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Impact of Atrioventricular Node Ablation and Pacing Therapy on Clinical Course in Patients with Permanent Atrial Fibrillation and Unstable Ventricular Tachycardia Induced by Rapid Ventricular Response: Follow-up Study

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Aim To evaluate prospectively the impact of atrioventricular (AV) node ablation and consequent pacing therapy on clinical course in patients with permanent atrial fibrillation and unstable ventricular tachycardia induced by rapid ventricular response.

Methods One hundred four patients with permanent atrial fibrillation and uncontrolled ventricular rate resistant to drug therapy underwent radiofrequency catheter ablation of the AV node and permanent pacemaker implantation. At baseline examination, 14 of them had unstable ventricular tachycardia induced by rapid ventricular response of atrial fibrillation (ventricular tachycardia group). The remaining 90 patients did not have this type of ventricular tachycardia (control group). After the ablation, all patients were followed-up without antiarrhythmic agents. The primary end point was sudden cardiac death.

Results Before the ablation, patients in ventricular tachycardia group had lower left ventricular ejection fraction ($P<0.013$), and higher ventricular rate at rest and during daily activities ($P<0.001$). During the follow up of 20 ± 8 months (mean ± standard deviation), the mortality rate of sudden cardiac death at two years was similar among the two groups (7% vs 5%, $P=0.703$). The observed cardiac and all-cause mortality were significantly higher in ventricular tachycardia group (21% vs 3.6%, $P=0.014$; 28.5% vs 4.4%, $P=0.038$; respectively) due to increased heart failure-related mortality ($P=0.013$).

Conclusion In patients with permanent atrial fibrillation and ventricular tachycardia induced by rapid ventricular response, AV node ablation and pacing therapy have beneficial effect in the elimination of this arrhythmia. It seems that these patients do not need a cardioverter defibrillator therapy.

Radiofrequency catheter ablation of the atrioventricular (AV) node followed by implantation of a ventricular rate-responsive pacemaker is an established therapy for the patients with permanent atrial fibrillation whose ventricular rate was not controlled by drug therapy, who cannot tolerate effective drugs, or who were resuscitated from sudden cardiac death due to a rapid ventricular response in the absence of an accessory pathway (1,2). While there are many studies underlining beneficial effects of this procedure in symptomatic patients with permanent atrial fibrillation who have fast and irregular ventricular rate, reduced functional capacity, or depressed cardiac performances (3-8), there is a lack of data concerning the impact of AV node ablation in patients with permanent atrial fibrillation and unstable ventricular tachycardia induced by rapid ventricular rate. The purpose of this study was to evaluate the clinical course in such patients, treated by AV node ablation and permanent cardiac pacing, in comparison with other patients with permanent atrial fibrilla-

tion, who underwent the same therapeutic procedures.

Patients and Methods

Patients

Consecutive patients with permanent atrial fibrillation and uncontrolled ventricular rate undergoing radiofrequency catheter ablation of the AV node and pacemaker implantation at our institution between April 1999 and April 2002 were eligible for the study. The patients enrolled gave their informed consent. Before therapeutic procedures, all patients underwent noninvasive cardiac examination and programmed ventricular stimulation at two cycle lengths (600 and 400 ms) with 2 extrastimuli. Permanent atrial fibrillation was defined as arrhythmia that persisted without interruption for at least 12 months and could not be converted to sinus rhythm by electrical cardioversion (9). Unstable ventricular tachycardia was defined as electrocardiographycally documented sustained ventricular tachycardia induced by rapid ventricular response of atrial fibrillation requiring termination because of hemodynamic compromise (Fig. 1).

