COMPARATIVE STUDY OF TWO TYPES OF PACING FOR THE TREATMENT OF UNEXPLAINED SYNCOPE (VASOVAGAL SYNDROME)

ISRCTN00029383

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1 – SUMMARY OF STUDY

Objective of the study: To compare the effectiveness of a dual chamber pacing (DDD) at 70 bpm and a single chamber atrial pacing (AAI) at 30 bpm in patients suffering from vasovagal syndrome related to a predominant cardio-inhibitory reflex determined by ATP test.

Assessment criteria: Onset and onset interval of recurrence of first vagal symptom of intensity at least as great as that of the spontaneous symptoms, following pacemaker implantation.

Treatments compared: Dual chamber pacing at 70 bpm and a single chamber atrial pacing at 30 bpm.

Programming: Group A: AAI mode - 30 bpm
Group B: DDD mode - 70 bpm

Type of study: Prospective multicentre comparative randomised single-blind study, with a direct individual benefit.

Number of patients: 200 patients (100 per group), positive on ATP test.

Study population:

1. Inclusion criteria

- Adult patients (≥ 18 yrs), agreeing to take part in the study and having signed the informed consent form.
- Patients having presented one or more episodes of syncope or pre-syncope unexplained by the usual screening tests: questionnaire, clinical examination, orthostatic hypotension investigation, biological tests, electrophysiological study (if necessary), echocardiogram, ECG, Holter, exercise test (optional), EEG (optional), and brain scan (optional).
- Negative sino-carotid massage (SCM) (Appendix A).
- Head-up tilt test conducted according to Appendix B protocol, whatever the result.
- Positive adenosine-5'-triphospate (ATP) test (Appendix C), confirmed by double reading by principal investigator.

2. Exclusion criteria

- Syncope etiology revealed by usual sc reening testings.
- Positive SCM (Appendix A).
- Atrial or ventricular tachyarrhythmia.
- Defibrillator implanted (DAI).
- Pacemaker previously implanted.
- Patient on waiting list for or having had heart transplantation.
- Sick sinus syndrome, brady-tachy syndrome.
- Atrial fibrillation, paroxysmal or permanent first and second-degree atrio-ventricular block, trifascicular block.
- Ongoing pregnancy. Women of childbearing age should be using reliable contraception.
- Acute systemic infection or other surgical contra-indication for pacemaker implantation.
- Chronic obstructive bronchopneumopathy.
- Asthma.
- Diabetes.

Randomisation: Rate and mode of cardiac stimulation (single blind study).

Follow-up protocol: - The first recurrence of a vagal symptom (at least as severe as spontaneous symptoms) must be checked in outpatient clinics; the patient will be systematically removes from the study.

- Besides this first recurrence, the pacemaker functioning will be checked as usual

at 2, 6, 12, 18 and 24 months in out patient clinics

Planned schedule:	Beginning of inclusions:	January 2000
	End of inclusions:	December 2002
	Final FU (at 2 yrs):	December 2004

Investigation centres:

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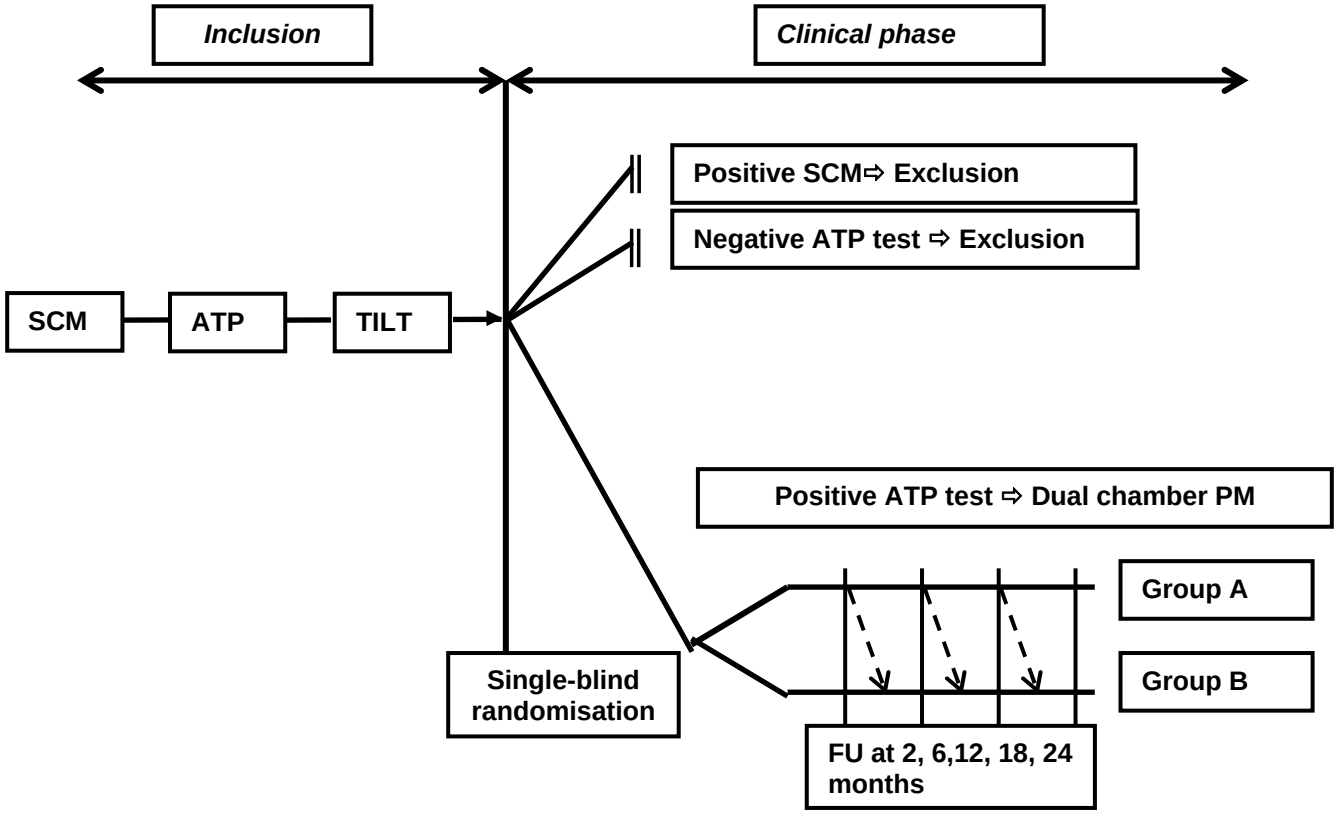
STUDY FLOWCHART



