News on cardiac arrhythmias - Part III

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SUDDEN CARDIAC DEATH IN STEINERT MUSCULAR DYSTROPHY: PRELIMINARY RESULTS OF THE RAMYD STUDY

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Background

Myotonic muscular dystrophy type 1 (DM1) is the most common type of autosomal dominant muscular dystrophies (1/8000 cases among Caucasians)[1]. The genetic defect associated with DM1 is an abnormal expansion of a cytosine-thymine-guanine (CTG) trinucleotide repeat located in the 3' end of the DMPK gene, on chromosome 19q13.3[2]. Normal alleles have from 5 up to 34 CTG, while DM1 alleles contain from 50 up to 2000 or more CTG repeats. In DM1 the muscle involvement is characterized by myotonia and muscle weakness. Usually symptoms become evident between the second and the fourth decade of life and slowly progress with time[3,4], but in a small number of cases DM1 occurs as a severe, congenital form, characterized by neonatal hypotonia, facial diplegia, joint contractures, psychomotor delay, respiratory failure[5]. Beside muscle, DM1 affects other organs, including eyes (cataract) endocrine (diabetes, thyroid dysfunction, hypogonadism) and nervous system (mental retardation), gastrointestinal tract (dysphagia, pseudo-obstruction) and the heart[3,4]. Cardiac involvement manifests as a selective and extensive impairment of the conduction system, usually not associated with any apparent structural heart disease. Such degeneration of the conduction system has been correlated with the significant incidence of sudden death (SD) observed in DM1 patients, ranging from 2 to 30% according to the literature data. In general, sudden cardiac death has been related to the development of conduction blocks, and in fact the implantation of a pacemaker is required with a relatively high prevalence in DM1 patients (from 3 to 22% of cases)[6-10]. Nevertheless, some studies have reported the occurrence of SD in patients with pacemaker[11,12]; these findings, together with reports of spontaneous or inducible ventricular tachycardia (VT)[11-16], would suggest a potential pathogenic role also of ventricular arrhythmias for the occurrence of SD in DM1. To this regard, several studies tried to characterize which type of cardiac conduction abnormality underlies the occurrence of SD in DM1[11,12], however, perhaps because of the small number of patients studied, they displayed a wide variability of results.

Another important issue is represented by the lack of prognostic factors useful to assess the risk of developing life-threatening arrhythmias either in individual or classes of DM1 patients. Some studies have attempted to ascertain the reliability of different markers, including clinical (age of symptom onset, degree of muscle severity)[5,17], genetic (number of CTG)[18,19] and instrumental (non-invasive cardiac tests) features[19-27], as prognostic indexes for the arrhythmic risk in DM1 patients, but again their results appeared controversial.

A last open question concerns the therapeutic approach versus life-threatening cardiac arrhythmias. A recent study by Lazarus et al.[15] seems to indicate that a more accurate evaluation of the arrhythmic risk in DM1 patients may be obtained through the use of invasive diagnostic procedures like electrophysiological study (EPS), and in fact by such procedure they were able to detect

both atrial and ventricular arrhythmias in many DM1 patients. These authors also pointed out that EPS may reveal conduction abnormalities not detectable by 12-lead standard ECG, and they suggested that the degree of severity of conduction defects estimated by EPS, particularly the lengthening of the HV interval, should be adopted as a major parameter for indicating the need of a prophylactic implant of a pacemaker in DM1 patients in order to prevent SD.

The usefulness of EPS both in the diagnosis and in the clinical management of cardiac complications in DM1 patients seems supported by other authors[16] who reported the successful treatment in a DM1 of a bundle branch reentry ventricular tachycardia (BBRVT) induced at EPS by radiofrequency ablation of the right or left bundle branch. The usefulness of devices with monitoring functions for diagnosis and treatment of cardiac arrhythmic complications in DM1 patients is supported by the results of the French multicenter study by Lazarus et al.[28]. In this study the authors have implanted pacemakers with a specific algorithm for Holter monitoring in 49 DM1 patients showing an HV interval > 70 ms at EPS, and they have been performing a 53-month clinical and instrumental follow-up. Data collected from pacemakers have documented paroxysmal atrioventricular (AV) blocks in 21 patients of cases and sino-atrial blocks in 4 patients. Furthermore analysis of the records of cardiac electric events revealed the presence of ventricular arrhythmias in 13 patients. Finally, no patient died of AV block during follow-up but 4 patients died suddenly and any arrhythmic cause has been possible excluded by pacemaker *post-mortem* interrogation in 2 cases of typical SD[28].

Based on these preliminary remarks, we propose[29], in collaboration with two other research groups and three UILDM sections (Rome, Naples, Milan) an Italian multicenter clinical research study, lasting 2 years, performed on a large group of DM1 patients (600 cases). Objectives of the study are: a) to estimate the incidence of arrhythmias and the clarification of the etiology of sudden cardiac death events occurring in DM1; b) to evaluate the usefulness of different non-invasive markers as prognostic indexes of the arrhythmic risk in DM1 patients; c) to identify therapeutic specific guidelines for the prevention and the treatment of arrhythmic events in DM1.