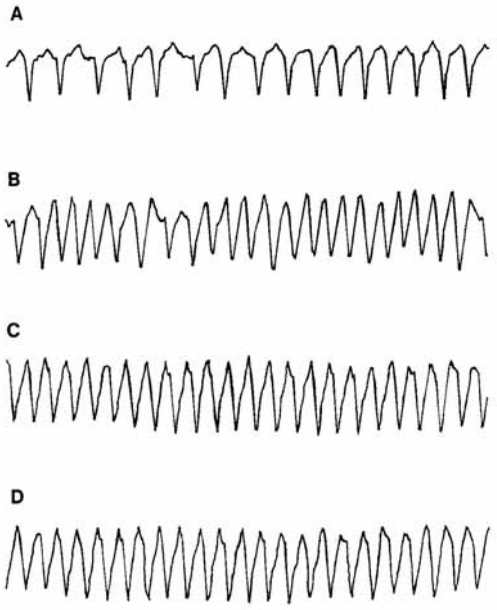

Figure 1. Holter recording of ventricular tachycardia induced by rapid ventricular response in patient with permanent atrial fibrillation. Trace A: an acceleration of the ventricular rate in permanent atrial fibrillation. Trace B: the onset of ventricular tachycardia with a progressive acceleration of ventricular rate. Traces C and D: established ventricular tachycardia with very fast rate (R-R interval of 270 ms).

Patients were included in the study if they had tachyarrhythmic episodes of permanent atrial fibrillation causing severe symptoms or heart failure, with medical therapy providing either inadequate control of symptoms or producing intolerable adverse effects, or rapid ventricular response of atrial fibrillation induced unstable ventricular tachycardia. The patients were excluded from the study if they had acute clinical disease during the previous 6 months, left ventricular ejection fraction <20%, Wolff-Parkinson-White-syndrome, or a life expectancy less than 12 months due to a non-cardiac medical condition, such as cancer or terminal lung disease.

Therapeutic Procedures

Catheter ablation of the AV node and permanent pacemaker implantation were performed by using the standard techniques (10). One or two days before the ablation, the permanent ventricular rate responsive pacemaker was implanted in all patients.

Radiofrequency generator (HAT 300, Dr. Osypka, Wyhlen, Germany) was used for the unipolar, temperature-guided radiofrequency ablation of the AV node. Actual power output, impedance, energy delivery, and catheter tip temperature were continuously monitored and displayed on a personal computer via an interface. Power output of 30 W was adjusted by the generator to reach and maintain the preselected temperature of 70° C in duration of 30-60 seconds. A deflectable, quadripolar 7-French electrode catheter (Dr. Osypka) with interelectrode spacing of 2 mm and integrated thermistor was used for the ablation. The goal of ablation was to induce a complete AV block at the suprahisal level. All patients were discharged from the hospital without antiarrhythmic drug therapy. Anticoagulant and other medical agents were administrated in accordance with the published guidelines (11,12).

Study End Points

The primary end point of the study was sudden death. The secondary end points were cardiac death, all-cause mortality, and the occurrence of symptomatic ventricular tachycardia requiring cardioverter defibrillator therapy. Sudden cardiac death was defined as death caused by documented ventricular tachyarrhythmia or death that occurred within one hour from the onset of symptoms or during sleep in a previously stable patient

free of hemodynamic collapse or myocardial infarction in the preceding 24 hours (13,14). Cardiac death was defined as death caused by congestive heart failure or by acute myocardial infarction (10). Progressive heart failure was defined as unstable clinical progression of deteriorating heart pump function under active therapy (15), as ascertained by evidence of either interstitial or alveolar edema on chest x-ray, which required admission to the intensive care unit.

Follow-up

The patients were prospectively followed up in our pacemaker center. Each control checkup every six months included medical history, physical examination, 12-lead electrocardiogram, Holter monitoring, and recording of any primary or secondary outcome event. The cause of death was determined by the review of hospital records and death certificates, and by telephone interviews of local physicians or family members.

Statistical Analysis

Continuous variables with normal distribution were presented as a mean with standard deviation (±SD), and those with non-normal distribution as a median with interquartile ranges (IQR). Categorical variables were presented as frequencies (%). Differences between the groups in normally and non-normally distributed variables were assessed with the independent t-test or the Mann-Whitney U-test. Categorical variables were compared with χ^2 test by using Yates correction. Differences in survival were analyzed with the Kaplan-Meier method. Data on surviving patients were censored at the date of the last follow-up visit. For the analysis of sudden death, data on deaths from other causes were censored on the date of death. A value of $P<0.05$ for two-sided comparison was considered significant. MedCalc program (MedCalc Software, Mariakerke, Belgium) was used for the statistical analysis.

Results

A total of 120 consecutive patients with permanent atrial fibrillation and uncontrolled ventricular rate underwent a pacemaker implantation and radiofrequency catheter ablation of the AV node (Fig. 2). Of these patients, 10 refused to participate and 6 patients were lost to follow-up.

