Effects of Epinephrine in Patients with an Accessory Atrioventricular Connection Treated with Quinidine

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The purpose of this study was to determine whether physiologic doses of epinephrine reverse the electrophysiologic effects of quinidine in patients with an accessory atrioventricular (AV) connection. Eighteen patients with an accessory AV connection who had inducible sustained orthodromic tachycardia underwent an electrophysiologic study in the baseline state and after at least 2 days of treatment with 1.4 to 1.9 g/day of quinidine gluconate. The effects of epinephrine were then determined. Epinephrine infusion rates of 25 and 50 ng/kg/min were used in 9 patients each because these doses of epinephrine previously have been demonstrated to result in elevated plasma epinephrine concentrations in the range that occurs during a variety of stresses in humans. Quinidine prolonged refractoriness in the atrium and accessory AV connection and slowed conduction through the accessory AV connection. These effects were partially or completely reversed by epinephrine. Among 8 patients in whom quinidine resulted in orthodromic tachycardia becoming noninducible or nonsustained, sustained tachycardia became inducible again in 5 patients after infusion of epinephrine. After quinidine, atrial fibrillation was either noninducible or nonsustained in 8 patients; however, sustained atrial fibrillation could be induced in 4 of these patients after infusion of epinephrine. The results of this study demonstrate that the therapeutic effect of quinidine in patients who have an accessory AV connection are often reversed by physiologic increases in circulating epinephrine.

(Am J Cardiol 1988;62:580–584)

Beta-adrenergic stimulation with isoproterenol has been demonstrated to accelerate paroxysmal supraventricular tachycardia[1] and to antagonize the therapeutic effects of antiarrhythmic drugs in patients with the Wolff-Parkinson-White syndrome.[2–6] However, because isoproterenol is not produced endogenously, the physiologic significance of the response to isoproterenol in quantitative terms is unclear. In contrast to isoproterenol, epinephrine is produced endogenously and prior studies have determined that infusions of 25 and 50 ng/kg/min result in elevations of the plasma epinephrine concentration within a physiologic range.[7,8] This study determines the effects of physiologic doses of epinephrine in patients with an accessory atrioventricular (AV) connection and symptomatic tachycardias treated with quinidine.

METHODS

Patients studied: Eighteen patients with an accessory AV connection underwent an electrophysiologic study because of recurrent, symptomatic tachycardia. A criterion for inclusion in this study was the ability to induce orthodromic reciprocating tachycardia in the baseline state. There were 15 men and 3 women, with a mean age of 40 ± 18 years (± standard deviation). None had any evidence of structural heart disease. Sixteen patients had overt ventricular preexcitation and 2 patients had a concealed accessory AV connection. The accessory AV connection was located in the left free wall in 14 patients, in the right free wall in 2 patients and in the posterior septum in 2 patients.

Electrophysiologic study: Electrophysiologic studies were performed in the fasting, unsedated state after informed consent had been obtained and at least 5 half-lives after all antiarrhythmic medications had been discontinued. The study protocol was approved by the Human Research Committee at the University of Michigan. Multiple quadripolar electrode catheters were positioned within the heart using conventional techniques. Leads V_1, I and III, and the intracardiac electrograms recorded at the right atrium, His bundle position, coronary sinus and right ventricular apex were displayed on an oscilloscope and recorded at a paper speed of 100 mm/s on a Siemens-Elema Mingograf 7 recorder. Pacing was performed with a programmable stimulator (Bloom Associates) using stimuli 2 ms in duration and twice the late diastolic threshold.

Electrophysiologic parameters measured: The AV nodal (AH) and infranodal (HV) conduction times

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were determined at an atrial paced cycle length of 500 and 600 ms. The minimum atrial and ventricular pacing cycle lengths associated with 1:1 AV and ventriculoatrial conduction through the accessory AV connection were determined by incremental pacing in steps of 10 ms. Refractory periods were measured using 8 beat drive trains at a cycle length of 500 ms and a single extrastimulus scanned in steps of 10 ms. Orthodromic reciprocating tachycardia was induced in each patient, and the cycle length and AH, HV and VA intervals during tachycardia were measured. The ventriculoatrial interval was determined using the low right atrial septal electrogram.

The effect of epinephrine on atrial fibrillation was not determined systematically in this study because of time constraints and in order to avoid patient discomfort and the need for direct current countershock. However, atrial fibrillation was induced either purposely or inadvertently before and after the administration of epinephrine in 8 patients, and in these patients the mean cycle length and the shortest cycle length between 2 consecutive preexcited QRS complexes were measured.

Induced tachycardias were considered nonsustained if there was spontaneous termination within 30 seconds and sustained if the duration was > 30 seconds.