Specific aims

Primary objective. Estimation of the magnitude of the risk to develop cardiac arrhythmias in DM patients, with special attention to the characterization of the brady-tachyarrhythmic mechanisms underlying the occurrence of SD.

Primary endpoint. Actual incidence of cardiac critical events in DM patients. Events considered to be major cardiac events are SD, resuscitated cardiac arrest, ventricular fibrillation, sustained VT, sino-atrial and AV blocks. SD is defined as natural death due to cardiac causes heralded by an abrupt loss of consciousness within 1 hour of the onset of acute symptoms. The diagnosis of ventricular arrhythmias, sino-atrial and AV block is based on implanted device diagnostics or Holter monitor data.

Secondary objectives. The prognostic significance of diagnostic non-invasive and invasive procedures will be tested in order to predict the risk to develop cardiac arrhythmias in DM patients.

Therefore we will verify the utility of the data available by non-invasive diagnostic cardiac procedures, such as standard ECG, 24-hour ECG monitoring, signal-averaged ECG, echocardiography. Regarding this issue, we will also evaluate the prognostic significance of genetic data, in particular the number of CTG repeats in leukocyte, as well as of several clinical data, including family history, with particular regard to the occurrence of cardiac events, age at onset of the disease, severity of muscle involvement, age at onset of cardiac symptoms. Finally, we will test the prognostic significance of the data obtained by invasive procedures (EPS and implantable loop recorders), performed in patients selected according to specific inclusion criteria (see study plans).

The last objective is the identification of therapeutic specific guidelines for the prevention and the treatment of arrhythmic events in DM1.

Study plan

Patient selection. The inclusion criteria are: patients affected by MD1 and patients willing to provide a signed informed consent. The exclusion criteria are: age < 18 or > 70 years; ischemic cardiomyopathy; cardiomyopathy due to chronic excess of alcohol consumption (> 100 g/day); congenital heart disease; acquired valvular heart disease; metabolic cardiomyopathy: thyrotoxicosis, hypothyroidism, adrenal cortical insufficiency, pheochromocytoma, acromegaly; familiar storage and infiltrative diseases (hemochromatosis, glycogen storage, Hurler's syndrome, Niemann-Pick disease; primary, secondary, familial and hereditary cardiac amyloidoses); systemic diseases (connective tissue disorder, sarcoidosis); *peripartum* cardiomyopathy.

Data management. Data will be collected on each patient and documented on case report forms. In each center the investigator will store in a binder all forms, to permit the access to data and sources for monitoring, verification and audit of IRB/IEC and regulatory authority. All data will be sent to the data analysis center by means of an electronic data management system via Internet and will be stored in an electronic database.

Methods. All patients fulfilling the study inclusion criteria were enrolled in the study according to the enrolment procedure.

The neurological status of DM1 patients was assessed according to the neurologic evaluation procedure specified in the protocol. This evaluation will be repeated at the end of the study.

A genetic testing was performed according to the genetic evaluation procedure.

At enrolment a cardiac evaluation was performed consisting of:
- clinical cardiac evaluation (clinical cardiac evaluation procedure) repeated every 6 months;
- non-invasive instrumental cardiac evaluation: a) standard 12-lead ECG (standard 12-lead ECG procedure) repeated every 6 months; b) ECG signal-averaging (ECG signal-averaging procedure) for the detection of late ventricular potentials, repeated every 12 months; c) 24-Hour ECG Holter monitoring (24-Hour ECG Holter monitoring procedure) repeated every 6 months, with heart rate variability analysis; d) echocardiographic evaluation (echocardiographic evaluation procedure) repeated every 12 months.

Enrolled patients did not receive antimyotonic medication even if in the presence of severe clinical myotonia.

At enrolment all antiarrhythmic therapies were suspended.

Based on results of non-invasive instrumental cardiac evaluation at the enrolment or at follow-up, all patients fulfilling the EPS inclusion criteria underwent an EPS according to the EPS procedure.

Electrophysiological study. *Inclusion criteria.* Sinus node dysfunction symptomatic or asymptomatic (sinusal pause > 3.0 s; sinus bradycardia < 40/min); symptomatic or asymptomatic AV conduction anomaly (first degree AV block with PR interval > 240 ms, higher grade AV block with or without intraventricular conduction defects); intraventricular conduction anomalies (left bundle branch block, bifascicular block); association of first degree AV block with left fascicular anterior or posterior block; patients referring symptoms suggestive of arrhythmic disorders (syncope, lipothymia, palpitations); patients with documented atrial and ventricular arrhythmias (atrial tachycardia, atrial fibrillation/flutter, frequent premature ventricular beats, non-sustained and sustained VT); positive family history for SD, ventricular fibrillation, sustained VT, pacemaker or cardioverter-defibrillator implant.

Methods. Introduction of three quadripolar catheters through the right femoral vein or, alternatively, through a different central access (jugular or subclavian vein, in this case a mono-catheter technique).

Positioning of the catheter in the right atrium, His and right ventricle using a fluoroscopic guide (apex and successively the outflow tract).

