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Propranolol Blocks Ventricular Refractory Period Changes With Orthostatic Stress in Humans

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The purpose of this study was to test the hypothesis that orthostatic stress shortens the right ventricular effective refractory period by reflex activation of beta-adrenergic receptors. Twelve patients undergoing electrophysiologic testing for standard clinical indications were studied. After a full electrophysiologic study, patients underwent graded lower body negative pressure before and after administration of either propranolol (0.2 mg/kg intravenously) in Group I or atropine (0.035 mg/kg intravenously) in Group II.

Before the addition of drugs, lower body negative pressure produced decreases in systolic blood pressure and significant increases in sinus rate. The effective refractory period shortened from 214 ± 8 (mean ± SEM) to 206 ± 7 ms at −40 cm H_2O and to 197 ± 4 ms at −60 cm H_2O lower body negative pressure. After propranolol, Group I patients had no change in right ventricular effective refractory period despite similar changes in sinus rate and systolic blood pressure. In Group II patients, atropine did not alter effective refractory period responses to lower body negative pressure.

Thus, reflex adjustments to orthostatic stress result in shortening of right ventricular effective refractory period mediated by way of beta-adrenergic mechanisms. These findings constitute the first evidence that sympathetic influences mobilized by the body can directly modulate ventricular electrophysiologic changes.

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Autonomic influences play an important role in ventricular arrhythmogenesis, particularly after myocardial infarction. Parasympathetic influences are believed to protect against arrhythmias and beta-adrenergic influences are thought to be arrhythmogenic in experimental animals (1–3) and in humans (4–7). The electrophysiologic mechanisms for these effects are not known, but they may be direct, acting on the tissue responsible for tachycardia (2), or indirect (3) by reduction of heart rate.

It is well known that beta-adrenergic influences shorten the ventricular effective refractory period in animals (8,9) and humans (7). Human studies like the latter have involved infusions of arbitrary doses of isoproterenol, which might have questionable physiologic significance. Even though propranolol prolongs baseline ventricular effective refractory period in anesthetized animals (1,8,9), it does not substantially affect that in humans at rest (10), perhaps because there is only a small amount of background sympathetic input to the ventricle in a patient undergoing clinical electrophysiologic testing of the ventricle. We reasoned that the beta-blocking effects of propranolol would be demonstrable in patients if background sympathetic influences were augmented by an autonomic reflex. We therefore studied the effects of lower body negative pressure on the right ventricular effective refractory period in patients because lower body negative pressure is an extremely well studied physiologic stimulus (11), that increases both circulating catecholamines (11,12) and sympathetic neural firing (13) in humans. We tested the hypotheses that lower body negative pressure would shorten right ventricular effective refractory period and that this shortening would be mainly due to sympathetic influences that could be blocked by propranolol.

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Table 1. Clinical Features of 12 Patients

Patient No.	Age (yr) & Gender	Cardiac Disease	Indication For EPS	Results of EPS
Group I				
1	71F	None	Syncope (VT-NS)	Negative
2	36M	Myocardial infarction	Palpitation (VT-NS)	Negative
3	33F	Mitral prolapse	Syncope (VT-NS)	Negative
4	24F	None	(VT-Sus)	VT Sus
5	69M	None	Syncope (SVT)	SVT (AVNR)
6	67M	None	Presyncope (VT-NS)	VT-NS
Group II				
7	23M	None	Syncope (unknown)	SVT (AVNR)
8	37M	Aortic regurgitation	Syncope (VT-NS)	VT-NS
9	49F	None	Cardiac arrest (VT-NS)	VT-NS
10	39M	None	Syncope (seizure)	Negative
11	50M	Cardiomyopathy	Syncope (VT-NS)	Negative
12	33F	None	Syncope (unknown)	Negative

AVNR = atrioventricular node reentry; EPS = electrophysiologic study; F = female; M = male; NS = nonsustained; Sus = sustained; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Methods

Study patients (Table 1). Twelve patients presenting with symptoms of syncope or palpitation or known arrhythmias were studied. The patients were invited to participate in the study after its goals were explained, and each gave written informed consent for the research protocol approved by the Human Use Committee of the University of Iowa.

