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Right atrial preference pacing algorithm in the prevention of paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients: a long term follow-up study

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Atrial Preference Pacing (APP) is a pacemaker (PM) algorithm that works by increasing the atrial pacing rate to achieve continuous suppression of a spontaneous atrial rhythm and prevent supraventricular tachyarrhythmias. We have previously shown that atrial preference pacing may significantly reduce the number and the duration of AF episodes in myotonic dystrophy type 1 (DM1) patients who are paced for standard indications. However, the role that APP therapies play in the prevention of AF in a long-term period remains still unclear. Aim of the present prospective study was to evaluate whether this beneficial effect is maintained for 24-months follow-up period.

To this aim, 50 patients with Myotonic Dystrophy type 1 who underwent dual-chamber PM implantation for first- and second-degree atrioventricular block, were consecutively enrolled and followed for 2 years. One month later the stabilization period, after the implantation, they were randomized to APP algorithm programmed *OFF* or *ON* for 6 months each, using a cross-over design, and remained in the same program for the second year. The results showed that while the number of AF episodes during active treatment (*APP ON phases*) was lower than that registered during no treatment (*APP OFF phases*), no statistically significant difference was found in AF episodes duration between the two phases. Furthermore, during the APP *OFF* and APP *ON* phases, the percentage of atrial pacing was 0 and 99%, respectively, while the percentage of ventricular pacing did not show differences statistically significant (11 vs. 9%, P = 0.2). Atrial premature beats were significantly higher during APP *OFF* phases than during APP *ON* phases. Lead parameters remained stable over time and there were no lead-related complications. Based on these 24-months follow-up data, we can conclude that, in DM1 patients who underwent dual-chamber PM implantation, APP is an efficacy algorithm for preventing paroxysmal AF even in long term periods.

Key words: myotonic dystrophy, atrial preference pacing, atrial fibrillation

Introduction

Myotonic dystrophy type 1 (DM1), or Steinert's disease, is an autosomal dominant neuromuscolar disorder with an incidence of 1 in 8.000 births and prevalence of 35/100.000 (1, 2). It is caused by an abnormal expansion of an unstable CTG repeats in the 3′ untranslated region of DMPK gene on chromosome 19 (3). This disease is characterized by myotonia and various multisystemic complications, most commonly of the cardiac, respiratory, endocrine, and central nervous systems. In addition, cardiac abnormalities, that can precede the skeletal-muscle one, contribute to a significant morbidity and mortality in these patients. The most frequent cardiac abnormalities in DM1 are conduction defects, such as first-degree atrioventricular block and/or arrhythmias (4-9) followed by less common manifestations such as dilated cardiomyopathy, heart failure, and mitral valve prolapsed (6). Heart block, the first and most clinically significant cardiac disease in this group of patients, is related to fibrosis of the conduction system and fatty infiltration of the His bundle (7). In order to identify patients affected by DM1 (10) or by other diseases (11,12) at risk of atrial or ventricular arrhythmias non-invasive electrocardiographic parameters as the value of P-dispersion, QT and JT dispersion could be useful. To prevent cardiac sudden death, the implantation of a pacemaker (PM) or cardioverter defibrillator (ICD) is required in 3-22% of cases (13-15). Paroxysmal atrial arrhythmias [atrial fibrillation (AF), atrial flutter, atrial tachycardia] frequently occur in DM1 patients. Pacemaker including

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detailed diagnostic functions may facilitate the diagnosis and management of frequent paroxysmal atrial tachyarrhythmias (ATs) that may remain undetected during conventional clinical follow-up. In a previous study (16), we showed that preference atrial pacing (APP) may significantly reduce the number and the duration of AF episodes in DM1 patients who are paced for standard indications during a 12-month follow-up period. However, the role that atrial pacing therapies play in the prevention of AF in a long-term period remains still unclear. Aim of the present prospective study was to evaluate whether this beneficial effect is maintained in the long term, during the 24-month follow-up period.

Patients and Methods

Patients selection and follow-up

From a large cohort of 212 genetically confirmed DM1 patients, periodically followed at the Cardiomyology and Medical Genetics of the Second University of Naples, 50 patients presenting first- or second-degree atrioventricular block and indication for permanent dual-chamber cardiac pacing, were consecutively included in the study. DM1 patients with patent foramen ovale, atrial septal aneurysm, severe mitral stenosis or regurgitation, left atrial enlargement, paroxysmal AF, sick sinus syndrome, and inducible ventricular tachycardia or who have undergone prior surgery involving the right atrium (coronary bypass or valvular heart surgery), were excluded. The study was conducted according to the Declaration of Helsinki and approved by the Institution's Ethical Committee. A written informed consent was obtained from the patients before implant, as requested by the Study protocol (8).