At the beginning of each study basal parameters (PR, QRS, QT, QTc, CL, AH, HV) were recorded.
1) Atrial study:
- evaluation of the functionality of the sinus node: calculation of the sinus node recovery time and corrected sinus node recovery time;
- anterograde evaluation of the 1:1 AV conduction until reaching the Wenckebach point;
- function curve of the AV node (double drive, if possible, 600 and 400) and measurements of the atrial refractory period and of the AV node;
- induction attempt of supraventricular arrhythmias with programmed atrial stimulation up to triple extrastimulation and double drive (600 and 400, always if possible);
- whenever an atrial arrhythmic substrate is evident, supporting the symptoms of patients (for example, evidence of double physiology of the AV node), repeat the atrial study after the infusion of isoproterenol (in increasing doses, starting from 1 μg/min up to a maximum of 5 μg/min to obtain a gradual increase of the heart rate of at least 30% with respect to the baseline).
2) Ventricular study:
- the study is obtained stimulating both from the apex and from the outflow tract of the right ventricle;
-measure the 1:1 ventriculo-atrial conduction until block;
- programmed ventricular stimulation using double drive (600 and 400) up to triple extrastimulus;
- because of the higher incidence of BBRVT in this pathology, a sequence of extrastimuli with long-short cycle will be used in addition to the one previously mentioned;
- if BBRVT is not obtained by such a way of stimulation, one should consider the opportunity to repeat the stimulation under isoproterenol infusion;
- in the case of occurrence of VT, the length of the tachycardia cycle, HV or VH interval, a possible retroconduction, axis and morphology, symptoms, and hemodynamic tolerability will be evaluated, and – if sustained – indicated the means of interruption (example: overdrive or DC shock).

Pacemaker implant criteria. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines will be adopted in patients with AV blocks, and in those with sinus node dysfunction. Furthermore, a pacemaker will be implanted in all patients showing an HV interval > 70 ms, even if asymptomatic.

Cardioverter-defibrillator implant criteria. The criteria for the implant of a cardioverter-defibrillator will follow the indications of class I of the ACC/AHA guidelines.

Loop recorder implant criteria. All patients submitted to EPS that, according to the results of the study, will not fit into the criteria for a pacemaker or implantable cardioverter-defibrillator, will receive the implant of a loop recorder if showing an HV interval between 55-70 ms.

All patients implanted with a device will be monitored via in hospital/clinic follow-up visits at 1 month from the implant and every 6 months (1 month for

patients implanted with loop recorder) according to the device follow-up procedure. Further controls will be also performed if required by the patients. In these patients an EPS will be repeated at the end of the study.

Procedures schedule. See figure 1.

Statistical analysis. Summary data will be expressed as means ± standard deviation or percentages of patients. Differences between mean data will be compared by Student's t-test for gaussian variables and by Mann-Withney or Wilcoxon non-parametric test for non-gaussian variables.

Differences in proportions will be compared by χ^2 analysis or exact Fisher's test, as appropriate.

Correlations between variables will be calculated by Pearson or Spearman method, respectively for gaussian or non-gaussian distributions. A p value of < 0.05 for two-sided comparisons is considered as statistically significant. Magnitude of arrhythmic risk and number of survival patients will be studied by calculating Kaplan-Meier curves which show the cumulative percentage of event-free patients during the follow-up. To compare differences between two or more Kaplan-Meier curves, the log rank test will be used and a p value of < 0.05 is considered as statistically significant.

Sample size. To determine the sample size for estimating a population proportion, based on a confidence interval, one requires the following information: desired interval width (d), desired confidence level ($1 - \alpha$), a crude estimate or a guess of the population proportion. With this information, the following formula can be used to estimate the needed sample size:

$$n = \frac{4z^2_{1-\alpha/2}pq}{d^2}$$

Each patient having a cardiac critical event is considered a failure. The failure rate estimate in this type of situation requires two-sided confidence interval. From previous studies[28,30] we assume that the incidence of critical cardiac events in a 2-year long observation period is 25%. We want to be 95% confident to characterize the critical cardiac events incidence within 30% of the true value, being our best prediction of the actual incidence equal to 25%. Sample size to measure an incidence in the range (25.0 ± 7.5%) is 537 patients. Considering a 10% of lost to follow-up patients, we want to enroll 600 patients.

Preliminary results

To date 174 patients with a genetic diagnosis of MD have been enrolled (104 males, 70 females, mean age 42 ± 15 years). All patients underwent a complete cardiac work-up. Heart rate variability analysis and ECG signal-averaged were performed in 90 and 59 patients respectively. Patients with symptoms or brady-tachyarrhythmias underwent an EPS.

