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Intracoronary Infusion of Catecholamines Causes Focal Arrhythmias in Pigs

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Abstract

Background—Acute ischemia causes myriad changes including increased catecholamines. We tested the hypothesis that elevated catecholamines alone are arrhythmogenic.

Methods and Results—A 504 electrode sock was placed over both ventricles in six open-chest pigs. During control infusion of saline through a catheter in the left anterior descending coronary artery (LAD), no sustained arrhythmias occurred, and the refractory period estimated by the activation recovery interval (ARI) was 175 ± 14 ms in the LAD bed below the catheter. After infusion of isoproterenol at $0.1 \mu\text{g/kg/min}$ through the catheter, the ARI in this bed was significantly reduced to 109 ± 10 ms. A sharp gradient of refractoriness of 43 ± 10 ms was at the border of the perfused bed. Sustained monomorphic ventricular tachycardia occurred after drug infusion in the perfused bed or near its boundary in all animals with a cycle length of 329 ± 26 ms and a focal origin. The maximum slope of the ARI restitution curve at the focal origins of the tachyarrhythmias was always <1 (0.62 ± 0.15). Similar results with a focal arrhythmia origin occurred in two additional pigs in which intramural mapping was performed with 36 plunge needle electrodes in the left ventricular perfused bed.

Conclusion—Regional elevation of a catecholamine, which is one of the alterations produced by acute ischemia, can by itself cause tachyarrhythmias. These arrhythmias are closely associated with a shortened refractory period and a large gradient of the spatial distribution of refractoriness but not with a steep restitution curve.

Keywords

catecholamines; ventricular tachycardia; swine; activation recovery interval

Introduction

Ventricular arrhythmias, especially ventricular fibrillation (VF), occurring during acute myocardial ischemia are potentially lethal. The mechanisms underlying arrhythmogenesis during acute regional myocardial ischemia are complex. Several factors including local potassium release, increased catecholamines and cellular uncoupling have been shown to be

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involved.^{1, 2} Elucidation of the relative roles of these various factors can help devise better management strategies to prevent these lethal arrhythmias in acute ischemia. Though catecholamines are known to be present in increased amounts locally during acute myocardial ischemia,³ their exact contribution to arrhythmias in this context is not well established. The effect of local and systemic catecholamine infusion in the setting of regional myocardial ischemia has been investigated in previous studies.^{4, 5} However, the effect of local catecholamine infusion in a nonischemic setting has not been well studied. In addition to acute ischemia, catecholamines have been shown to be involved in arrhythmogenesis in other clinical situations such as heart failure and in some idiopathic forms of ventricular tachycardia (VT) such as exercise-induced VT and catecholaminergic VT.⁶ The purpose of this study was to determine if catecholamine infusion in a single vascular bed could induce arrhythmias in pigs in the absence of ischemia. Epicardial mapping was performed in six hearts and intramural mapping in two hearts to determine the activation pattern and site or origin of any arrhythmias.

Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee at the University of Alabama at Birmingham Medical Center. Preoperative and operative care complied with Section 6 of the Animal Welfare Act of 1989 and adhered to the guiding principles outlined in the “Guide for the Care and Use of Animals” (NIH Publication No. 85–23, revised 1996).

Epicardial Mapping Study

Six pigs of either gender were studied. Aspirin (325 mg) was administered orally the night before the study. Anesthesia was established using telazol (4.4 mg/kg), xylazine (4.4 mg/kg), and atropine (0.04 mg/kg) intramuscularly and maintained with isoflurane in 100% oxygen by inhalation. The chest was opened via a median sternotomy and the heart was suspended in a pericardial cradle.

An Endotak (Guidant Corp., St. Paul, MN, USA) defibrillation catheter was placed with the proximal coil electrode in the superior vena cava (SVC) and the distal coil electrode in the RV apex. A nylon sock containing 504 Ag/AgCl unipolar electrodes of approximately 1.5-mm diameter and 6-mm interelectrode spacing was placed to cover the entire ventricular epicardium. Two electrodes were sutured to the atrial epicardium in close proximity to each other to record a bipolar atrial electrogram. The left anterior descending coronary artery (LAD) was cannulated and an infusion catheter was placed with its tip just distal to the first diagonal branch.