Infusion of epinephrine: The infusion rates of epinephrine used in this study were 25 and 50 ng/kg/min. These infusion rates were used because previous studies have demonstrated that these doses result in elevations in the plasma epinephrine concentration comparable to a variety of stresses in humans.[7,8]

After measurement of baseline electrophysiologic parameters, 25 ng/kg/min of epinephrine was infused in 8 patients to determine the effects of epinephrine in the absence of quinidine. Prior studies have found that 10 minutes are required to obtain a steady-state plasma epinephrine concentration,[9,10] therefore, the infusion was continued for 14 minutes to ensure that a steady-state concentration had been reached before remeasurement of the electrophysiologic parameters.

In each of the 18 patients, electrophysiologic parameters were measured in the baseline state and after at least 2 days of treatment with 1.4 to 1.9 g/day of quinidine gluconate (mean daily dose 1.7 ± 0.2 g). Immediately after measurement of quinidine's effects, epinephrine was infused at a rate of 25 or 50 ng/kg/min in 9 patients each. The plasma quinidine concentration immediately after measurement of quinidine's electrophysiologic effects was 3.0 ± 1.2 mg/liter, and 2.9 ± 1.1 mg/liter after measurement of epinephrine's effects. The elapsed time between these 2 determinations of the plasma quinidine concentration was 24 to 30 minutes.

Analysis of data: The effects of epinephrine in the absence of quinidine were analyzed using a paired *t* test. The effects of quinidine and quinidine plus epinephrine on each variable were analyzed using a repeated measures analysis of variance.[11] The effects of the 2 doses of epinephrine were compared also using a repeated measures analysis of variance. Multiple comparisons were performed using Fisher's least significant difference procedure.[11] A mixed model analysis of variance was used to analyze the data for the variables that had missing data.[12] A p value <0.05 was considered significant.

TABLE I Effects of 25 ng/kg/min of Epinephrine in the Absence of Quinidine in 8 Subjects

	Baseline	Epinephrine	p Value
Sinus cycle length (ms)	972 ± 163*	708 ± 91	<0.001
MAP (mm Hg)	99 ± 11	103 ± 10	NS
AH (ms)†	111 ± 25	86 ± 13	<0.01
HV (ms)†	4 ± 32	28 ± 17	<0.05
Atrial ERP (ms)	199 ± 16	184 ± 15	<0.001
Atrial FRP (ms)	245 ± 13	231 ± 14	<0.01
1:1 AV conduction (ms)‡	286 ± 29	273 ± 23	<0.05
AAVC ERP (ms)	290 ± 14	275 ± 21	NS
1:1 VA conduction (ms)†	290 ± 38	262 ± 33	<0.05
Retrograde AAVC ERP (ms)	277 ± 28	273 ± 35	NS
Orthodromic tachycardia			
Cycle length (ms)	359 ± 36	333 ± 30	<0.001
AH (ms)	160 ± 35	139 ± 31	<0.001
HV (ms)	42 ± 5	40 ± 5	NS
VA (ms)	158 ± 34	154 ± 30	NS

* Mean ± standard deviation.
† Measured during atrial pacing at the same cycle length (500 or 600 ms).
‡ Shortest pacing cycle length associated with 1:1 conduction through the accessory AV connection.
AAVC = accessory atrioventricular conduction; AV = atrioventricular; ERP = effective refractory period; FRP = functional refractory period; MAP = mean atrial pressure; NS = not significant; VA = ventriculoatrial.

RESULTS

Effects of epinephrine in the absence of quinidine: A 25 ng/kg/min infusion of epinephrine resulted in a significant decrease in the mean sinus cycle length, AH interval, atrial refractory periods and the shortest pacing cycle length associated with 1:1 AV and ventriculoatrial conduction through the accessory AV connection. The mean HV interval increased because of shortening of the AH interval and a lesser degree of ventricular preexcitation. Measurement of the antegrade effective refractory period of the accessory AV connection before and after epinephrine was often limited by atrial refractoriness and was possible in only 2 patients; in these 2 patients, the effective refractory period shortened by 10 to 20 ms.

The mean orthodromic tachycardia cycle length decreased from 359 ± 36 to 333 ± 30 ms. During orthodromic tachycardia, the AH interval decreased significantly, whereas the HV and AV intervals were unchanged by epinephrine (Table I).

In 3 patients, the mean cycle length and the shortest cycle length between 2 consecutive preexcited QRS complexes during atrial fibrillation decreased from 362 ± 21 and 238 ± 19 ms, respectively, to 320 ± 14 and 216 ± 16 ms during infusion of epinephrine (p <0.05).

Electrophysiologic effects of quinidine and epinephrine: Quinidine resulted in a significant increase in the shortest pacing cycle length associated with 1:1 conduction in the accessory AV connection and a lengthening of refractory periods of the atrium and accessory AV connection.

