

Effect of Adrenergic Stimulation on Action Potential Duration Restitution in Humans

Peter Taggart, MD, DSc, FRCP; Peter Sutton, PhD; Zaid Chalabi, PhD; Mark R. Boyett, PhD; Ron Simon, BSc, MBBS, MRCP; Donna Elliott, MSc; Jaswinder S. Gill, MA, MD, FRCP

Background—Enhanced sympathetic activity facilitates complex ventricular arrhythmias and fibrillation. The restitution properties of action potential duration (APD) are important determinants of electrical stability in the myocardium. Steepening of the slope of APD restitution has been shown to promote wave break and ventricular fibrillation. The effect of adrenergic stimulation on APD restitution in humans is unknown.

Methods and Results—Monophasic action potentials were recorded from the right ventricular septum in 18 patients. Standard APD restitution curves were constructed at 3 basic drive cycle lengths (CLs) of 600, 500, and 400 ms under resting conditions and during infusion of isoprenaline (15 patients) or adrenaline (3 patients). The maximum slope of the restitution curves was measured by piecewise linear regression segments of sequential 40-ms ranges of diastolic intervals in steps of 10 ms. Under control conditions, the maximum slope was steeper at longer basic CLs; eg, mean values for the maximum slope were 1.053 ± 0.092 at CL 600 ms and 0.711 ± 0.049 at CL 400 ms (\pm SEM). Isoprenaline increased the steepness of the maximum slope of APD restitution, eg, from a maximum slope of 0.923 ± 0.058 to a maximum slope of 1.202 ± 0.121 at CL 500 ms. The effect of isoprenaline was greater at the shorter basic CLs. A similar overall effect was observed with adrenaline.

Conclusions—The adrenergic agonists isoprenaline and adrenaline increased the steepness of the slope of the APD restitution curve in humans over a wide range of diastolic intervals. These results may relate to the known effects of adrenergic stimulation in facilitating ventricular fibrillation. (*Circulation*. 2003;107:285-289.)

Key Words: action potentials ■ arrhythmia ■ catecholamines ■ electrophysiology

Substantial evidence links enhanced sympathetic activity with ventricular arrhythmias and sudden cardiac death.¹⁻⁴ Several studies have demonstrated an increased susceptibility to complex arrhythmias and ventricular fibrillation as a result of sympathetic stimulation.¹ One mechanism that has been shown to underlie the destabilization of activation wavefronts relates to the restitution properties of action potential duration (APD), which may be described as the change in APD in response to an abrupt change in the preceding diastolic interval. Steeply sloped restitution curves, ie, a large change in APD for a relatively small change in diastolic interval, have been shown to be associated with complex unstable dynamics.⁵⁻⁹ Computer modeling and experiments have shown that increasing the steepness of APD restitution results in progressive instability and spiral wave breakup,^{9,10} whereas reducing the slope by drugs suppresses ventricular fibrillation attributable to suppressing spiral breakup.^{11,12} We have previously shown in a porcine model that adrenaline increases the slope of the ventricular APD

restitution curve.¹³ If adrenergic stimulation exerts a similar effect in humans, it could have an important bearing on the role of the sympathetic nervous system in arrhythmogenesis. It has been proposed that the destabilizing effect of steep APD restitution does not only depend on the steepness of the slope; also important is that the slope is steep over a wide range of diastolic intervals.¹⁰ We have examined the effect of the β -adrenergic agonist isoprenaline or the α - and β -adrenergic agonist adrenaline on the APD restitution curve in patients with normal ventricles over a wide range of diastolic intervals. We found that both isoprenaline and adrenaline steepen the APD restitution curve over a minimum range of diastolic intervals of 40 ms.

Methods

Patients

Patients were selected at random from the waiting list for radiofrequency ablation procedures for supraventricular arrhythmias. Eighteen patients, 10 men and 8 women, age 22 to 65 years (mean, 49

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From the Department of Cardiology (P.T., P.S.), University College London Hospitals; Centre for Nonlinear Dynamics and its Applications (Z.C.), University College London; School of Biomedical Sciences (M.R.B.), University of Leeds; and Department of Cardiology (R.S., D.E., J.S.G.), Guys and St Thomas's Hospitals, London, UK. Dr Chalabi is now at the Department of Public Health and Policy, London School of Hygiene and Tropical Medicine.

