

Effect of β -adrenergic blockade on dynamic electrical restitution in vivo

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Hao, Steven C., David J. Christini, Kenneth M. Stein, Peter N. Jordan, Sei Iwai, Orville Bramwell, Steven M. Markowitz, Suneet Mittal, and Bruce B. Lerman. Effect of β -adrenergic blockade on dynamic electrical restitution in vivo. *Am J Physiol Heart Circ Physiol* 287: H390–H394, 2004. First published March 4, 2004; 10.1152/ajpheart.00749.2003.—The slope of the action potential duration (APD) restitution curve may be a significant determinant of the propensity to develop ventricular fibrillation, with steeper slopes associated with a more arrhythmogenic substrate. We hypothesized that one mechanism by which β -blockers reduce sudden cardiac death is by flattening the APD restitution curve. Therefore, we investigated whether infusion of esmolol modulates the APD restitution curve in vivo. In 10 Yorkshire pigs, dynamic APD restitution curves were determined from measurements of APD at 90% repolarization with a monophasic action potential catheter positioned against the right ventricular septum during right ventricular apical pacing in the basal state and during infusion of esmolol. APD restitution curves were fitted to the three-parameter (a , b , c) exponential equation, $APD = a \cdot [1 - e^{(-b \cdot DI)}] + c$, where DI is the diastolic interval. Esmolol decreased the maximal APD slope, 0.68 ± 0.14 vs. 0.94 ± 0.24 (baseline), $P = 0.002$, and flattened the APD restitution curve at shorter DIs, 75 and 100 ms ($P < 0.05$). To compare the slopes of the APD restitution curves at similar steady states, slopes were also computed at points of intersection between the restitution curve and the lines representing pacing at a fixed cycle length (CL) of 200, 225, 250, 275, and 300 ms using the relationship $CL = APD + DI$. Esmolol decreased APD restitution slopes at CLs 200–275 ms ($P < 0.05$). Esmolol flattens the cardiac APD restitution curve in vivo, particularly at shorter CLs and DIs. This may represent a novel mechanism by which β -blockers prevent sudden cardiac death.

action potentials; sudden death; antiarrhythmia agents; arrhythmia

β -BLOCKERS IMPROVE SURVIVAL in patients after myocardial infarction and in patients with congestive heart failure and are useful in the treatment of electrical storm (2, 23, 24). However, the precise mechanism by which β -blockers prevent sudden cardiac death has not been elucidated.

Ventricular fibrillation has been shown in both numerical and animal models to be due to wave break of reentrant wave fronts (8, 33). In addition to tissue heterogeneities, important factors causing wave break are action potential duration (APD) and conduction velocity (CV) restitution properties of myocardial tissue (8). Wave break can be independent of electrophysiological heterogeneities, particularly when the APD restitution curve is steep, with slopes >1 (5). It has been suggested that flattening of the APD restitution curve with diacetyl monoxime, bretylium, verapamil, and amiodarone, as shown in vivo and computer models, prevents degeneration of ventricular tachycardia to ventricular fibrillation and organizes ven-

tricular fibrillation to ventricular tachycardia (13, 21, 26, 28). On the basis of these findings, as well as the recent observation that isoprenaline or norepinephrine increases the slope of APD restitution curves (30), we hypothesized that modulation of APD restitution is one mechanism by which β -blockade may reduce the risk for sudden cardiac death.

METHODS

Sixteen Yorkshire swine (40–60 kg) were sedated with an intramuscular injection of tiletamine (4.4–8.8 mg/kg), zolazepam (4.4–8.8 mg/kg), and methylparaben (2.2–4.4 mg/kg). The pigs were intubated and ventilated, and sedation was maintained throughout the protocol with 0.5–2.0% isoflurane. The femoral artery and vein were surgically exposed and vascular access obtained. All procedures were approved by the Institutional Animal Care and Use Committee of Weill Medical College of Cornell University.