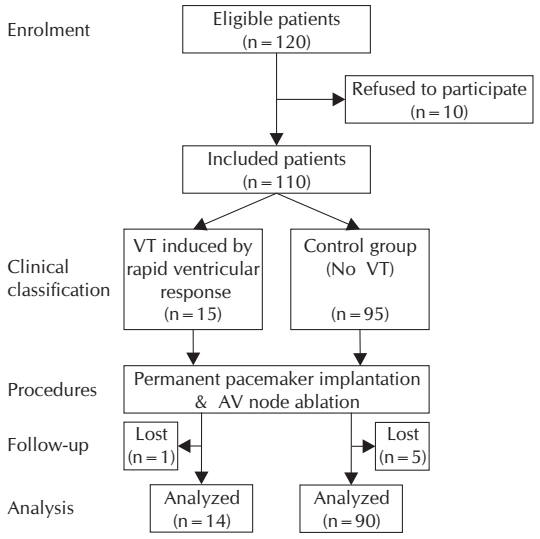

Figure 2. Flow chart of the study. VT – ventricular fibrillation; AV – atrioventricular.

Thus, data analysis is based on 104 consecutive patients with permanent atrial fibrillation, of whom 14 patients had unstable ventricular tachycardia induced by rapid ventricular response of atrial fibrillation (ventricular tachycardia group), and 90 patients were without this type of ventricular tachycardia (control group).

The analysis of baseline clinical data demonstrated several significant differences between the two patient groups (Table 1). Patients in ventricular tachycardia group had lower ejection fraction ($P<0.013$), more often syncope ($P<0.001$), higher class according to the New York Heart Association (NYHA) classification ($P<0.001$), and higher ventricular rate at rest ($P<0.001$) and during daily activities ($P<0.002$). The other clinical variables, including age, sex, type of structural heart disease, history of heart failure and His-ventricular interval did not differ between the two groups. Ventricular tachycardia was not inducible by routine right ventricular pacing in any patient in either group. The mean follow up period was 20±8 months (median, 18; range, 5-36 months). Follow-up was completed in April 2004.

At discharge from the hospital, there was no significant difference in the medical therapy between the two patient groups, but there was a trend of more frequent use of spironolactone in the ventricular tachycardia group. During the follow-up period, the similar distribution of medical therapy was held in the both patient groups.

Table 1. Baseline data of patients with permanent atrial fibrillation according to the presence of ventricular tachycardia induced by rapid ventricular response*

Characteristic	No. (%) of patients: ventricular tachycardia group (n=14)	control group (n=90)	P†
Age (mean±SD, years)	64±10	62±12	0.555
Men	7 (50.0)	64 (71.0)	0.207
Underlying heart disease:			
ischemic heart disease	4 (29.0)	26 (29.0)	0.751
hypertensive heart disease	7 (50.0)	52 (58.0)	0.785
dilated cardiomyopathy	3 (21.0)	8 (9.0)	0.373
other	0	4 (4.0)	0.980
History of heart failure	7 (50.0)	23 (26.0)	0.128
Presenting symptoms:			
syncope	14 (100.0)	26 (29.0)	<0.001
effort dyspnea	14 (100.0)	90 (100.0)	0.999
rest dyspnea	7 (50.0)	23 (26.0)	0.128
Ejection fraction	41±12	51±14	<0.013
NYHA classes (mean±SD)	2.7±0.7	2.0±0.7	<0.001
Ventricular rate (mean±SD, beats/min):			
at rest	130±20	110±15	<0.001
daily activity	199±34	176±24	<0.001
Baseline HV (mean±SD, ms)	55±14	53±14	0.620
Inducible VT	0	0	
Medical therapy at discharge:			
ACE inhibitors	10 (71.0)	60 (67.0)	0.993
beta blockers	7 (50.0)	40 (44.0)	0.896
anticoagulans	11 (79.0)	72 (80.0)	0.786
loop diuretics	6 (43.0)	20 (22.0)	0.174
spyronolactone	4 (29.0)	8 (9.0)	0.058

*Abbreviations: SD – standard deviation; NYHA – New York Heart Association; HV – His-ventricular interval; VT – sustained ventricular tachycardia; ACE - angiotensin converting enzyme.
†χ^2 test for frequencies and Mann-Whitney for continuous variables.

