

# Isoprenaline and inducibility of atrioventricular nodal re-entrant tachycardia

H Hatzinikolaou, L-M Rodriguez, J L R M Smeets, C Timmermans, G Vrouchos, G Grecas, H J J Wellens

## Abstract

**Objectives**—To examine the effect of isoprenaline on slow and fast pathway properties and tachycardia initiation.

**Design**—Consecutive patients, prospective study.

**Setting**—Referral centre for cardiology, academic hospital.

**Patients**—24 patients suffering from common type atrioventricular nodal re-entrant tachycardia (AVNRT).

**Interventions**—Programmed electrical stimulation and radiofrequency catheter ablation of the slow pathway.

**Measurements and main results**—AVNRT was induced before and after the administration of isoprenaline in nine patients (group 1), before isoprenaline only in five (group 2), and after isoprenaline only in 10 (group 3). The anterograde effective refractory period of the fast pathway was prolonged significantly during isoprenaline administration in group 1 (405 (31) *v* 335 (34) ms, *p* < 0.001) and shortened in group 2 (308 (57) *v* 324 (52) ms, *p* = 0.005). There was also significant shortening in group 3 (346 (85) *v* 395 (76) ms, *p* < 0.001). Isoprenaline administration did not result in a significant change of the anterograde effective refractory period of the slow pathway in groups 1 and 3, but eliminated slow pathway conduction in group 2. Isoprenaline significantly shortened the minimal and maximal atrial to His bundle conduction interval recording in response to each extrastimulus of the slow pathway (210 (24) *v* 267 (25) ms, *p* < 0.001 and 275 (25) *v* 328 (25) ms, *p* < 0.001, respectively) in group 1 and significantly prolonged these intervals (331 (34) *v* 274 (34) ms and 407 (33) *v* 351 (33) ms, respectively) in group 3. In all groups only minimal changes in the refractory period of the atrium occurred after isoprenaline administration. The effect of isoprenaline was also measured on the ventricular effective refractory period and on the minimal and maximal length of the ventriculoatrial ( $V_2$ - $A_2$ ) interval during ventricular pacing. Isoprenaline did not result in a significant change of the ventricular effective refractory period in groups 1 and 2 nor of the shortest and longest  $V_2$ - $A_2$  interval. In group 3, however, the ventricular effective refractory period and the shortest and longest  $V_2$ - $A_2$

interval shortened significantly after isoprenaline administration.

**Conclusions**—In group 1 isoprenaline did not affect inducibility of AVNRT because it prolonged the fast pathway refractory period without affecting slow pathway conduction. In group 2 isoprenaline shortened the fast pathway refractory period and appeared to abolish slow pathway conduction. Consequently, isoprenaline prevented induction of AVNRT. In group 3 isoprenaline facilitated induction of AVNRT. This effect seemed primarily to be the result of shortening of retrograde refractoriness of the fast pathway with prolongation of slow pathway anterograde conduction and refractory period.

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Keywords: atrioventricular re-entrant tachycardia; isoprenaline

Patients with atrioventricular nodal re-entrant tachycardia (AVNRT) usually have a discontinuous atrio-His (AH) bundle conduction interval in response to programmed atrial stimulation, a finding that is compatible with dual atrioventricular (AV) nodal pathways.<sup>1</sup> Initiation of tachycardia during atrial pacing is usually dependent on induction of a critical delay in the AH interval.<sup>2</sup> These characteristics led to our understanding of the mechanism of tachycardia as one based on re-entry with anterograde AV conduction over a slowly conducting (slow) pathway and retrograde conduction over a rapidly conducting (fast) pathway.<sup>3</sup> These fast and slow AV nodal pathways have different properties, with differences in conduction time, refractoriness,<sup>3</sup> and the site of earliest atrial activation during retrograde conduction.<sup>4</sup> AV nodal pathways may also have different responses to pharmacological agents.<sup>5–13</sup> Few data compare quantitatively the response of the fast and slow pathways to adrenergic stimulation.<sup>14</sup> In addition, it is not certain whether the effects on refractoriness parallel the effects on conduction. The present study was performed to quantify the effect of adrenergic stimulation using isoprenaline on AV and ventriculoatrial conduction in patients with clinically documented AVNRT and to study its effect on the initiation of tachycardia during pacing.