ECG and intracardiac electrograms. A 7-Fr monophasic action potential (MAP) catheter (EP Technologies) was advanced in the right ventricle and positioned against the right interventricular septum. A 6-Fr quadripolar catheter (Bard Electrophysiology) was also positioned in the right ventricular apex. Right ventricular apical unipolar (0.05–400 Hz) and bipolar (40–400 Hz) intracardiac electrograms and ECG leads I and aVF were continuously displayed on an electrophysiology monitor. All tracings were digitized at 1 kHz and stored on a computer using a custom-designed computer-acquisition program (4).

Pacing protocol. The right ventricle was paced from the right ventricular apex with a rectangular pulse of 2.0 ms at twice the diastolic threshold or 2.0 mA, whichever was higher, via a Bloom (Fischer Imaging) or Bard stimulator. The protocol consisted of a drive train of 20 beats interrupted by an 8-s pause between drive trains to generate dynamic APD restitution curves (19). The cycle length (CL) of each drive train was decremented in 20-ms intervals from 500 to 300 ms and then by 10 ms until 2:1 capture was achieved. In six pigs, the CL of successive drive trains was decremented by 1 ms until 2:1 capture was reached. Data from six pigs were eliminated from analysis because 1) ventricular fibrillation was induced with rapid ventricular pacing, in one of the pigs, which could not be defibrillated, whereas the other became persistently hypotensive after receiving multiple shocks, and 2) MAP recordings were inadequate in four pigs (vide infra). Thus 10 pigs were included in the final analysis.

Drug infusion. The pacing protocol was performed in the basal state and during esmolol infusion for each pig [low dose ($n = 4$): $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 1 min, followed by a continuous infusion at $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ intravenous infusion, or high dose ($n = 6$): $500 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 4 min, followed by a continuous infusion at $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$].

Computer-assisted annotation and measurement. Adequate MAP tracings were defined as having an amplitude >10 mV, a sharp upstroke, and flat baseline. If $>30\%$ of the MAP recordings were substandard, the pig was removed from further analysis (total of 4 pigs). The last two beats of a drive train were selected for analysis. If

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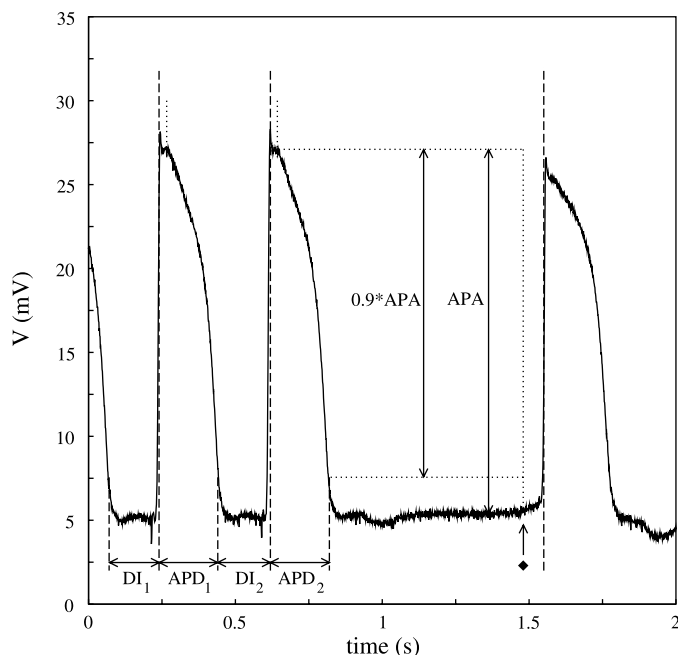


Fig. 1. Monophasic action potential voltage signals with measurement of action potential duration (APD) and diastolic interval (DI). Monophasic action potential voltage signals from the last 2 beats of a 20-beat train, followed by a sinus beat. The dashed vertical lines extending above the action potentials represent the manually annotated fiducial points. APD was measured from the fiducial point to 90% of repolarization. To determine 90% repolarization, action potential amplitude (APA) was computed as the difference between the action potential peak and the baseline. The peak for each action potential was set as the voltage a fixed time (10–30 ms, as set by the operator) after each fiducial point; this is shown at the dotted vertical line immediately after the fiducial point. The baseline for all action potentials in a given train was set as the voltage a fixed time (10–50 ms) preceding the first postpacing sinus beat (◆). The dotted lines illustrate the determination of APD₉₀ (APD₂) for the last beat of this train. The corresponding DI₂ is illustrated and corresponds to the time from the fiducial point back to the previous monophasic action potential signal at a voltage corresponding to 90% repolarization.

either beat was preceded by a premature or noncaptured beat, it was eliminated from further analysis.