Correspondence to Dr Peter Taggart, The Hatter Institute, Department of Cardiology, University College Hospital, Grafton Way, London, WC1E 6DB. E-mail peter.taggart@ucl.org

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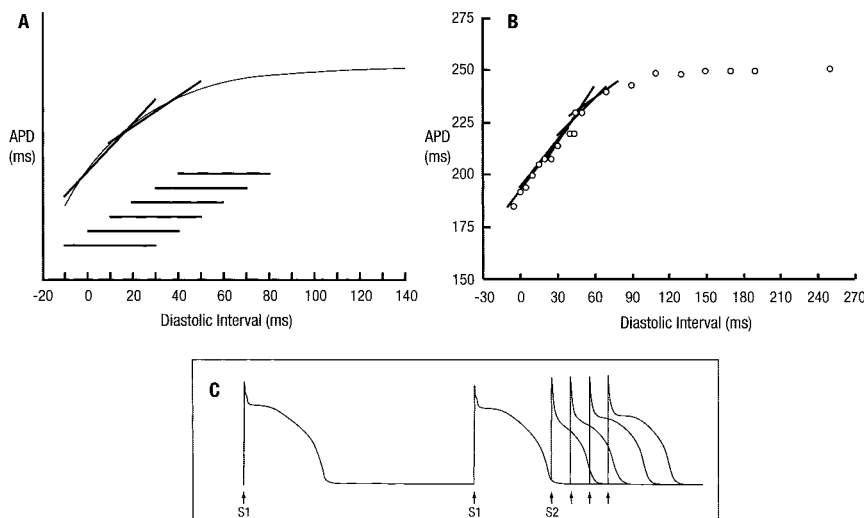


Figure 1. Measurement of APD slope. A, Diagrammatic representation of APD restitution curve. The slope of the rising portion of the APD restitution curve is measured by fitting linear regression sequentially to points on the curve over 40-ms ranges of diastolic interval, beginning at a diastolic interval range of -10 to 30 ms and up to a diastolic interval range of 40 to 80 ms, as indicated by the horizontal lines. Only the first and third of these lines on the curve are shown for clarity. B, Control restitution curve from one patient is shown, to which the line for the steepest segment of the slope and the lines on either side of it are fitted. The steepest segment of the curve was between diastolic intervals of 20 to 60 ms (slope 0.902 ms/ms). C, Diagrammatic illustration showing increase in APD as the diastolic interval between repolarization of S_1 and the upstroke of S_2 increases.

years) participated in the study. Cardioactive drugs were discontinued 72 hours before the procedure. The hospital ethics committee approved the study protocol, and each patient gave written informed consent.

Monophasic Action Potential Recording

Monophasic action potential (MAP) signals from the right ventricular septum were recorded on a Prucka Cardiolab system set to a frequency response of DC–500 Hz. The MAP is an established technique for the measurement of APD in humans.^{14,15}

Restitution Curves

Standard restitution curves at 3 basic paced cycle lengths (CLs) were constructed as follows. Ventricular pacing was established from the catheter electrode at a basic drive CL of 600 ms using a stimulus strength of twice diastolic threshold and 2-ms pulse width. After a 3-minute run-in period, test pulses, S_2 , were introduced after 9 beat trains of S_1 stimuli decrementing by 20 ms from S_1 – S_2 intervals of 400 to 300 ms and then by 5 ms from S_1 – S_2 intervals of 300 ms to refractoriness. The protocol was repeated for basic drive CLs of 500 and 400 ms. Either isoprenaline (15 patients) or adrenaline (3 patients) was then infused in incremental doses of 0.025, 0.05, and 0.10 $\mu\text{g/kg}$ per minute. The pacing protocol was then repeated at the 3 basic drive CLs at each of the 3 dose levels. Because of the increase in intrinsic heart rate during infusion, it was not always possible to obtain restitution curves at the longer basic drive CLs.

Data Analysis

The maximum effect on the slope was observed at the first dose level during almost all infusions. When the maximum effect was not attained during the first dose, it was invariably achieved by the second dose. The data presented are comparison of control with maximum effect. Monophasic action potentials were measured at 90% repolarization. Diastolic interval was measured as the S_1 – S_2 interval minus the APD of S_1 with appropriate correction for latency at very short S_1 – S_2 intervals. Signals without a smooth and stable baseline and amplitude of >10 mV were excluded from the analysis. In 2 patients, deflections during the repolarization phase resembling afterdepolarizations developed during the infusion. To avoid ambiguity attributable to uncertainties as to whether such deflections are real or artifact, these patients have not been included.