Standard ECG documented sinus bradycardia (< 50 b/min) (7%), AV conduction defects (27%) and supraventricular tachycardia (3%), sustained VT in 1 case. Holter ECG showed bradyarrhythmias, AV conduction defects and ventricular pauses in 49% of patients; sustained VT (12%), non-sustained supraventricular tachycardia (18%) and sustained supraventricular tachycardia (3%) were found. At echocardiographic evaluation 9 patients had an ejection fraction < 50%. A significant decrease

				Every			
		Enrolment	1 month (± 15 days)	1 month (± 15 days)	6 months (± 1 month)	12 months (± 2 months)	End study (2 years)
Neurological evaluation		√					√
Genetic evaluation		√*					
Cardiac evaluation	Clinical evaluation	√			√		√
	12-lead ECG	√			√		√
	ECG signal-averaging	√				√	√
	24-hour Holter ECG	√			√		√
	Echocardiography	√				√	√
	EPS (for patients fulfilling inclusion criteria)	√ (when criteria are fulfilled)					√
	Devices follow-up	√	√	√**	√		√

Figure 1. *EPS = electrophysiological study. * in all patients who received a genetic testing 2 years earlier or more; ** for implantable loop recorder holders.*

in SDNNi was found in MD patients compared to 50 healthy age-matched controls (61.5 ± 21.5 vs 122.2 ± 46.6), as well as a depression of parasympathetic activity (high frequency components 526.6 ± 595.9 vs 997.3 ± 289.4 ms^2) (both $p < 0.05$). ECG signal-averaged showed the presence of late potentials in 20 patients (34%). EPS was performed in 69 patients, showing a sinus node dysfunction in 9% of patients, an abnormal 1:1 AV conduction in 23% of patients and abnormal HV interval (> 70 ms) in 49% of patients. Syncopal VT were induced in 19 patients (28%) and supraventricular tachycardia in 7 patients (10%). The proportion of patients with positive late potentials was similar in patients with normal and abnormal HV interval. All the patients with inducible VT at EPS had presence of late potentials while in the group without inducible VT the prevalence of late potentials was 41% ($p = 0.02$).

Pacemaker, implantable cardioverter-defibrillator and loop recorder follow-up. In 45 patients (24 males, 21 females, mean age 48 ± 10 years) 25 pacemakers, 12 cardioverter-defibrillators and 8 loop recorders were implanted. During 13 ± 8 months of follow-up, 3 patients died for no arrhythmic cause.

Among pacemaker holders, a progressive pathological lengthening of the AV interval was documented in 7 patients, a sinus block and a complete AV block in 2 patients; sustained supraventricular tachyarrhythmias (supraventricular tachycardia) (n = 11), non-sustained (n = 2) and sustained VT (n = 2), not documented at EPS, were also recorded by the pacemaker diagnostics.

A symptomatic sinus pause of 4.7 s was documented in a patient with a loop recorder who consequently underwent pacemaker implant.

Three out of the 12 patients implanted with a cardioverter-defibrillator received therapeutic interventions due to VT and ventricular fibrillation (2 appropriate DC shock, 1 antitachycardia pacing). Sustained supraventricular tachycardia were documented in 5 patients with implantable cardioverter-defibrillator.

Conclusion

Conduction system abnormalities, arrhythmias and, less commonly, myocardial dysfunction and angina are observed in patients with DM1 and may occasionally represent the initial manifestations of disease, even in the absence of overt neuromuscular involvement. Thus, cardiologists should be aware of this diagnosis. Conversely, in all patients presenting with DM1 a careful clinical and diagnostic evaluation needs to be performed for the identification of patients at risk of major cardiac events. An attitude of a low threshold for invasive procedures is suggested, considering the unclear rate of cardiac disease progression and the risk of SD in some subsets of patients. Several questions are still unanswered. Future studies are needed in order to improve the identification of patients at risk of SD. The prospective, long-term Italian multicenter RAMYD study (risk of arrhythmia in myotonic dystrophy) is now ongoing which will hopefully contribute to the formulation of evidence-based guidelines for the management of cardiac conditions associated with DM1.

The preliminary results of this study support the high prevalence of arrhythmic disorders. Heart rate variability and late potentials might help stratifying the arrhythmic risk in these patients. Furthermore the severe progression of bradyarrhythmias and the occurrence of spontaneous tachyarrhythmias in MD1 patients strongly suggest the prophylactic use of implantable devices with diagnostic and therapeutic capabilities.

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References

1. Ashizawa T, Epstein HF. Ethnic distribution of myotonic dystrophy gene. (letter) Lancet 1991; 338: 642-3.
2. 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.
3. Steinert H. Myopathologische Beitrge 1. ber das klinische und anatomische Bild des Muskelschwunds der Myotoniker. Dtsch Z Nervenheikld 1909; 37: 58-104.
4. Harper PS. Myotonic dystrophy. 2nd edition. London: WB Saunders, 1989.
5. de Die-Smulders CE, Hweler CJ, Thijs C, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain 1998; 121: 1557-63.
6. Prystowsky EN, Pritchett EL, Roses AD, Gallagher J. The natural history of conduction system disease in myotonic muscular dystrophy as determined by serial electrophysiologic studies. Circulation 1979; 60: 1360-4.
7. Florek RC, Triffon DW, Mann DE, Ringel SP, Reiter MJ. Electrocardiographic abnormalities in patients with myotonic dystrophy. West J Med 1990; 153: 24-7.
8. Hawley RJ, Milner MR, Gottdiener JS, Cohen A. Myotonic heart disease: a clinical follow-up. Neurology 1991; 41: 59-62.
9. Fragola PV, Autore C, Magni G, Antonini G, Picelli A, Cannata D. The natural course of cardiac conduction disturbances in myotonic dystrophy. Cardiology 1991; 79: 93-8.
10. Fragola PV, Luzi M, Calo L, et al. Cardiac involvement in myotonic dystrophy. Am J Cardiol 1994; 74: 1070-2.
11. Grigg LE, Chan W, Mond HG, Vohra JK, Downey WF. Ventricular tachycardia and sudden death in myotonic dystrophy: clinical, electrophysiologic and pathologic features. J Am Coll Cardiol 1985; 6: 254-6.
12. Hiromasa S, Ikeda T, Kubota K, et al. Ventricular tachycardia and sudden death in myotonic dystrophy. Am Heart J 1988; 115: 914-5.
13. Motta J, Guilleminault C, Billingham M, Barry W, Mason J. Cardiac abnormalities in myotonic dystrophy. Electrophysiologic and histopathologic studies. Am J Med 1979; 67: 467-73.
14. Perloff JK, Stevenson WG, Roberts NK, Cabeen W, Weiss J. Cardiac involvement in myotonic muscular dystrophy