The MAP tracings were annotated, and APD at 90% repolarization (APD₉₀) and the preceding diastolic interval (DI) at APD₉₀ were measured according to the methods outlined in Fig. 1. No beat had a negative DI, and beats inappropriately annotated by the computer, as verified by an investigator, were eliminated from further analysis.

APD restitution curves and slopes. The APD and DI for each beat were plotted to define the APD restitution curve in the basal state and during esmolol infusion. The curves were fitted with the three-parameter (*a*, *b*, and *c*) exponential equation $APD = a \cdot [1 - e^{(-b \cdot DI)}] + c$ using Matlab version 6.1 (see Fig. 2). The slope of the curve at each data point was determined as the derivative of the exponential curve: $slope = a \cdot b \cdot e^{(-b \cdot DI)}$. The maximal slopes (which occur at the shortest DI for a single-exponential fit) in the basal state and during infusion of esmolol were computed. Slopes of the curves and APDs were computed at DIs of 75, 100, 125, and 150 ms. In addition, to compare the slopes of the APD restitution curves in the basal state and during infusion of esmolol at similar steady-state heart rates (HR), the slopes of the curves were computed at the points of intersection between the restitution curve and the lines representing pacing at a fixed CL of 200, 225, 250, 275, and 300 ms using the relationship $CL = APD + DI$.

Statistical analysis. Statistical comparisons were performed using Student's *t*-test for paired values. For all comparisons, a *P* value <0.05 was required for rejection of the null hypothesis.

RESULTS

There was no significant difference in HR or systolic blood pressure (SBP) during the basal state vs. infusion of esmolol. There was no difference in HR or SBP between pigs receiving low-dose (pigs 1-4) or high-dose esmolol (pigs 5-10) (Table 1).

APD restitution slopes. Examples of representative MAP tracings, annotated fiducial points, and annotated maximum and minimum voltages are illustrated in Fig. 1. Sample dynamic APD restitution curves of APD₉₀ in the basal state and during infusion of esmolol are illustrated in Fig. 2. The APDs were shorter at longer DIs during infusion of esmolol but were similar to the basal state at shorter DIs. The maximal slopes of the curves in all 10 pigs during infusion of esmolol were less than at baseline (0.68 ± 0.14 vs. 0.94 ± 0.24 , *P* = 0.002; see Fig. 3). Low- and high-dose esmolol reduced the maximal slope of the APD restitution curve to a similar degree. Esmolol flattened the APD restitution curve primarily at the shorter DIs, i.e., 75 and 100 ms, *P* < 0.05 (Fig. 4 and Table 2). APD alternans were not observed in any animal at baseline or after esmolol infusion.

Given that slopes measured at the same DI may not correlate to the same APD and thus CL, the slopes of the APD restitution curves during the basal state and esmolol were compared at the same CL. Therefore, the intersection of the APD restitution curve and the line defined for CLs of 200, 225, 250, 275, and 300 ms by $CL = APD + DI$ represent steady-state points at a given paced CL (see Fig. 2). Similar to the analysis of restitution based on DI, the slopes of the dynamic APD restitution curve referenced to CL during esmolol infusion were less than the basal state, particularly at shorter steady-state CLs (Fig. 5 and Table 2).