Heparin was administered intravenously, initially as a bolus of 5,000 units immediately before cannulation of the LAD, followed by hourly boluses of 500 units throughout the period of the study. Body temperature, blood gases, pH, and electrolytes were monitored and maintained within physiological limits throughout the study.

Experimental Procedure

Normal saline (NS) was initially infused through the catheter in the LAD at 0.5 mL/min and served as the control. The restitution relationship was determined as described in the next paragraph. Following this, NS was stopped and isoproterenol (ISO) was infused into the LAD through this catheter at 0.1 µg/kg/min. The restitution relationship was again determined. The baseline rhythm and any spontaneous arrhythmias occurring during these infusions were recorded.

The restitution relationship was determined using the dynamic restitution protocol. We chose the dynamic restitution protocol since APD dynamics at short coupling intervals during fixed

pacing and during VF have been shown to correlate with the dynamic, but not the standard, restitution relation.⁷ During each infusion, a unipolar cathodal pacing train was delivered via the tip of the Endotak catheter using a 5 ms pulse-width stimulus at twice diastolic threshold. Depending on the intrinsic heart rate, pacing started at 400 or 350 ms and was decreased to 300 ms by 50 ms steps. The pacing interval was decreased by 10 ms steps after 300 ms to an interval that induced VF or lost 1:1 capture. To capture during shorter pacing intervals, the S1–S1 interval was initially 300 ms and then decreased in 10 ms steps to the target interval, and thereafter kept at the target interval for 30 beats. After 30 stimuli were delivered at this cycle length, pacing was stopped and the last paced beat was used to measure the activation-recovery interval (ARI). Pacing was then reduced decrementally to a shorter length, and the ARIs were determined after 30 stimuli were delivered at this new cycle length. Because blood pressure dropped during the rapid pacing, there was a 30–60 seconds interval after each pacing sequence to let blood pressure return to normal levels.

At the end of the study, the sock was removed and the orientation of the sock with respect to the LAD was carefully noted. In four animals, green dye was then infused through the catheter in the LAD to stain the perfused area green, and a digital image was recorded.

Data Acquisition and Analysis

Unipolar epicardial potentials from the 504 electrodes were bandpass filtered between 0.5 and 500 Hz and recorded on a 528-channel mapping system at a sampling rate of 2-kHz and a gain of 50×, with the ground electrode on the right lower limb. The atrial electrogram, surface electrocardiogram lead II and femoral arterial blood pressure were also recorded.

The local electrograms during events of interest were visualized by a color-coded animation of the first temporal derivative (dV/dt) of the recordings on a scientific workstation. Activation maps were also constructed for these events. Local activation times were first identified based on a slope threshold of ≤ -0.5 V/s and then corrected manually. From the animated displays and the activation maps, the following characteristics were noted: the site of earliest activation, the pattern of activation spread for each cycle, the total activation time (defined as the time required for activation to spread completely across the ventricles), and the cycle length (defined as the time interval between the first recorded activation of two consecutive cycles).

Conduction block was identified when the difference in activation times between adjacent electrodes was so great that the computed conduction velocity was <10 cm/s and the activation front appeared to stop in the animation. Reentry was identified if a continuous, closed path of activation was observed in which the conduction velocity was always >10 cm/s and the activation front continued to reactivate some regions more than once. A focal origin of an arrhythmic cycle was identified if the earliest activation was remote from the site of the last activation of the previous cycle and the activation front radiated in all directions from the early site.