Analysis of Restitution Curves

The standard methods of fitting a single function such as an exponential, a polynomial, or a sigmoid may not always be suitable for modeling the cardiac restitution data, for several reasons. The first reason is that a single-function model is too restrictive. For example, the implicit assumption in an exponential model is that the

maximum slope always occurs at the lowest bound of the diastolic interval and then monotonically decreases with increasing diastolic interval. This assumption may not always be true.^{16,17} The second reason is that a single function is unable to track faithfully the fluctuations in the data, which could have a physiological basis. There is of course a balance to achieve between the goodness of fit of the model and the smoothness of fit of the model. On the one hand, if the model overfits the data, it is sensitive to noisy data oscillations that are not physiologically based. On the other hand, if the model underfits the data, it may smooth out physiologically meaningful fluctuations. The third reason is that any procedure that fits a single function to the data over a wide range of diastolic intervals is unlikely to be robust. This is because the support of a single function is not local; any data scatter in one region of the diastolic interval may affect greatly the fit in another region. The lack of robustness in the fit of a single function is often reflected in large standard errors in the least-squares estimates of the parameter values of that function and in high correlations between its estimated parameter values. Because of the above-mentioned reasons, the data were fitted using overlapping least-squares linear segments (Figure 1). The restitution curves were analyzed in 40-ms diastolic interval segments in steps of 10 ms, commencing from the shortest diastolic interval range that contains data points.

Results

APD Restitution Under Control Conditions

Under control conditions (ie, before the infusion of isoprenaline or adrenaline), the maximum slope of the APD restitution curve was steeper at the longer basic CLs, ie, at slower heart rates. An example from one subject at basic CL of 600 and 400 ms is shown in Figure 2A. The regression lines for the steepest segment of each curve are superimposed, showing a steeper maximum slope at the longer basic CL (600 ms) compared with the shorter CL (400 ms). Mean values \pm SEM for the maximum slope of the APD restitution curves during control conditions for each of the 3 basic CLs were 1.053 ± 0.092 ms/ms (CL 600 ms), 0.923 ± 0.058 (CL 500 ms), and 0.711 ± 0.049 (CL 400).

Effect of Isoprenaline

Isoprenaline increased the maximum slope of APD restitution. The intrinsic sinus rate increased from 77 ± 3 (mean \pm SEM) before infusion to 108 ± 5 during isoprenaline infusion. An example showing APD restitution before and during isoprena-