DISCUSSION

The principal finding of this study is that intravenous β-blockade (esmolol) flattens the APD restitution curve as measured along the right ventricular septum. These effects

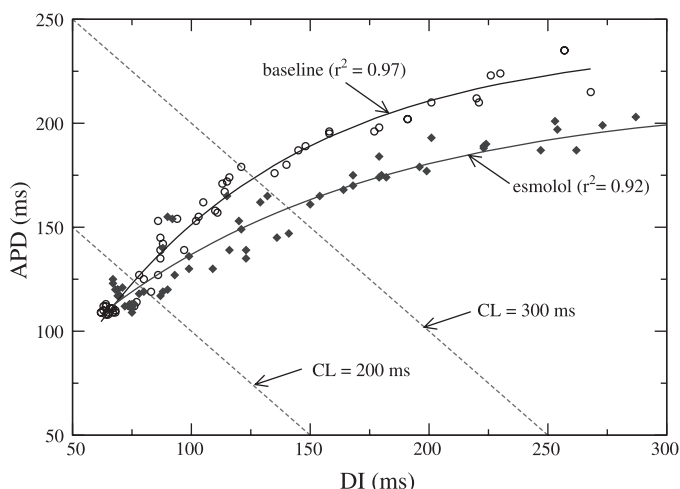


Fig. 2. Representative APD restitution curves before and after infusion of esmolol. ○, Data before infusion of esmolol; ◆, data after infusion of esmolol. APD and DI were measured from monophasic action potentials during decremental ventricular pacing. The curves represent exponential curve fits to the data, where $APD = a \cdot [1 - e^{(-b \cdot DI)}] + c$. The hatched lines represent pacing or heart rates at a specific cycle length (CL; 200 and 300 ms shown), where $CL = APD + DI$ (see text).

Table 1. Effect of esmolol on heart rate and blood pressure

	<i>n</i>	Baseline HR, beats/min	Esmolol HR, beats/min	<i>P</i> Value	Baseline SBP, mmHg	Esmolol SBP, mmHg	<i>P</i> Value
Low-dose esmolol	4	84 ± 8	84 ± 6	0.50	91 ± 3	97 ± 3	0.11
High-dose esmolol	6	94 ± 10	90 ± 11	0.24	107 ± 20	109 ± 17	0.71
Esmolol (high and low doses combined)	10	90 ± 10	87 ± 9	0.27	100 ± 17	104 ± 15	0.27

Values represent means ± SD; *n* = no. of pigs. HR, heart rate; SBP, systolic blood pressure.

occur primarily at short DIs and short CLs. Flattening of the APD restitution curve occurred independent of β -blocking effects on HR or SBP. Given that a decrease in the slope of the APD restitution curve is thought to reduce the likelihood of wave break and destabilization of excitation waves, this effect of β -blockade may provide one potential mechanism for its antifibrillatory actions and its ability to prevent sudden cardiac death in patients with structural heart disease.

APD restitution and ventricular fibrillation. Ventricular fibrillation is an aperiodic rhythm whose onset has been thought to result from "wave break." Wave break has been described as wave fronts of depolarization that continually split into multiple other wave fronts (8, 33). At least two mechanisms are thought to link wave breaks to ventricular fibrillation. The focal source hypothesis suggests that wave fronts propagate from a relatively stable mother rotor that rotates at a high frequency. Wave break is due to static and dynamic heterogeneity of tissue peripheral to the mother rotor as well as the core size and frequency of the mother rotor. Modulation of the core size and frequency of the mother rotor with drugs, such as verapamil, have been shown to organize ventricular fibrillation into ventricular tachycardia (17, 29).

An alternative theory suggests that the continuous production of multiple small rotors, or wavelets, maintains ventricular fibrillation, and a stable reentrant circuit, like a mother rotor, is not necessary to drive fibrillation. The wave break of multiple depolarizing fronts produces wavelets that propagate, collide, extinguish, and produce more wavelets (8, 33). Wave break can be caused by static heterogeneities, such as anatomic obstacles or fibrosis, but can also occur due to spontaneous, dynamic changes in wavelength that are dependent on APD and CV restitution (3, 9, 33). Steep APD restitution, that is, slopes >1, amplify oscillations of wavelength that lead to large gradients of repolarization and wave break.