	Selection phase	Inclusion M0	M2	M6	M12	M18	M24
Carotid massage Chest X-ray Exclusion of syncope of known origin	7						
ECG	7		7	7	7	7	7
ATP Test followed by Tilt Test		7					
Informed consent		7					
PM implantation Randomisation programming		7					
Clinical assessment	7	7	7	7	7	7	7
PM reprogramming (HR)			7	7	7	7	7
Adverse events		7	7	7	7	7	7

2. INTRODUCTION

2.1. STUDY RATIONALE

Vasovagal syndrome (VVS), as described by Sir Lewis in 1932, refers to an intense vasoplegia resulting in a sudden and severe drop in blood pressure ("vaso"), and to a negative dromotropic and chrontropic phenomenon represented by a bradycardia of varying severity, ranging from simple sinus bradycardia to an atrio-ventricular or sino-atrial blockage ("vagal"). It is generally found that, even for a single given patient, a number of different factors affect the vasovagal symptoms, the severity of which may depend upon the underlying mechanism. Also, despite the complexity and central processing of the vagal afferents, clinical signs tend to concern a vasodilative reflex more than a cardio-inhibitory reflex, although the two components may also be combined (1).

The head-up tilt test (TT) is effective for reproducing the symptoms and so, for confirming the diagnosis. However, it cannot distinguish the underlying mechanism, even if a positive test is usually associated to a vasodepressive phenomenon (2,3).

The adenosine-5'-triphospate (ATP) test has been demonstrated to be interesting in revealing the cardio-inhibitory origin of VVS (4-6). It consists on a 20mg iv bolus of ATP (Striadyne®, Wyeth Lab.) designated to provoke a severe cardio-inhibitory vagal response (see appendix C for the the ATP test description) (7). It has been demonstrated that this test is able to identify those vasovagal patients with the highest risk of heart sensitivity to the vagal tone, as indicated by a cardiac pause longer than 10 seconds (positive test).

Therapeutically, 1) for the vasovagal symptoms refering to a severe drop in blood pressure (positive TT), no treatment or various drug regimen have been tried out with varying success. Of these, beta-blockers have proved effective in 50% of cases, and mainly when the TT is positive under beta stimulation (isuprel®). Other drugs are also effective: etaphylline, serotonine re-uptake inhibitors, midodrine, etc..

2) When the TT fails to reproduce the symptoms (negative test) and when there is significant cardiac pause under ATP (appendix C), the most effective treatment consists on implanting a permanent pacemaker (4).

2.2. VASOVAGAL SYNDROME EVOLUTIONARY HYPOTHESIS

A preliminary study found a significant correlation between patients' age and ATP test result, while no such relation was found for the TT (8). These findings suggest that the vaso-depressive form of VVS is not age-linked, whereas the cardio-inhibitory form predominates with aging. This may lead to the following evolutionary hypothesis: VVS may be due to a simple ortho-parasympathetic balance instability in youth, deteriorating with age to result in autonomic nervous system hypersensitivity to any vagal influx. Thus an initial inotropic and vascular disregulation may give way to chrontropic and dromotropic disregulation. In this case, the TT may be more effective during the first phase for detecting the vasoplegic forms predominating at that time, whereas the ATP test would become more appropriate as the patient ages for screening for an abnormal cardio-inhibitory reflex of vagal origin.