Electrophysiologic testing. All patients underwent electrophysiologic testing in the postabsorptive and nonsedated state and were not receiving cardioactive medications. Two quadripolar catheters were placed in the femoral veins by the Seldinger technique under local lidocaine anesthesia (1 to 2 ml of 1% solution). The extrastimulus protocol for the clinical electrophysiologic study was performed as previously reported from this laboratory (7,14).

The study protocol followed completion of the clinical study. A quadripolar catheter was placed in the right ventricular apex and thresholds were recorded to the nearest 0.1 mA. Pacing was performed at four times threshold to decrease the variability of refractory period measurements occurring at two times threshold, owing to the varying shape of the strength-interval relation in normal and abnormal ventricular myocardium (15). The current for pacing set at the beginning of the study was maintained throughout all subsequent testing including threshold determinations. Preliminary extrastimulus testing was performed to assure stable pacing without artificial repetitive responses. The catheter was then fixed to the skin and sterile drape with a plastic adhesive sheet that prevented catheter movement. The sterile drape was folded so that it lay immediately above the patient, exposing the lateral aspects of the patient's legs and hips. The patient was placed in a lower body negative pressure chamber, which was advanced to the level just below the iliac crest. A seal was formed by applying adhesive tape circumferentially around the patient's abdomen. The folded sterile sheet containing the catheters exiting from the pressure chamber was placed under the seal.

Lower body negative pressure. After satisfactory seal resulting in a range of lower body negative pressure from −20 to −60 cm H_2O, repeat threshold testing was performed at the right ventricular apex at a basic cycle length of 450 ms (lasting approximately 20 to 30 s). Then a premature stimulus (followed by a train delay) was administered to the same electrodes at a coupling interval approximately 30 to 50 ms longer than the estimated effective refractory period. After capture occurred, the premature stimulus interval was shortened in decrements of 5 ms after each eight basic stimuli until failure to capture occurred. After this sequence, the premature interval was prolonged by 10 ms and the procedure of decrementing the premature interval was repeated. The effective refractory period was defined as the longest premature interval for which the premature stimulus did not evoke a response. The data reported herein are those that were reproducible, defined as obtaining the same value of refractoriness on two separate trials. In addition, threshold measurements were unchanged, defined as varying ≤0.1 mA throughout the course of testing with lower body negative pressure; threshold is not altered by sympathetic influences (8).

Protocols. The sequence of study was as follows: control period; lower body negative pressure at three levels, −20, −40 and −60 cm H_2O; and recovery 5 min after cessation of lower body negative pressure. During each period, the spontaneous heart rate was measured for 60 s while blood pressure was measured by the inflatable cuff technique. Then ventricular pacing was begun to measure the effective refractory period. These measurements were performed after 1 min at each level of lower body negative pressure.

Table 2. Systolic Arterial Pressure Responses (mm Hg)

	LBNP 0	LBNP −20	LBNP −40	LBNP −60	Recovery
Group I (n = 6)					
Baseline	119 ± 7	122 ± 4	119 ± 5	110 ± 3*	119 ± 9
Propranolol	114 ± 5	116 ± 8	106 ± 6	108 ± 7	113 ± 4
Group II (n = 6)					
Baseline	118 ± 7	119 ± 7	110 ± 4	110 ± 7	124 ± 14
Atropine	127 ± 5	116 ± 7*	106 ± 3*	Not done	128 ± 5

*$p < 0.05$ vs. LBNP 0 for baseline or drug. LBNP = lower body negative pressure (cm H_2O).

After completion of measurements at each level, the next level of lower body negative pressure was applied without interruption. The time at each level of lower body negative pressure averaged 5 min.

The patients were classified into two groups. The first group of six patients received propranolol at a dose of 0.2 mg/kg. Repeat testing with lower body negative pressure was performed 20 min after administration of propranolol. In Group II, atropine (0.035 mg/kg intravenously) was administered by bolus injection and lower body negative pressure was repeated at levels of −20 and −40 cm H_2O. At lower body negative pressure of −60 cm H_2O, control of heart rate during ventricular pacing was inadequate.