## Patients and methods

### STUDY POPULATION

Twenty four consecutive patients (16 female, eight male, mean (SD) age 44 (16) years, range

Department of  
Cardiology, G  
Papanikolaou General  
Hospital, Exohi,  
Thessaloniki, Greece  
H Hatzinikolaou

Department of  
Cardiology, Academic  
Hospital Maastricht,  
PO Box 5800, 6202 AZ  
Maastricht,  
Netherlands  
L-M Rodriguez  
J L R M Smeets  
C Timmermans  
G Vrouchos  
G Grecas  
H J J Wellens

Correspondence to:  
Dr Rodriguez.

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Table 1 Results during the electrophysiological study

	Group 1 (n = 9)	Group 2 (n = 5)	Group 3 (n = 10)
ERP <sub>A</sub> (ms)			
Basal	240 (25)	260 (36)	280 (64)
Isoprenaline	250 (25)	245 (24)	260 (75)
AntERP <sub>FP</sub> (ms)			
Basal	335 (34)	324 (52)	395 (76)
Isoprenaline	405 (31)*	308 (57)†	346 (85)*
AntERP <sub>SP</sub> (ms)			
Basal	269 (11)	274 (50)	290 (63)
Isoprenaline	297 (11)	No duality	322 (64)
Min A <sub>2</sub> -H <sub>2</sub> <sub>SP</sub> (ms)			
Basal	267 (25)	280 (38)	274 (34)
Isoprenaline	210 (24)*	No duality	331 (34)*
Max A <sub>2</sub> -H <sub>2</sub> <sub>SP</sub> (ms)			
Basal	328 (25)	335 (45)	351 (33)
Isoprenaline	275 (25)*	No duality	407 (33)*
ERP <sub>V</sub> (ms)			
Basal	376 (61)	340 (25)	370 (58)
Isoprenaline	360 (48)	325 (45)	276 (46)*
Max V <sub>2</sub> -A <sub>2</sub> (ms)			
Basal	365 (40)	324 (27)	385 (33)
Isoprenaline	348 (32)	318 (18)	335 (44)*
Min V <sub>2</sub> -A <sub>2</sub> (ms)			
Basal	288 (25)	295 (20)	320 (35)
Isoprenaline	274 (11)	280 (14)	255 (11)*

Mean (SD) values of the refractory periods are given at 500 ms basic pacing cycle length.

\*p < 0.001; †p < 0.005.

A, atrium; Ant, anterograde; ERP, effective refractory period; FP, fast pathway; Max, maximal; Min, minimal; SP, slow pathway; V, ventricle.

18–72) with common type (slow-fast) AVNRT were referred for electrophysiological evaluation and catheter ablation. Inclusion criteria were: each patient suffered from symptomatic recurrent common type AVNRT; each had been treated unsuccessfully with antiarrhythmic drugs; and each had no signs of pre-excitation during sinus rhythm or atrial pacing, or both. Patients without a discontinuous AV nodal conduction pattern during baseline electrophysiological study were excluded.

#### ELECTROPHYSIOLOGICAL STUDY PROTOCOL

Informed consent was obtained from each patient. Diagnostic electrophysiological study was performed with the patient in the fasting state and after discontinuation of all antiarrhythmic medication for at least five half lives. Six patients had received amiodarone (four from group 1 (n = 9), one from group 2 (n = 5), and one from group 3 (n = 10)), which was stopped one to two weeks before the study. After local anaesthesia four multipolar electrode catheters for recording and stimulation were inserted percutaneously into the femoral veins (right and left), and positioned in the high right atrium, across the tricuspid valve at the site of the His bundle, in the right ventricular apex, and the coronary sinus. Our stimulation protocol for supraventricular tachycardia has been described elsewhere.<sup>15</sup> The 12 lead electrocardiogram and four unipolar and four bipolar intracardiac electrograms were recorded simultaneously on a 20 channel Mingograph (Siemens AG) recorder. Measurements were made at a paper speed of 100 mm/s and stored on disk.

