments that were assigned by blinded observers with a standardized technique to achieve co-registration. Some of the variability in our study might thus be attributed to inaccuracies of localization, but results remain conclusive and software advances and the application of PET-computed tomography for bio-morphologic imaging might refine regional assessment in the future. Finally, VT in our model was electrophysiologically characterized by a re-entry mechanism. We were not able to map the entire re-entry circuit in our study, probably owing to a deeper intramural course. Therefore, we
chose the earliest activation site and thus the endocardial exit site as the best available parameter for regional VT localization, which is in line with general clinical practice.

**Conclusions**

In conclusion, mapping of cardiac sympathetic nerve terminals provides regional biological information about the substrate of ventricular arrhythmia in ischemic heart disease. The site of inducible VT correlated with the area of viable but denervated myocardium measured by PET. Our results provide a rationale for clinical trials to evaluate the use of noninvasive innervation imaging in the work-up of post-infarct ventricular arrhythmia.

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