Patients were discharged 2 days post-implantation after confirming the electrical lead parameters. If required, a reprogramming was done to adjust atrial sensitivity and to optimize AV synchronous pacing. The conditions of the wound at the site of PM implantation were verified 7 days after. Patients were randomized – 1month post stabilization – to AT/AF prevention pacing features programmed OFF or ON. Patients crossed over to the opposite pacing program, six months later and remained in the same pacing program till the end of the study. Pharmacological therapy was not changed. Patients were re-examined at 1, 6, 12, 18 and 24 months thereafter, by clinical assessment, standard 12-lead electrocardiogram, 24h-Holter monitoring and echocardiogram. The device performance was assessed at every visit.

Device characteristics

All patients with DM1 underwent dual-chamber PM system implantation (Medtronic Adapta ADDR01, Medtronic Inc., Minneapolis, MN, USA). The right ventricular lead (Medtronic 4074 CapSure Sense) was positioned in the apex, under fluoroscopic guidance; the bipolar atrial screw-in lead (Medtronic 5076 CapSureFix) was positioned in the right atrial appendage (RAA) or on the right side of the interatrial septum (Bachmann's bundle – BB – region), according to optimal site, defined as the location with lowest pacing and highest sensing thresholds. To reduce atrial lead over-sensing, the sensitivity configuration was bipolar. To minimize confounding variables with different electrode materials and inter-electrode spacing, the identical model lead was used in all the patients. Similarly, PMs with identical behaviour and telemetric capabilities were used to assure accuracy in comparing measurements between the two groups of patients.

All the devices were programmed in AAI-DDD mode; the lower rate was set to 60 b.p.m. Mode switches were programmed to occur for atrial rates > 200 b.p.m. persisting for > 12 ventricular beats. Managed Ventricular Pacing algorithm (MVP, Medtronic Inc.) was enabled to promote the intrinsic conduction and to reduce the possible influence of high-percentage ventricular pacing on AF incidence. Atrial Preference Pacing (APP, Medtronic Inc.) was enabled according to the prospective programming compliance criteria. The devices used in this study were programmed to detect the episodes of atrial tachycardia and to record summary and detailed data, including atrial and ventricular electrograms (EGMs).

Endpoints

The primary endpoints were the number and the total duration of AF episodes recorded by PM diagnostics in APP ON phases compared with APP OFF phases during the 24-month follow-up period. The overall number of premature atrial beats, the number and the total duration of AF episodes and the percentage of atrial and ventricular pacing in synchronous rhythm during the observation period were carefully noted. For each AF episode, the device stored simultaneous atrial and ventricular EGMs. Atrial tachycardia episodes, identified by regular atrial activity, were excluded from the analysis. Data from the first 2 weeks of each 3-month cross-over period were excluded from the analysis to minimize carry-over effects.

Statistical analysis

Statistical analysis was performed using Student's t-test. P values < 0.05 were considered to be statistically significant. Continuous variables are expressed as mean ± standard deviation. Analyses were performed using the statistical package SPSS 11.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

From the cohort of 50 patients with DM1, first enrolled in the study, 10 were excluded due to following reasons: far-field ventricular sensing, despite refractory periods reprogramming (3 cases); atrial undersensing (4 cases); and persistent AF during follow-up (3 cases). The remaining 40 patients (29M:11F; age 51.3 ± 7.3) underwent dual-chamber PM implantation for first-degree atrio-ventricular block (AVB) with a pathological infra-Hissian conduction (18 patients), symptomatic type 1 AVB (12 patients), and type 2 second degree AVB (10 patients). No statistically significant differences in the electrical parameters (P-wave amplitude, pacing threshold, and lead impedance) nor in the medication intake were found at implantation, between the group of patients with RAA and in the group with BB lead placement. The baseline characteristics of the study population are shown in Table 1.

Atrial pacing and atrial fibrillation

A statistically significant difference was found in the number of AF episodes between no treatment (*APP OFF phases*) group and active treatment (*APP ON phases*) group, during the follow-up period. In fact during active treatment a lower number of AF episodes was registered compared with that registered during no treatment (134 ± 21 vs. 302 ± 35; p = 0.03).

