

## Is isoproterenol really required during electrophysiological study in patients with Wolff-Parkinson-White syndrome?☆

Maheshwar Pauriah, MD, Gabriel Cismaru, MD, Jean-Marc Sellal, MD, Christian De Chillou, MD, Béatrice Brembilla-Perrot, MD\*

CHU Nancy, Service de Cardiologie, Nancy, France

### Abstract

We have studied the results of electrophysiological study (EPS) in patients with Wolff-Parkinson-White syndrome (WPW) and spontaneous adverse clinical presentation and determined whether isoproterenol added incremental value.

**Methods:** EPS was performed in 63 patients with WPW and adverse clinical presentation at baseline. EPS was repeated after infusion of isoproterenol in 37 patients, including 25 without criteria for a malignant form at baseline.

**Results:** Atrioventricular orthodromic tachycardia was induced 44%, antidromic tachycardia in 11%, atrial fibrillation (AF) in 68% at baseline. At baseline EPS, criteria for a malignant form (AF induction and shortest CL <250 ms) were noted in 60%; tachycardia was not inducible in 16%. All the patients met the criteria for a malignant form after isoproterenol.

**Conclusions:** EPS at baseline missed 16% of patients at risk of life-threatening arrhythmias who had no inducible tachyarrhythmia and 40% without classical criteria for malignant form.

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### Keywords:

Wolff-Parkinson-White syndrome; Electrophysiological study; Isoproterenol; Sudden death

Although most patients with pre-excitation will not have adverse clinical presentation, sudden cardiac death can occur and can be a presenting feature in some individuals.<sup>1–3</sup> It is very difficult to determine the exact risk, but estimates range between 0.02–0.1% per year.<sup>1,4</sup> Various risk markers have been identified over the years. These include male sex, multiple accessory pathways, refractory period less than 250 ms and shortest RR interval during atrial fibrillation of <250 ms.<sup>5</sup> The risk of sudden cardiac death is thought to be due to ventricular fibrillation, secondary to rapidly conducting atrial fibrillation (AF),<sup>1,6</sup> which is itself thought to arise secondary to an episode of supraventricular tachycardia in mostly young patients.<sup>5</sup>

Several non invasive tests are available, but they lack specificity.<sup>7</sup> Therefore, electrophysiological study remains a very powerful tool in investigations of asymptomatic patients with Wolff-Parkinson-White syndrome (WPW) type ECG when non-invasive tests are equivocal.<sup>7</sup> beta-

Adrenergic stimulation that occurs during exercise activity or stress may result in shortening of the anterograde refractory period of the accessory pathway, leading to increased ventricular rates during AF. Isoproterenol infusion has been used by several groups<sup>7–9</sup> to reproduce the effects of beta-adrenergic stimulation and has been shown to shorten the refractory period of the accessory pathway. However, none of these studies have conclusively shown that data obtained after isoproterenol infusion are associated with a risk of death.

Therefore, the diagnostic value of isoproterenol in electrophysiological testing of patients with WPW is not well defined. Initial studies did not use isoproterenol and the follow-up did not indicate an adverse prognosis in studied patients.<sup>7,8</sup> Recent studies used isoproterenol but the data about the prognostic significance of the infusion are unknown.<sup>9</sup> Moreover, the adverse prognosis reported in some patients of the last study concerned patients with documented rapid AF at Holter monitoring.

In the past years, the treatment for pre-excitation syndrome has changed with the development of ablation techniques. The number of accessory pathway ablations has considerably increased. Therefore, the natural history of the pre-excitation syndrome became difficult to evaluate.

☆ Conflicts of Interest: None.

\* Corresponding author. CHU of Brabois, 54500, Vandoeuvre lès Nancy, France. Tel.: +33 383153256; fax: +33 383154226.

E-mail address: [b.brembilla-perrot@chu-nancy.fr](mailto:b.brembilla-perrot@chu-nancy.fr)

The aim of this study was a confirmative study to determine whether testing with isoproterenol in addition to baseline testing added any incremental value in identifying electrophysiological malignant features in high risk patients. To do this, we looked at a group of patients with WPW who had already manifested a being high risk (having presented with adverse clinical features) who underwent electrophysiological study with a view to ablation.

## Methods

### *Study population*

The study population consisted of patients with spontaneous adverse presentation-related WPW referred to a single centre in 1990 and 2011.

Inclusion criteria were the patients with WPW who presented with a documented life-threatening hemodynamically not tolerated arrhythmia, with collapse or syncope and requiring emergency treatment (cardioversion or intravenous drug).

