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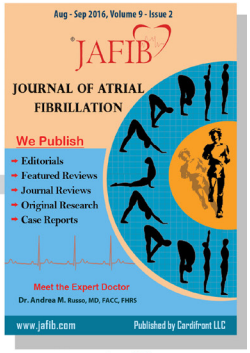

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Implantable Loop Recorder: Diagnostic Yield And Possible Therapeutic Effect In Patients With Neurally Mediated Reflex Syncope

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Abstract

Through a retrospective study concerning the experience of our center in patients affected by Neurally Mediated reflex Syncope (NMS) we wanted to verify not only the diagnostic yield of the Implantable Loop Recorder (ILR) but its possible placebo therapeutic effect.

In the context of patients affected by a severe clinical presentation of NMS identified through a careful clinical evaluation, we selected those who followed a diagnostic iter using the ILR.

We analysed 84 patients (39 male and 45 female, mean age 71 years), during the period 2009-2013. 34 patients (40.5%) had no recurrences after a mean follow-up (FU) of 35 months, among these 17 concluded a FU of 4 years. 50 patients (59.5%) had recurrences and a specific diagnosis after an average period of 7 months.

We found an important number of patients who showed a disappearance of syncope during an observation period of 2-3 and 4 years. At first glance this results could be explained considering the possible placebo therapeutic effect of ILR.

Introduction

The ILR represents the golden standard in syncope work-up according to the ESC 2009 guidelines.[1] It plays an important and unique role in the context of uncertain diagnosis in high risk patients and in moderate risk after all the invasive and non-invasive diagnostic procedures have been performed but there is not sufficient information to treat the patient. The ILR is also used in certain or suspected NMS with severe clinical presentation: invalidating recurrences of episodes, unpredictable forms, traumatic effects or syncope occurring during high risk activities.

In the past a carefully selected group of patients with severe clinical presentation of likely neurally mediated reflex syncope was stratified following a specific diagnostic path guided by Tilt Table Test (TTT). After a careful initial evaluation (clinical history, physical examination, electrocardiogram and echocardiogram) a TTT was performed to investigate the underlying physiopathological mechanism: cardioinhibitory or vasodepressive form. In most cases patients with a documented cardioinhibitory activity by TTT underwent a pacemaker implantation (PM) but the efficacy of cardiac pacing for prevention of syncopal recurrences is still controversial. It was already questioned approximately 15 years ago: two important randomized, multicenter, open label studies (SYDIT[1] and VASIS[2]) showed results in favour of pacing, but in the same period other two randomized, multicenter, double-blind studies (VPS-[2,3] SYNPACE[4]) failed to demonstrate the superiority of cardiac pacing to over placebo.

ISSUE-2 Trial[5] changed the medical history in the context of reflex syncope. It showed the capacity of ILR to guide the specific therapy and confirmed that there is not always a clear correlation between the results of TTT and the mechanism documented by ILR at the time of the syncope. The main objective was to verify the value of ILR in assessing the mechanism of syncope and the efficacy of ILR-guided therapy after syncope recurrence. ISSUE 2 was set up to verify risk stratification and diagnosis of NMS based on initial evaluation; early implantation of an ILR (irrespective of the results of tilt testing and the adenosine triphosphate ATP test), and therapy delayed until after ILR documentation of the apparent basis of the syncope with a FU period of 2 years.

Out of an initial enrollment of 392, about 143 (36,5%) of patients had recurrence of syncope, 57 (40%) of whom had asystole.

Starting from the important experience of the ISSUE-2 Trial a new international, multicenter, controlled, double blind study was organized: the ISSUE-3 Trial.[6] It showed that pacing is effective in reducing recurrence of syncope in patients in the category of 40 years and above and severe asystolic NMS documented by ILR. There was 32% absolute risk reduction and 57% relative risk reduction, with evidence of a clear, statistical difference between the two groups: Pm

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on and Pm off arm. Concerning the two-year diagnostic yield of ILR in the ISSUE-3 Trial it was found that about a half of patients who received an ILR had a specific diagnosis within two years of observation, of these about an other half (25%) underwent a PM implantation due to a documented significant pause.[8]

Aim of the Study

Through a retrospective study concerning the experience of our center in patients affected by severe clinical presentation of NMS, we wanted to verify not only the diagnostic yield of ILR but its possible placebo therapeutic effect.