Furthermore, while no statistically significant difference was found in the *overall* duration of AF episodes between the two phases (7987 ± 963 vs. 8690 ± 612 minutes; P = 0.07), a difference statistically different was obtained in the *mean* duration of AF episodes, that during *APP ON phases* was longer than that registered during *APP OFF phases* (95 ± 16 vs. 32 ± 11 min; p < 0.004). On the other hand, the ventricular pacing percentage did not show statistical variation (11% vs. 9%; P = 0.2) during both phases.

Atrial premature beats were significantly higher during *APP OFF* phases than during *APP ON* phases (58.651 ± 41.724 vs. 13.731 ± 9.652 beats; P = 0.005). No significant differences in atrial pacing capture, sensing threshold, and atrial lead impedances at both the implant and 24-month follow-up were found. Lead parameters remained stable over time and no lead-related complications were observed (see Table 2).

No differences were found in the number and duration of AF episodes and in the ventricular pacing rate concerning the site of implantation (RAA DM1 vs. BB DM1 subgroups).

Table 1. Characteristics of the study population.

Patients (n)	40
Age (years)	51.3 + 7.3
Sex (m/ f)	29/11
First degree AV block	18
Type 1 second degree AV block	12
Type 2 second degree AV block	10
QRS duration (ms)	91 ± 13
LVEDD (mm)	43,2 ± 3,5
LVESD (mm)	25,2 ± 2,5
IVSEDD (mm)	7,3 ± 1,1
LVPWEDD (mm)	6,7 ± 1,5
LAD (mm)	3,5 ± 0,3
Ejection fraction (%)	56 ± 3
ACE inhibitor therapy (%)	79
Angiotensin II receptor antagonists (%)	21
Magnesium Pidolate (%)	45
Coenzyme Q10 (%)	31

Discussion

Our clinical experience on a large group of implanted DM1 patients confirmed the data of literature (16) about the high occurrence of paroxysmal AF in patients implantated with PM.

Several studies (17-20) have documented that cardiac involvement in DM1 patients is not limited to the conduction system, as initially supposed, but cardiomyopathy, characterized by progressive selective fibrosis and scar replacement of initially unaffected areas, facilitating the onset and perpetuation of AF, is a peculiar part of the disease, as it happens for other neuromuscular disorders (21-24).

Because one of the causes of AF episodes could reside in the site of stimulation, recent papers (25-30) demonstrate that an alternative stimulation site, i.e the interatrial septum, in the region of Bachmann's bundle (BB) is the atrial site with better sensing and pacing threshold compared with the RAA and presents a low rate of sensing and pacing defects in a long term follow-up. These results were not confirmed by a recent work (31) that, comparing the right atrial appendage and Bachmann's bundle atrial pacing as sites of stimulation in 30 DM1 patients, failed to demonstrate a beneficial effect of BB stimulation in preventing atrial fibrillation.

Other studies (32, 33) have shown that atrial preference pacing (APP) may prevent the onset of AF through different mechanisms: prevention of the relative bradycardia that triggers paroxysmal AF; prevention of the bradycardia-induced dispersion of refractoriness; suppression or reduction of premature atrial contractions

that initiate re-entry and predispose to AF; preservation of atrioventricular synchrony, which in turn may prevent switch-induced changes in atrial repolarization, predisposing to AF. However the efficacy of the automatic atrial overdrive algorithms remains controversial (32-35). The ADOPT Trial (32) demonstrated that overdrive atrial pacing decreased significantly symptomatic AF burden in patients with sick sinus syndrome and AF by 25% and total atrial arrhythmia burden by 26.5%. In the SAFARI trial, Gold et al. (33) showed a statistically significant reduction in the AF burden only in the subgroup of patients with a high AF burden (≥ 6%). In the low AF burden group (≤ 6%), activation of prevention pacing algorithms did not result in the prevention of AF episodes.

On the other hand, Ogawa et al. (33) in the APP study, showed that, altough the total duration of AT tended to be reduced in patients with the APP algorithm ON, the reduction failed to reach statistical significance. Similarly, Camm et al. (35) in evaluating four atrial pacing algorithms-pace conditioning, premature atrial complexes (PAC) suppression, post-PAC response, and post-exercise response-demonstrated a 37% lower mean AF burden in the therapy group, but once again the difference did not reach a statistical significance (AFTherapy study). The same results were obtained by Sulke et al. (36) who evaluated the efficacy of atrial overdrive and ventricular rate stabilization pacing algorithms in patients with AF burden 1-50% and showed no difference in total AF burden between therapy and control groups of patients (PAFS study).