Patients with WPW who presented with hemodynamically well-tolerated arrhythmia or patients who presented with syncope without documented arrhythmia or asymptomatic patients with pre-excitation in whom rapid AF was induced were excluded from the study.

Patients were studied as part of standard of care. Written informed consent was obtained in all patients.

### *Electrophysiological study*

Electrophysiological study (EPS) was carried out without sedation as previously described.<sup>10</sup> Briefly incremental atrial pacing was performed until the highest rate conducted 1/1 through the accessory pathway and/or the atrioventricular node. Programmed atrial stimulation at a basic cycle length of 600 and 400 ms with the introduction of one and two extrastimuli was performed. When a fast supraventricular tachycardia was induced, the protocol was generally stopped, except in patients studied several years earlier. In the absence of induction of a tachycardia conducted through the accessory pathway at a rate higher than 250 bpm, isoproterenol (0.02 to 1  $\mu\text{g}\cdot\text{min}^{-1}$ ) was infused to increase the sinus rate to at least 130 bpm and the pacing protocol was repeated.<sup>11,12</sup> Arterial blood pressure was continuously monitored during the study by an external sphygmomanometer (Baxter HealthCare, Tokyo, Japan). Ablation was recommended for all patients presenting with malignant forms of WPW. The first ablations were performed in 1994 in our department. Catheter ablation of accessory pathway was proposed during the same time in patients with induced rapid supraventricular tachycardia and those with a spontaneous or detected malignant form.

### *Definitions*

The location of the accessory pathway was determined with the 12-lead ECG recorded in maximal preexcitation. The diagnosis of multiple pathways was retained only if ECGs in maximal preexcitation were clearly different or if the sites of ablation were also clearly different. In the left free

wall location, the ablation could require the application of radiofrequency energy apparently at two sites, but it could be the same large accessory pathway. Sustained AF or reciprocating tachycardia was defined as a tachycardia that lasted longer than 1 minute. Anterograde conduction was evaluated by the measurement of the shortest atrial cycle length at which there was 1 to 1 conduction over the accessory pathway and the shortest atrial tachycardia cycle length at which there was 1 to 1 conduction over the accessory pathway. Accessory pathway effective refractory period was determined at a cycle length of 600 ms and 400 ms in control state and only 400 ms after isoproterenol. WPW syndrome was considered as malignant and at risk of sudden death at electrophysiologic study when the following association was observed<sup>5</sup>: induced sustained AF or atrial tachycardia and the shortest RR interval between pre-excited beats was less than 250 ms in the control state or less than 220 ms after isoproterenol during atrial pacing. Orthodromic atrioventricular re-entrant tachycardia (AVRT) induction alone was not considered as a criterion for a high-risk form of preexcitation syndrome.

### *Statistical analysis*

Data are expressed as means  $\pm$  standard deviation (SD). All variables were tested for a Gaussian distribution by visual inspection of the histogram and Shapiro Wilk test. Non-normally distributed data are reported as median (interquartile range). For categorical variables, the chi-squared ( $\chi^2$ ) test was performed. The paired t-test procedure was used to analyse variables. A P value  $<0.05$  was considered statistically significant. All statistical analyses were performed by using the SPSS package for Windows (version 17.0.1, SPSS Inc., Chicago, IL, USA).

## Results

### *Clinical characteristics*

Sixty three patients (mean age  $38 \pm 18$  years, 68% males) were included in the study. Age range varied from 11 to 74 years and 26 (41%) were more than 40 years of age at the time of presentation (Table 1). Fifty seven presented with syncope and documented arrhythmia and 6 other patients were resuscitated from a ventricular fibrillation (VF). Presenting arrhythmia was ventricular fibrillation in 6, AF in 46, antidromic tachycardia in 4, wide atrial tachycardia in 3 and other supraventricular tachycardia without clear mechanism in 4 patients. In the latter cases, ECG was recorded in one lead in emergency before cardioversion and was of poor quality. Cardioversion was required in 31 patients to stop the tachycardia.

Pathway location in all patients is shown in Table 1. Thirty nine were left-sided, 2 were right-sided and 22 were septal. One of the patients with septal accessory pathway had 2 accessory pathways, (postero-septal and antero-septal). The total number of patients with WPW referred to the centre within this time period was 782. Seven hundred nineteen patients were excluded because they were asymptomatic ( $n=278$ ) or they have presented a syncope without documented

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