Adrenaline Versus Atropine for AVNRT Induction

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Jennifer Asamoah

10.1 Introduction

AVNRT is the most frequent form of paroxysmal supraventricular tachycardia. In French the term is TRIN (tachycardie par reentre intra-nodale) and in English AVNRT (atrioventricular node reentrant tachycardia). It can be induced in the EP lab by atrial or ventricular stimulation in the basal state or after drug administration. The drug of choice is isoprenaline, but in some European countries, the lack of the drug produced efforts to search for another options. There is no study that compares efficacy of atropine versus adrenaline for AVNRT induction in the EP lab. In our study, we compared the two drugs in terms of efficacy and side effects.

J. Asamoah (✉)
New York University School of Medicine,
550 1st Avenue, New York, NY, USA

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10.2 Hypothesis

In order to compare atropine with adrenaline, we took patients with AVNRT that received atropine and compared them with patients that received adrenaline, without corresponding placebo matching per intervention group. The investigators hypothesized that adrenaline would be a better and more convenient for the induction of arrhythmias since adrenaline is administered as an intravenous infusion over several minutes, in comparison to atropine, which is administered as a bolus. We demonstrated our hypothesis by statistical analysis.

10.3 Materials and Method

10.3.1 Study Population and Methodology

This study was a retrospective, observational study which analyzed 216 consecutive patients who underwent AVNRT ablation and received either adrenaline (49 patients) or atropine (167 patients) for arrhythmia induction. It was ensured that informed consent was obtained before EP study for every subject included in the analysis. Each subject had a history of AVNRT with an ECG showing retrograde P wave in inferior leads: D2, D3, avF, or rsR' in lead V1. Patients that required both atropine and adrenaline for AVNRT induction were excluded from the study. Further exclusion criteria included the presence of prostatic adenoma or glaucoma with closed angle when chosen to have received atropine. Due to retrospective nature of the study, the authors note the limitations in statistical analysis due to the differing numbers of subjects that received adrenaline and atropine.

10.3.2 Electrophysiological Study

Electrophysiological study was performed without general anesthesia or sedation. The only anesthetic used was local anesthesia (lidocaine 1%) that was administered subcutaneously. All patients were noted to be in sinus rhythm at the beginning of the electrophysiological study. Catheters were introduced via femoral, subclavian or jugular venous access sites. The right side was preferred over the left side. For most of the procedures, four catheters were used according to our department's protocol: one in the superior right atrium, one in the region of the His bundle, one inside the coronary sinus, and one at the apex of the right ventricle.

We performed atrial and ventricular stimulation to measure the refractory period of the atrium, ventricle, and AV node. We excluded the presence of an accessory pathway by atrial and ventricular stimulation and by demonstrating absence of retrograde conduction to the atrium or when present decremental conduction with the first atrial depolarization at the level of the His bundle. After arrhythmia

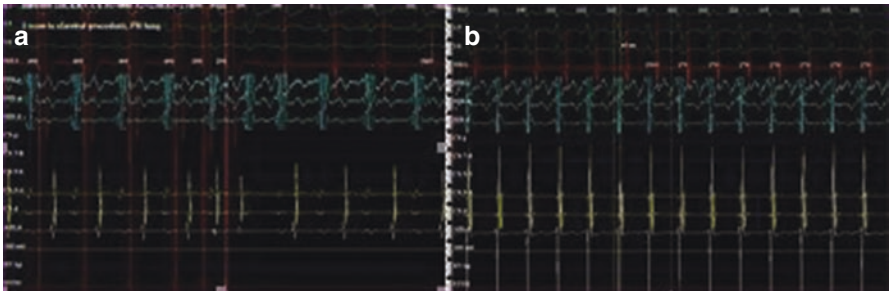


Fig. 10.1 Atrial stimulation for AVNRT induction. Surface and intracardiac derivations can be seen (from up to down): the first three derivations in green are surface ECG; the following in red is high right atrium (HRA); in blue the His derivations, proximal Hisp, medium Hism, and distal His, Hisd; in yellow the coronary sinus, distal and proximal; in white the ablation catheter. The tachycardia cycle length is 270 ms with the ventricular electrogram superimposed with the atrial electrogram which is suggestive of typical AVNRT. (**a**) Before adrenaline infusion, atrial extrastimuli could not induce AVNRT; (**b**) after adrenaline infusion, programmed atrial stimulation induces AVNRT

