

Arrhythmia induction using isoproterenol or epinephrine during electrophysiology study for
supraventricular tachycardia

Parin J. Patel^a, MD; Rachel Segar^a; Jyoti Kandlikar Patel^b, MD; Benzy J. Padanilam^a, MD, FHRS; Eric N.
Prystowsky^a, MD, FHRS

From the ^aSt. Vincent Medical Group, Department of Cardiology; and ^bIndiana University School of
Medicine, Department of Pediatrics, Section of Cardiology

Correspondence to: Parin J. Patel, parin.patel@post.harvard.edu, 8333 Naab Rd, Suite 400, Indianapolis,
IN 46260.

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Abstract

Background: Electrophysiology study (EPS) is an important part of the diagnosis and workup for supraventricular tachycardia (SVT). Provocative medications are used to induce arrhythmias when they are not inducible at baseline. The most common medication is the beta-1 specific agonist isoproterenol, but recent price increases have resulted in a shift toward the nonspecific agonist epinephrine.

Objectives: We hypothesize that isoproterenol is a better induction agent for SVT during EPS than epinephrine.

Methods: We created a retrospective cohort of 131 patients who underwent EPS and required medication infusion with either isoproterenol or epinephrine for SVT induction. The primary outcome was arrhythmia induction.

Results: Successful induction was achieved in 71% of isoproterenol cases and 53% of epinephrine cases ($p = 0.020$). Isoproterenol was significantly better than epinephrine for SVT induction during EPS (odds ratio 2.35 [95% CI 1.14-4.85, $p = 0.021$]). There was no difference in baseline variables or complications between the two groups. Other variables associated with successful arrhythmia induction included longer procedure duration and AVNRT as the clinical arrhythmia. In a multivariable model, isoproterenol remained significantly associated with successful induction (OR 2.57, 1.002-6.59, $p = 0.05$).

Conclusions: Isoproterenol was significantly better than epinephrine for SVT arrhythmia induction. However, epinephrine was safe and successfully induced arrhythmias in the majority of patients who received it. Furthermore, when atropine was added in epinephrine-refractory cases, in a post hoc analysis there was no difference in arrhythmia induction between medications. Cost savings could be significant without compromising safety.

Keywords:

Supraventricular tachycardia

Isoproterenol

Epinephrine

Atrioventricular nodal reentry tachycardia

Abbreviations

Electrophysiology study (EPS)

Supraventricular tachycardia (SVT)

Atrioventricular nodal reentry tachycardia (AVNRT)

Introduction

Electrophysiologic characteristics of the heart may change under various physiologic states. Sympathetic and parasympathetic influences alter heart rate and blood pressure in response to exercise, for example (1-8). The basic electrophysiology study (EPS) includes careful measurement of both baseline conduction intervals as well as intervals under stressful conditions. Because of its nearly pure beta adrenergic stimulation, isoproterenol is the sympathomimetic drug of choice for infusion during EPS. To date, the largest series of cases involving tilt table testing, electrophysiology study and supraventricular tachycardia (SVT) ablation, and premature ventricular contraction ablation all used isoproterenol as the primary provocative drug (9-16). Even under conditions of deep sedation or general anesthesia, isoproterenol is effective for arrhythmia induction (17). However, as noted in prior publications (18), a dramatic price increase in March 2015 (19) resulted in the wholesale acquisition cost of isoproterenol increasing from \$26.20 per milligram to \$1,790.11 per milligram. The nonspecific alpha and beta adrenergic stimulant epinephrine (priced at \$14.96 per milligram) is one alternative to isoproterenol. There is evidence that epinephrine induces sympathomimetic changes in heart rate and blood pressure (7,20), but the effect on SVT arrhythmia induction during EPS remains unclear. Replacing isoproterenol with less costly epinephrine seems a reasonable, but previously untested, option. The effect of this replacement on outcomes has not previously been reported. We evaluated the safety and efficacy of using epinephrine compared to isoproterenol for SVT arrhythmia induction during EPS.

Methods

We conducted a retrospective cohort study of all patients with evidence of clinical SVT who presented to St. Vincent Hospital (Indianapolis, IN) for EPS and were tested with either isoproterenol or epinephrine, in an approximately 1 year period after the isoproterenol price change (6/1/2015-8/31/2016). SVT was defined as atrial tachycardia (AT), atrioventricular nodal reentry tachycardia (AVNRT), or bypass tract

mediated tachycardia (AVRT). We included those patients in whom drug infusion was required to assess baseline arrhythmia inducibility; patients in whom drug infusion was used only to test efficacy after ablation were excluded (21). Choice and dosing of drug infusion was at the discretion of the provider. Typically, antiarrhythmic drugs (Class I [flecainide, propafenone, disopyramide, mexilitine] or Class III [sotalol, dofetilide]) were discontinued five half-lives prior to EPS, and beta blockers and non-dihydropyridine calcium channel blockers discontinued 24 hours prior to EPS.

