● 特別演題

New Development in Pacing and Defibrillation for the Next Century

－Point of View of a European Company：ELA－

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History and major breakthroughs

ELA has been involved in Pacing since the early sixties. The company is based at Paris, and manufactures pacemakers, defibrillators, leads and Holter systems. ELA today owns 11％ of the European bradycardia market.

ELA was the first company to introduce lithium battery in pacemakers (PM) in 1972. In 1980, the company launched the first pacemaker controlled by a microprocessor. Chorus, implanted in 1988, was the first dual-chamber pacemaker featuring all modern algorithms：mode switch, rate smoothing, automatic detection and termination of endless-loop tachycardias and rate-responsive atrio-ventricular (AV) delay.

His dual-chamber strategy led the company to the development of the first DDD implantable cardioverter-defibrillator (ICD), Defender, implanted in January 1995. In the meantime the company became the world specialist of minute ventilation (MV) sensor, with a unique rate-response pacemaker line, starting with Chorus RM, launched in 1992. The last model, Talent, proposes a unique dual-sensor technology, using both MV and acceleration information.

ELA started clinical studies in new pacing indications, such as the treatment of Congestive Heart Failure (CHF) patients as early as 1994, and prevention of ventricular and atrial arrhythmias with pacing algorithm through RAM loaded functions.

Future developments

1 Pacing for arrhythmia prevention

Compensatory pauses prevention algorithms have been tested in the atrium and in the ventricle in the early 90's. If these study demonstrated promising results in preventing arrhythmic events[1], they also showed some limitations in the design of these functions[2,3].

An other idea to decrease refractory periods dispersion, at the origin of some arrhythmias, consists in providing a permanent overdriving, just above spontaneous sinus rate.

Overdriving：PROVE study[4]

< Methods >

The aim of this study is to evaluate the hypothesis of the antiarrhythmic effect of overdrive pacing in patients implanted with Chorum® or Talent pacemakers during two 3-month phases (Ⅰ and Ⅱ).

Table 1 PROVE population

Class	I	II
Patients	16	33
Sex (males)	8	22
Age (years)	73.9±7.6	72.7±6.9
Indication for implantation	2 AV block, 4 SND, 4 BTS, 5 AV block & SND, 1 other	10 AV block, 12 SND, 2 BTS, 9 AV block & SND
Previous history of SVT	13	10
Patients receiving antiarrhythmic drugs	10	15

sinus node dysfunction (SND), brady-tachy syndrome (BTS)

All patients are monitored during 1 month (Phase 0) in order to identify the number and duration of supra-ventricular tachycardias (SVT) during this period.

Then the patients are classified in 2 classes and randomized with respect to the order in which two different pacemaker settings are applied：class I = patients with at least 2 mode switch episodes and class II all other patients. Therefore the number and the duration of SVTs can be quantified by monitoring the mode switchs on SVTs.

Class I patients are programmed with their basic rates (BR) at 60 bpm or set with an atrial overdriving at 10 bpm over the mean atrial rate, with the automatic rest rate being activated.

Class II patients are also randomized and programmed with a higher basic rate of 70 bpm associated with the rest rate (phase II c) in comparison to a standard programming at 60 bpm (phase II d).

During this study, the results of Phase I monitoring will be compared to Phase II within the two classes of patients.

＜Results＞

49 patients have been included so far (see **Table 1**).

14/16 patients of class I developed SVTs during both phase I and II. During the phase with overdrive the number of SVTs was reduced by 43% (75 to 43) and the total SVT duration was reduced by 79%.

These preliminary results show that Overdriving combined with the Automatic Rest Rate are useful to prevent SVTs. But more data must be collected before statistical significance. If the definite results are positive, the prevention of SVTs might become a new indication for pacing.

Multisite pacing

Two concepts have been tested recently to control dispersion of refractory periods：bi-focal[5] and bi-atrial[6] pacing (SYNBIAPACE). In the first case, 2 leads are inserted in the right atrium. In the second case, 1 classical lead is inserted in the right atrium, and a second one close to the left atrium through the coronary sinus (CS). Recent studies have been conducted for both techniques, and have shown promising results, even if the optimal pacing site and mode are not established today.

ELA Recherche conducts a study evaluating these different pacing sites and overdrive pacing (PIPAF).

2　Multisite pacing in heart failure（HF）

State of the Art, new studies（MUSTIC...）

Today, admitted multi-site pacing（MSP）indications are drug refractory HF patients presenting with an inter-ventricular block. Recent studies[7] report a significant decrease in NYHA class, an improved quality of life and exercise tolerance. However, studies failed to demonstrate a significant increase in patients longevity. May be because about 1/3 of those patients dead from sudden cardiac death（SCD）. This supports the development of MS ICDs（see below）. And is bi-ventricular pacing the clue? Some specialists propose multi-focal systems, with 4 pacing sites in the 4 cardiac chambers[8].