induction, we used atrial and ventricular entrainment to confirm AVNRT by measuring the post-pacing interval with orthodromic reentrant tachycardia and atrial tachycardia excluded. We stimulated the atrium with up to three extrastimuli at the level of high right atrium and coronary sinus on a 600 and 400 ms imposed rhythm. If the clinical arrhythmia could not be induced with extrastimuli, then burst atrial or ventricular pacing was performed. If clinical arrhythmias could not be induced, a bolus of either atropine 1 mg or infused adrenaline to facilitate arrhythmia induction. The choice between the two drugs was left at the discretion of the interventionist. Adrenaline was infused at an initial dose of 0.05 μg/kg/min and increased by 0.05 μg/kg/min until the heart rate increased by 50% to at least 100 bpm but not more than 150 bpm (cycle length of 400 ms). The dose of adrenaline that permitted increase of the heart rate was noted to be 0.1–0.3 μg/kg/min (Fig. 10.1). If atropine was injected, a bolus of 1–2 mg was used. The medium dose of atropine used was 1.5 mg with a minimum of 1 mg and a maximum of 3 mg. If the clinical arrhythmia cannot be induced with one of the two drugs, then the other one was added, but patients that received both atropine and adrenaline were excluded from the study.

10.3.3 Statistical Analysis

Statistical analysis was done using SPSS version 22. For descriptive statistics we used mean and standard deviation in case of normally distributed values. For continuous variables without normal distribution, we used median and interquartile range. For comparison between atropine and adrenaline, we used either the

chi-square test or the Fisher's exact test. For comparison of normally distributed variables, we used the Student's *T*-test and, in case of abnormal distribution, the Mann-Whitney test.

10.4 Results

10.4.1 Patients' Characteristics

A total of 49 patients received adrenaline, and 167 patients received atropine for AVNRT induction. Due to the retrospective nature of this study, no baseline population matching between the two groups could be done. The median dose of adrenaline was 0.2 μg/kg/min, and the median dose of atropine was 1.5 mg/patient.

The mean age of the adrenaline group was 50.4 years (range 17–68), and the mean age of the atropine group was 46.3 years (range 15–82) with a significant difference between groups ($p = 0.0002$) (Fig. 10.2). In the atropine group, 63.3% were females (33 of 49), and in the adrenaline group, 58.9% (99/167) were females. We compared both groups in terms of sex distribution, and we found a nonsignificant difference with a p value of 0.586 (Fig. 10.3, Table 10.1).

The group of patients that was given adrenaline was able to achieve their primary endpoint (AVNRT induction) in 40 out of 49 patients (81.5%), while the atropine group achieved the endpoint in 143 out of 167 patients (85.7%). Although the percentage is higher in the atropine group, the statistical chi-square test showed a nonsignificant difference between the two groups with a *p* value of 0.494 (Figs. 10.4 and 10.5, Table 10.2).

10.4.2 Side Effects of Atropine and Adrenaline

The adrenaline infusion had to be stopped in 2 of the 49 patients (4%) because of they developed headache at blood pressure values of more than 180/110 mmHg, for infusion rates of more than 0.2 μg/kg/min. Blood pressure was subsequently lowered

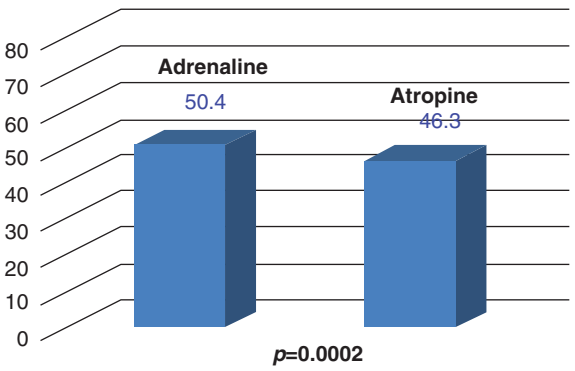
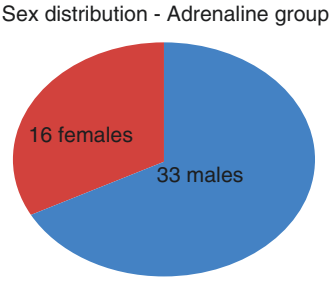


Fig. 10.2 Comparison of age between the two groups found a significant *p* value of 0.0002