Cohort design

We used a stepwise approach to cohort selection and database creation. First, we queried procedure billing codes for Current Procedural Terminology codes 93653 (Electrophysiology study and supraventricular tachycardia ablation) and 93620 (Electrophysiology study with attempted arrhythmia induction), and selected those cases with add on code 93623 (Intravenous drug infusion for diagnostic programmed stimulation and pacing). Then we selected cases where there was a billing charge for either isoproterenol or epinephrine. This comprised the cohort of patients eligible for the study (n = 208). Exclusions were made for those with incorrect billing codes for either the drug (n = 50) or procedure (n = 27) after manual chart review (Figure 1). Incorrect drug comprised cases where EPS and ablation was performed, and then medicines were infused to assess arrhythmia inducibility post ablation only (and not pre ablation). Incorrect procedure comprised cases where atrial fibrillation or atrial flutter ablation were performed.

Manual chart review was then performed to ascertain baseline clinical variables including age, gender, medications, and comorbidities. All patients were required to undergo a history and physical examination by a cardiologist within the one month prior to their procedure; baseline demographics and clinical variables were abstracted from that visit. Additional clinical data including EPS results and clinical follow up were ascertained from the electronic medical record. After database creation, a random

number generator was used to choose 10% of the population for repeated manual chart review by a second abstractor, which resulted in no changes to the original database. Institutional Review Board approval was obtained prior to the start of data collection.

Electrophysiology Study

EP study and ablation was performed according to standard clinical practice. Conscious sedation was achieved using intravenous fentanyl and midazolam as needed. Femoral venous access was achieved using modified Seldinger technique. Three quadripolar pacing catheters and one decapolar pacing catheter (6F, Inquiry, Abbott, Abbott Park, Illinois) were inserted and fluoroscopically advanced to the high right atrium, His position, right ventricular apex, and coronary sinus respectively (the decapolar catheter was optional, per operator preference). All EP studies included assessment of baseline clinical parameters including spontaneous sinus cycle length, assessment of AH and HV intervals, and anterograde atrio-ventricular conduction and retrograde ventriculo-atrial conduction using both incremental pacing as well as extrastimulus pacing. SVT induction was attempted at baseline, and if no arrhythmias were inducible, either isoproterenol or epinephrine infusion was begun. Infusion was titrated at the discretion of the operator, targeting a 10% increase in baseline cycle length or maximum tolerated dose, and EPS was performed again.

Outcome parameters

The primary outcome was arrhythmia inducibility during EPS. Clear documentation of a sustained, clinical SVT by the primary operator was required to bin it as a positive study. Safety outcomes included procedural complications (vascular injury, cardiac tamponade requiring intervention, severe regurgitant valvular disease following ablation, hypotension, heart attack, stroke, or death).

Statistical methods

Categorical variables are represented by frequency, and continuous variables by mean and standard deviation if normally distributed, and by median and interquartile range if not normal. The primary outcome was arrhythmia inducibility, which was self-reported by the primary operator of the EPS. Logistic regression was used to correlate outcome to baseline variables. Continuous variables were compared using the Mann-Whitney U test, and Pearson chi-square test was used for categorical variables. Variables that had two-tailed P value <0.05 in bivariate analysis were considered in the multivariable regression model. Two-tailed P values of <0.05 were considered statistically significant. Analyses were conducted using SPSS v 24 (IBM, Armonk, NY).

Results

The cohort included 131 patients, with mean age 40.1 +/- 21.9 years and median follow up 0.97 yr (0.2, 1.3) (Table 1). There were more female than male patients, and beta blockers were the most common preoperative medications. Isoproterenol was given in 72 patients, epinephrine in 56 patients, and 3 patients received both epinephrine and isoproterenol (all three were given epinephrine, failed arrhythmia induction, and were then given isoproterenol; counted as epinephrine group for baseline variables). The frequency of isoproterenol and epinephrine use is charted over time in Figure 2. There is a clear reduction in isoproterenol use during EPS after January 2016. Of note, ECG or event monitor documentation of SVT was confirmed in 100/131 (76%) patients prior to EPS, and 31 (24%) patients were brought to the EP lab based on clinical suspicion for SVT only.

The median maximum dose of isoproterenol was 2 mcg/min (1, 4); median maximum dose of epinephrine was 0.3 mcg/kg/min (0.2, 0.4). The median maximum dose of epinephrine was inversely associated with successful arrhythmia induction ($p = 0.029$), with median dose 0.2 mcg/kg/min in those who had successful induction, and 0.5 mcg/kg/min in those who were not successfully induced. There was no such association in the isoproterenol group.