Major clinical events during the follow-up included sudden death in one patient in the ventricular tachycardia group on day 150, and in 4 patients in the control group on days 150, 160, 240 and 510 (Table 2). The calculated mortality rate of sudden death at two years was similar in two groups (7% vs 5%, log-rank test, $P=0.703$). The distribution of sudden cardiac death as a percentage of the all-cause mortality was 25% (1 of 4 patients) in the ventricular tachycardia group and 57% (4 of 7 patients) in the control group (log-rank test, $P=0.692$).

Table 2. Major clinical events in patients with permanent atrial fibrillation according to the presence of ventricular tachycardia induced by rapid ventricular response before therapeutic procedures

Clinical event	No. (%) of patients: ventricular tachycardia group (n=14)	control group (n=90)	P†
Sudden death	1 (7.1)	4 (4.4)	0.703
Cardiac death	3 (21.4)	3 (3.3)	0.014
Progressive heart failure	3 (21.4)	2 (2.2)	0.013
Acute myocardial infarction	0	1 (1.1)	0.240
All-cause mortality	4 (28.5)	7 (7.7)	0.038
VT occurrence	0	2 (2.2)	0.570

VT – sustained ventricular tachycardia.
†χ^2 test.

For the cumulative incidence of the secondary end points in the two patients groups, the patients in the ventricular tachycardia group had significantly higher incidence of cardiac death (log-rank test, $P=0.014$) and all-cause mortality (log-rank test, $P=0.038$; Fig. 3). These patients also had a significantly higher incidence of death due to progressive heart failure (log-rank test, $P=0.013$), which accounted for 75% of their all-cause mortality. During the observational period, sustained ventricular tachycardia requiring cardioverter defibrillator therapy developed only in two patients in the control group. In both of them, a cardioverter defibrillator was properly activated by ventricular tachycardia.

Discussion

This prospective study is one of the first to show that radiofrequency catheter ablation of the AV node followed by permanent cardiac pacing

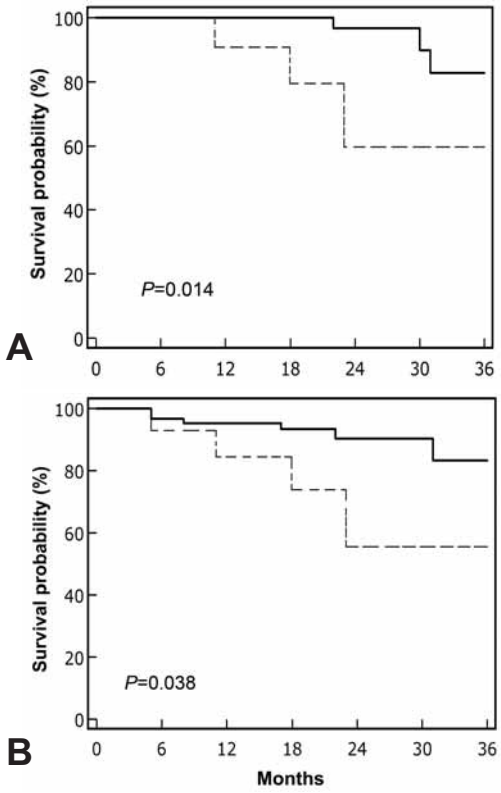

Figure 3. Kaplan-Meier estimates of cardiac death mortality (**A**) and of all-cause mortality (**B**) in patients with permanent atrial fibrillation according to the presence (ventricular fibrillation group – dashed line) or absence (control group – full line) of ventricular tachycardia induced by rapid ventricular response before therapeutic procedures.

has beneficial effect in patients with permanent atrial fibrillation and unstable ventricular tachycardia induced by rapid ventricular response in the elimination of this arrhythmia. In these patients, the mortality rate of sudden death at two years was comparable with the mortality rate of sudden death in other patients with permanent atrial fibrillation but without the history of such ventricular tachycardia, who underwent AV node ablation. These data suggest that patients with unstable ventricular tachycardia induced by rapid response of atrial fibrillation are not candidates for the cardioverter defibrillator therapy (16). Previous studies on radiofrequency and pacing therapy for atrial fibrillation provided insufficient data on the clinical course of such patients after these therapeutic procedures (17). However, the sudden death rates for studies with more than one year of follow-up were comparable with that in our study (18-20).