3 – STUDY OBJECTIVES

Main objective:

The study seeks to compare the effectiveness of dual chamber 70 bpm pacing in preventing syncope recurrence as compared to absence of pacing in patients suffering from VVS related to a predominant cardio-inhibitory reflex as shown by positive ATP test. Absence of stimulation is simulated by a temporary pacing (i.e. until the first symptom recurrence) at 30 bpm single atrial pacing mode (AAI).
The multicentre design of the study will enlarge the scale reproduction of the generally positive results published to date. The investigation centers have been chosen for their clearly manifest interest and great experience in the treatment of this kind of pathology, guaranteeing the success of the project.

Secondary objectives:

- To assess the impact of the following factors on head-up tilt test and ATP test results:

  - age,
  - sex,
  - anatomic parameters (cardio-thoracic ratio: CTR),
  - heart disease and cardiovascular risk factors.
- To determine to what extent positive or negative tilt test results relate to syncope recurrence rates in positive ATP-test patients implanted with pacemakers programmed at two possible settings.

4 – PATIENT SELECTION

4.1. INCLUSION CRITERIA

- Adult patients (≥ 18 yrs), agreeing to take part in the study and having signed the informed consent form.
- Patients having presented one or more episodes of syncope or pre-syncope unexplained by the usual screening testings: questionnaire, physical examination, orthostatic hypotension investigation, biological tests, electrophysiological study (if necessary), echocardiogram, ECG, Holter, exercise test (optional), EEG (optional), and head CT scan (optional).
- Negative sino-carotid massage (SCM).
- Positive adenosine-5'-triphospate (ATP) test, confirmed by double reading by principal investigator. (ATP test must be performed 15 min before tilt test.)
- Tilt test conducted as per Appendix B.

4.2. NON-INCLUSION CRITERIA

- Syncope etiology revealed by usual screening testings.
- Positive SCM.
- Atrial or ventricular tachyarrhythmia.
- Defibrillator implanted (DAI).
- Pacemaker previously implanted.
- Patient on waiting list for or having had heart transplantation.
- Sick sinus syndrome, brady-tachy syndrome.
- Atrial fibrillation, paroxysmal or permanent first and second-degree atrio-ventricular block, trifascicular block.
- Ongoing pregnancy. Women of childbearing age should be using reliable contraception.
- Acute systemic infection or other surgical contra-indication for pacemaker implantation.
- Chronic obstructive bronchopneumopathy.
- Asthma.
- Diabetes.

5 – STUDY PROCEDURES

5.1. PRACTICAL PROCEDURES

Before including a patient in the study, carotid sinus hypersensitivity or any other obvious syncope etiology are to be excluded. There is nothing specified as to the time between SCM and inclusion.

5.1.1. INCLUSION CONSULTATION

- Investigator review of patient's inclusion/exclusion criteria.
- Obtaining patient's informed consent.
- For each ATP test, a photocopy of the ECG shall be sent for double reading to the Principle Investigator. The patient will be randomised only after confirmation of the positive ATP test result has been received.

So, the ATP test is the practical means for selecting patients who may be included.
- Random allocation to one of the two treatment groups if the patient accepts to be implanted.

5.1.2. RANDOMISATION: PACING RATE AND MODE SETTING (SINGLE-BLIND RANDOMISATION)

All positive ATP patients will be implanted with a dual-chamber pacemaker. PM setting will be randomised prior to implantation. The patients will be divided into 2 groups:

Group A: AAI mode at 30 bpm
Group B: DDD mode at 70 bpm

Numbered randomisation envelopes will be given to each centre, specifying the setting for the implanted pacemaker (Group A: AAI mode at 30 bpm; Group B: DDD mode at 70 bpm).
These envelopes are to be opened just prior to implantation, according to the patients' chronological order of inclusion (envelope n°1 for the 1st implanted patient, envelope n° 2 for the 2nd, and so on).

The randomised order must be respected so as to preclude any bias in the study.

Once implanted, patients have to call the investigator at the first symptom recurrence. Only symptoms as severe as spontaneous symptoms are to be considered as recurrence. In such case:

- **group A patients**, initially programmed at 30 bpm AAI mode, will be reprogrammed at 70 bpm DDD mode, and are not to be subsequently reset for 30 bpm AAI mode.
- **group B patients** may be reprogrammed in an upgraded mode (DDDR), if available on the model of implanted PM), with or without increase in heart rate and/or associated medical treatment. At all events, they are not to be programmed at a rate inferior to 70 bpm without being removed from the study.

So far as possible, throughout the duration of the study, the patients are not to be informed as to their PM programming.

Spontaneous symptom recurrence being the index parameter to be assessed, the study objective is then met and the patient is discharged from the study.