(Steinert's disease): a prospective study of 25 patients. Am J Cardiol 1984; 54: 1074-81.
15. 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.
16. Merino JL, Carmona JR, Fernandez-Lozano I, Peinado R, Basterra N, Sobrino JA. Mechanisms of sustained ventricular tachycardia in myotonic dystrophy: implications for catheter ablation. Circulation 1998; 98: 541-6.
17. Church SC. The heart in myotonia atrophica. Arch Intern Med 1967; 119: 176-81.
18. Melacini P, Villanova C, Menegazzo E, et al. Correlation between cardiac involvement and CTG trinucleotide repeat length in myotonic dystrophy. J Am Coll Cardiol 1995; 25: 239-45.
19. Clarke NR, Kelion AD, Nixon J, Hilton-Jones D, Forfar JC. Does cytosine-thymine-guanine (CTG) expansion size predict cardiac events and electrocardiographic progression in myotonic dystrophy? Heart 2001; 86: 411-6.
20. Colleran JA, Hawley RJ, Pinnow EE, Kokkinos PF, Fletcher RD. Value of the electrocardiogram in determining cardiac events and mortality in myotonic dystrophy. Am J Cardiol 1997; 80: 1494-7.
21. Baciarello G, Villani M, Di Maio F, Sciacca A. Late surface potentials in myotonic dystrophy with ventricular tachycardia. Am Heart J 1986; 111: 413-4.
22. Fragola PV, Calo L, Antonini G, et al. Signal-averaged electrocardiography in myotonic dystrophy. Int J Cardiol 1995; 50: 61-8.
23. Babuty D, Fauchier L, Carbi DT, et al. Significance of late ventricular potentials in myotonic dystrophy. Am J Cardiol 1999; 84: 1099-101.
24. Hiromasa S, Ikeda T, Kubota K, et al. Myotonic dystrophy: ambulatory electrocardiogram, electrophysiologic study, and echocardiographic evaluation. Am Heart J 1987; 113: 1482-8.
25. Viitasalo MT, Kala R, Karli P, Eisalo A. Ambulatory electrocardiographic recording in mild or moderate myotonic dystrophy and myotonia congenita (Thomsen's disease). J Neurol Sci 1983; 62: 181-90.
26. Fragola PV, Ruscitti GC, Autore C, et al. Ambulatory electrocardiographic monitoring in myotonic dystrophy (Steinert's disease). A study of 22 patients. Cardiology 1987; 74: 362-8.
27. Forsberg H, Olofsson BO, Andersson S, Henriksson A, Bjerle P. 24-Hour electrocardiographic study in myotonic dystrophy. Cardiology 1988; 75: 241-9.
28. Lazarus A, Varin J, Babuty D, Anselme F, Coste J, Duboc D. 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.
29. Pelargonio G, Dello Russo A, Sanna T, De Martino G, Bellocci F. Myotonic dystrophy and the heart. Heart 2002; 88: 665-70.
30. Mammarella A, Paradiso M, Paoletti V, et al. Cardiac critical events in myotonic dystrophy: relationship with the severity of neuromuscular disease. Eur J Intern Med 1999; 10: 198-201.

LASER CATHETER ABLATION OF ARRHYTHMIAS

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Purpose of the study was to compare safety and effectiveness of various methods of transcatheter ablation of arrhythmias including DC shock, radiofrequency current, microwave, ultrasound, laser, and cryoablation.

From July 1986 to August 2000, 1232 endo/epimyocardial lesions in 104 dogs and 661 endocardial laser applications in 69 patients (atrial fibrillation 37, atrioventricular node reentrant tachycardia 24, atrial flutter 12, accessory pathway 7, ventricular tachycardia 4, atrial tachycardia 2, inappropriate sinus tachycardia 1) were evaluated. Results were compared with those of the other above-mentioned methods, obtained in our or in other electrophysiology laboratories when applying the same or comparable techniques and a similar amount of energy. For Nd:YAG, 1064 nm, laser application at 5-25 W, 5-60 s a special catheter was developed for non-contact irradiation, simultaneous local ECG recordings and saline irrigation. Left heart catheterization was performed by using a novel transseptal laser puncture set. Gross pathology and histology of lesions were examined after 2-3 hours, 2-3 days and up to 3.5 years. Follow-up included clinical exam, Holter, ECG at rest, and, in addition, in patients event recorder, echo, exercise tests, and D-dimer serum levels.

