Inducibility of Paroxysmal Atrial Fibrillation by Isoproterenol and its Relation to the Mode of Onset of Atrial Fibrillation

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Inducibility of Paroxysmal Atrial Fibrillation. ***Background:*** **Isoproterenol has been used to assess inducibility during catheter ablation for paroxysmal PAF. However, no studies have determined the sensitivity and specificity of isoproterenol for the induction of AF. It also is not clear whether isoproterenol is equally effective in inducing AF in the clinical subtypes of vagotonic, adrenergic, and random AF.**

Objective: **To determine the sensitivity and specificity of isoproterenol for the induction of atrial fibrillation (AF).**

Methods: **Isoproterenol was infused at 5, 10, 15, and 20 μg/min at 2-minute intervals or until AF was induced in 20 control subjects with no history of AF and in 80 patients with PAF.**

Results: **Among the 20 control subjects, AF was induced by isoproterenol in one patient (5%). Among the 80 patients with PAF, persistent AF was induced in 67 patients (84%, $P < 0.001$). Isoproterenol induced AF in 15 of 17 patients (88%) with vagotonic AF, 11 of 11 patients (100%) with adrenergic AF, and 41 of 52 patients (79%) with random episodes of AF ($P = 0.2$). The yield of AF was 11% (9/80) after 5 μg/min, 28% (22/80) after 10 μg/min, 51% (40/78) after 15 μg/min, and 88% (67/76) after 20 μg/min of isoproterenol ($P < 0.01$). Isoproterenol had to be discontinued in four patients (5%) before reaching the maximum dose due to reversible chest pain or systolic blood pressure <85 mmHg.**

Conclusions: **Isoproterenol at infusion rates up to 20 μg/min has a high sensitivity (88%) and specificity (95%) for induction of AF in patients with PAF, regardless of whether the clinical subtype is vagotonic, adrenergic, or random.** *(J Cardiovasc Electrophysiol, Vol. 19, pp. 466-470, May 2008.)*

atrial fibrillation, isoproterenol, inducibility, arrhythmia, ablation

Introduction

Several studies have used isoproterenol to assess for residual atrial fibrillation (AF) triggers after pulmonary vein isolation in patients with paroxysmal AF.[1-6] However, there has been no systematic evaluation of the sensitivity and specificity of isoproterenol for the induction of AF prior to radiofrequency ablation. It is recognized that paroxysmal AF may be vagotonic in some patients and adrenergic or random in others,[7-11] but no prior studies have compared the inducibility of AF by isoproterenol in these clinical subtypes. The purpose of this study was to determine the sensitivity and specificity of isoproterenol for the induction of AF and to compare AF inducibility by isoproterenol between patients with the vagotonic, adrenergic, and random varieties of paroxysmal AF.

Methods

Study Subjects

The subjects of this study were 80 patients who underwent radiofrequency catheter ablation of paroxysmal AF. There were 59 men and 21 women, and their mean age was 58 $\pm$ 11 years. The mean left atrial size and left ventricular ejection fraction were 40 $\pm$ 5 mm (range: 29–51 mm) and 0.59 $\pm$ 0.07 (range: 0.45–0.80), respectively. AF had been first diagnosed 7 $\pm$ 6 years prior to presentation. Among the 80 subjects, hypertensive heart disease was present in 20 (25%), coronary artery disease in 5 (6%), a nonischemic cardiomyopathy in 1, and a repaired atrial septal defect in 1. Patients with coronary artery disease were excluded unless there was documentation of a negative stress test. Patients with hypertrophic obstructive cardiomyopathy or aortic or mitral valve stenosis were excluded from the study, as were patients who had been treated with amiodarone within the prior 3 months.

The clinical subtype of paroxysmal AF was classified based on a detailed clinical history as described previously.[10] Episodes of AF that exclusively occurred nocturnally or postprandially were considered vagotonic, whereas episodes of

Dr. Oral has received research grants from St. Jude Medical and Boston Scientific. Drs. Oral and Morady are founders and equity owners of Ablation Frontiers, Inc.

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Manuscript received 17 October 2007; Revised manuscript received 12 November 2007; Accepted for publication 15 November 2007.

doi: 10.1111/j.1540-8167.2007.01089.x

AF that exclusively were triggered by exercise or adrenergic stimulation were considered adrenergic. The remaining patients were considered to have random paroxysmal AF.[7-9,11]

A group of 20 otherwise healthy subjects with no history of AF who underwent radiofrequency catheter ablation of paroxysmal supraventricular tachycardia constituted a control group. The mean age of the control subjects was 46 ± 17 years ($P < 0.001$, Mann-Whitney *U* test, compared with patients with AF). There were 16 men and 4 women. The mean left ventricular ejection fraction was 0.56 ± 0.06. Among these 20 patients, 14 had atrioventricular nodal reentrant tachycardia, 4 had an accessory pathway, 1 had atrial tachycardia, and 1 had no inducible supraventricular tachycardia.