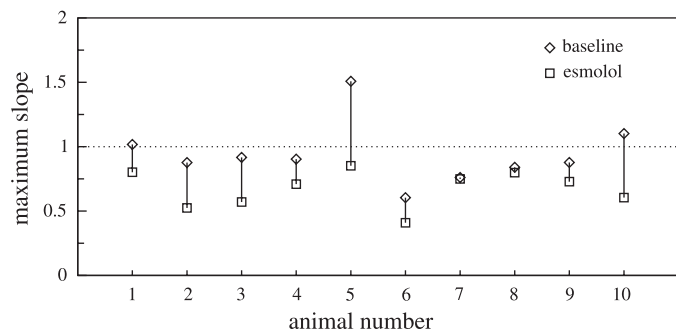


Fig. 3. Maximum slopes of the APD restitution curve for the dynamic pacing protocol for all 10 animals at baseline and after esmolol infusion. The maximum slope decreased after esmolol infusion for all animals. The dotted horizontal line represents slope = 1.

Measurement of APD restitution slopes. There are at least two distinct conditions by which the slope of the APD restitution curve may have implications for tachyarrhythmias, each of which was considered in our study. In the first condition, the effect of a perturbation on APD restitution was analyzed with respect to a given DI (Fig. 4). Over a wide range of DIs, relatively steep slopes of the APD restitution curve result in amplification of heterogeneity and destabilization of wave fronts (5, 13, 21, 26, 28). This is relevant for the response of a wave front to a premature extrastimulus, when an abrupt change of the DI in the region of steep slope could destabilize the wave and initiate a disorganized tachyarrhythmia. An alternative scenario is that of a rotating wave front from a spiral or scroll wave advancing at a fixed CL. The slope of the APD restitution curve at a given CL (as opposed to a fixed DI) of the advancing wave front would then be the determinant of whether wave break occurs along the wave front. Note that spiral wave CLs are not always constant: frequency can vary because it is an intrinsic function of dynamic electrophysiological properties of the tissue, including APD restitution and CV restitution. Nevertheless, to compare the effects of drug infusion on the breakup of stable wave fronts into disorganized rhythms, we believe that it is informative to compare slopes of the APD restitution curve at fixed cycle lengths (Fig. 5) as well as at fixed DIs (Fig. 4). Esmolol preferentially flattened the APD restitution slopes in this study at short CLs (as well as at short DIs), consistent with the expectation that its antiarrhythmic effects should be more pronounced at CLs comparable to those observed during episodes of ventricular tachycardia and ventricular fibrillation.

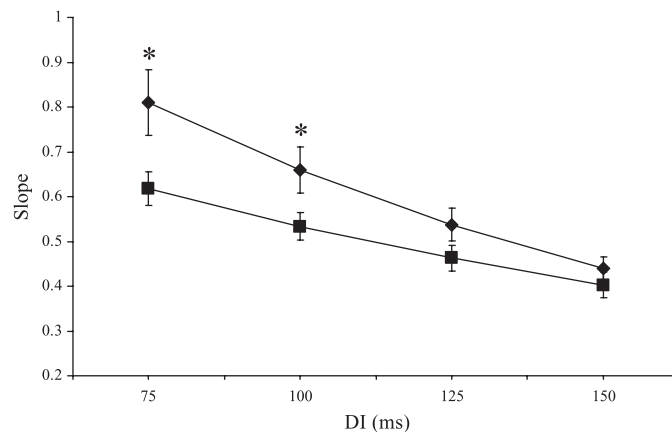


Fig. 4. APD restitution slopes at fixed DIs before and after infusion of esmolol. Comparison of slopes of the APD restitution curve at fixed DIs before and after infusion of esmolol (◆, baseline; ■, esmolol). The slopes of the APD curve were less during infusion of esmolol and reached statistical significance at the shortest DIs, 75 and 100 ms; **P* < 0.04.