5.1.3. FOLLOW-UP IN OUTPATIENT CLINICS

Patients are to be followed up as follows:
- Those *presenting recurrence* of the original symptom are, like any implanted patient, to be followed up at 2 months and every 6 months in outpatients clinics, out of the present protocol.
- Implanted patients *not presenting recurrence* of the original symptom are to be followed up at 2 mpnths and every 6 months in outpatients clinics, as part of the present study (per protocol), for 24 months, each visit comprising:

- a physical examination for adverse events;
- pacemaker control;
- report of patient's symptoms (clinical questionnaire and review of patients self-report diary) so as to confirm or not any symptom recurrence. In case of confirmed recurrence, the PM is to be reprogrammed acording to § 5.1.2 and the study is to be considered as terminated as of this date.

So, to avoid any unnecessary delay between symptoms recurrence and control, an effort is suggested to inform the patient's GP to respect the protocol and to reduce the time for the investigator visit.

5.2. END OF STUDY AND THE VARIOUS DISCHARGE CRITERIA

5.2.1. DEFINITION OF END OF STUDY

A patient shall be deemed to have terminated the study when he or she has presented a vagal symptom recurrence at least as severe as the spontaneous symptoms and leading to reprogrmming the pacemaker according to § 5.1.2, or when, not having presented any such recurrence, he or she has completed 24 months' follow-up.

5.2.2. CONDITIONS FOR PREMATURE DISCHARGE

A patient may leave prematurely the study for one of the following reasons:
- consent withdrawn during study period *
- lost to follow-up
- serious adverse event
- PM explantation
- investigator decision.

* *certified and signed by the patient on the initial consent form*

The reason for withdrawal has to be noted at the end of the case report form (CRF) and the data obtained for such patients up to their withdrawal may be used in the statistical analysis as “intention ot treat”.

5.2.3. PATIENT LOST TO FOLLOW-UP

A patient is considered lost to follow-up when he or she fails to attend two FU consultations despite at least two written and/or telephone reminders for each control visit. Data gathered are in that case to be used in the Per Protocol analysis up to the date at which follow-up ceased.

5.2.4. NON-INCLUSION CRITERION DISCOVERED DURING STUDY PERIOD

The discovery of a non-inclusion criterion in a patient who has been included and implanted will not necessarily entail their removal from the study. The decision may be discussed with the principal investigator. If the patient is in fact removed, their data collected up to the time of such removal may still be used in the Per Protocol analysis.

6 – STATISTICAL CONSIDERATIONS

The forecast inclusion rate is of 15 to 20 patients per month. It is estimated that 10% of these will be ATP positive.

6.1. ANALYSIS GROUPS

The main analysis will be of the Per Protocol type, applying solely to patients who:
- have been treated as per protocol, or
- present only minor protocol deviations.

A further analysis in “intention to treat” will also be made, including all implanted patients.

- Protocol deviations

Minor protocol deviations are such as do not bias the assessment of the principal study criterion. An example might be a control visit missed or arrived at late.

Major protocol deviations are such as do bias the assessment of the principal study criterion because of a failure to respect all of the inclusion and exclusion criteria of the study. Patients presenting any such major deviation will be withdrawn from the Per Protocol analysis.

Any protocol deviation has to be clearly noted down in the CRF, specifying the reasons and type.

6.2. STATISTICAL ANALYSIS (T. Church, Ph.D.)

The statistical analysis will be conducted by the project manager. Descriptive analysis will be made of all variables recorded in either treatment group. Groups A and B will be compared by appropriate methods.

Recurrence rates during each setting period will be compared for each patient. If necessary, the sequence of the PM settings will be examined in the whole study population, to see whether it is a factor influencing recurrence rates.

6.3. SAMPLE SIZE

Null hypothesis:
The cumulative percentage syncope recurrence in the 30 bpm AAI-mode stimulated group, r_p, equals that in the 70 bpm DDD-mode group, r_w. Thus, $r_p=r_w=r_0$.

Alternative hypothesis: $r_p=ar_w$, where $a\neq1$.

The required number of subjects was calculated using Wu, Fisher and DeMets' method, with a first order relative risk of α, power 1-β, r_0 and *a*. Based on Flammang et al's (1997) findings, α=0.05, r_0=0.40, the values chosen for 1-β et 1-*a* show that n = 200 subjects gives a reasonable 95 % power of demonstrating a difference in recurrence rates between the two groups.

		Power				
		0.75	**0.80**	**0.85**	**0.90**	**0.95**
	0.50	164	184	*210*	246	304
	0.55	132	150	170	*198*	244
	0.60	108	122	140	162	*200*
1-a	**0.65**	90	102	116	136	166
	0.70	76	86	98	114	140
	0.75	64	72	82	96	118

Sample-size calculation for sample of ATP-positive patients randomised between 2 PM frequencies.

7 – Study RISK / BENEFIT analysis

A preliminary retrospective single-centre study (4), confirmed by a prospective single-centre study (5), showed the interest of double-chamber pacemakers in this kind of vasovagal pathology in which the cardio-inhibitory reflex is predominant. In both study groups, risk is identical and related to the PM implantation technique. Experience shows that this kind of pathology and management rarely jeopardise the patient's life expectancy.