Induced arrhythmias

Arrhythmias were inducible in 84/131 of patients (64%), but 22/75 (29%) of those given isoproterenol and 28/59 (47%) of those given epinephrine were found to be noninducible at EPS (3 patients were given both isoproterenol and epinephrine). By Pearson chi-square analysis, this was statistically significant ($p = 0.020$), and the odds ratio for successful induction by isoproterenol compared to epinephrine was 2.35 (95% CI 1.14-4.85, $p = 0.021$). Nonclinical arrhythmias were noted in 1/75 patients given isoproterenol and 1/59 given epinephrine ($p = 0.90$).

AVNRT comprised the most common arrhythmia that was ablated ($n=87$ [66%]), followed by AVRT ($n=13$ [10%]), and then Atrial tachycardia ($n=9$ [7%]). Operator self-reported acute ablation success rate was 95% (98/103 ablations performed). Even in some cases where SVT could not be induced, clinical suspicion and the presence of a slow pathway lead to empiric slow pathway modification (16/47=34%), as previously reported (22,23).

There were no significant baseline clinical differences between those who received isoproterenol and those who received epinephrine during EPS. There were no significant differences in major complications between the two groups (one patient in the isoproterenol group had pericardial tamponade requiring pericardiocentesis; one patient in the epinephrine group had severe abdominal pain and hypotension during the case, and the procedure was terminated early). This was not significant (1/72 v 1/59, $p = 0.90$). No patients died in the follow up period.

Covariates that were significantly associated with successful arrhythmia induction on bivariate analysis included type of arrhythmia, with AVNRT being much more likely to be induced than the other arrhythmias ($p = 0.000$, Table 2). Additionally, longer procedure time was associated with successful induction (OR 1.009, 1.003-1.015, $p = 0.002$).

Induction agent, type of arrhythmia, and procedure duration were included in a multivariate logistic regression model. Only isoproterenol use remained significantly associated with successful arrhythmia induction (OR 2.57, 1.002-6.59, $p = 0.05$).

Discussion

The dramatic increase in price of isoproterenol after March 2015 has resulted in cost-effectiveness evaluations for its routine use during EPS. In our electrophysiology laboratory, for example, there has been a rapid decline in isoproterenol use during EPS, replacing it with the nonspecific alpha and beta adrenergic stimulant epinephrine. This study demonstrates that isoproterenol is more effective than epinephrine in inducing SVT during EPS. However, epinephrine was effective for arrhythmia induction in the majority of patients (53%, 31/59) and there was no difference in safety outcomes.

Furthermore, it should be noted that in 2 out of 3 patients who received both drugs, isoproterenol was also unable to induce an arrhythmia. And in 4/28 patients who had no inducible arrhythmias with epinephrine, 1.0 milligram of atropine administration resulted in successful arrhythmia induction (all were AVNRT). Because this was not the standard practice across all cases, the strategy of “epinephrine +/- atropine” was not formally assessed in this study. Older studies have included small series of patients requiring atropine for arrhythmia induction, but to our knowledge no formal comparison to isoproterenol has been published (14,24). Nevertheless, routine use of atropine in addition to epinephrine may diminish the apparent advantage of isoproterenol use. An exploratory analysis reclassifying those 4 failures as successes would render the induction rates insignificantly different (59% v 71%, $p = 0.12$).

Also, complication rates were not significantly different between the isoproterenol and epinephrine groups. However, this cohort was relatively young (mean age 40 years old) and healthy (only 8% had preexisting coronary artery disease); see Table 1. In this study, neither drug was stopped because of new

myocardial ischemia during infusion, but they should both be used with caution when myocardial ischemia may be present.

Interestingly, we found a correlation between length of procedure and likelihood of successful arrhythmia induction. This may have been because of more time spent in performing maneuvers or titrating medications, though there was an inverse correlation between maximum dose of epinephrine and successful induction. It appears that if epinephrine is going to work, it will work at lower doses (0.2 mcg/kg/min) and titrating to higher doses may not give incremental benefit. There was no such relationship between isoproterenol dose and induction success.

Cost Savings

The current cost savings associated with epinephrine use in place of isoproterenol are significant, approaching \$1,620 per procedure. Prior to isoproterenol price changes, this difference was only \$140 per procedure, at our institution. This study highlights the broader implications of pharmaceutical price control and how this affects patient care. In the absence of clear data about effectiveness, trends in our EP laboratory reflect a switch from isoproterenol to epinephrine because of manufacturer related changes in isoproterenol price. It does appear that there has been a reduction in successful arrhythmia induction as a result of this switch. However, a strategy of adding atropine in refractory cases, or switching to isoproterenol only after epinephrine failure, may be reasonable options.