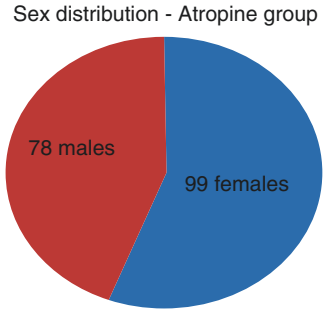


Fig. 10.3 Sex distribution between the two groups shows a nonsignificant difference with a *p* value of 0.586

Table 10.1 General characteristics of patients that received Atropine or Adrenaline

	Adrenaline	Atropine	*P*
Number of patients	49	168	
Mean age	50.4 (17–68)	46.3 (15–82)	0.0002
Females	31 (63.3%)	99 (58.9%)	0.586
Males	18 (36.7)	69 (41.1)	0.586

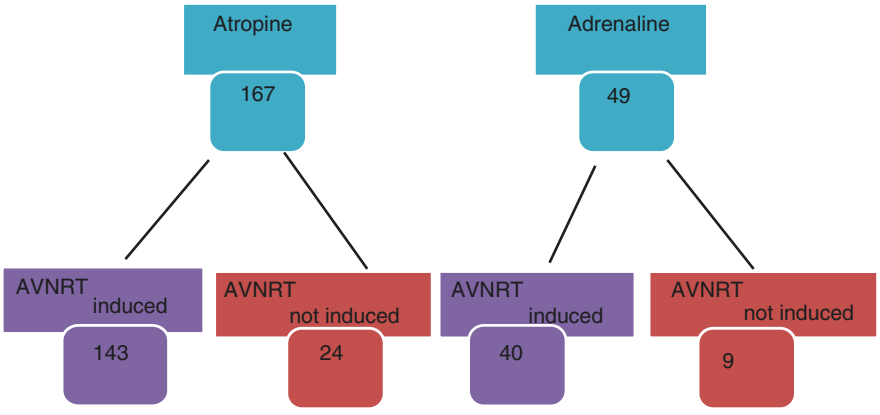


Fig. 10.4 AVNRT induction with atropine and with adrenaline

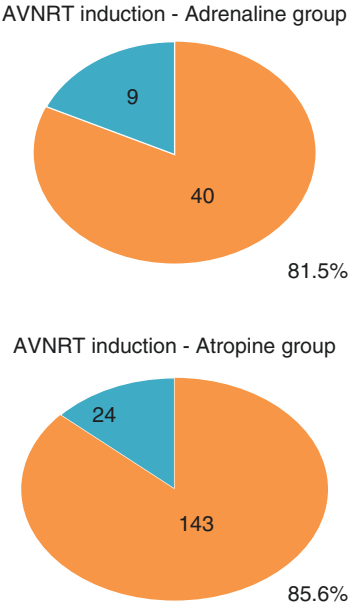


Fig. 10.5 AVNRT induction with atropine and adrenaline. Chi-square test shows a nonsignificant difference between the two groups with a *p* value of 0.494

Table 10.2 The chi-square test for comparison between the 2 groups shows a non-significant *p* value of more than 0.4

		Levene's test for equality of variances		*t*-test for Equality of Means						
									95% confidence interval of the difference	
		F	Sig.	*t*	df	Sig. (2-tailed)	Mean difference	Std. error difference	Lower	Upper
ATROPINE_ vs._ ADRENALINE	Equal variances assumed	1.752	0.187	0.681	214	0.496	0.03996	0.05866	−0.07567	0.15559
	Equal variances not assumed			0.643	72.309	0.522	0.03996	0.06217	−0.08396	0.16388

with intravenous enalapril. Tremors also appeared at doses >0.1 μg/kg/min. Because tremors are well tolerated by the patients, the infusion was not stopped for this particular side effect.

In the atropine group, the most frequent side effect was dry mouth, which was well tolerated by the patients during all the electrophysiological studies.

During the adrenaline infusion, atrial premature beats and ventricular premature beats were rarely seen at doses >0.2 μg/kg/min. After atropine administration, no patients presented with atrial or ventricular premature beats. No patients in the atropine group had closed-angle glaucoma. None of the patients with prostatic adenoma that received atropine had acute retention of urine.

10.5 Discussion

10.5.1 Results Interpretation

Our study demonstrated that both atropine and adrenaline had significant capabilities to induce AVNRT: 81.6% for adrenaline and 85.7% for atropine. The difference of 4% between the two drugs is nonsignificant, despite atropine having a higher percentage. However, the investigators understand the limitations of the study and understand that a higher number of patients in the adrenaline group would be necessary to confirm differences between the two groups.