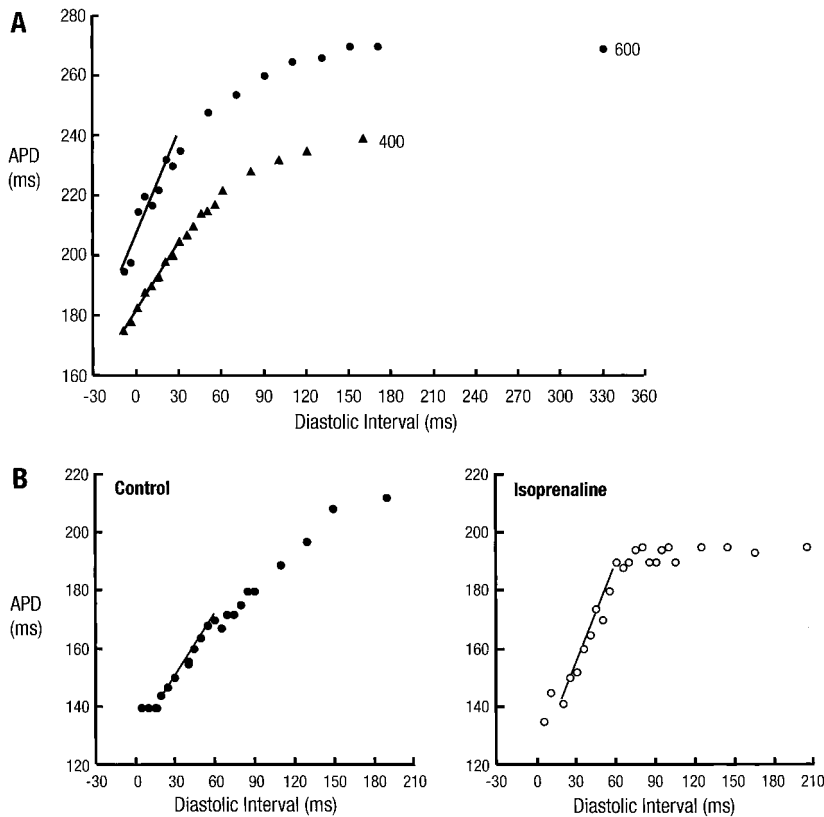


Figure 2. A, APD restitution curves from one subject under control conditions at basic CLs of 600 ms (●) and 400 ms (○). The maximum slope of APD restitution is steeper at the longer CL; ie, at a basic CL of 600 ms, the curve has a maximum slope of 1.114 compared with a maximum slope of 0.850 at a basic CL of 400 ms. B, APD restitution curves under control conditions (●) and during isoprenaline infusion (○) showing steepening of the maximum slope of the curve in response to isoprenaline. The maximum slope increased from 0.707 before isoprenaline infusion to 1.120 during isoprenaline. Basic CL, 400 ms. The lines for the segments of maximum slope for each curve are shown.

line infusion at a paced CL of 400 ms is shown in Figure 2B. In the example, the maximum slope increased from 0.707 (control) to 1.12 during infusion of isoprenaline. Mean values and 95% confidence intervals for the maximum slopes of the APD restitution curves obtained during control and in response to isoprenaline are shown in Figure 3A. Isoprenaline increased the maximum slope of restitution from 0.711 ± 0.049 (control) to 1.076 ± 0.101 (isoprenaline) at CL 400 ms and from 0.923 ± 0.058 (control) to 1.202 ± 0.121 at CL 500 ms, both significant at the 95% confidence level for the mean difference of paired samples. At a basic CL of 600 ms, although isoprenaline increased mean values for the slope from 1.053 ± 0.092 (control) to 1.228 ± 0.098 (isoprenaline), this was not statistically significant. In 5 patients, the restitution curve could be reasonably fit by a monoexponential during both control and isoprenaline at a CL of 600 and 400 ms. Isoprenaline increased the slope from 1.496 (control) to 1.837 (isoprenaline) at 600 ms and from 1.314 (control) to 2.277 (isoprenaline) at 400 ms. The range of diastolic intervals over which the slope was >1 increased from 15.971 (control) to 22.067 (isoprenaline) at 600 ms and from 11.017 (control) (slope <1 in two) to 17.331 (isoprenaline) (slope <1 in one) at 400 ms.

Effect of Adrenaline

In the 3 patients studied with adrenaline infusion, the intrinsic sinus rate increased from a mean value of 89 before infusion to 102 during infusion. Adrenaline resulted in a similar overall effect on the steepness of APD restitution, increasing the maximum slope in 3 of 3 subjects at a CL of 400 ms and in 3 of 3 subjects at a CL of 500 ms (Figure 3B). Mean values for the maximum slopes were 0.669 (control) and 0.987

(adrenaline) at CL 400 ms and 0.854 (control) and 1.142 (adrenaline) at CL 500 ms. It was only possible to obtain a restitution curve at a CL of 600 ms in 1 patient who showed no change in response to adrenaline.

Discussion

The main finding of the present study is that in humans, the adrenergic agonists isoprenaline and adrenaline steepened the maximum slope of the APD restitution curve over a wide range of diastolic intervals. The effect seemed to interact with basic CL such that the steepening of APD restitution was greater at shorter basic CLs.

Methodological Considerations

A limitation of the present study is that recordings were obtained from a single ventricular endocardial site, whereas heterogeneity of both ion channel expression and structure (both of which may affect APD) has been implicated in arrhythmias in many studies. Regional differences in the slope of APD restitution have been demonstrated on the epicardium in guinea pig hearts using optical mapping.¹⁸ It is possible therefore that regional differences may exist in the slope of APD restitution in humans and the response to adrenergic agonists.