The mean dose of epinephrine in the 9 patients who received the 25 ng/kg/min infusion of epinephrine was 2.2 ± 0.6 μg/min, and 4.1 ± 0.7 μg/min in the 9 patients who received the 50 ng/kg/min infusion of epinephrine. The electrophysiologic effects of the 2 infu-

TABLE II Effects of Quinidine and Quinidine Plus Epinephrine in 18 Subjects

				p Values		
	B	Q	Q & E	Q vs B	Q & E vs Q	Q & E vs B
Sinus cycle length (ms)	798 ± 179*	790 ± 154	661 ± 93	NS	<0.01	<0.001
MAP (mm Hg)	96 ± 12	94 ± 8	90 ± 11	NS	NS	<0.05
AH (ms)†	104 ± 28	111 ± 22	88 ± 18	NS	<0.001	<0.05
HV (ms)†	7 ± 30	11 ± 26	18 ± 27	NS	NS	<0.05
Atrial ERP (ms)	197 ± 19	230 ± 22	201 ± 23	<0.001	<0.001	NS
Atrial FRP (ms)	241 ± 19	278 ± 29	253 ± 27	<0.001	<0.001	<0.05
1:1 AV conduction (ms)‡	268 ± 29	345 ± 75	298 ± 56	<0.001	<0.001	<0.01
AAVC ERP (ms)	276 ± 18	316 ± 46	280 ± 31	<0.01	<0.01	NS
1:1 VA conduction (ms)‡	279 ± 49	369 ± 82	312 ± 65	<0.001	<0.001	<0.01
Retrograde AAVC ERP (ms)	264 ± 38	363 ± 64	316 ± 56	<0.001	<0.01	<0.01

* Mean ± standard deviation.
† Measured during atrial pacing at the same cycle length (500 or 600 ms).
‡ Shortest pacing cycle length associated with 1:1 conduction through the accessory AV connection.
B = baseline; Q = quinidine; other abbreviations as in Table I.

TABLE III Effects of Epinephrine on the Induction of Orthodromic Tachycardia in 8 Patients in Whom Quinidine Suppressed the Induction of Sustained Tachycardia

		Quinidine		Quinidine and Epinephrine		
Pt	Baseline* CL (ms)	CL (ms)	Duration†	CL (ms)	Duration†	Epi Dose (ng/kg/min)
1	330	—	Noninducible	310	Sustained	25
2	280	—	Noninducible	330	Sustained	50
3	400	—	Noninducible	290	15 beats	50
4	290	—	Noninducible	—	Noninducible	50
5	390	420	5 beats	390	Sustained	25
6	390	490	5 beats	370	Sustained	25
7	240	330	7 beats	260	Sustained	50
8	320	350	20 beats	320	23 beats	25

* The tachycardia was sustained in each patient in the baseline state.
† Maximum duration on multiple induction attempts.
CL = cycle length; Epi = epinephrine.

sion rates of epinephrine were not significantly different and therefore the results are presented in combined fashion (Table II). All of quinidine's electrophysiologic effects were completely or partially reversed by epinephrine.

Effects of quinidine and epinephrine on orthodromic tachycardia: The effects of the 2 doses of epinephrine on orthodromic tachycardia were similar and therefore the results are presented in combined fashion. Quinidine lengthened the mean orthodromic tachycardiac cycle length from 337 ± 51 to 389 ± 48 ms ($p < 0.001$). Epinephrine resulted in a shortening of the mean tachycardia cycle length to 340 ± 43 ($p > 0.05$ ms vs baseline), indicating complete reversal of quinidine's effects on tachycardia cycle length. The changes in mean tachycardia cycle length that occurred with quinidine and epinephrine were associated with concomitant significant changes in the mean AH interval during tachycardia, but not in the HV or ventriculoatrial intervals.

Sustained orthodromic tachycardia no longer was inducible in 8 patients after treatment with quinidine. However, when epinephrine was infused, sustained orthodromic tachycardia again became inducible in 5 of these patients (Table III).

Effects of quinidine and epinephrine on atrial fibrillation: The effects of epinephrine were determined in patients who had either noninducible (4) or nonsustained (4) atrial fibrillation after treatment with quinidine. The mean cycle length and the shortest cycle length between 2 consecutive preexcited QRS complexes during atrial fibrillation were 365 ± 28 and 242 ± 19 ms, respectively, after quinidine. These values shortened to 343 ± 13 and 228 ± 16 ms, respectively, after the addition of epinephrine ($p < 0.05$ for each). Among the 4 patients with noninducible atrial fibrillation, atrial fibrillation became sustained or nonsustained in 1 patient each after the infusion of epinephrine. Among the 4 patients with nonsustained atrial fibrillation, the atrial fibrillation became sustained in 3 after the infusion of epinephrine.