Limitations

We created a retrospective cohort using billing codes. Incorrect billing could decrease the yield of the study population. We limited our study time to one year, to better assess the change in isoproterenol usage patterns, but a true effect was not seen until 8 months after the new pricing announcement. Also, this cohort excludes all those who underwent successful EPS and ablation without the need for

medication testing. Therefore, the overall noninducibility rate may be lower when taken in the context of all EPS/ablation procedures performed. Finally, there was ECG or event monitor documentation of SVT in only 100 (76%) of patients. The remainder of patients were referred for EPS based on clinical suspicion only. This may have influenced arrhythmia induction rates.

Conclusion

Isoproterenol was more likely than epinephrine to induce SVT during EPS in those patients who were not inducible without medications. This difference persisted in a limited multivariable model of associated covariates. However, if atropine is added to epinephrine, any advantage to isoproterenol may be diminished, and further study is warranted. And potential cost savings of epinephrine are significant. A strategy of using epinephrine and adding atropine or changing to isoproterenol when necessary may result in potential cost savings without compromising safety. Further randomized prospective data may aid in our understanding of SVT induction using various medications.

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Table 1: Baseline characteristics of patients given isoproterenol or epinephrine for SVT induction during EPS

	Isoproterenol	Epinephrine	Total	P value
	N = 72	N = 59	N = 131	
Age (yr)	39.0 +/- 21	41.4 +/- 23	40.1 +/- 21.9	0.6
Female	40 (56%)	39 (66%)	79 (60%)	0.27
Arrhythmia type				0.23
AT	4 (5.6%)	5 (8.5%)	9 (6.9%)	
AVNRT	53 (74%)	34 (58%)	87 (66%)	
AVRT	5 (6.9%)	8 (14%)	13 (10%)	
Procedure time (min)	192 +/- 77	203 +/- 79	198 +/- 78	0.6
Congestive heart failure	2 (3%)	3 (5%)	5 (4%)	0.49
Diabetes	5 (7%)	3 (5%)	8 (6%)	1
Hypertension	13 (18%)	14 (24%)	27 (21%)	0.41
Coronary artery disease	4 (6%)	7 (12%)	11 (8%)	0.25
Obesity	9 (13%)	4 (7%)	13 (10%)	0.72
Beta blocker	24 (33%)	16 (27%)	40 (31%)	0.81
Calcium channel blocker	7 (10%)	5 (8%)	12 (9%)	1
Class 1 antiarrhythmic drug	5 (7%)	4 (7%)	9 (7%)	0.72
Class 3 antiarrhythmic drug	2 (3%)	1 (2%)	3 (2%)	1
Successful arrhythmia induction	52 (72%)	31 (53%)	84 (64%)	0.025

Table 2: Cohort characteristics of successful and unsuccessful SVT induction during EPS

	Successful Induction	Unsuccessful induction	Total	P value
Age (yr)	41.1 +/- 22.4	38.2 +/- 21.1		0.46
Female	45 (54%)	34 (72%)	79 (60%)	0.052
Arrhythmia type				0.000
AT	6 (7%)	3 (6%)	9 (7%)	
AVNRT	70 (83%)	17 (36%)	87 (66%)	
AVRT	7 (8.3%)	6 (13%)	13 (10%)	
Procedure time (min)	214.8 +/- 75	169.7 +/- 75		0.001
Congestive heart failure	3 (4%)	2 (4%)	5 (4%)	0.91
Diabetes	6 (7%)	1 (2%)	7 (5%)	0.14
Hypertension	20 (24%)	6 (13%)	26 (20%)	0.14
Coronary artery disease	6 (7%)	5 (11%)	11 (8%)	0.59
Obesity	9 (11%)	4 (9%)	13 (10%)	0.66
Beta blocker	28 (33%)	11 (23%)	39 (30%)	0.76
Calcium channel blocker	6 (7%)	5 (11%)	11 (8%)	0.16
Class 1 antiarrhythmic drug	5 (6%)	4 (9%)	9 (7%)	0.32
Class 3 antiarrhythmic drug	0 (0%)	3 (6%)	3 (2%)	0.007

Figure Legend

Figure 1: Cohort design.

Billing codes were queried for procedures that included electrophysiology study and concurrent medication administration. Exclusions included those for whom medication administration was not required for induction of the arrhythmia, but instead was used to test inducibility after ablation (= incorrect drug, 50); and those studies that did not involve supraventricular tachycardia (SVT) (= atrial flutter or atrial fibrillation, 27). Total study population included 131 patients.

Figure 2: Frequency of isoproterenol and epinephrine use over time.

Procedure date is plotted against cumulative frequency in an area graph. Isoproterenol price increase was announced in 4/2015. Behavior changes occurred on 1/2016, with a clear shift away from isoproterenol to epinephrine.

Figure 1: Cohort design



Figure 2: Frequency of isoproterenol and epinephrine use over time.