A second limitation is that the relationship between APD and diastolic interval is not straightforward but is influenced by other factors, including a history of previous excitation (memory function) and wave curvature. As a result, the APD restitution characteristics may not be represented truly by APD restitution curves obtained using pacing protocols. The optimum method to assess the APD restitution properties at

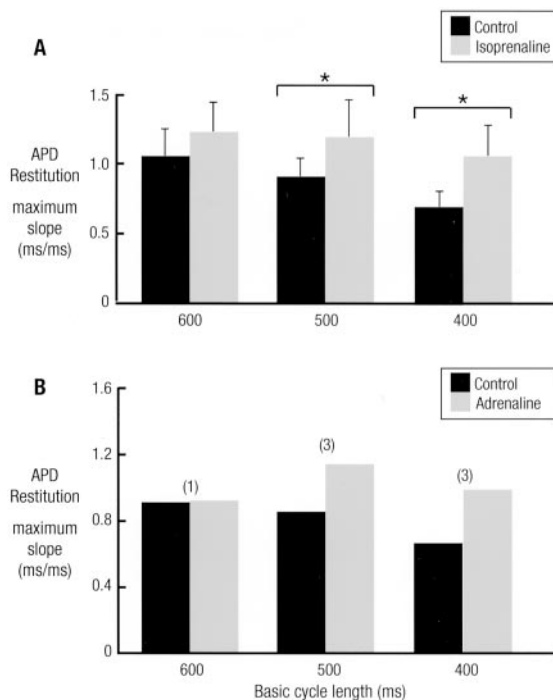


Figure 3. A, Mean values and 95% confidence intervals for the maximum slope of the APD restitution curves at basic CLs of 600, 500, and 400 ms before and after isoprenaline. Isoprenaline increased the maximum slope of the restitution curves, the increase in slope being greater at the shorter basic CLs. *Significant for the 95% confidence intervals for the mean difference of paired samples. B, Effect of adrenaline on the maximum APD restitution slope in 3 patients showing an increase in the maximum slope at basic CLs of 500 and 400 ms. Data at a CL of 600 ms were obtained from only 1 patient.

different phases of evolution of reentrant wavefronts and at different sites along the wave remains to be determined. Dynamic restitution constructed using continuous pacing at each S_1 - S_2 interval to incorporate a component of memory has been shown to correspond more closely with APD restitution during ventricular fibrillation¹⁷ but is technically not appropriate to humans.

Electrical Restitution in Humans and the Effect of the Basic Cycle Length

Several studies have described APD restitution in humans, although in none of these were measurements of the steepness of the slope reported.^{19,20} Theory, based on experiments and computer modeling, predicts that a restitution slope steeper than 1 promotes wave break and fibrillation.¹⁰ Inspection of illustrated examples in reported human studies suggests a range of maximum slopes varying from less than unity to greater than unity. In one report of patients with cardiomyopathy and a propensity to arrhythmia, the illustrated examples show an APD restitution slope that is clearly >1 in regions of abnormal myocardium.²⁰ Our results showed an intersubject variability in the maximum slope of APD restitution under control conditions ranging from <1 to >1 in a manner that seemed to interact with CL such that the maximum steepness was significantly greater at longer basic CLs (Figure 2). This is in keeping with in vitro observations.²¹ Several

studies of APD restitution show that the early rising phase of the curve is sometimes interrupted by a dip, creating a pattern referred to as a hump.^{19,20} In the patient population we studied, a hump was sometimes observed but was relatively inconspicuous, being prominent in only 3 patients.

Effect of Adrenergic Agonists

The effect of the adrenergic agonists isoprenaline and adrenaline in humans was to steepen the slope of the restitution curve. A similar effect on APD restitution has previously been reported on the epicardium in an in-vivo porcine model in response to adrenaline infusion¹³ and recently during sympathetic nerve stimulation in a guinea pig heart preparation.²² In the present studies, we observed a rate-dependent effect in that the steepening of the APD restitution curve by adrenergic agonists was more marked at shorter CLs.