#### ASSESSMENT OF ANTEROGRADE ATRIOVENTRICULAR NODAL FUNCTION

The extrastimulus method was used during right atrial pacing to assess refractoriness and anterograde conduction properties of the fast and slow AV nodal pathways. The extrastimulus interval was decremented in steps of 10 ms

until atrial refractoriness. The AH bundle conduction interval in the His bundle recording in response to each extrastimulus (A<sub>2</sub>-H<sub>2</sub> interval) was recorded and plotted against the coupling interval of the atrial extrastimulus (A<sub>1</sub>-A<sub>2</sub> interval) to construct an anterograde AV nodal function curve. An increase in the A<sub>2</sub>-H<sub>2</sub> interval of more than 50 ms in response to a decrease in the A<sub>1</sub>-A<sub>2</sub> interval of 10 ms was defined as a discontinuous AV nodal function curve and taken as evidence of dual anterograde AV nodal conduction pathways.

#### ASSESSMENT OF VENTRICULOATRIAL CONDUCTION

Programmed stimulation was performed from the right ventricular apex using the extrastimulus method. A ventriculoatrial conduction curve was constructed by plotting the ventriculoatrial conduction interval (V<sub>2</sub>-A<sub>2</sub>) in relation to the coupling interval (V<sub>1</sub>-V<sub>2</sub>) of the ventricular extrastimulus.

#### ISOPRENALINE

Isoprenaline infusion was started after baseline recordings. The initial dose (1 µg/min) was increased gradually until a stable sinus rate 25% higher than the rate immediately before drug administration was achieved. Individual isoprenaline dosage ranged from 1 to 5 µg/min. Measurements during isoprenaline infusion were made using the same atrial and ventricular stimulation site and the same pacing cycle length and test stimulus intervals as those before drug treatment.

#### DEFINITIONS

*Effective refractory period of the atrium*—the longest A<sub>1</sub>-A<sub>2</sub> interval that failed to capture the atrium.

*Anterograde effective refractory period of the fast pathway*—the longest A<sub>1</sub>-A<sub>2</sub> interval that failed to propagate to the His bundle by way of the fast pathway (followed by conduction over the slow pathway).

*Anterograde effective refractory period of the slow pathway*—the longest A<sub>1</sub>-A<sub>2</sub> interval that failed to propagate to the His bundle.

*Minimal A<sub>2</sub>-H<sub>2</sub> interval over the slow pathway*—the shortest A<sub>2</sub>-H<sub>2</sub> interval over the slow pathway during atrial extrastimulation, measured in the His bundle recording.

*Maximal A<sub>2</sub>-H<sub>2</sub> interval over the slow pathway*—the longest A<sub>2</sub>-H<sub>2</sub> interval over the slow pathway during atrial extrastimulation, measured in the His bundle recording.

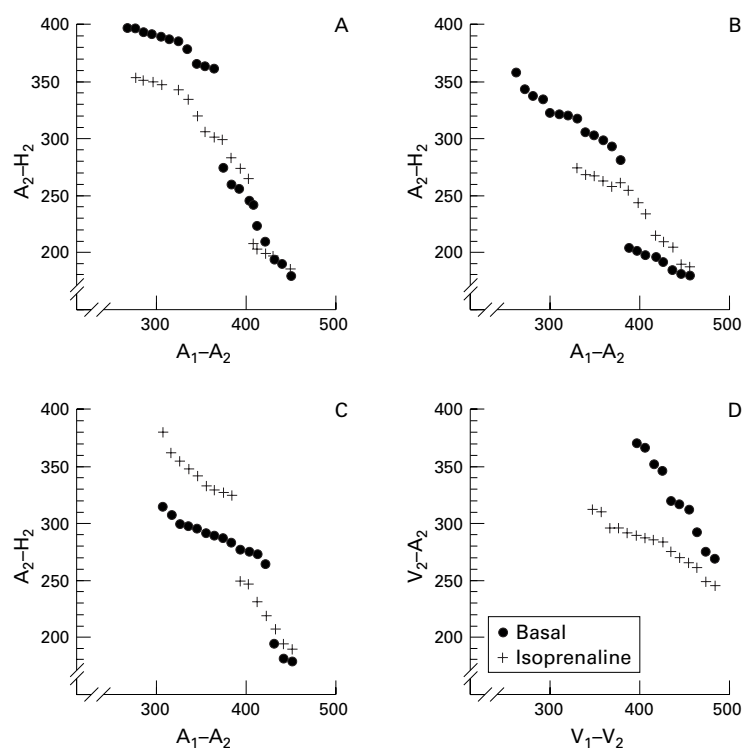
*Effective refractory period of the ventricle*—the longest V<sub>1</sub>-V<sub>2</sub> interval that failed to capture the ventricle.