Adrenaline was generally well tolerated, with the investigators noting that the infusion had to be stopped in only 2 out of the 49 cases where it was administered. None of the patients from the atropine group had significant side effects.

We believe that both atropine and adrenaline can be used in the EP lab for arrhythmia induction when isoprenaline, being the current gold standard, is not readily available. However, the main disadvantage of adrenaline is the necessity of an infusion and a longer time to achieve its full effect compared with atropine, which is administered as a bolus with a rapid onset of action. As previously reiterated, in patients with closed-angle glaucoma and prostatic adenoma, adrenaline may be preferred over atropine.

10.5.2 Prior Studies with Atropine

The first study that demonstrated the utility of drugs for arrhythmia induction in the EP lab was that of Akhtar et al. [1] published in 1975, which demonstrated that atropine was capable of increasing patient susceptibility to paroxysmal supraventricular tachycardia during programmed stimulation. Hariman et al. [2] showed that atropine could be used for atrioventricular node reentrant tachycardia induction because it facilitates retrograde ventriculoatrial conduction. Wu et al. [3] showed increased conduction through the antegrade and retrograde conduction after atropine. Patients that were inducible after atropine showed a similar refractory period of both fast and slow nodal pathways after atropine. In the study of Kim et al. [4], atropine added to programmed stimulation facilitated reentry through an accessory pathway and paroxysmal supraventricular tachycardia in 2 of 18 patients with asymptomatic WPW syndrome.

10.5.3 Prior Studies with Adrenaline

The effects of adrenaline in patients with supraventricular tachycardias were previously studied, but at present, there is no data showing the efficacy of this drug for PSVT induction. Increase in plasma concentration of adrenaline leads to a decrease in atrial refractory period, a decrease in refractory period of the AV node, and an increase in the conduction velocity through the AV node.

In the study by Cismaru et al. [5], an increase in the plasma concentration of adrenaline can lead to PSVT induction in patients that are non-inducible in the basal state.

10.5.4 Prior Studies with Isoprenaline

Hariman et al. [2] were the first to show that isoprenaline was effective for PSVT induction for cases that were non-inducible in the basal state or after atropine injection. They documented a 79-year-old patient that received isoprenaline infusion with PSVT subsequently induced. Toda et al. [6] demonstrated a 50% sensitivity for isoprenaline in the induction of paroxysmal supraventricular tachycardia presented on exertion. Huycke et al. [7] noted a sensitivity of 67% and a specificity of 100% for PSVT induction in a case series of 20 patients with dual nodal pathway, without any arrhythmia induced in the basal state. In the same year, Brembilla-Perot et al. [8] published their results obtained in Nancy Center, France, and demonstrated a sensitivity of 90% for PSVT induced on exertion (28 out of 31 patients). In the control group (of 37 patients without PSVT), after isoprenaline infusion, no arrhythmia was induced which further permitted to calculate a 100% specificity for isoprenaline for PSVT induction. Stellbrink et al. [9] demonstrated induction of AVNRT via isoprenaline infusion in 93% of cases. Katz et al. [10] reported a 46% induction rate of PSVT in patients with ventricular preexcitation. Oral et al. [11] demonstrated a sensitivity of 80% and a specificity of 95% for atrial fibrillation induction after 20 μg/min of isoprenaline was administered to patients with paroxysmal, persistent or long-term persistent atrial fibrillation.

10.5.5 Limitations

This study has two important limitations: Firstly, the investigators acknowledge that this is a non-randomized study, with information obtained in a retrospective manner. There were therefore significant differences in baseline characteristics with large differences in the population for both groups analyzed.

Second, in patients that received atropine for arrhythmia induction, the absence of a slow pathway at the end of procedure could be questionable. Lin et al. showed that after atropine injection, the refractory period of the slow pathway is close to the refractory period of the fast pathway and conduction jumps could be absent in this case. At the end of the procedure, the absence of the conduction jump may be the

effect of high atropine concentration in the blood of the patient and not the sign of an effective slow pathway ablation [12].

10.6 Conclusion

Adrenaline and atropine demonstrated similar efficacies for AVNRT induction in the EP laboratory. Both may be used when isoprenaline is not available, as is seen in some Eastern and Western European countries. The study reports an induction rate of 81.5% for adrenaline and 85.6% for atropine with no significant differences between each drug. However, the investigators recognize the limitations of the retrospective manner of data collection, particularly in the differences among baseline characteristics between compared groups and the number of subjects per groups.

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