ELA Recherche and Medtronic co-sponsor a European cross-over study（MUSTIC）which objective is to assess the interest of MSP compared to classical DDD pacing in CHF patients[9].

PM constraints

The development of MS PMs introduces new constraints[10]：(i) Pacing output must be higher for MS PMs, compromizing the device longevity. (ii) An other problem is that right and left pacing impedance are not the same. In order to provide the same voltage on both tip electrodes, a parallel design must be used. (iii) But this parallel design divides sensed R wave amplitudes. If this is not a main constraint for PMs, it must be taken into account for MS ICD design where ventricular fibrillation（VF）waves are very low（see below）.

Left-ventricular leads

Two endocardial approaches are used today to pace the LV：the LV epicardium through the CS veins, or a transeptal approach.

The design of CS leads for left ventricular or atrial pacing must respect very specific constraints：the shape and the stiffness or the lead must allow an easy approach of the CS but also of the collateral veins, and the lead must be thin enough to enter these veins up to an optimal pacing/sensing position. The transeptal approach is also a promising possibility to enter the LV. It is easier to choose a good pacing position with this approach, but it also needs very specific tools to go through the atrial septum to the LV.

3　Defibrillation

Arrhythmia detection

ELA Médical developed in the early 90's the first dual-chamber ICD, Defender, providing DDD pacing mode and an innovative dual-chamber tachycardia classification algorithm, PARAD（P And R Arrhythmia Detection, see **Fig. 1**）. In January 1995, the first device was implanted in France[11]. During the following clinical studies, the device demonstrated the highest overall efficacy（see example in **Fig. 2**）：specificity on SVT and ST is around 92%, with a sensitivity on VT higher than 99%[12].

Specificity on ST and SVT is nowadays high enough to extend the field of application of VT therapy to slow VTs. These tachycardias, which rates range within 120 to 150 mn^{-1}, were not formerly addressed by single-chambre ICDs which are not specific enough on slow SVT and ST. However, slow VTs can dramatically decrease cardiac output, even if not compromising patient survival. Defender reaches a high sensitivity on slow VTs, preserving specificity on SVT/ST[13]. Ongoing European clinical studies should demonstrate the interest of treating such slow VTs.

Full ICDs：Atrial ATP & shocks

In the early 90's, an American company, Incontrol, designed and manufactured an ICD not treating

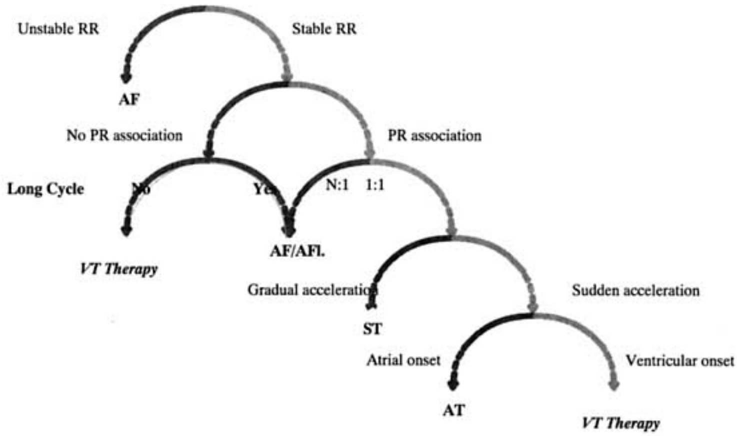

Fig. 1 PARAD＋ algorithm, implemented in the Defender ICD line, which classifies arrhythmias from 1) stability of the RR interval, 2) P-R association, 3) acceleration and, if present, its chamber of origin