*Maximal V<sub>2</sub>-A<sub>2</sub> interval*—the longest ventriculoatrial interval during single test stimulation of the ventricle during ventricular pacing.

*Minimal V<sub>2</sub>-A<sub>2</sub> interval*—the shortest ventriculoatrial interval during single test stimulation of the ventricle during ventricular pacing.

#### STATISTICAL ANALYSIS

Continuous variables expressed as means (SD) were compared before and after infusion of



**Figure 1** (A) Effect of intravenous isoprenaline on anterograde atrioventricular (AV) nodal conduction in a patient of group 1. The effective refractory period of the fast pathway was prolonged and conduction time of the slow pathway shortened after drug administration. (B) Effect of isoprenaline on anterograde AV nodal conduction in a patient of group 2. Slow pathway conduction was eliminated after drug administration. (C) Effect of isoprenaline on anterograde conduction in a patient of group 3. The effective refractory period of the fast pathway was shortened and conduction time over the slow pathway prolonged after drug administration. (D) Effect of isoprenaline on retrograde conduction. The ventricular effective refractory period and the retrograde conduction time were shortened after drug administration. Measurements of anterograde and retrograde AV nodal conduction were obtained using a basic cycle length of 500 ms.  $A_2-H_2$ , atrio-His bundle conduction interval in the His bundle recording in response to each extrastimulus;  $A_1-A_2$ , atrial extrastimulus;  $V_2-A_2$ , ventriculoatrial conduction interval;  $V_1-V_2$ , coupling interval of the ventricular extrastimulus.

isoprenaline using the Wilcoxon sign rank test. A p value of less than 0.05 was considered significant.

## Results

### HEART RATE BEFORE AND AFTER ISOPRENALINE

Heart rates before isoprenaline ranged from 65 to 80 beats/min in group 1, from 60 to 80 beats/min in group 2, and from 75 to 86 beats/min in group 3. Heart rates after isoprenaline perfusion increased in all groups (from 90 to 100 beats/min in group 1, from 88 to 115 beats/min in group 2, and from 90 to 110 beats/min in group 3).

### INDUCIBILITY OF ATRIOVENTRICULAR NODAL RE-ENTRANT TACHYCARDIA

AVNRT was induced before and after administration of isoprenaline in nine patients (group 1). Before drug administration AVNRT was reproducibly induced at three different atrial pacing cycle lengths (600, 500, and 430 ms) and one atrial extrasystole having a coupling interval of 310, 300, and 280 ms, respectively. Tachycardia could be induced after isoprenaline infusion at basic cycle lengths of 500 and 430 ms and one atrial extrasystole with a coupling interval of 370 and 360 ms, respectively. AVNRT was initiated in only five patients

before administration of isoprenaline (group 2). AVNRT in this group was also reproducibly induced at three basic cycle lengths (600, 500, and 430 ms) and one atrial extrasystole with a coupling interval of 320, 320, and 290 ms, respectively. AVNRT could be induced only after isoprenaline oterenol perfusion in 10 patients (group 3). Tachycardia was induced at two cycle lengths (500 and 430 ms), with one atrial extrasystole with a coupling interval of 290 and 270 ms, respectively.

### EFFECTIVE REFRACTORY PERIODS OF THE ATRIUM AND VENTRICLE AND ANTEROGRADE AND RETROGRADE EFFECTIVE REFRACTORY PERIODS OF THE FAST AND SLOW PATHWAYS BEFORE AND AFTER ISOPRENALINE