Only the laser method met all the following criteria: 1) stable orthogonal positioning of the steerable catheter system upon the area of interest in the beating heart; 2) linear growth of the lesion with the amount of energy delivered; 3) the largest homogeneous lesions of clear-cut coagulation necrosis; 4) without unwanted effects on the heart: without tissue vaporization and crater formation, thrombogenic or arrhythmogenic effects; no damage of chordae or heart valves, nor of intramural or epicardial coronary vessels even after direct irradiation; 5) controllability of lesion formation by the dwindling of the amplitudes of potentials in the local electrograms; 6) reversibility of the heights of the amplitudes after 5-10 s of irradiation (laser mapping); 7) easy handling, no need of: back-paddle, atena, gas supply, etc.; 8) the best prospects for development of other cardiovascular laser applications such as the transseptal approach.

In patients (37 males, 32 females, mean age 59 ± 17 years) repeated ablation procedures were needed because of another arrhythmia in 9 and because of recurrences in 2. The mean procedure duration was 118 ± 72 min and X-ray exposure times were 13.2 ± 12.2 min. Laser applications at 15-20 W, 7.2 ± 6.2/patient; irradiation times were 155 ± 186 s. Total energy applied was 2769 ± 2862/patient. Laser application were without any kind of complications and were effective except in one attempt at atrial fibrillation ablation. In the follow-up of 3.5-15.8 years 62 of 69 patients were cured from the arrhythmia, whereas 7 improved. One died 6 months after the laser treatment in a home accident and anoth-

er patient 7 months thereafter at the intensive care unit, several hours following attempted antiarrhythmic surgery for accessory pathway/atrial fibrillation.

As compared to the other methods tested, the laser method is the most effective and best controllable technique for catheter ablation of arrhythmias and it bears the lowest risk, acutely and in the long term, when using the laser catheter system described. The laser method has become the therapy of choice in our electrophysiology laboratories.

Cardiac resynchronization therapy utilizing the right ventricular outflow tract combined with left ventricular pacing: which patients can benefit?

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Background. Multisite biventricular stimulation has been recognized as a valid non-pharmacological alternative for treating patients with congestive heart failure, NYHA functional class III-IV, optimal medical therapy and left bundle branch block. Although much has been researched on the best location for the left ventricular lead (LVL), virtually no studies have been made to find the optimal position for the right ventricular leads (RVL).

Aim. To evaluate the acute hemodynamic effect of cardiac resynchronization therapy (CRT) in patients with RVL placed in the anterior-septal outflow tract.

Methods. Eleven patients with severe congestive heart failure, sinus rhythm, QRS ± 120 ms were implanted with a CRT device (Renewal, Guidant). Tissue Doppler imaging and M-mode have shown a higher asynchrony when in proximity to the septal wall. Thus the RVLs were placed in the anterior-septal outflow tract position, while the LVLs in the post-lateral wall to obtain the higher delay between the two ventricular electrograms. The effect of CRT has been assessed with color Doppler echocardiography and tissue Doppler imaging using ejection fraction, stroke volume and dP/dT parameters.

Results. A shortening of the QRS and a significant improvement of in ejection fraction, stroke volume and dP/dT was observed.

Conclusions. In patients with a higher asynchrony in proximity to the septal wall, the placing of the RVL in the anterior-septal right ventricular outflow tract position has been found to be effective in resynchronizing the septal wall and in improving ejection fraction, stroke volume and dP/dT.

Catheter ablation of chronic atrial fibrillation: how far are we?

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Introduction

Radiofrequency catheter ablation (RFCA) is a well-established treatment for atrial fibrillation (AF). Different electrophysiologic mechanisms are advocated for the initiation and maintenance of AF. Firing foci located in the pulmonary veins can trigger paroxysms of AF, and radiofrequency current delivered at these foci can eliminate the arrhythmia. Even with a high success rate of this approach, some triggering foci could remain undiscovered if the mapping study is carried out with conventional techniques. Therefore, modification of the atrial substrate responsible for the maintenance of AF may become an effective therapeutic alternative[1-3]. In chronic AF, the clinical scenario is more complicated, because macroreentrant fibrillatory process involving the atrial musculature is critical to sustain the arrhythmia. Previous surgical interventions have already shown that chronic AF can be prevented by multiple incisions in the atria, especially in the left atrium that is crucial for the maintenance of AF, achieving a success rate of 71-91%[4]. In the most recent years, several investigators have attempted to mimic the surgical procedures[4], by creating linear lesions by RFCA[1-3]. A critical step to make left linear lesions work is the continuity of the lesions, because it is well proved that the occurrence of gaps along the lines can be proarrhythmic, causing new clinical atrial arrhythmias. The clinical availability of a non-contact mapping (NCM) system (EnSite, Endocardial Solution, Inc., St. Paul, MN, USA) that detects farfield endocardial potentials from a multielectrode array catheter and provides three-dimensional reconstruction of cardiac chambers, can allow immediate and simultaneous identification of a propagation vector along all sites of the ablation line. Based on these considerations, the aim of this pilot study was to assess the feasibility and safety of using a NCM system in the left atrium, investigate the ability of the system in guiding creation of linear lesions and determine the impact of linear lesion continuity on ablation success.