Nonsustained ventricular tachycardia (NSVT) was defined, by convention, as a tachycardia lasting ≥ 3 cycles at a rate >100 beats/min that terminated spontaneously within 30 seconds. Sustained ventricular tachycardia (VT) was defined as a tachycardia lasting >30 seconds or degenerating into VF.⁸

ARIs, which have been reported to correlate with effective refractory periods, were determined at each recording site for the last activation of the pacing episode using the method developed by Millar *et al.*⁹ Briefly, local activation was identified as the maximal negative derivative of the QRS complex and local recovery as the maximal positive derivative of the T wave. The local recovery time minus the local activation time was taken as the ARI. The diastolic interval (DI) was calculated as the passing cycle length minus the ARI.

Restitution curves were constructed from the electrodes showing initial activation during sustained VT.

Intramural mapping

In an additional two pigs, intramural mapping instead of epicardial mapping was performed with 36 plunge needles inserted into the left ventricular perfused LAD bed. Each needle contained 12 unipolar electrodes spaced 1 mm apart along the needle shaft with the most epicardial electrode 1 mm from the epicardial surface. The protocol was similar to the epicardial mapping protocol except that ARIs were not determined. Arrhythmic cycles for which the earliest recorded activation was at the border of the intramural array of electrodes were not analyzed, because yet earlier activation could have occurred outside the mapped volume. Those arrhythmic cycles with earliest activation not at the boundary of the mapped volume were analyzed to see if the activation pattern was reentrant or focal.

Statistical Analysis

Data were reported as mean $\pm$ SD. Statistical comparisons were made using the Student's *t*-test for paired and/or unpaired data or ANOVA, as appropriate. $P \leq 0.05$ was considered statistically significant.

Results

Epicardial Mapping Study

The border of the perfused area in each of the six animals in which epicardial mapping was performed was plotted as the line along which there was a maximal disparity in ARI between adjacent electrodes during isoproterenol infusion. Perfusion maps thus constructed closely correlated with the perfusion maps drawn from the digital images obtained after green-dye perfusion in four of the hearts. They also correlated with the electrodes showing ST-T changes in the local electrograms during isoproterenol infusion.

Spontaneous Arrhythmias

No arrhythmias occurred during NS infusion. During infusion of isoproterenol into the LAD, sustained monomorphic VT occurred in all six pigs, with a mean cycle length of 329 ± 26 ms. Before sustained VT was established, PVCs and NSVT occurred during ISO infusion in all pigs. In activation maps recorded from the sock electrodes, the arrhythmias appeared to have a focal origin with activation first appearing on the epicardium at a single point and then propagating away in all directions. The earliest site of activation was near the boundary of the perfused bed in three pigs (Fig. 1A), and within the perfused bed in the other three pigs (Fig. 2A). The mean total activation time was 53 ± 11 ms. VT spontaneously terminated in all pigs upon stopping the infusion of isoproterenol. None of the episodes of VT degenerated into VF.

ARIs

In each animal, the ARIs were measured at the longest pacing cycle length that could capture during both infusions (260 ms in three animals, 300 ms in the other three animals). The mean ARI in the LAD bed below the catheter, measured while pacing at this cycle length during control infusion of NS, was 175 ± 14 ms. This was similar to the mean ARI in the nonperfused area (173 ± 14 ms, Fig. 1B and 2B). Upon infusion of isoproterenol into the LAD, the mean ARI in the perfused bed, measured while pacing at the same cycle length, was significantly shorter (109 ± 10 ms) than in the nonperfused bed (151 ± 9 ms, $P < 0.05$, Figs. 1C and 2C). When compared with the mean ARI during control infusion, the mean ARI during isoproterenol infusion significantly shortened both in the perfused and in the nonperfused areas, but the shortening was significantly greater in the perfused bed compared with the nonperfused bed.

A sharp gradient of refractoriness of 43 ± 10 ms was present at the border of the perfused region during ISO infusion.

Restitution Curves

As shown in Figure 3B, restitution curves for the electrode showing earliest activation during sustained VT had a maximum slope that was greater than 1 during NS infusion in all pigs (1.19 ± 0.27) but less than 1 during ISO infusion in all pigs (0.62 ± 0.15 , $P < 0.05$).