Table 1 summarises the findings of the effective refractory periods of the atrium and ventricle and anterograde and retrograde conduction over the AV junction before and after isoprenaline. Mean values are given at 500 ms basic pacing cycle length. In group 1 the anterograde effective refractory period of the fast pathway showed significant prolongation during isoprenaline infusion (405 (31) v 335 (34) ms), while the anterograde effective refractory period of the slow pathway did not change significantly (297 (11) v 269 (11) ms). The conduction time over the slow pathway expressed as the minimal and maximal  $A_2-H_2$  interval significantly shortened during drug administration (210 (24) v 267 (25) ms, and 275 (25) v 328 (25) ms respectively (fig 1A)). In group 2 there was significant shortening of the anterograde effective period of the fast pathway during isoprenaline infusion (324 (52) v 308 (57) ms), and elimination of slow pathway conduction (fig 1B). In group 3 significant shortening of the anterograde effective refractory period of the fast pathway was measured during isoprenaline infusion (346 (85) v 395 (76) ms), without significant changes in the anterograde effective refractory period of the slow pathway (322 (64) v 290 (63) ms). Significant prolongation of the conduction time over the slow pathway, as seen by behaviour of the minimal and maximal  $A_2-H_2$  interval (331 (34) v 274 (34) ms and 407 (33) v 351 (33) ms, respectively), was observed during isoprenaline administration (fig 1C). There were no significant differences in the effect of isoprenaline on the effective refractory period of the atrium.

A gradual increase in ventriculoatrial conduction time was observed in 23 of the 24 patients during single test stimulation of the ventricle at baseline. One patient (group 2) had a dual retrograde conduction curve. The ventricular effective refractory period showed significant shortening (276 (46) v 370 (58) ms) after isoprenaline only in group 3. This was accompanied by ventriculoatrial conduction of extrasystoles given at these shorter intervals. The minimal and maximal  $V_2-A_2$  intervals also shortened considerably after drug administration (255 (11) v 320 (35) ms, 335 (44) v 385 (33) ms, respectively (fig 1D)).

## Discussion

The results indicate that isoprenaline may have individually different effects on the antero-grade effective refractory period of the fast pathway, antero-grade conduction time over the slow pathway, and ventriculoatrial conduction time and that these changes determine the ability to initiate AVNRT. The effect of isoprenaline could not be predicted from findings of the basal state.

Induction of AVNRT is facilitated when isoprenaline considerably prolongs the antero-grade effective refractory period of the fast pathway, widening the difference in fast and slow pathway refractoriness. But also, as shown in group 3, a decrease in this difference can be accompanied by initiation of AVNRT if the drug produces a decrease in antero-grade conduction velocity over the slow pathway and improvement in retrograde conduction. It has been reported that isoprenaline improved ventriculoatrial conduction by improving conduction through the retrograde limb of the re-entrant pathway.<sup>14</sup> By doing so, isoprenaline also allowed induction of AVNRT.

In about one fifth of patients isoprenaline shortened the antero-grade effective refractory period of the fast pathway to such an extent that no differences in the antero-grade refractory period of the fast and slow pathway could be found. This obviously resulted in the inability to initiate AVNRT during atrial pacing.

Beta adrenergic stimulation had a greater effect on antero-grade refractoriness of the fast than of the slow AV nodal pathway. This suggests that there is a difference in effect of isoprenaline on refractoriness of the AV nodal pathways. The physiological mechanism responsible for this apparent greater susceptibility of the fast pathway to such stimulus is unknown. More anterior located fibres entering the AV node may possibly have a richer innervation or more adrenergic receptors than fibres approaching the compact node from the posterior direction. By contrast, some features seen in this study may be the result of the effect of isoprenaline on vagal tone.<sup>16, 17</sup> Cardiac vagal activity during intravenous isoprenaline administration is dependent on the method by which the drug is given. A bolus injection causes withdrawal of vagal tone,<sup>16</sup> but with continuous perfusion there is an increase in vagal tone.<sup>16, 17</sup> Although, this phenomenon was not explored here, this is an aspect that deserves further study. Our findings emphasise the importance of the delicate interplay between refractoriness and conduction velocity in initiating and perpetuating re-entry. Initiation of the arrhythmia by programmed electrical

stimulation and pharmacological manipulation of that interplay is sometimes required in patients with AVNRT to interrupt the re-entry circuit by radiofrequency catheter ablation.

In conclusion, isoprenaline did not affect inducibility of AVNRT in group 1 because it prolonged the fast pathway refractory period without affecting slow pathway conduction (group 1). In group 2, isoprenaline shortened the fast pathway refractory period and appeared to abolish slow pathway conduction. As a consequence isoprenaline prevented induction of AVNRT. In a third group of patients isoprenaline facilitated the induction of AVNRT. Induction seemed primarily to be the result of shortening of retrograde refractoriness of the fast pathway with prolongation of the slow pathway antero-grade conduction and refractory period.

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