Data analysis. Data are expressed as mean ± SEM and were analyzed with an analysis of variance employing Dunnett's test for multiple comparisons (16). Paired Student's *t* tests were employed to compare variables before and after drug administration. Unpaired *t* tests were used to compare the two groups. A p value <0.05 was considered significant.

Results

Clinical features (Table 1). Our patients' ages ranged from 23 to 71 years; patients in Group I tended to be older, but this difference was not significant ($p > 0.25$). Moreover, the magnitude of baseline reflex responses (Tables 2 to 4) did not differ between the groups. Four patients had heart disease and all had clinical indications for electrophysiologic study. Six patients had no abnormalities at the electrophysiologic study, whereas three had nonsustained ventricular tachycardia, two had atrioventricular (AV) node reentrant tachycardia and one had sustained ventricular tachycardia induced.

Arterial pressure responses (Table 2). In Group I, systolic arterial pressure decreased reversibly at a lower body negative pressure of −60 cm H_2O, whereas in Group II, a similar magnitude of change did not result in a significant decrease. After propranolol administration in Group I, systolic blood pressure did not decrease significantly during lower body negative pressure. In Group II, systolic blood pressure decreased at lower body negative pressures of −20 and −40 cm H_2O after atropine.

Heart rate responses (Table 3). In Group I, sinus node rate increased at a lower body negative pressure of −60 cm H_2O. After propranolol administration, spontaneous heart rate slowed significantly compared with that before the drug was given. The sinus rate was not significantly altered by lower body negative pressure after propranolol. In Group II, sinus rate increased at all levels of lower body negative pressure. After atropine, baseline heart rate increased, but it did not increase further with lower body negative pressure. At a lower body negative pressure of −60 cm H_2O, spontaneous heart rate exceeded that during ventricular pacing; therefore data after atropine were not recorded.

Effective refractory period responses (Fig. 1, Table 4). Before propranolol or atropine, the effective refractory period shortened in both groups during lower body negative pressures of −40 and −60 cm H_2O. Twenty minutes after intravenous administration of propranolol, the effective refractory period was not significantly altered. Lower body negative pressure produced no change in effective refractory period at any negative pressure level after propranolol

Table 3. Heart Rate Responses (beats/min)

	LBNP 0	LBNP −20	LBNP −40	LBNP −60	Recovery
Group I (n = 6)					
Baseline	90 ± 6	86 ± 6	96 ± 5	109 ± 7*	89 ± 9
Propranolol	70 ± 3†	66 ± 4	74 ± 3	77 ± 3	69 ± 5
Group II (n = 6)					
Baseline	76 ± 4	87 ± 3*	87 ± 4*	104 ± 8*	77 ± 6
Atropine	117 ± 5†	121 ± 6	126 ± 7	Not done	107 ± 5

*$p < 0.05$ vs. LBNP 0; †$p < 0.05$ vs. recovery baseline. LBNP = lower body negative pressure (cm H_2O).

Table 4. Right Ventricular Effective Refractory Period Responses (ms)

	LBNP 0	LBNP −20	LBNP −40	LBNP −60	Recovery
Group I (n = 6)					
Baseline	214 ± 8	213 ± 7	206 ± 7*	197 ± 4*	215 ± 6
Propranolol	218 ± 3	220 ± 7	218 ± 5	223 ± 6	226 ± 6
Group II (n = 6)					
Baseline	209 ± 5	202 ± 5	200 ± 4*	196 ± 3*	210 ± 8
Atropine	199 ± 2	193 ± 2	192 ± 2*	Not done	201 ± 2

*$p < 0.05$ vs. LBNP. LBNP = lower body negative pressure (cm H_2O).