Electrophysiologic Study

All patients provided informed written consent prior to the study. Electrophysiologic studies were performed in the postabsorptive state. Antiarrhythmic drug therapy was discontinued at least 4–5 half-lives before the study. Conscious sedation was achieved with fentanyl and midazolam. Vascular access was obtained through a femoral vein. In patients undergoing an electrophysiologic study for treatment of supraventricular tachycardia, quadripolar catheters were positioned in the high right atrium, His bundle position and the right ventricular apex. In patients with AF, catheter placement was as previously described.[1]

Study Protocol

The study protocol was approved by the Institutional Review Board. Only patients who presented in sinus rhythm were included in the study. Isoproterenol was infused through a femoral vein at rates of 5, 10, 15, and 20 μg/min for 2 minutes at each infusion rate. The isoproterenol infusion was discontinued upon induction of AF, a decrease in systolic blood pressure to <85 mmHg, complaints of severe chest tightness, electrocardiographic changes suggestive of ischemia, or upon completion of the infusion protocol. Episodes of AF that occurred during the first 10 minutes of isoproterenol washout were considered to have been induced by isoproterenol.

In the control group, isoproterenol was infused upon completion of the clinically indicated portion of the electrophysiology procedure. AF and frequent atrial ectopy (bigeminy or trigeminy) were considered to be a positive response to isoproterenol.

Statistical Analysis

Continuous variables are expressed as mean ± 1 standard deviation and were compared by Student's *t*-test. Normality of distribution was tested using Shapiro-Wilk's test. Nonparametric Mann-Whitney *U* test or Wilcoxon-matched pairs test was used as appropriate when the distribution was not normal. Categorical variables were compared by chi-square analysis or with Fisher's exact test where appropriate. A P value of <0.05 indicated statistical significance.

Results

Effects of Isoproterenol in Control Subjects

Among the 20 control subjects, the mean baseline sinus cycle length was 743 ± 134 ms and progressively decreased to a mean of 399 ± 50 ms with infusion of isoproterenol up to 20 μg/min ($P < 0.0001$). AF was induced in one patient (5%) and frequent premature atrial depolarizations were induced in another patient (5%), in both cases during an infusion rate of 20 μg/min (Fig. 1). AF persisted for >5 minutes and transthoracic cardioversion was performed to restore sinus rhythm.

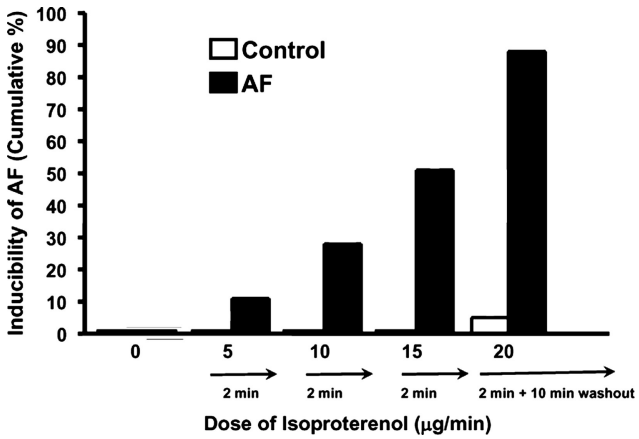

Figure 1. *Effect of isoproterenol dose on inducibility of AF. The cumulative dose of isoproterenol that resulted in initiation of sustained AF in control subjects or patients with PAF is shown. Because the isoproterenol infusion was discontinued prematurely in four patients, only 78 and 76 of the 80 patients received isoproterenol at 15 μg/min and 20 μg/min, respectively.*

Effects of Isoproterenol in Patients with Paroxysmal AF

Among the 80 patients with paroxysmal AF, the baseline sinus cycle length progressively decreased from 892 ± 207 ms to 407 ± 121 ms after infusion of isoproterenol at 20 μg/min ($P < 0.0001$, Wilcoxon pairs test). There was not a significant difference in the mean cycle length after infusion of isoproterenol between the control subjects and the patients with paroxysmal AF.

Among the 80 patients with paroxysmal AF, isoproterenol induced persistent AF in 67 (84%) and frequent premature atrial depolarizations or short bursts of AF in two (2%) patients ($P < 0.0001$, compared with control subjects, Fig. 1). Persistent AF was induced by rapid atrial pacing in 8 of the 11 patients who did not have AF induced by isoproterenol.