Table 2. Effect of esmolol on slopes at fixed DIs and CLs

Fig	DI(B)	DI(E)	DI(B)	DI(E)	DI(B)	DI(E)	DI(B)	DI(E)	CL(B)	CL(E)	CL(B)	CL(E)	CL(B)	CL(E)	CL(B)	CL(E)	CL(B)	CL(E)
	75	75	100	100	125	125	150	150	200	200	225	225	250	250	275	275	300	300
1	0.74	0.70	0.59	0.60	0.46	0.52	0.37	0.45	0.95	0.81	0.84	0.75	0.74	0.69	0.65	0.63	0.56	0.57
2	1.11	0.53	0.87	0.50	0.68	0.48	0.54	0.45	0.90	0.54	0.79	0.52	0.69	0.50	0.59	0.48	0.51	0.46
3	0.74	0.52	0.61	0.44	0.50	0.37	0.41	0.31	0.70	0.52	0.62	0.46	0.55	0.41	0.49	0.36	0.43	0.31
4	0.74	0.64	0.63	0.54	0.53	0.45	0.45	0.38	0.84	0.79	0.77	0.72	0.70	0.65	0.63	0.58	0.57	0.52
5	1.30	0.80	0.99	0.65	0.75	0.52	0.56	0.42	1.29	0.77	1.13	0.68	0.99	0.60	0.86	0.53	0.73	0.46
6	0.55	0.42	0.50	0.38	0.45	0.35	0.40	0.32	0.58	0.42	0.55	0.40	0.51	0.37	0.47	0.35	0.44	0.32
7	0.67	0.59	0.55	0.46	0.45	0.36	0.37	0.28	0.74	0.63	0.66	0.53	0.58	0.45	0.51	0.38	0.44	0.32
8	0.67	0.79	0.55	0.71	0.46	0.64	0.38	0.57	0.75	0.85	0.67	0.80	0.60	0.75	0.53	0.71	0.46	0.66
9	0.66	0.60	0.53	0.50	0.43	0.42	0.35	0.35	0.73	0.65	0.65	0.58	0.57	0.52	0.49	0.46	0.43	0.41
10	0.92	0.59	0.78	0.56	0.67	0.53	0.57	0.50	1.04	0.62	0.96	0.60	0.89	0.58	0.81	0.56	0.74	0.54

Values represent slopes at fixed diastolic intervals (DI) and cycle lengths (CL). DI(B), DI (in ms) at baseline; DI(E), DI (in ms) during esmolol infusion; CL(B), CL (in ms) at baseline; CL(E), CL (in ms) during esmolol infusion.

Absence of APD alternans. The restitution hypothesis posits that APD alternans should occur whenever the slope of the APD restitution curve exceeds 1 (25). On the basis of this hypothesis alone, it is surprising that no alternans were observed during the dynamic pacing protocol for animals 1, 5, and 10 at baseline. The maximum restitution slopes for these trials were 1.02, 1.51, and 1.10, respectively (Fig. 3). One potential reason for the absence of alternans may be the explanation proposed in recent experimental (1, 14) and theoretical (6, 10, 31) studies in which restitution slopes exceeding one were not always accompanied by alternans. These studies proposed that APD is not a unique function of the previous DI (as assumed by the restitution hypothesis) and that additional factors, such as cardiac memory and CV restitution, may contribute to prevent alternans from occurring when APD restitution slope exceeds 1. Thus, as in this study, even when APD restitution slope exceeds 1, alternans may not occur.

Modulation of the APD restitution slope. Diacetyl monoxime, bretylium, verapamil, and amiodarone have been shown to organize ventricular fibrillation into ventricular tachycardias and prevent the initiation of ventricular fibrillation in ex vivo and computer studies (13, 21, 26, 28). Because those antiarrhythmic effects occurred along with flattening of the

APD restitution curve, it was suggested that restitution flattening might be antiarrhythmic. Propranolol has also been shown to qualitatively flatten APD restitution curves in a single small clinical study (7). Contrary effects are observed clinically with isoprenaline or norepinephrine, where there is an increase in slope, consistent with the known effects of adrenergic stimulation in facilitating ventricular fibrillation (30).