On the other hand, it has been shown that more than 80% of patients suffering from this kind of pathology show remission or cessation of symptoms under effective double-chamber stimulation.

8 – ADVERSE EVENTS AND ADVERSE TREATMENT EFFECTS - DEFINITION AND NOTIFICATION

8.1. ADVERSE EVENTS

An **adverse event** is any adverse clinical manifestation, *apart from recurrence of spontaneous vasovagal symptoms,* occurring in a subject, whether or not the event is deemed to be related to the device or to the procedure. An adverse event may be a sign or a symptom, several associated symptoms, recurrence or development of an illness or pre-existing condition or of a new illness, occurring during the study period. The following such adverse events are considered **serious**:

- **death** of patient,
- **hospitalisation** or extension of hospitalisation,
- permanent or potential **disability** or intervention required to prevent such disability, or **organ damage**,
- **life-threatening risk**,
- **cancer**

8.2. ADVERSE TREATMENT EFFECTS

An **adverse treatment effect** is any dysfunction or alteration in the characteristics or performance of the study device such as might lead or have lead to a degradation in the patient's state or health: e.g., infection of implantation site or displacement of a stimulation lead.

All adverse events and/or adverse treatment events are to be **reported in the CRF**, whether reported by the patient or by the investigator. The minimum to be reported is: type of event, duration (onset, offset), severity, location, action (treatment) undertaken by investigator, results in patient, and possible treatment link. The investigator shall follow up all adverse events and adverse treatment effects throughout the study period, and note them in the CRF.

The investigator shall use the appropriate form in the observations notebook to report, **as soon as he becomes aware of it,** any serious adverse event to the study monitor. The minimum to be reported is: type of event, duration (onset, offset), severity, location, action undertaken by investigator, results, and possible link with device, possible link with protocol and medical treatment administered prior to event. After validation of the data, the investigator shall **fax** the form to the principle investigator **within 24 hours.**

In line with French regulations (*Code de la Santé Publique - Livre II bis - Loi Huriet-Sérusclat* and *livre V bis - Dispositions relatives aux dispositifs médicaux*), the project manager and the principle investigator are to inform the competent authority (i.e., the CCPPRB) and the other investigators of any serious device-linked adverse event.

9 – CONDUCT OF STUDY

9.1. CASE REPORT FORMS (CRF)

Paper CRF shall be used and the data transmitted to the Principal Investigator by mail.

9.2. MONITORING PROCEDURES

The appended forms (informed consent, and inclusion/exclusion criteria, etc.) shall be checked by the project manager via the network of technical sales engineers.
The investigator has to keep all the source documents at the project manager's and the principle investigator's disposal, including the informed consent form, the surgical report, the follow-up reports, and so on. The monitor shall respect the confidentiality of all of this information.

The investigator has the responsibility of filling in the CRF in due time and sending them to the principle investigator on request. On reception, each CRF has to be archived for 10 years by each investigator.

9.3. QUALITY ASSURANCE

The study may be audited at any time by the regulatory authorities or by the project manager, to evaluate the Good Clinical Practices, the EN 540 standard and the respect of the protocol. Any change to the protocol is to be agreed by the project project manager and by the principal investigator.

The principle investigator undertakes to submit any amendment to the CCPPRB of Poitou-Charentes (France).

9.4. STUDY REPORT AND PUBLICATION OF RESULTS

The property of the data collected in this study shall shared between the sponsor and the investigators. The data analysis and the statistical report will be prepared by D. Flammang, M.D., the principal investigator, who shall also present and publish the clinical report of the study in association with the other investigators.

9.5. ADMINISTRATION OF STUDY MATERIAL

The pacemaker and the Striadyne® needed for the ATP test will be provided by the respective hospitals. The pacemekers to be implanted must be CE-labelled commercial dual-chamber models

10 – REGULATORY CONSIDERATIONS

10.1. HELSINKI DECLARATION

The study is to be conducted in agreement with the recommendations to physicians performing biomedical research on human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964 and subsequent revisions thereto.

10.2. ETHICAL COMMITTEE - C.C.P.P.R.B.

The principal investigator shall secure the ethical committee (CCPPRB) approval and report any device-linked adverse effects. The informed consent form and the information letter are to be approved by the CCPPRB prior to any inclusion. The curriculum vitae of all of the investigators, along with their Medical Council registration numbers are to be sent to the CCPPRB on submission.

10.3. PATIENT'S INFORMED CONSENT AND INFORMATION

Before inclusion in the study, the patient shall be given all verbal and written information by each investigator regarding the study's aims and procedures and the risks involved therein. All patients taking part in the study must sign the informed consent form prior to their inclusion. The investigator shall keep the original and a copy has to be given to the patient. Appendix A presents an example of the patients' letter of information and informed consent form.