Intramural Mapping Study

Arrhythmias occurred in both of the animals in which intramural mapping was performed. For those arrhythmia cycles in which earliest recorded activation was within the central portion of the mapping array instead of at the boundary of the mapping array, activation propagated away from the earliest activation site in a focal pattern (Fig. 4).

Discussion

The key findings of our study are as follows: (i) intracoronary infusion of isoproterenol in pigs caused spontaneous monomorphic ventricular tachycardia that appeared to be focal in origin, arising from within, or at the border of, the perfused region, and (ii) intracoronary infusion of isoproterenol caused a significant shortening of ARI within the perfused region, a large gradient of ARI near the boundary of the perfused region, but decreased the slope of the restitution curve to < 1 .

In the first few minutes of ischemia, plasma catecholamine concentrations are increased to about five times the normal levels.^{3, 10, 11} This is due to increased activity of the whole sympathetic nervous system, and, more importantly, a reflex increase in cardiac sympathetic nerve activity (both afferent and efferent) that leads to local exocytotic release of norepinephrine from sympathetic nerve endings of the heart.¹⁰ However, excessive accumulation of catecholamines is prevented by rapid removal by neuronal catecholamine reuptake, by accumulation of adenosine in the ischemic myocardium, which suppresses exocytotic catecholamine release, and by depletion of adenosine triphosphate in the sympathetic neurons.¹⁰ After 10 minutes of ischemia, the myocardium is no longer protected against excess catecholamine accumulation by the above mentioned mechanisms, because of local metabolic release mechanisms. The extracellular catecholamine levels increase to 100–1,000 times the normal plasma concentrations within 20–30 minutes of ischemia.¹⁰ There also is a temporary supersensitivity of the myocardium to catecholamines during ischemia that is mediated by a twofold increase in alpha receptors and a 30% increase in beta receptors.¹⁰

Previous studies have shown the role of catecholamines in promoting arrhythmogenesis during ischemia.^{4, 12} Catecholamine induced ventricular arrhythmias may differ from the monomorphic VT we observed and may be caused by a differential sensitivity to normal levels of catecholamines rather than to an increased level of catecholamines as in our study. Our study showed that local elevation of a catecholamine alone can cause VT, suggesting that local catecholamine excess during ischemia is, by itself, sufficient to cause tachyarrhythmias. Studies of the mechanism of arrhythmogenesis by catecholamines suggest that delayed afterdepolarization is the predominant mechanism.¹³ However, catecholamines also facilitate abnormal automaticity and reentry.¹⁴ In our study, the mechanism of VT induced by isoproterenol infusion appeared to be focal, based on both epicardial and intramural activation maps. However, we cannot exclude microreentry that was smaller than the distance between the electrodes, which was approximately 6 mm. A finding against the presence of microreentry is that activation spread away from the early site in a centrifugal pattern (Fig. 1A). If reentry were present, a more spiral spread of activation would be expected unless the reentry consists

of a small figure-of-eight with rapid conduction around the outside of the reentry circuit with extremely slow conduction through the common isthmus.

Ischemia decreases the APD and increases the dispersion of refractoriness.^{15, 16} Systemic catecholamine infusion also decreases the APD and the refractory period.¹⁷ Sympathetic stimulation during ischemia increases the dispersion of refractoriness, due to a decrease in refractoriness in the normal myocardium and an increase in refractoriness in the ischemic myocardium.¹⁸ In this study, we used the ARI as a measure of the APD and of the refractory period. ARIs have been shown to correlate closely with APD and with the refractory period, even during ischemia.^{9, 19, 20} In our study, there was some shortening of APD outside the perfused area, probably due to the increased heart rate during isoproterenol infusion; but the decrease in the perfused area was much more marked, so that there was a sharp gradient of APD near the border of the perfused region. This sharp APD gradient correlated closely with the perfused/nonperfused border on digital images recorded after infusion of green dye in the four animals in which dye was perfused in the LAD bed and was taken as the border between the perfused and nonperfused areas in our study.