The mean age of the patients with AF who did and did not have inducible AF in response to isoproterenol was similar (58 ± 10 years vs 56 ± 11 years, $P = 0.54$). AF was inducible in a similar proportion of patients with AF who were younger and older than 50 years ($P = 1.0$).

Among the 69 patients in whom isoproterenol induced AF or frequent premature atrial depolarizations, AF persisted beyond 30 minutes after discontinuation of isoproterenol in 67 (97%).

Dose-Response Relationship

Among the 80 patients with paroxysmal AF, the mean maximum infusion rate of isoproterenol in the patients with and without AF inducible by isoproterenol was 15 ± 5 μg/min and 17 ± 4 μg/min, respectively ($P = 0.14$).

Among the patients with paroxysmal AF, the cumulative rates of inducibility were 11% (9 of 80) after 5 μg/min, 28% (22 of 80) after 10 μg/min, 51% (40 of 78) after

TABLE 1
Diagnostic Accuracy of Isoproterenol for Induction of AF

Isoproterenol Dose (μg/min)	Sensitivity	Specificity	PPV	NPV
5	11	100	100	22
10	28	100	100	26
15	51	100	100	66
20	88	95	99	73

Data shown are in %. PPV = positive predictive value; NPV = negative predictive value.

15 μg/min, and 88% (67 of 76) after 20 μg/min ($P < 0.01$, Fig. 1, Table 1).

Clinical Subtypes of Paroxysmal AF

Among the 80 subjects, 17 (21%) had vagotonic AF, 11 (14%) had adrenergic AF, and the remaining 52 (65%) had random AF. AF was induced by isoproterenol in 15 of the 17 patients (88%) with vagotonic AF, in each of the 11 patients with adrenergic AF (100%), and in 41 of the 52 patients with random AF (79%, $P = 0.2$, Table 2). The mean dose of isoproterenol required to induce AF was similar between the patients with vagotonic (15 ± 6 μg/min), adrenergic (16 ± 5 μg/min) and random (15 ± 5 μg/min, $P = 0.7$) AF.

Diagnostic Accuracy

The sensitivity and specificity of isoproterenol for the induction of AF were 88% and 95%, respectively. The positive and negative predictive values were 99% and 73%, respectively (Table 1). The overall diagnostic accuracy was 90%.

Adverse Effects

The isoproterenol infusion was discontinued prematurely in 4 of the 80 patients (5%) because of chest discomfort in two and a systolic blood pressure <85 mmHg in two patients during infusion at rates of 10–15 μg/min. The symptoms and hypotension quickly resolved after discontinuation of isoproterenol. There were no electrocardiogram changes suggestive of ischemia in any of the patients.

Discussion

Main Findings

This study demonstrates that isoproterenol has a high sensitivity and specificity for the induction of AF in patients with paroxysmal AF. Induction of AF by isoproterenol is dose-dependent and requires infusion rates of 20 μg/min in ~50% of the patients. Isoproterenol generally was well tolerated and the infusion was discontinued prematurely in only 5% of patients.

Despite differences in autonomic tone during spontaneous initiation of AF in the three clinical subtypes of paroxysmal AF, isoproterenol induced AF in a similar proportion of patients with vagotonic, adrenergic, and random episodes of AF.

TABLE 2
Diagnostic Accuracy of Isoproterenol at 20 μg/min for Induction of AF in Patients with Vagotonic, Adrenergic, or Random AF

Clinical Subtype of AF	Sensitivity	Specificity	PPV	NPV
Vagotonic AF	88	95	94	90
Adrenergic AF	100	95	92	100
Random AF	79	95	100	63

Data shown are in %. PPV = positive predictive value; NPV = negative predictive value.

Isoproterenol, Inducibility, and Mode of Onset of AF

The mechanism by which isoproterenol induces sustained AF may be multifactorial. Isoproterenol decreases the sinus cycle length, shortens the refractory period in the PVs and atrium, facilitates calcium release from the sarcoplasmic reticulum, and promotes early after-depolarizations.[6,12,13] An experimental study demonstrated that isoproterenol results in a rise of intracellular calcium concentrations prior to the initiation of focal PV discharges, leading to phase singularities at the PV-left atrium junction due to anisotropic reentry.[14] Isoproterenol may facilitate automaticity and triggered activity.[15] A clinical observation has been the suppression of premature depolarizations and bursts of AF with propranolol and verapamil in patients with paroxysmal AF, suggesting that both automaticity and triggered activity may play a role in mediating proarrhythmic effects of isoproterenol.[2,16] In another study, dissociated rhythms in PVs after isolation had a similar response to isoproterenol as the sinus node, suggesting automaticity as a potential mechanism.[17]