10.4. INVESTIGATOR'S RESPONSIBILITIES

The investigator shall fill in the CRF per follow-up visits and inform the principal investigator and the project manager within 24 hours of any serious adverse event or adverse effect related to the device. The investigator shall ensure that the source data, observations notebooks and investigator's file are kept in a safe place throughout the study. These documents are then to be archived for 10 years.

The investigator shall keep informed the staff involved in the study. He/she shall also ensure that his/her staff conducting the study are properly qualified. He/she shall inform the patient's GP of the patient's participation.

10.5. PROTECTION OF PATIENT DATA

The study documents are to remain strictly confidential. In the CRF, the patients will be identified by a number and their initials. The investigator has to keep an up to date patient identification list, with the corresponding hospital form numbers, in the investigator's file.

The data from the study are to undergo computerised processing. In line with the French "Informatique et Liberté" (IT and Liberty) law, they remain strictly confidential. The patients' identities shall at no time be disclosed in any data processing report.

10.6. PROTOCOL DEVIATION

Should a patient's medical condition require a deviation from the protocol, the investigator has to inform the principal investigator as quickly as possible, and the latter shall determine whether the patient may remain within the study. Any protocol deviation has to be clearly reported in the CRF. Repeated unjustified protocol deviations may result in the closure of the centre concerned.

11 - SIGNATURES

PROTOCOL TITLE: Comparative study of two types of pacing for the treatment of unexplained syncope (vasovagal syndrome)

PROTOCOL VERSION: 1st October 1999

Having read the present protocol, we understand its requirements and the study performance conditions. Our signature below confirms our adherence to the terms of the protocol and our agreement to perform the study in accordance with the EN 540 standard, Good Clinical Practice and the French Public Health Code. We understand that any alteration to the present protocol has to take the form of a written amendment with prior agreement from the project manager and the co-ordinator, who are to inform the CCPPRB of Poitou-Charentes thereof. We understand that any violation of the present protocol may entail early closure of the centre in question.
We further undertake that all of the devices and accessories used in the framework of the present study shall be used only in accordance with the present protocol. We undertake to meet the demands of the Medtronic company and of the Health Authorities regarding the checking of the data collected in the study, and the auditing or inspection thereof.
We undertake to inform the project manager and the principal investigator of any serious adverse event as of its observation, whether expected or not, and deemed device-linked or not

_____ _____/_____/_____
Principal Investigator Date (dd/mm/yyyy)
Dr Daniel Flammang

_____ _____/_____/_____
Dr Jacques Victor Date (dd/mm/yyyy)

_____ _____/_____/_____
Pr Jean-Jacques Blanc Date (dd/mm/yyyy)

_____ _____/_____/_____
Dr Pierre Graux Date (dd/mm/yyyy)

_____ _____/_____/_____
Pr Jean Luc Rey Date (dd/mm/yyyy)

_____ _____/_____/_____
Pr Luc De Roy Date (dd/mm/yyyy)

_____ _____/_____/_____
Dr Roland Carlioz Date (dd/mm/yyyy)

_____ _____/_____/_____
Dr Robert Frank Date (dd/mm/yyyy)

_____ _____/_____/_____
Dr Guilly Date (dd/mm/yyyy)

_____ _____/_____/_____
Dr Richard Sutton Date (dd/mm/yyyy)

_____ _____/_____/_____
Pr Rosanne Kenny Date (dd/mm/yyyy)

_____ _____/_____/_____
Project manager Date (dd/mm/yyyy)
Dr. Cécile Laiter de Monclin, Medtronic France

_____ _____/_____/_____
Sponsor Date (dd/mm/yyyy)
M. Yves Drapp, Director Medtronic France

INFORMATION LETTER

TITLE OF CLINICAL STUDY: Comparative study of two types of pacing for the treatment of unexplained syncope (vasovagal syndrome)

Lady or Gentleman,

In view of your clinical examination and of the syncopes you suffer from, your physician suggests that you take part in a clinical study of syncope management by means of an implanted pacemaker.

This letter is intended to inform you about the advantages and disadvantages that you may incur by your participation in this clinical trial. Please read it carefully, and ask your physician any questions before you make your decision; if you decide to participate, then sign the consent form below to indicate that you agree to take part in the study. A copy of this document will be given to you.

You are subject to recurrent syncope or pre-syncope. The term “syncope” refers to a sudden loss of consciousness and of hearing, while “pre-syncope” refers to a fainting or vertigo without actual loss of consciousness. The various examinations were unable to identify any cardiac, neurological or metabolic cause. The fact that your cardiac assessment, including your reaction to the carotid massage, were normal rules out any known cause reponsible for your symptoms.