Methods

The patient population consisted of 11 patients (8 males, mean age 56 ± 8 years) with chronic AF, refractory to several antiarrhythmic drugs. All patients were considered eligible for RFCA of the atrioventricular junction with subsequent pacemaker implantation and

were symptomatic for severe palpitations, dyspnea and reduced daily activity. Patients were excluded if there was evidence of left atrial thrombus detected by transesophageal echocardiogram, severe mitral or aortic valve disease, or any other cardiac condition requiring open heart surgery. All patients had already had one or more previous RFCA attempts. In detail, each patient underwent pulmonary vein isolation procedure, in 2 patients also an attempt of right side compartmentalization was previously performed. In one patient, a left side compartmentalization by cryoenergy was carried out 2 years earlier. Each patient was asked to discontinue warfarin treatment 4 days before the procedure and start low-molecular heparin subcutaneously as to ensure an almost normal international normalized ratio at time of ablation.

Non-contact mapping system and its placement. The NCM system has been already validated and elsewhere described[5,6]. It consists of a 9F catheter with a braid of 64 insulated wires woven over a 7.7 ml balloon. Once the system has remotely sensed electrical potentials from the endocardium, it provides a method to establish a three-dimensional geometry of the left atrium by tracing the inner surface with a standard ablation catheter from which a locator signal is transmitted. Once the transseptal puncture was performed, under the fluoroscopic guidance, the NCM catheter was advanced over the guidewire across the interatrial septum into the left atrium and positioned as close as possible to the center of the chamber. A second transseptal puncture was provided as to permit the ablation catheter to be properly maneuvered in the left atrium. The left atrial geometry was then established and care was taken to accurately define the four pulmonary veins, the left posterior free wall and the mitral annulus. Throughout the study, heparin was continuously infused as to maintain an activated clotting time of about 300 s.

Ablation procedures: left atrial line design. On the basis of previous surgical experience[7], we chose to create two linear lesions in the left atrium. A line connecting the two superior pulmonary veins and a line connecting the most lateral portion of the mitral annulus and the base of the left atrial appendage, passing by the ostium of the inferior pulmonary vein. Guided by the NCM system, radiofrequency current was delivered through an irrigated tip electrode catheter, setting a temperature of 45°C and power of 40 W for 60-90 s. At the beginning of the procedure, a 20-pole diagnostic catheter was placed as to record in within the coronary sinus with the distal 10 poles and the right antero-lateral wall with the proximal 10 poles. Sinus rhythm was restored by external cardioversion in each patient as to ensure baseline activation sequence analysis during regular sinus rhythm and during pacing from distal coronary sinus, right atrial appendage and left atrial appendage. The same stimulation protocol was carried out after creation of each ablation line and pacing was also performed from each side of lines as to prove an effective bidirectional block and exclude any gap along the lines. After ablation, a transthoracic echocardiogram was performed, and each patient was monitored for 24 hours. Continuous telemetric monitoring was ensured for the following days and, each patient was maintained on antiarrhythmic medications, warfarin and beta-blocker treatment was added when possible.

Follow-up. Patients were seen in outpatient clinic at 1, 3 and 6 months after ablation, thereafter every 6 months or anytime the patient had symptoms that could be related to recurrence or documentation of AF. Due to the clinical presentation of the arrhythmia (i.e. chronic and refractory to medication) the success of the procedure was considered the maintenance of regular sinus rhythm with or without antiarrhythmic medications.

Results

In all patients, RFCA was carried out during sinus rhythm as to allow the NCM system to properly analyzed the activation pattern before and after creation of linear lesions. In all patients, the EnSite catheter was successfully positioned in the left atrium, allowing the three-dimensional reconstruction of the chamber. For the left isthmus line, activation pattern was analyzed off-line during sinus rhythm and during pacing from the distal coronary sinus and compared with the activation pattern after creation of the line. Completeness of this line was achieved with a mean number of 11 ± 5 radiofrequency applications. Pacing anteriorly and posteriorly to the line ensured the presence of bidirectional conduction block along the line, as clearly shown by the color-coded isopotential maps from NCM system. In all instances, the continuity of the line was associated with double potentials along the line and, in 8/11 patients pacing from the left atrial appendage showed reversion of the coronary sinus activation, being the distal portion of the coronary sinus, the area with the latest activation. Interestingly, in the remaining 3 patients, complete reversion of the coronary sinus activation was achieved only once the roof line was created. The roof line was completed with a mean number of 15 ± 7 radiofrequency current applications and a mean number of 3 ± 1 gaps was identified by NCM system. Lack of a standardized activation pattern reference (as the coronary sinus activation for the left isthmus line), made NCM the pivotal system to prove the continuity of the roof line and the occurrence of bidirectional block along the line. Also for this line, continuity of the lesion was associated with double potentials. The procedural parameters are reported in table I.