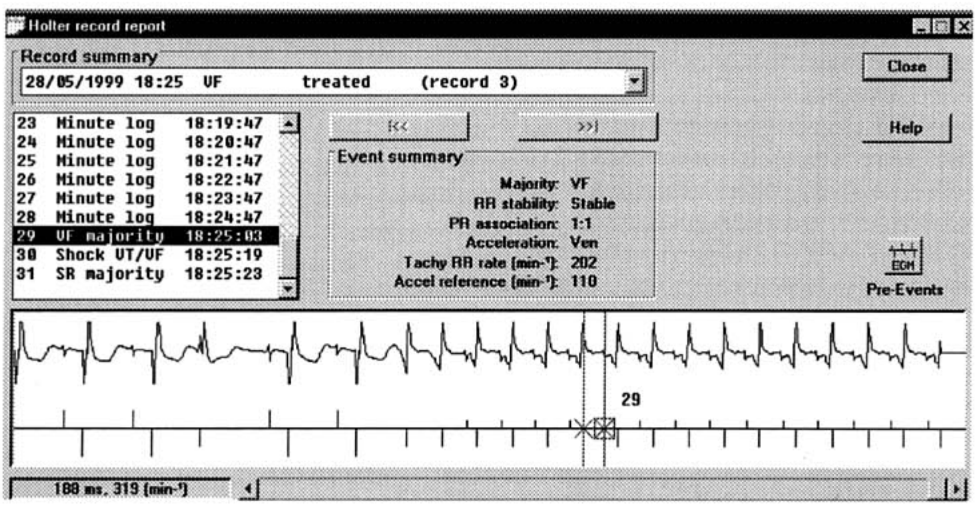

Fig. 2 Fast VT episode stored by an ELA Defender ICD mode 612
The top panel shows the diagnosis provided by the device (from PARAD classification algorithm): stable 1/1 tachycardia with a sudden onset (event 29). The episode is correctly identified even if RP is long (188 ms), as shown by the AV EGM morphology and event markers displayed on the bottom panel (bars to the top are A sensed events, and bars to the bottom are V sensed events). The VT has been reduced by a high energy shock (event 30).

ventricular arrhythmias, but atrial fibrillation (AF). However, it has not been possible to obtain painless atrial therapies to reduce permanent AF. Assuming that most of symptomatic AF do not require immediate termination, these atrial only ICDs failed to find a significant market.

However, patients suffering from ventricular arrhythmias and implanted with a ventricular ICD can also present symptomatic AF. In this case, a ventricular ICD also providing atrial therapies (ATP and shocks) can be useful. But the acceptance of such therapies by the patients has still to be demonstrated.

MS ICDs

By the way, the reasons justifying a multi-site pacing function in ICD patients can justify to implant a MSP ICD. However, design of such devices is much more complex that classical ventricular ICD. Ventricular sensing in these MSP patients, presenting with an long inter-ventricular delay exceeding the post-R wave refractory periods can lead to double R wave counting. The risk of inappropriate therapy is thus important. ELA Médical will launch next year the Alto MSP ICD, which will sense only in the RV in order to avoid all oversensing problems, but will pace both ventricles for CHF patients presenting with a risk of life-threatening ventricular arrhythmia.

4 Technology

Device downsizing

One of the key objectives of manufacturers is to decrease device size in order to increase patient acceptance. If ICDs volume decreases rapidly it becomes more and more difficult to go on preserving high shock output and short charge time.

On one hand, batteries represent about $1/3^{rd}$ of ICD size. On the other hand, high voltage capacitors represent $1/3^{rd}$ of the ICD volume. So the clue for ICDs downsizing is partly to use a new capacitor technology, such as the "flat cap", which presents the same energy density as classical electrolytic capacitors, but can be designed as a flat component, decreasing the volume lost in the ICD case. This technology allows smaller and thicker ICD design.

An other way to decrease device size is to decrease battery volume. But classical battery electrolytes (Li/I for PMs and Li/SVO for ICDs) present energy and current densities which do not allow very small volumes without compromising device longevity and charge time. An other battery technology with higher energy and current densities is necessary. However, no such reliable technology is available today for active implants.

Sensors

ELA Médical pioneered the development of the two sensors which are now the reference for rate-response : (i) the minute ventilation[14] (Chorus RM, 1991) and (ii) the accelerometer[15] (Opus & Sonata g, 1993). These two sensors, if combined, should provide the best rate-response. Such a function is proposed by the Talent (1998).

But the most promising field of application concerns ICDs, which need an hemodynamic sensor. An immediate therapy is always needed in case of cardiac output decrease, not only in case of very fast ventricular arrhythmia. But manufacturers are still looking for a fast and reliable sensor to measure such an information, even if some interesting systems (oxygen saturation, ventricular contractility, stroke volume measurement...) are now under studies.

Xtended RAM and fast telemetry

Active devices appear more and more as "implantable cardiac disease management" tools. Now, powerful and reliable static RAM are available, allowing the implementation of innovative functions. We can imagine that within 10 years PM and ICDs will provide intra-cardiac data comparable to external Holter recordings, not only for 24 hours but for 1 month follow-up or more. These devices will provide a complete range of data (atrial and ventricular high resolution EGM, annotated markers...).