Increased dispersion of refractoriness can facilitate reentry and promote maintenance of arrhythmias.²¹ A steep slope of the restitution curve (>1) has also been shown to promote spiral wave breakup and fibrillation.^{22, 23} However, ischemia flattens the slope of the electrical restitution curve.²⁴ The effect of catecholamines on the restitution relationship has not been well studied. Taggart *et al.* showed that systemic catecholamine infusion caused an increase in the slope of the APD restitution curve over a wide range of diastolic intervals in humans.²⁵ In our study, however, ISO infusion significantly decreased the maximum slope of the restitution curve from >1 with NS infusion to <1 (Fig. 3B). Therefore, the origin of spontaneous arrhythmias was associated with a decreased APD and a sharp gradient in APD, but not with a steep restitution slope.

There were no episodes of VF during catecholamine infusion in our study. The VT we observed is slower than that seen in pigs with acute ischemia,⁸ which may partly explain why it did not degenerate into VF. The faster VT rate in acute ischemia may be due to factors other than catecholamine excess during ischemia. The restitution hypothesis for fibrillation states that a steeply sloped restitution curve creates unstable wave propagation that results in wave break, the event that is necessary for fibrillation.^{22, 23} Interventions that flatten the APD restitution slope have been shown to convert VF to VT.²⁶ A paradox with this hypothesis is that ischemia flattens the slope of the restitution curve and, yet, causes VF. It has been proposed that ischemia promotes wavebreak in the surrounding normal tissue (whose restitution slope is not flattened) and the decreased APD in the ischemic region accelerates spiral wave reentry.²⁷ Though a decreased APD in the perfused bed was present in our study, there were no episodes of spontaneous VF. Local catecholamine release is strongly related to the development of ischemic VF.¹² Our results suggest that while catecholamines are arrhythmogenic, they are not sufficient to cause VF during ischemia, and that alterations during ischemia, in addition to catecholamine excess, are essential to promote wavebreak and VF.²⁸

Limitations

Our study has several limitations. (1) Though the mechanism of spontaneous arrhythmias during isoproterenol infusion appeared to be focally based on epicardial and intramural activation maps, we cannot exclude microreentry. (2) Regional isoproterenol infusion was not compared with acute regional ischemia, which could have illustrated the role of noncatecholamine factors in acute ischemia. (3) The APD and refractory period were not measured directly, but were estimated from the ARI, which may not precisely correspond with the APD or refractory period. Though the ARI was measured after pacing at the same cycle length for 30 beats as during control, the effect of memory may not have been completely

abolished. (4) The ARI dispersion was only determined during the longest cycle length of pacing, because we were interested in the dispersion of refractoriness at the time of onset of the arrhythmia, not at the shorter cycle length during VF. (5) The perfusion maps were constructed indirectly, based on the gradient in ARI, and are thus imprecise.

Despite these limitations, we believe that this study indicates that regional elevation of a catecholamine by itself causes spontaneous ventricular tachyarrhythmias. However, other factors occurring during ischemia may be essential for the degeneration of VT into VF.