The ionic mechanisms by which drugs modulate APD restitution have not been elucidated, predominantly due to an incomplete understanding of how individual ionic currents contribute to the restitution curve. Computer simulations have demonstrated that numerous ionic currents influence the rate dependence of APD and therefore determine the slope of the APD restitution curve (11). One possibility for the effect observed in this study is that the esmolol, by blocking sympathetic tone, reduces the L-type Ca²⁺ current (*I*_{Ca,L}), which could have the same restitution-flattening effect of the Ca²⁺ channel blocker verapamil. Also, it has previously been shown that a reduction of Ca²⁺ or K⁺ currents decreases the range of DIs over which the APD restitution curve is steep (22). The reduction in Ca²⁺ current produced shortened APDs at long DIs compared with control (22), whereas the reduction in K⁺ current lead to a lengthening of APD at long DIs compared with control (22, 32). Incomplete Na⁺ channel activation also contributes to the shortening of the action potential at short DIs (12), and thus drugs that modulate Na⁺ current are likely to significantly influence the restitution curve. The restitution curve is also affected by the action potential history through ionic memory (18, 20); this complicates any understanding of how individual currents influence the restitution curve.

β-Adrenergic stimulation increases permeation of multiple ion channels, including *I*_{Ca,L} and the slow outward K⁺ channel (16, 22, 30). Shortening of APD at longer CLs and flattening of the APD restitution curve in this study with esmolol was likely due to its inhibitory effects on *I*_{Ca,L} (15, 16, 22).

Limitations. Most prior studies have examined APD restitution in computer models, myocardial fibers or excised segments of hearts and have shown maximal APD restitution slopes >1. This study was performed in anesthetized and sedated pigs with normal hearts and demonstrated mean maximal slopes that approached, but did not exceed, 1. The effect of anesthesia or the autonomic response to anesthesia were not systematically measured (except for HR and SBP) and could have affected the APD restitution slopes such that maximal

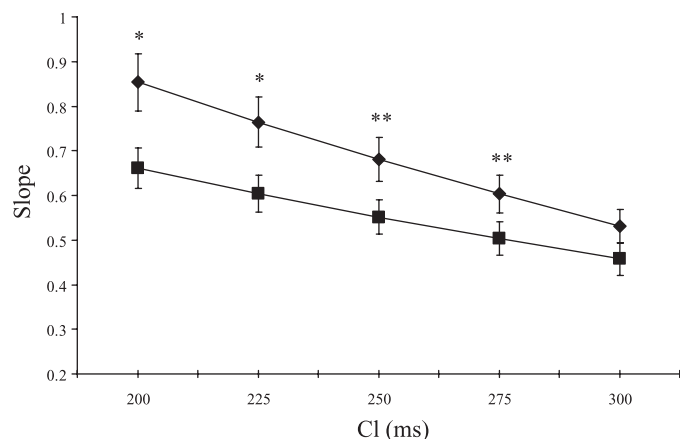


Fig. 5. APD restitution slopes at fixed CLs before and after infusion of esmolol. Comparison of slopes of the APD restitution curve at fixed CL before and after infusion of esmolol (◆, baseline; ■, esmolol). The slopes of the APD restitution curves at CLs 200, 225, 250, 275, and 300 ms before and after infusion of esmolol were compared. There was a significant decrease in slope at CLs 200, 225, 250, and 275 ms (**P* < 0.02 and ***P* < 0.05).

slopes did not exceed 1. Nonetheless, intravenous esmolol flattened the maximal slope of the APD restitution slope as well as the slopes of the APD restitution curve at CLs that are consistent to those observed during episodes of ventricular tachycardia and fibrillation in vivo.

Flattening of the APD restitution slope in the right ventricular septum in response to esmolol would presumably also occur throughout the left and right ventricular myocardium. However, given the technical considerations in this in vivo experiment, only one MAP recording could be obtained and the global effects of intravenous esmolol cannot be definitively confirmed.

Low- and high-dose esmolol resulted in similar flattening of the APD restitution curve that could be consistent with a threshold effect and complete β -adrenergic blockade. However, given that only two doses of esmolol were used in this study, the effect of lower doses could not be determined.

GRANTS

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