Table 2. Comparison between patients' characteristics during APP ON phases and APP OFF phases.

	APP ON phase	APP OFF phase	*P value*
P-wave amplitude (mV)	3.4 ± 1.3	2.9 ± 1.3	0.3
R-wave amplitude (mV)	10.7 ± 1.9	11.7 ± 3.0	0.07
Atrial capture threshold (V)	0.49 ± 0.30	0.55 ± 0.37	0.4
Ventricular capture threshold (V)	0.9 ± 0.29	1.2 ± 0.37	0.3
Atrial lead impedance (V)	600.89 ± 146.52	560.5 ± 192.87	0.2
Ventricular lead impedance (V)	780 ± 176	840 ± 189	0.4
Atrial pacing (%)	99	0	0,03
Ventricular pacing (%)	11	9	0,2
AF episodes (n)	134 ± 21	302 ± 35	0.03
Total duration AF (min)	7987 ± 963	8690 ± 612	0.07
Mean duration AF (min)	95 ± 16	32 ± 11	0.004
Atrial premature beats (n)	58651 ± 41724	13731 ± 9652	0.005

Conclusion

The present study has confirmed the data of literature about the preventive effect of atrial preference pacing on the number and the duration of AF episodes in DM1 patients who are paced for standard indications. Furthermore, based on 24-months follow-up period data, these data show that in DM1 patients who need dual-chamber PM implantation, atrial preference pacing is an efficacy algorithm for preventing paroxysmal AF, even in the long period.

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References

1. Emery AE. Heritability of common neuromuscular diseases. Neuromuscul Disord 2010;20:476.
2. Harper PS. Myotonic Dystrophy: some genetic problems. Birth Defects Orig Artic Ser 1974;10:120-5.
3. Harley HG, Brook JD, Rundle SA, et al. Expansion of an unstable DNA region and phenotypic variation in myotonic dystrophy. Nature 1992;355:545-6.
4. Phillips MF, Harper PS. Cardiac disease in myotonic dystrophy. Cardiovasc Res 1997;33:13-22.
5. Hawley RJ, Gottdiener JS, Gay JA, et al. Families with myotonic dystrophy with and without cardiac involvement.Arch Intern Med 1983;143:2134-6.
6. Nigro G, Comi LI, Politano L, et al. Cardiomyopathies associated with Muscular Dystrophies. In: Engel A, Franzini-Armstrong C. Myology. New York: Mac Graw-Hill 2004, pp. 1239-56 and references therein.
7. Nguyen HH, Wolfe JT III, Holmes DR Jr, et al. Pathology of the cardiac conduction system in myotonic dystrophy: a study of 12 cases. J Am Coll Cardiol 1988;11:662-71.
8. Dello Russo A, Mangiola F, Della Bella P, et al. Risk of arrhythmias in myotonic dystrophy: trial design of the RAMYD study. J Cardiovasc Med (Hagerstown) 2009;10:51-8.