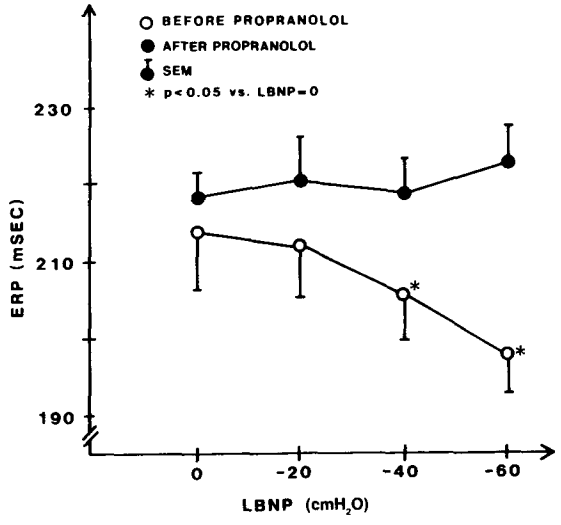
administration. At no time did the configuration of the surface electrocardiogram (ECG) or intracardiac electrogram change during pacing and at no time did the late diastolic threshold vary by >0.1 mA.

In Group II after atropine administration, the effective refractory period did not shorten significantly ($p = 0.1$). Lower body negative pressure still shortened the effective refractory period at −40 cm H_2O after administration of atropine; this shortening expressed as percent of lower body negative pressure 0 (3.5 ± 1.1%) was not different from that occurring before atropine was given (4.5 ± 0.8%, $p > 0.2$).

Discussion

This study demonstrates two new observations. First, orthostatic stress (lower body negative pressure) shortens right ventricular effective refractory period through activation of beta-adrenergic receptors. Second, parasympathetic influences are not involved in controlling effective refractory period responses to orthostatic stress. These studies clearly demonstrate a physiologic role for the sympathetic nervous system in direct modulation of the duration of the ventricular refractory period.

Figure 1. Right ventricular effective refractory period (ERP) responses (in ms) at various levels of lower body negative pressure (LBNP) before and after propranolol administered intravenously. Before propranolol, there were graded decreases in effective refractory period. After propranolol, effective refractory period did not change.



Comparison with previous studies. Lower body negative pressure in the present study was solely performed during electrophysiologic testing with the use of single extrastimuli to measure the ventricular effective refractory period. Because all measurements and extrastimulus testing were performed in 4 to 5 min at each level of lower body negative pressure, near syncope did not occur, although others (17) observed it commonly when lower body negative pressure at levels of −40 and −60 mm Hg continued for >5 min. This lack of presyncope during lower body negative pressure in our study may have been due to our use of pacing at a cycle length of 450 ms, which reversed the bradycardia and hypotension occurring in the prior study (17).

In our study, lower body negative pressure produced reversible shortening of the right ventricular effective refractory period measured at a constant pacing rate. Others (18) have measured the right ventricular effective refractory period during tilt and found that it also shortened to a similar degree. Although there are differences between these two interventions in that tilt stimulates the vestibular system and produces differential stimulation of carotid and aortic baroreceptors (11,19), these apparently do not influence the ventricular effective refractory period responses. In addition, our study demonstrated that shortening of the effective refractory period was blocked entirely by intravenous propranolol in a dose that slowed baseline sinus rate.

We did not demonstrate the significant alteration in ventricular effective refractory period with intravenous atropine as previously reported by others (10). This lack of effect might have been due to the small number of patients in Group II, but a similar number of patients (five) was studied previously (10). More likely, because our patients underwent lower body negative pressure before the administration of atropine, this procedure may have conditioned them to have less parasympathetic influence at rest to the ventricle. We also did not observe atropine to potentiate the response to lower body negative pressure (greater shortening of effective refractory period); we did not see a blockade of the restrain-

ing influence of the parasympathetic nerves on sympathetic function with atropine. This result may be due to the ventricular effects of parasympathetic influences produced by baroreflexes, which are small as compared with sympathetic influences as manifested by previous animal experiments (9). This disparity in magnitude of parasympathetic and sympathetic effects is especially prominent when there is coincident parasympathetic withdrawal and sympathetic activation during lower body negative pressure.