DISCUSSION

The results of this study demonstrate that elevation of the plasma epinephrine concentration to levels within the range that occurs during a variety of stresses in humans may reverse the electrophysiologic effects of quinidine in patients with symptomatic tachycardias involving an accessory AV connection. Although plasma epinephrine concentrations were not measured in the present study, prior studies have determined the plasma epinephrine concentrations that result from infusion of the same doses of epinephrine under similar conditions

used in this study.[7,8] The 25 ng/kg/min infusion of epinephrine increases the plasma epinephrine concentration to levels within the range that occurs during cigarette smoking,[13] public speaking,[14] submaximal exercise,[7] mild hypoglycemia,[13] dental extraction,[15] and surgery.[16] A 50 ng/kg/min infusion of epinephrine increases the plasma epinephrine concentration to levels within the range that occurs during maximal exercise,[7] acute myocardial infarction,[17,18] diabetic ketoacidosis[13] and severe hypoglycemia.[13] Therefore quinidine's therapeutic effects in patients who have an accessory AV connection may be markedly attenuated by physiologic and pathophysiologic increases in circulating epinephrine.

Electrophysiologic effects of epinephrine: Both in the absence and presence of quinidine, epinephrine significantly shortened the refractory periods of the accessory AV connection and atrium and accelerated conduction through the accessory AV connection. Because the majority of patients in this study had overt ventricular preexcitation, the electrophysiologic effects of epinephrine on the AV node-His-Purkinje axis could not be studied in a systematic fashion. However, a prior study demonstrated that epinephrine also shortens refractoriness and accelerates conduction in the AV node.[8]

There were no significant differences in the effects of the 2 infusion rates of epinephrine used in this study. This may indicate that the relation between the epinephrine dose and its electrophysiologic effects may not be monotonic. However, it also is possible that a significant difference in the effects of the 2 infusion rates would have been demonstrated had the sample sizes been larger.

During the period of time that the effects of epinephrine were determined, the mean quinidine plasma concentration fell only slightly from 3.0 ± 1.2 to 2.9 ± 1.1 mg/liter. Therefore, it is unlikely that the reversal of quinidine's effects during infusion of epinephrine was related to a time-dependent decrease in quinidine's tissue effects.

Effects of epinephrine on orthodromic tachycardia and atrial fibrillation: As would be expected given epinephrine's effects on conduction through the accessory AV connection and the normal conduction pathway, the effect of epinephrine on orthodromic tachycardia was to accelerate its rate and to reverse completely the lengthening of the tachycardia cycle length that occurred with quinidine.

Of note is that quinidine resulted in orthodromic tachycardia becoming either noninducible or nonsustained in 8 of 18 patients in this study. However, with the addition of epinephrine, sustained tachycardia became inducible again in 5 of these 8 patients. In addition, in the subset of patients in whom the effects of the epinephrine on atrial fibrillation were determined, epinephrine accelerated the ventricular rate and often facilitated the induction of sustained atrial fibrillation. These results indicate that although quinidine may be effective in suppressing orthodromic tachycardia or atrial fibrillation in the electrophysiology laboratory, its efficacy may be lost when patients are exposed to a heightened degree of sympathetic activation.

Prior studies with isoproterenol: No prior studies have examined the interaction between epinephrine and antiarrhythmic drugs in patients with an accessory AV connection. However, there have been prior studies of the effects of isoproterenol in patients with the Wolff-Parkinson-White syndrome treated with various antiarrhythmic drugs. Similar to the interaction between epinephrine and quinidine in the present study, isoproterenol often reversed the therapeutic effects of amiodarone, flecainide and encainide.[2–6]

Mechanism of epinephrine's effects: Loss of antiarrhythmic drug efficacy in response to isoproterenol in prior studies suggests that the reversal of quinidine's electrophysiologic effects by epinephrine in the present study was related to the β-adrenergic stimulation properties of epinephrine. However, it was beyond the scope of the present study to determine whether epinephrine's effects in the presence of quinidine were mediated solely by β-receptor stimulation, by a specific interaction at sites of quinidine binding or by some other mechanism.

Limitations: This study has 2 principal limitations. First, the effects of quinidine and epinephrine on atrial fibrillation were determined in only 6 of the 16 patients in this study who had overt ventricular preexcitation. In the other 10 patients the effects of epinephrine on atrial fibrillation were not determined in order to avoid lengthy studies, hemodynamically unstable atrial fibrillation or the need for general anesthesia and direct current countershock to terminate atrial fibrillation.

A second limitation of the study is that no meaningful follow-up data are available to determine whether the response to epinephrine in the electrophysiology laboratory may have correlated with clinical recurrences of tachycardia during periods of sympathetic activation. This was because most patients elected to undergo either surgical or catheter ablation of their accessory AV connection.

Acknowledgment: The authors are grateful to Beverly Burgie, Joan Bergeron, Linda Abbott and Donna Felbaum for technical assistance and to Lisa Hackbarth for her excellent secretarial assistance.

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