At this point, according to standard practice, it is assumed that the reason for the symptoms may be a hypersensitivity of the heart itself to the vagal system. In order to offer you an appropriate treatment, your cardiologist undertook routine tests intended to reproduce the symptoms of syncope (or pre-syncope). Two such tests were carried out to confirm the diagnosis:
1 – the head-up tilt test, in which a change in body position can rproduce the same symptoms, is one example;
2 – the other test is performed without changing position, using a drug which is regularly used since 1950: ATP (Adenosine-5'-triphospate), administered intravenously, can also cause a cardiac pause or a slowing down of your heart rate.

If this ATP test is positive, your cardiologist considers that implanting a pacemaker could be helpful, as this would reduce the number of syncopes or pre-syncopes. If you agree to take part in this study, a pacemaker will be implanted in your thoracic region (usually under the right clavicle), under the skin, by means of a small incision of about 5 or 6 cm, causing no aesthetic damage. Implantation requires a surgical operation under local anaesthetic, with a very low risk of infection, rejection or local haemorrhage.

Several different pacemaker settings are possible, and we want to find out which one best reduces the number of recurrences of syncope. Two types of setting have been chosen for the study, and a randomisation procedure (drawing lots) will decide which one you will have:
-either a dual chamber stimulation at a rate of 70 beats per minute
-or a single chamber stimulation at 30 beats per minutes, which in principle does not pace your heart, but which will be immediately re-set at 70 bpm as soon as a first attack recurs.

Your cardiologist will follow you for 2 years and will modify the pacemaker programming if necessary. This programming is done via a programmer which communicated with the pacemaker through the skin, and requires no surgery.

Following implantation, it is important to avoid strong electromagnetic sources, such as scanners, diathermy, therapeutic radiation and certain apparatus used during surgery. You should inform all of your physicians that you are bearing a pacemaker; mobile phones and household equipment (microwaves, etc.) do not affect the pacemaker.

After implantation, you will be asked to come to five follow-up visits, at 2, 6, 12, 18 and 24 months). On these occasions, you will be asked whether you have experienced recurrence of syncope. By taking part in this study, you will enjoy a frequent and very attentive follow-up. Your physician will be able to find the optimal programming for your type of syncope, according to the tests carried out at inclusion.

Your physician is of course at your disposal to explain the alternative possibilities, such as medical treatment of syncope.

FURTHER INFORMATION

All of the elements of this study are confidential, and the cardiologist following you will be bound to secrecy. Some nominal data concerning you will undergo computerised processing. According to the French "*Informatique et Liberté*" (IT and Liberty) law, these data will remain strictly confidential. Your identity will at no time be disclosed in any data processing report, whether to the Ministry of Health or to Dr Flammang, the principal investigator of the study.

According to the provisions of *Livre II bis* of the French Public Health Code (*Huriet-Sérusclat* law), the sponsor has taken out a third party insurance policy (nº 5.323.759) with the CIGNA Insurance Company of Europe (Le Colisée, 8 Rue de l'Arche, 92419 Courbevoie Cedex, France). The Ethical Committee (Consultative Committee for the Protection of Persons in Biomedical Research - C.C.P.P.R.B.) of Poitou-Charentes (France), in charge of examining the study, gave its approval for implementation on 7th October 1999. .
200 patients with unexplained syncope will be taking part in the study. Participation is voluntary; you can refuse to take part or withdraw at any time, for whatever reason, and without explanation. Your decision will in no way affect the quality of care you will receive.
Should your physician consider that taking part in the study is not in your best interest, he or she can decide to stop it. The project manager or the Ministry of Health may also decide to interrupt the study if necessary. Should the study end before the scheduled date, you will continue to receive medical care adapted to your condition.

INFORMED CONSENT FORM

<u>TITLE OF STUDY</u>: Comparative study of two types of pacing for the treatment of unexplained syncope (vasovagal syndrome)

Surname and first name(s): …….

Date of birth: ……/……/…… Telephone: _____
Address: _____
_____

Dr ……..……..of……. [name of institution] has suggested I take part in a study on the treatment of unexplained syncope by two types of pacemaker setting.

He specified that I am free to accept or to decline; that will in no way affect the care I shall receive. Should I so wish, I shall be free at any time to withdraw from the study. I shall in that case inform Dr …….. , who will offer me, if I so wish, another treatment. I may at any time ask for further information from Dr …… at the following telephone number:
……..….

I have received and understood the information regarding the aims of study, its duration, the methods used, the benefits, the disadvantages and possible risks. Data concerning me will remain strictly confidential.

I am also aware of the opinion of the Ethical Committee (Consultative Committee for the Protection of Persons in Biomedical Research) of Poitou-Charentes (France), which examined the project and approved it on 7th October 1999.

I AGREE TO TAKE PART IN THE STUDY UNDER THE CONDITIONS SPECIFIED IN THE ABOVE LETTER OF INFORMATION WHICH I HAVE READ AND INITIALLED AND WHICH WAS HANDED TO ME PERSONALLY.

I certify that I am not under any form of legal guardianship. My consent does not discharge the study organisers from their responsibilities. I retain all of my legal rights.