If today PM and ICDs generally propose RAM ranging between 8 to 128 Kb, more than 1 Mb will be

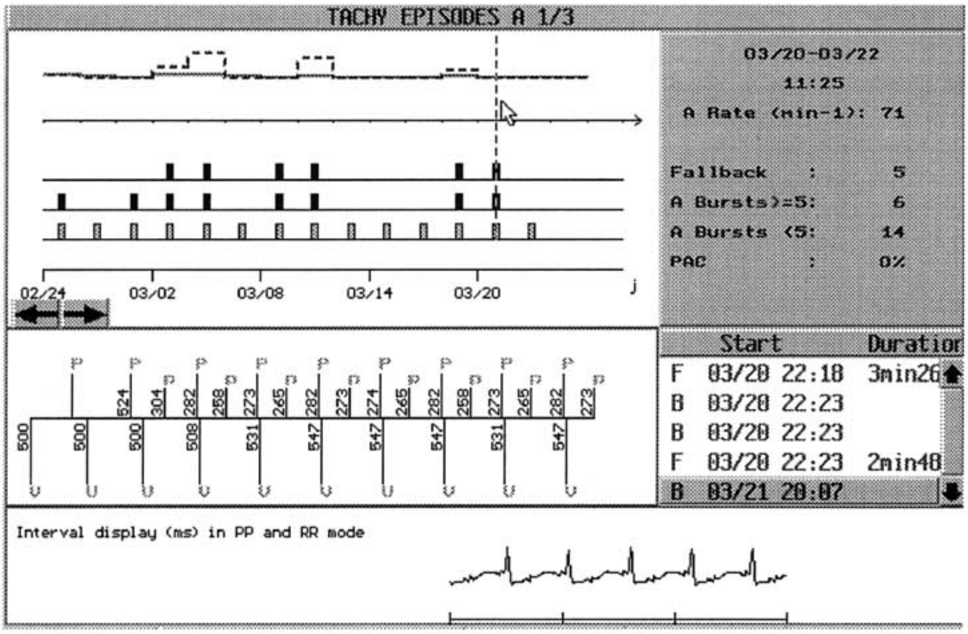

Fig 3. Data displayed by the AIDA software, for a 1 month follow-up, in a patient suffering from atrial tachycardias

The top panel displays the A and V rate curves, summarizes data concerning atrial arrhythmias：Fallback Mode Switchs, long A bursts, short A bursts and isolated Premature Atrial Contractions. The bottom panel displays the AV markers and EGM stored during an atrial burst：tachycardia coupling interval is around 280 ms, and the device paces the ventricle in 2/1 (at 550 ms) thanks to the Mode Switch features provided by the device (ELA Talent PM).

necessary to store these new data. Thus, the challenge will be to develop very fast telemetry functions.

5 Build-in memories and expert systems

The PM/ICD system environment can be summarized in three entities, managed by the physician：(i) the patient, with his clinical profile, (ii) the device programming and (iii) the data memorized by the implant.

ELA Médical proposed, in the early 90's, a software integrated in the Chorus programming system, called Clinical Programming (CLIP). This software uses the patient's profile entered by the physician and proposes a programming of the pacing and memory parameters which fit with the patient and planned follow-up duration. A study showed that such a software can be satisfying in most of the cases[16], and has been updated for all new ELA PMs (Talent/Brio).

The second step consists in analyzing stored data, in order to provide an automatic interpretation to the physician. ELA Médical proposes a software integrated to the programming system, called Automatic Interpretation for Diagnostic Assistance (AIDA). This assistance mainly covers (i) A and V arrhythmias (see **Fig. 3**) and (ii) PM functioning analysis. A preliminary study has shown that this tool is reliable, and can be helpful[17]. A later multicenter study gave very interesting insights for atrial arrhythmias in paced patients[18].

The last step of the process will consist in proposing an automatic reprogramming of the device according to the diagnosis provided by AIDA.

But one of the objectives of the manufacturers must be to decrease the number of proposed programmable parameters, which are very complex to master, and can lead to some unanticipated behavior. The activity of physician should not be to understand how functions the implant, but much more to retrieve and analyze easily the follow-up data provided by the implants, in order to improve the therapy proposed to the patient.

Conclusions

The progress of implantable technology is so fast that new functions & tools will be soon available. Devices will become still smaller, but with an increased longevity. As dual-chamber development has been fast in the 90's, it seems logical to forecast a rapid extension of MSP implants. The development of atrial and ventricular arrhythmia prevention will also be amazing in a close future. The availability of fast and reliable hemodynamic sensors should dramatically transform the ICDs applications within a few years.

But, may be, the most impressive progress will concern diagnostic tools. Implantable monitoring devices will be proposed, which objective will not be to pace or to shock, but to store intracardiac data or ECG records.

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