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References

1. Ehlert FA, Goldberger JJ. Cellular and pathophysiological mechanisms of ventricular arrhythmias in acute ischemia and infarction. *Pacing Clin Electrophysiol* 1997;20:966–975. [PubMed: 9127403]
2. Verkerk AO, Veldkamp MW, Coronel R, Wilders R, van Ginneken AC. Effects of cell-to-cell uncoupling and catecholamines on Purkinje and ventricular action potentials: Implications for phase-1b arrhythmias. *Cardiovasc Res* 2001;51:30–40. [PubMed: 11399245]
3. Lameris TW, de Zeeuw S, Alberts G, Boomsma F, Duncker DJ, Verdouw PD, Veld AJ, Van Den Meiracker AH. Time course and mechanism of myocardial catecholamine release during transient ischemia in vivo. *Circulation* 2000;101:2645–2650. [PubMed: 10840018]
4. Podzuweit T, Els DJ, McCarthy J. Cyclic AMP mediated arrhythmias induced in the ischaemic pig heart. *Basic Res Cardiol* 1981;76:443–448. [PubMed: 6116488]
5. Vegh A, Parratt JR. Noradrenaline, infused locally, reduces arrhythmia severity during coronary artery occlusion in anaesthetised dogs. *Cardiovasc Res* 2002;55:53–63. [PubMed: 12062708]
6. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995;91:1512–1519. [PubMed: 7867192]
7. Koller ML, Riccio ML, Gilmour RF Jr. Dynamic restitution of action potential duration during electrical alternans and ventricular fibrillation. *Am J Physiol* 1998;275:H1635–H1642. [PubMed: 9815071]
8. Zhang S, Skinner JL, Sims AL, Rollins DL, Walcott GP, Smith WM, Ideker RE. Three-dimensional mapping of spontaneous ventricular arrhythmias in a canine thrombotic coronary occlusion model. *J Cardiovasc Electrophysiol* 2000;11:762–772. [PubMed: 10921794]
9. Millar CK, Kralios FA, Lux RL. Correlation between refractory periods and activation-recovery intervals from electrograms: Effects of rate and adrenergic interventions. *Circulation* 1985;72:1372–1379. [PubMed: 4064279]
10. Schomig A, Richardt G. The role of catecholamines in ischemia. *J Cardiovasc Pharmacol* 1990;16 (Suppl 5):S105–S112. [PubMed: 11527112]
11. Schomig A, Richardt G, Kurz T. Sympathoadrenergic activation of the ischemic myocardium and its arrhythmogenic impact. *Herz* 1995;20:169–186. [PubMed: 7635399]
12. McDonald FM, Knopf H, Hartono S, Polwin W, Bischoff A, Hirche H, Addicks K. Acute myocardial ischaemia in the anaesthetised pig: Local catecholamine release and its relation to ventricular fibrillation. *Basic Res Cardiol* 1986;81:636–645. [PubMed: 3814056]
13. Priori SG, Corr PB. Mechanisms underlying early and delayed afterdepolarizations induced by catecholamines. *Am J Physiol* 1990;258:H1796–H1805. [PubMed: 2163219]
14. Podrid PJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. *Circulation* 1990;82:I103–I113. [PubMed: 1973640]
15. Sutton PM, Taggart P, Opthof T, Coronel R, Trimlett R, Pugsley W, Kallis P. Repolarisation and refractoriness during early ischaemia in humans. *Heart* 2000;84:365–369. [PubMed: 10995401]