Signed at…… , on ___/___/____

Dr/Pr _____ _____

Signature of Investigator or Co-Investigator

Signature of Patient:
(Preceded by the words “Read and understood”

(a copy of this document will be given to the patient, who is to keep it)

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APPENDIXES

A. SINO-CAROTID MASSAGE

Contra-indications: Carotid murmur, history of ventricular tachycardia, or recent cardiovascular accident or myocardial infarctus.

Preparation: Cardiac rescue conditions. BP and ECG continuously monitored before and during the procedure.
Procedure: Successive massage of both carotid sinuses ≥ 6 seconds, patient inclined at 60º.
Assessment: Positive if asystole ≥ 3 seconds.

B. TILT TEST: WESTMINSTER PROTOCOL (3)

Contra-indications: None known.

Preparation: Test performed in quiet room, outside of any period of dominant orthosympathetic activity; the room is to be equipped for cardiac resuscitation, at a temperature of 20°C. Patient stays in lying position on the tilt table for 15 min prior tilting, during which time a 5% glucose flush into the brachial vein, ECG recording and continuous BP recording are set up. Patient attached to table by waist strap and knee strap, with feet on foot-rest. ECG and BP are recorded every minute.

Procedure: The table is tilted to 60° for 45 min and ECG and BP recorded at least every minute. The table is returned to horizontal at end of test or if positive.

Assessment: Test is considered positive if it reproduces spontaneous symptoms or similar, associated to severe hypotension and/or bradycardia. Severe hypotension is defined as SBP ≤ 90 mm Hg (or fall in BP of at least 40%). Bradycardia is defined as a rate of <50 bpm.
For all patients included in the study, a negative passive tilt test is to be followed by a second tilt test under isoproterenol up to a maximum dose of 3 γ/mn or under Trinitrine Spray 0.4 mg.

C. ATP TEST

Contra-indications: Atrial or ventricular tachyarrythmia, atrial fibrillation, transitory or permanent second-degree atrio-ventricular blockade, trifascicular blockage. Coronary insufficiency and asthma are relative contra-indications. In this study, the ATP test is performed in sinus rhythm only.

Preparation: same as for the tilt test. Continuous ECG recording at 25 mm/sec. To avoid any anticipatory sympathetic reaction, patient is not warned of transitory vagal signs accompanying the ATP effect.

Procedure: Injection of 20 mg bolus of ATP (0.3 mg/kg) in 2 seconds, followed by 5% glucose flush.

Assessment: Initial negative chromotropic or dromotropic effect comes on in under 30 sec. ECG response is in 5 phases, concentrating on the analysis of phase III, when present.

- **Phase I:** gradual slowing of sinus rhythm.
- **Phase II:** 1st or 2nd degree AV blockade.
- **Phase III:** cardiac pause of variable duration due to complete AV or SA block; this phase may be absent.

Complete AV block during cardiac pause is defined as follows:
- number of blocked P waves ≥ 3
- association or not to a supraventricular or ventricular escape rhythm of ≤ 25 bpm (i.e., cycle of ≥ 2.400 msec)
- Calculation of total cardiac pause duration may include a brief 2nd degree AVB (Mobitz I or II) sandwiched between 2 complete AV block episodes.

- **Phase IV:** return to initial sinus rhythm via transitory 2nd and 1st degree AV block.
- **Phase V:** reflex sinus tachycardia.

Clinical response varies from a simple flush to true dizziness or syncope. At the end of the test, the patient is asked to describe the functional signs experienced and compare them to the spontaneous functional signs.
In all cases, the final result is based **only on the presence of an ECG phase III**. Response is abnormal (positive) when ATP causes a cardiac pause of > 10 seconds and normal (negative) when ATP causes cardiac pause of ≤ 10 seconds or when there is no cardiac pause (simple bradycardia of any type).

Recommendations: The patient should be in a quiet environment.
In case of technical problem (bad venous flush, etc), do not conduct more than 3 consecutive tests in one patient.

ATP: Adenosine-5'-triphospate.

TT: Tilt test.

CTR: Cardio-Thoracic Ratio

SCM: Sino-Carotid Massage.

BP: Blood Pressure.

Cardiogenic, neuro-cardiogenic or vasovagal syndrome: Synonyms for unexplained syncope, excluding carotid sinus hypersensitivity. According to the symptoms reproduced in the laboratory, a vasodepressive syndrome (severe hypotension) is distinguished from the cardio-inhibitory reflex (severe bradycardia or asystolia).

Programming 30: Pacing in AAI mode at 30 bpm

Programming 70: Pacing in DDD mode at 70 bpm

Group A: Group A patients' pacemakers will be set with the 30 bpm programming. They will be reprogrammed to 70 bpm at the first symptom recurrence. A return to 30 bpm is not allowed in the present study.

Group B: Group B patients' pacemakers will be set with the 70 bpm programming from the start of the study. Reprogramming to 30 bpm is not allowed in the present study.