9. Cudia P, Bernasconi P, Chiodelli R, et al. Risk of arrhythmia in type I myotonic dystrophy: the role of clinical and genetic variables. J Neurol Neurosurg Psychiatry 2009;80:790-3.
10. Magrì D, Piccirillo G, Bucci E, et al. Increased temporal dispersion of myocardial repolarization in myotonic dystrophy type 1: beyond the cardiac conduction system. Int J Cardiol 2012;156:259-64.
11. Nigro G, Russo V, Rago A, et al. Heterogeneity of ventricular repolarization in newborns with severe aortic coarctation. Pediatr Cardiol 2012;33:302-6.
12. Russo V, Rago A, Pannone B, et al. Dispersion of repolarization and beta-thalassemia major: the prognostic role of QT and JT dispersion for identifying the high-risk patients for sudden death. Eur J Haematol 2011;86:324-31.
13. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American college of Cardiology/ American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation 2002;106:2145-61.
14. Russo V, Rago A, D'Andrea A, et al. Early onset "electrical" heart failure in myotonic dystrophy type 1 patient: the role of ICD biventricular pacing. Anadolu Kardiyol Derg 2012;12:517-9
15. Lazarus A, Varin J, Babuty D, et al. Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: a multicenter diagnostic pacemaker study. J Am Coll Cardiol 2002; 40:1645-52.
16. Russo V, Rago A, Politano L, et al. The effect of atrial preference pacing on paroxysmal atrial fibrillation incidence in myotonic dystrophy type 1 patients: a prospective, randomized, single-bind cross-over study. Europace 2012;14:486-9.
17. Lazarus A, Varin J, Ounnoughene Z, et al. Relationships among electrophysiological findings and clinical status, heart function and extent of DNA mutation in myotonic dystrophy. Circulation 1999;99:1041-6.
18. Vignaux O, Lazarus A, Varin J, et al. Right ventricular MR abnormalities in myotonic dystrophy and relationship with intracardiac electrophysiologic test findings: initial results. Radiology 2002;24:231-5.
19. Vinereanu D, Bajaj BP, Fenton-May J, et al. Subclinical cardiac involvement in myotonic dystrophy manifesting as decreased myocardial Doppler velocities. Neuromuscul Disord 2004;14:188-94.
20. Dello Russo A, Pelargonio G, Parisi Q, et al. Widespread electroanatomic alterations of right cardiac chambers in patients with myotonic dystrophy type1. J Cardiovasc Electrophysiol 2006;17:34-40.
21. Rotundo IL, Faraso S, De Leonibus E, et al. Worsening of cardiomyopathy using deflazacort in an animal model rescued by gene therapy. PLoS One 2011;6:e24729.
22. Vitiello C, Faraso S, Sorrentino NC, et al. Disease rescue and increased lifespan in a model of cardiomyopathy and muscular dystrophy by combined AAV treatments. PLoS One 2009;4:e5051.
23. Lancioni A, Rotundo IL, Kobayashi YM, et al. Combined deficiency of alpha and epsilon sarcoglycan disrupts the cardiac dystrophin complex. Hum Mol Genet 2011;20:4644-54.
24. Politano L, Nigro G. Treatment of dystrophinopathic cardiomyopathy: review of the literature and personal results. Acta Myol 2012;31:24-30.
25. D'Andrea A, Salerno G, Scarafile R, et al. Right ventricular myocardial function in patients with either idiopathic or ischemic dilated cardiomyopathy without clinical sign of right heart failure: effects of cardiac resynchronization therapy. Pacing Clin Electrophysiol 2009;32:1017-29.
26. Nigro G, Russo V, Vergara P, et al. Optimal site for atrial lead implantation in myotonic dystrophy patients: the role of Bachmann's Bundle stimulation. Pacing Clin Electrophysiol 2008;31:1463-6.
27. Nigro G, Russo V, Politano L et al. Right atrial appendage versus Bachmann's bundle stimulation: a two-year comparative study of electrical parameters in myotonic dystrophy type-1 patients. Pacing Clin Electrophysiol 2009;32:1191-6.
28. Nigro G, Russo V, Rago A, et al. The main determinant of hypotension in nitroglicerine tilt-induced vasovagal syncope. Pacing Clin Electrophysiol 2012;35:739-48.
29. Sopher SM, Camm AJ. Atrial pacing to prevent atrial fibrillation? J Intervent Card Electrophysiol 2000;4:149-53.
30. Mehra R, Hill MRS. Prevention of atrial fibrillation/flutter by pacing techniques. In: Saksena S, Luderlitz B, eds. Interventional Electrophysiology: A Textbook, 2nd ed. Armonk, NY: Futura Publishing 1996, pp. 521-40.
31. Nigro G, Russo V, Politano L, et al. Does Bachmann's bundle pacing prevent atrial fibrillation in myotonic dystrophy type 1 patients? A 12 months follow-up study. Europace 2010;12:1219-23.
32. Carlson M, Ip J, Messenger J, et al. A new pacemaker algorithm for the treatment of atrial fibrillation. Results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). J Am Coll Cardiol 2003;42:627-33.
33. Gold M, Adler S, Fauchier L, et al. Impact of atrial prevention pacing on atrial fibrillation burden: primary results of the Study of Atrial Fibrillation Reduction (SAFARI) trial. Heart Rhythm 2009;6:295-301.
34. Ogawa H, Ishikawa T, Matsushita K, et al. Effects of right Atrial Pacing Preference in prevention of paroxysmal atrial fibrillation Atrial Pacing Preference Study (APP Study). Circ J 2008;72:700-4.
35. Camm AJ, Sulke N, Edvardsson N, et al. Conventional and dedicated atrial overdrive pacing for the prevention of paroxysmal atrial fibrillation – the AFTherapy study. Europace 2007;9:1110-8.
36. Sulke N, Silberbauer J, Boodhoo L, et al. The use of atrial overdrive and ventricular rate stabilization pacing algorithms for the prevention and treatment of paroxysmal atrial fibrillation: the Pacemaker Atrial Fibrillation Suppression (PAFS) study. Europace 2007;9:790-7.