Bidirectional block along each line was assessed by placing the “virtual” electrodes at the opposite side of the stimulation site, by demonstrating that the recruit-

Table I. Procedural parameters.

Duration of the procedure (min)	234 ± 50
Fluoroscopy time (min)	52 ± 12
Time to yield geometry (min)	18 ± 12
No. radiofrequency applications	27 ± 14

ment of the tissue at the virtual electrodes was very late (> 150 ms) as compared to the area where the pacing was performed. For each patient, bidirectional block was demonstrated for each line with the color-code isopotential maps. No complications procedure-related were documented. In 3 patients, recurrence of AF was documented in the first 48 hours, then sinus rhythm was successfully restored with external cardioversion. In the remaining 8 patients, regular sinus rhythm was documented by continuous ECG telemetry. Before discharge, pericardial effusion was ruled out by a transthoracic echocardiogram. Each patient was discharged on warfarin nand antiarrhythmic medications, 6 patients with amiodarone, 3 with flecainide and 2 with propafenone. Beta-blocker treatment was added when possible (8 patients).

Follow-up. Over a mean follow-up of 10 ± 2 months, 8 patients are in stable sinus rhythm on antiarrhythmic drugs, 1 patient has paroxysmal episodes of AF, 1 patient recurrences of atypical atrial flutter and the remaining patient is in chronic AF.

Discussion

The study proves the feasibility and safety of NCM navigational system for guiding creation of linear lesions in the left atrium to cure chronic AF. One the most striking findings was the usefulness of the system to assess the continuity of the predesigned lines and the ability to disclose gaps along the lines. Furthermore, the NCM system allowed to markedly reduce the fluoroscopy time, since the three-dimensional reconstruction permits to reliably navigate in the left atrium without the aid of the fluoro images. These findings can be of value when linear lesions are deemed to be critical for curing chronic AF. This concept has been already demonstrated by surgical experience, where atriotomies are intended to reduce the area available for the completion of wavelet circuits, and therefore their number has to be reduced. Based on the surgical results, several investigators have devised different transcatheter approaches to produce compartments in the left atrium as to control chronic AF. In very few instances, the continuity of the left atrial lesions has been validated[8]. Other authors have previously used the NCM navigation system in the right atrium to validate linear lesions[9], but this approach is usually poorly effective in curing chronic AF. The use of NCM as a navigation system in the left atrium may favor creation of lesions without gaps and, therefore may greatly improve the clinical outcome. The absence of complications in our pilot study could boost the use of the system in the left atrium and represent a reliable guide for treating chronic AF. One of the advantages of using the NCM is that the system can reliably distinguish conduction delay from conduction block as defined by contact mapping; this may have great impact when compartments are created in the left atrium. At the present time, catheter ablation of chronic AF is still an investigational approach with long procedural time and associated with potential clinical risks. NCM is a feasible and reliable support to guide catheter ablation of chronic AF in the left atrium, because the cure of the arrhythmia is strictly linked to continuity of linear lesions and the system allows identification of gaps, which are mainly responsible for arrhythmia recurrences.

References

1. Swartz JF, Pellersel G, Silvers J, et al. A catheter-based curative approach to atrial fibrillation in humans. (abstr) Circulation 1994; 90: I-335.
2. Haissaguerre M, Jais P, Shah DC, et al. Right and left atrial radiofrequency catheter therapy of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 1996; 7: 1132-44.
3. Kottkamp H, Hindricks G, Hamel D, et al. Intraoperative radiofrequency ablation of chronic atrial fibrillation: a left atrial curative approach by elimination of anatomic "anchor" reentrant circuits. J Cardiovasc Electrophysiol 199; 10: 772-80.
4. Cox JL, Boineau JP, Schuessler RB, et al. Five-year experience with the Maze procedure for atrial fibrillation. Ann Thorac Surg 1993; 56: 814-24.
5. Schilling RJ, Peters NS, Davies DW. Simultaneous endocardial mapping in the human left ventricle: comparison of contact and reconstructed electrograms during sinus rhythm. Circulation 1998; 98: 887-98.
6. Schilling RJ, Khadish AH, Peters NS, et al. Endocardial mapping of atrial fibrillation in the human right atrium using a non-contact catheter. Eur Heart J 2000; 21: 550-64.
7. Gaita F, Gallotti R, Calò L, et al. Limited posterior left atrial cryoablation in patients with chronic atrial fibrillation undergoing valvular heart surgery. J Am Coll Cardiol 2000; 36: 159-66.
8. Seidl K, Schwacke H, Zahn R, et al. Catheter ablation of chronic atrial fibrillation with noncontact mapping: are continuous linear lesions associated with ablation success? Pacing Clin Electrophysiol 2003; 26 (Part I): 534-43.
9. Gasparini M, Coltorti F, Mantica M, et al. Noncontact system guided simplified right atrial lesions using radiofrequency transcatheter ablation for treatment of refractory atrial fibrillation. Pacing Clin Electrophysiol 2000; 23: 1843-7.