In patients with adrenergic AF, adrenergic stimulation by isoproterenol would be expected to induce AF. However, it is not intuitively obvious that isoproterenol would induce AF in a large proportion of patients with vagotonic AF. A possible mechanism by which isoproterenol may facilitate the initiation of AF in patients with vagotonic AF may be accentuated antagonism.[18–22] Stimulation of ganglionated plexi and an increase in parasympathetic tone have been demonstrated to facilitate the initiation and perpetuation of AF by shortening the effective refractory period and promoting triggered activity and spontaneous depolarizations.[23–25] It is possible that the increase in parasympathetic tone that occurs during infusion of isoproterenol promotes AF in these patients.

Initiation of AF may primarily depend on the instantaneous balance between sympathetic and parasympathetic tone. During spontaneous episodes of vagotonic AF, the effects of an increase in parasympathetic tone may be clinically more apparent. On the other hand, infusion of high-dose isoproterenol may lead to a marked increase in parasympathetic effects through accentuated antagonism. However, these increased parasympathetic effects may not be clinically manifest due to prevailing adrenergic stimulation. It also is possible that the parameters often used to assess vagal tone, such as changes in sinus cycle length, may not have sufficient accuracy to detect instantaneous changes in parasympathetic tone.

In a prior experimental study, pretreatment with atropine abolished the inducibility of AF by isoproterenol in open-chest dogs.[26] Pretreatment with a beta-blocker did not have a similar effect, but led to an increase in the concentration of acetylcholine necessary to induce AF. On the other hand, coadministration of isoproterenol decreased the acetylcholine concentration needed to induce

AF. These observations suggest that parasympathetic activation is necessary for induction of AF and that isoproterenol may have a synergistic or facilitatory role. Isoproterenol may facilitate triggered activity due to an increase in intracellular calcium concentration, whereas shortening of the action potential duration and effective refractory period by parasympathetic activation may further promote spontaneous depolarizations and the perpetuation of AF. Adrenergic neurons also appear to be prevalent in the ganglionated plexi often located in the venoatrial junction.[24]

Another finding of this study is that AF induced by isoproterenol usually persisted beyond the point of complete isoproterenol washout. This indicates that once AF was triggered, self-perpetuating mechanisms, such as intermittent pulmonary vein tachycardias,[27] were activated.

Limitations

A limitation of this study is that the effects of isoproterenol were examined in patients who underwent an electrophysiologic study under conscious sedation. It is not clear whether isoproterenol would have similar effects if administered to patients under general anesthesia.

It may be argued that the depth of sedation may not have been the same between the control and AF groups. However, sedation was kept to a minimum in both groups, and the changes in sinus cycle length in response to isoproterenol were similar in both groups.

The findings are applicable only to patients with paroxysmal AF. It remains to be determined if isoproterenol would also exert similar effects in patients with chronic AF.

Another limitation may be that patients in the control group with no history of AF were younger than patients with AF. However, the mean age of the patients with AF who did and did not have inducible AF in response to isoproterenol was similar; and AF was inducible in a similar proportion of patients with AF who were younger and older than 50 years. Therefore, it is unlikely that age had a significant effect on inducibility of AF.

Clinical subtypes of AF were determined based on patient's history. However, continuous electrocardiographic monitoring for extended period of time to capture the initiation of AF would not have been feasible.

Finally, because the effects of isoproterenol may be time-dependent, it is possible that AF may have been induced at lower infusion rates if more time was allowed before increasing the infusion rate.

Clinical Implications

Isoproterenol has been used in prior studies to assess the inducibility of AF after ablation at widely divergent infusion rates of 2–20 μg/min.[1-4] The findings of this study demonstrate that an isoproterenol infusion of 20 μg/min is necessary to induce AF in >50% of the patients. This high infusion rate rarely induces AF in patients without a history of AF and generally is tolerated.

Because isoproterenol may not induce AF in ~15% of patients with paroxysmal AF even at an infusion rate of 20 μg/min, it is important to assess the inducibility of AF before ablation if noninducibility of AF is to be used as an endpoint of the ablation strategy.

Infusion of high-dose isoproterenol to assess inducibility of AF may also be considered in patients who undergo an electrophysiologic study to determine the mechanisms of their palpitations and/or syncope after having undergone a negative noninvasive workup.

Finally, the prognostic significance of reassessment of inducibility of AF using isoproterenol with and without rapid atrial pacing after ablation for AF remains to be determined in future studies.

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