Underlying Mechanisms

The processes involved in the shortening of the premature action potential are the following: (1) inactivation of L-type Ca^{2+} current ($i_{\text{Ca,L}}$); (2) reduction of inward Na^+ - Ca^{2+} exchange current (i_{NaCa}); and (3) activation of rapid and slow delayed-rectifier K^+ currents ($i_{\text{K,r}}$ and $i_{\text{K,s}}$).^{10,23} Inward i_{NaCa} is reduced as a result of a reduction of the intracellular Ca^{2+} transient (the driving force behind inward i_{NaCa}).^{23,24} The APD restitution curve is governed by reactivation of $i_{\text{Ca,L}}$, recovery of the Ca^{2+} transient, and thus inward i_{NaCa} and deactivation of $i_{\text{K,r}}$ and $i_{\text{K,s}}$. In ferret ventricular cells, 80% recovery of $i_{\text{Ca,L}}$, i_{NaCa} , and i_{K} ($i_{\text{K,r}}$ and $i_{\text{K,s}}$) occurs after ≈ 32 , ≈ 189 , and ≈ 93 ms, respectively, at -80 mV (close to the resting potential of a ventricular cell).²³ A possible reason for the increase in the steepness of APD restitution at longer basic CLs is that different processes with different recovery kinetics may dominate APD restitution at different basic CLs. For example, at shorter basic CLs there could be a buildup of ultraslow inactivation of $i_{\text{Ca,L}}$ ²⁵ and the slow activation of $i_{\text{K,s}}$ (because the time between regular action potentials is too short for recovery of $i_{\text{Ca,L}}$ from ultraslow inactivation and deactivation of $i_{\text{K,s}}$). As a consequence, the slow recovery of $i_{\text{Ca,L}}$ from ultraslow inactivation and slow deactivation of $i_{\text{K,s}}$ may come to play a more dominant role in APD restitution. The increase in the steepness of APD restitution by isoprenaline and adrenaline could be the result of an acceleration in the kinetics of recovery of one or more of the currents involved in APD restitution. Isoprenaline has been reported to accelerate deactivation of i_{K} in rabbit sinoatrial node cells and guinea-pig ventricular cells,^{26,27} and in human ventricular muscle, adrenaline accelerates the mechanical restitution curve.²⁸ This suggests that adrenaline accelerates the recovery of the Ca^{2+} transient, and, in turn, this is expected to accelerate recovery of inward i_{NaCa} . Alternatively, the increase in the steepness of APD restitution by isoprenaline and adrenaline could be the result of their well-known increase of $i_{\text{Ca,L}}$.¹⁰ The interaction discussed above between the effects of basic CL and isoprenaline may arise because both basic CL and isoprenaline affect the restitution curve by affecting the same currents (eg, i_{K}).

In the intact heart, the effect of isoprenaline and adrenaline on the steepness of the restitution slope would be expected to be the

sum of the direct effects (which steepen the slope) and indirect effects as a consequence of an increase in heart rate (which reduces the slope). Although there is considerable evidence that steep APD restitution is proarrhythmic and in particular pro-fibrillatory, the concept of a critical restitution slope of <1 or >1 continues to be disputed.²⁹ Other mechanisms may be important, such as the maintenance of VF by one or more rapidly activating foci.²⁹ In addition, other variables, such as the influence scarring and fibrosis and heterogeneity of ion channel expression, may also be important. In the context of focal mechanisms, the effect of catecholamines in inducing both early and delayed afterdepolarizations is well known and may be crucial to adrenergically mediated arrhythmias. In extrapolating our data to the context of clinical arrhythmias, two limitations should be kept in mind. First, no arrhythmias were recorded in our study group. This may relate in part to the fact that the subjects had essentially normal hearts and the proarrhythmic effect of steepening APD restitution relates to the transition from VT to VF, not the initiation of VT. Second, the transition from VT to VF often occurs at heart rates faster than those that we studied.

Clinical Implications

Abundant evidence implicates the autonomic nervous system as playing an important role in ventricular arrhythmias and sudden death. The adverse effects of enhanced sympathetic activity demonstrated experimentally are reflected clinically by the effectiveness of adrenergic blockade in preventing fatal arrhythmias. Although several mechanisms are likely to be involved, the present results showing a steepening of APD restitution over a wide range of diastolic intervals in response to adrenergic agonists suggest a mechanism whereby the sympathetic nervous system may contribute to the destabilization of arrhythmias and ventricular fibrillation. There is strong evidence that vagal influences are protective and may suppress the development of ventricular fibrillation.³ A recent study in an isolated rabbit heart model²² has shown that stimulation of the sympathetic nerves steepens APD restitution in the left ventricle, whereas stimulation of the parasympathetic nerves exerts the opposite effect and reduces the steepness of the slope. In this model, steepening of the APD restitution slope facilitates the initiation of ventricular fibrillation, whereas reducing the slope suppresses it. It is tempting, therefore, to speculate that fluctuations in autonomic tone and autonomic balance may influence susceptibility to lethal arrhythmias by modulating the APD restitution properties.

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