The main trigger for the induction of ventricular tachycardia was a rapid ventricular activation initiated by fast and uncontrolled transport of atrial fibrillation impulses across the AV node, which directly reduced ventricular refractoriness (21). By means of the same mechanism, atrial fibrillation can induce life-threatening ventricular tachycardia in patients with Wolff-Parkinson-White syndrome and otherwise normal heart, when conduction runs over an accessory pathway with a short refractory period (22). Although conduction properties of the AV node are different from those of accessory pathways, the potential of atrial fibrillation to induce ventricular tachycardia by a rapid ventricular activation is substantially higher in patients with structural heart disease, reduced left ventricular function, and high concentration of circulating catecholamines (7,23). A rapid ventricular response of permanent atrial fibrillation may also indirectly affect ventricular electrophysiology through their associated hemodynamic changes. A decrease in cardiac output during the fast rate may increase preload susceptibility to ventricular arrhythmias through mechanoelectrical coupling (24). Our patients with permanent atrial fibrillation and ventricular tachycardia induced by rapid ventricular activation fulfilled some of these conditions. At baseline examination, their ejection fraction was significantly lower and ventricular rate considerably higher than those in the control group. After ventricular rate controlling by AV node ablation and pacemaker implantation, these patients were free of rapid ventricular activation and its negative electrophysiological and hemodynamic consequences, and therefore were prone to similar risk of sudden cardiac death as the control group patients, who underwent the same therapeutic procedures.

Another pathophysiological mechanism related to irregular ventricular activation can also be responsible for the development of ventricular tachycardia in permanent atrial fibrillation. Even at well-controlled ventricular rate, atrial fibrillation results in irregular ventricular activation leading to marked short-long-short sequences (25). Irregular ventricular activation leads to inhomogeneous repolarization and thus to higher vulnerability predisposing to sustained ventricular tachycardia (26). This pathophysiologic mechanism for initiation of ventricular tachycardia has been recently supported by the analysis of stored cardioverter defibrillator electrograms with a documented onset of ventricular tachycardia or ventricular fibrillation in patients with persistent atrial fibrillation (27). Although we did not observe this mechanism in our patients with ventricular tachycardia, it is reasonable to presume that regulation of ventricular rate by AV nodal ablation could reduce the short-long-short sequences related to irregular ventricular activation in permanent atrial fibrillation.

In this study, the incidence of cardiac death and all-cause mortality was significantly higher in patients who had ventricular tachycardia induced by rapid ventricular response before the ablation than in patients without such a ventricular tachycardia. The main reason for that was a substantially higher incidence of deaths due to progressive heart failure in the patients with ventricular tachycardia induced by rapid ventricular response. This was concordant with the lower ejection fraction and higher NYHA classes in these patients at baseline evaluation as compared with that in the control group patients.

The main limitation of this study was a relatively small number of patients in the ventricular tachycardia group, which did not permit the analysis of end points in the prespecified subgroups of patients. Another potential limitation of this study was the fact that sudden cardiac death occurred in 7 patients within six months after ablation. Therefore, we cannot exclude the possibility that some instances of sudden cardiac death in this study could have been related to the ablation pro-

cedure itself (19,28). However, the lesions produced by radiofrequency current have not been shown to be arrhythmogenic, even when the current was delivered in the right or left ventricle (2,29). Furthermore, we did not observe a pacemaker malfunction in these patients, and most of them had a satisfactory junctional escape rhythm. Thus, we would suggest that the majority of sudden cardiac death episodes in our two study groups were related to the associated underlying heart disease.

In conclusion, radiofrequency catheter ablation of the AV node followed by pacemaker implantation had a beneficial effect in the treatment of patients with permanent atrial fibrillation and ventricular tachycardia induced by rapid ventricular response, whereby eliminating this arrhythmia. The clinical course of these patients was not influenced by sudden cardiac death, but by progressive heart failure. These data suggest that patients with permanent atrial fibrillation and ventricular tachycardia induced by rapid ventricular activation do not require cardioverter defibrillator therapy.

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