16. Elharrar V, Gaum WE, Zipes DP. Effect of drugs on conduction delay and incidence of ventricular arrhythmias induced by acute coronary occlusion in dogs. *Am J Cardiol* 1977;39:544–549. [PubMed: 848439]
17. Hillsley RE, Bollacker KD, Simpson EV, Rollins DL, Yarger MD, Wolf PD, Smith WM, Ideker RE. Alteration of ventricular fibrillation by propranolol and isoproterenol detected by epicardial mapping with 506 electrodes. *J Cardiovasc Electrophysiol* 1995;6:471–485. [PubMed: 7551316]
18. Opthof T, Coronel R, Vermeulen JT, Verberne HJ, van Capelle FJ, Janse MJ. Dispersion of refractoriness in normal and ischaemic canine ventricle: Effects of sympathetic stimulation. *Cardiovasc Res* 1993;27:1954–1960. [PubMed: 8287403]
19. Haws CW, Lux RL. Correlation between in vivo transmembrane action potential durations and activation-recovery intervals from electrograms. Effects of interventions that alter repolarization time. *Circulation* 1990;81:281–288. [PubMed: 2297832]
20. Ejima J, Martin D, Engle C, Sherman Z, Kunimoto S, Gettes LS. Ability of activation recovery intervals to assess action potential duration during acute no-flow ischemia in the in situ porcine heart. Experimental Cardiology Group, University of North Carolina at Chapel Hill. *J Cardiovasc Electrophysiol* 1998;9:832–844. [PubMed: 9727662]
21. Janse MJ, Wit AL. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989;69:1049–1169. [PubMed: 2678165]
22. Garfinkel A, Kim YH, Voroshilovsky O, Qu Z, Kil JR, Lee MH, Karagueuzian HS, Weiss JN, Chen PS. Preventing ventricular fibrillation by flattening cardiac restitution. *Proc Natl Acad Sci USA* 2000;97:6061–6066. [PubMed: 10811880]
23. Gilmour RF Jr. A novel approach to identifying antiarrhythmic drug targets. *Drug Discov Today* 2003;8:162–167. [PubMed: 12581710]
24. Taggart P, Sutton PM, Boyett MR, Lab M, Swanton H. Human ventricular action potential duration during short and long cycles. Rapid modulation by ischemia *Circulation* 1996;94:2526–2534.
25. Taggart P, Sutton P, Chalabi Z, Boyett MR, Simon R, Elliott D, Gill JS. Effect of adrenergic stimulation on action potential duration restitution in humans. *Circulation* 2003;107:285–289. [PubMed: 12538429]
26. Swissa M, Qu Z, Ohara T, Lee MH, Lin SF, Garfinkel A, Karagueuzian HS, Weiss JN, Chen PS. Action potential duration restitution and ventricular fibrillation due to rapid focal excitation. *Am J Physiol Heart Circ Physiol* 2002;282:H1915–1923. [PubMed: 11959659]
27. Xie F, Qu Z, Garfinkel A, Weiss JN. Effects of simulated ischemia on spiral wave stability. *Am J Physiol Heart Circ Physiol* 2001;280:H1667–H1673. [PubMed: 11247778]
28. Clements-Jewery H, Hearse DJ, Curtis MJ. Independent contribution of catecholamines to arrhythmogenesis during evolving infarction in the isolated rat heart. *Br J Pharmacol* 2002;135:807–815. [PubMed: 11834629]

Figure 1.

Activation map of spontaneous VT during isoproterenol infusion (A) and the ARI distribution during infusion of normal saline (B) and isoproterenol (C). The perfused area is outlined. The site of earliest activation during VT is at the border of the perfused area. Marked shortening of ARI in the perfused area is noted during isoproterenol infusion.

Figure 2.

Epicardial activation map of spontaneous VT during isoproterenol infusion (A) and the ARI distribution during infusion of normal saline (B) and isoproterenol (C) in another animal. The perfused area is outlined. The site of earliest activation during VT in this pig is within the perfused area. Marked shortening of ARI in the perfused area is noted during isoproterenol infusion.

Figure 3.

Restitution during NS and ISO infusion. In (A), an example is shown of an electrode recording from which the ARI was determined while pacing at a cycle length of 130 ms. The asterisks indicate the time of minimum downslope of activation and the maximum downslope of repolarization. The arrows indicate the pacing artifacts. In (B), the mean restitution curves from the earliest site of activation during spontaneous VT are shown for all six animals. The maximum slope of the restitution curve is greater than 1 during NS infusion but less than 1 during ISO infusion.

Figure 4.

Intramural activation map of spontaneous VT during isoproterenol infusion (A) unipolar recordings from five plunge needle electrodes during the onset of the arrhythmia (B), and times of activation for the first arrhythmic cycle (C). In (A), two views of the plunge needle array are shown with activation times indicated by the color code shown to the right. Earliest activation (blue) was recorded near the endocardium after which activation spread away from this early site in a focal activation pattern. The locations of the electrodes shown in (B) are indicated by the numbers in (A). The first cycle of the monomorphic arrhythmia is cycle 4 in (B). In (C), the Xs indicate the time of most negative dV/dt during the fourth cycle for the electrode tracings shown in (B).