Possible limitations of this study. We considered other possibilities to explain our results with propranolol in Group I. It could be argued that propranolol prevented lower body negative pressure from being an effective stress because of the blunted (nonsignificant) responses of the systolic blood pressure to lower body negative pressure. However, at a lower body negative pressure of −60 cm H_2O, a similar level of systolic arterial pressure was produced before and after propranolol, indicating that the stimulus of the lower body negative pressure was very similar before and after propranolol. A second possible concern was that the lack of effective refractory period response after propranolol reflected effects of the repeated application of lower body negative pressure and not drug effect (11). This possibility is unlikely because responses of the effective refractory period were preserved after atropine. The third possibility was that the stimulus of lower body negative pressure was altered because propranolol decreased left ventricular contractility and the sensitivity of cardiac afferents (20). However, effects on effective refractory period occurred at −40 and −60 cm H_2O (corresponding to −29 and −44 mm Hg) when the arterial and cardiac baroreflexes are activated by lower body negative pressure (20–22). Propranolol does not desensitize the arterial baroreflex (20); thus, it is unlikely that the effects of propranolol on cardiac sensory receptors accounted for its effect on the ventricular effective refractory period. Therefore, we conclude that propranolol prevented right ventricular effective refractory period shortening during lower body negative pressure because of blockade of beta-receptors, which prevented expression of augmented sympathetic neural and humoral influence.

With the use of catheter techniques, any change in the position of the heart, such as that which might occur with lower body negative pressure, may alter the recording and pacing sites. In this study, we carefully performed the following procedures to document that results of lower body negative pressure were accurately reflecting ventricular electrophysiologic changes. First, threshold changes were measured with each intervention and found not to alter over the course of each study. Second, the effective refractory period returned to control level and lower body negative pressure. Third, the surface ECG and intracardiac electrograms did not change during ventricular pacing in any of the patients studied. Thus, the positional changes of the heart in the chest occurring with lower body negative pressure did not change the catheter position to another site which might have altered our data.

Increases in sympathetic neural influence to the ventricles may produce dispersion of ventricular refractoriness and may predispose to ventricular fibrillation (23). Changes in the right ventricular effective refractory period do not necessarily demonstrate dispersion because lower body negative pressure also increases circulating epinephrine (11,12). We did not measure dispersion of refractory periods; however, we did not observe any QT interval or T wave changes consistent with altered sympathetic neural input to the heart.

Clinical implications. Recent observations in patients have suggested that parasympathetic influences do modulate ventricular refractoriness (10) and interrupt ventricular tachycardia (24,25). The present study documents the modulating effect of physiologically activated sympathetic influences on duration of ventricular refractory period, but we did not investigate such influences on spontaneous or inducible arrhythmias in our patients. However, in a preliminary series of patients with repetitive monomorphic ventricular tachycardia from our laboratory (26), lower body negative pressure appeared to be similar to infusion of isoproterenol in facilitation of tachycardia. Specifically, both interventions shortened right ventricular refractoriness and tachycardia cycle length and facilitated induction of ventricular tachycardia during extrastimulus testing. At this time, we do not know whether lower body negative pressure will facilitate induction of clinically occurring ventricular tachycardias associated with prior myocardial infarction. Because nearly all such ventricular tachycardias are induced with premature stimulation alone and because at least short-term administration of a beta-blocking agent is not effective in preventing tachycardia induction, the frequency of facilitation of such induction may not be common. However, reentry is the likely mechanism of these inducible ventricular tachycardias, and shortening of refractoriness in tissue critical to the circuit may facilitate tachycardia induction on occasion (7).

Further work is needed to assess whether physiologic augmentation of sympathetic influences by lower body negative pressure during extrastimulus testing will be useful in predicting efficacy of adrenergic blockade, as has been demonstrated with isoproterenol (7). Because of the physiologic activation of sympathetic influences, lower body negative pressure may be a better means than infused isoproterenol of testing responses of arrhythmias to beta-adrenergic blocking drugs.

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