Methods

The selection of patients was made according to the ISSUE-3 criteria: certain or suspected reflex syncope (except of "Carotid Sinus Syndrome" because this is an already accepted indication for cardiac pacing), age more than 40 years, and severe clinical presentation. The severity of the clinical presentation was based on the definition of high frequency or risk provided by guide lines: invalidated quality of life because of the recurrences, unpredictable syncope, syncope exposing patients to risk of trauma, occurence of syncope during "high risk activity".

The exclusion of patients involved cardiac abnormalities which suggested cardiac syncope, symptomatic orthostatic hypotension, non-syncopal loss of consciousness.

All patients followed a diagnostic iter guided by ILR and were followed till the first documented syncopal recurrence or an occurrence of a diagnostic arrhythmic event. Events were classified according to the ISSUE classification[9] as: type 1 (asystole > 3 s and recurrence of syncope or > 6 s without recurrence of syncope or presyncope), type 2 (bradycardia), type 3 (slight o no rhythm variations) and type 4 (tachycardia).

Results

We analysed 84 patients (39 male and 45 female, mean age 71 years), during the period 2009-2013. 34 patients (40.5%) had not recurrences after a mean follow-up (FU) of 35 months, among these 17 patients concluded a FU of 4 years. 50 patients (59.5%) had recurrences and a specific diagnosis after an average period of 7 ±8 months.

The prevalent form of neurally mediated syncope was the cardioinhibitory form (26 patients, 31%), followed by vasodepressive NMS (21 patients, 25%).

Tachyarrhythmias were diagnosed in 2 patients (2,4%) and 3rd degree- AV- Block (2 patients, 2,4%).

Discussion

In our clinical experience we have found an important number of patients with disappearance of syncope during an observation period of 2,3 and 4 years. At first glance this results may suggest a possible placebo effect of the ILR and can be disappointing in the everyday clinical setting.

Still, this is the most controversial explanation for this phaenomenon.

The ISSUE-2 experience gave us the possibility to use ILR as therapy- guiding device.

From one hand we have learnt that ILR is able to warrant a specific diagnosis in about a half of patients during a follow-up period of 2 years, and among these another half undergo a PM implantation because of evidence of an asystolic event as cause of syncope.

On the other hand we must bear in mind that there is about half of patients without diagnosis at the end of this period. We are talking about patients selected maintaining the same inclusion criteria: frequent recurrences and invalidated quality of life. The question is what happened at these patients and why patients with frequent recurrences of syncope haven't had any more episodes after the ILR implantation.

In our study we have not found important differences prolonging the follow-up until the 4th year: about 40% of patients haven't had recurrences after a mean follow-up (FU) of 53 months.

At first glance this result could be explained considering the possible placebo therapeutic effect of ILR. The way we see things is that we should investigate and interpret the results using common sense and applying larger scientific considerations.

Recently the SUP-2 Study[10,11] has been completed; it is a multicenter, prospective, observational study which wanted to verify the utility of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope. The Syncope Unit Project 2 (SUP 2) showed the benefit of cardiac pacing at 3 years in patients selected according to the ESC-guide lines: carotid sinus massage (CSM) , followed by Tilting Table Test (TTT) if CSM was negative, followed by implantation of an Implantable Loop Recorder (ILR), if TTT was negative; those who had an asystolic response to one of these tests received a dual-chamber pacemaker. The 3-years recurrence of syncope in the treated group was 20% and was significantly lower than in the group of patients who did not receive the pacemaker and were observed by ILR.

Focusing on the total syncope burden of the SUP-2 we observed that it fell dramatically in the year before and after cardiac pacing. The number of syncopes also decreased in the ILR group (Figure A). It is likely that other mechanisms contributed to this reduction.

First of all it is necessary to remember that the syncopal recurrence is not constant because of an important feature of NMS that is the "cyclicity": in the typical subject affected by NMS during the life-time there are phases of concentrated frequent recurrences of syncope, a long period without events and then an important high burden of syncope again.

Second point could concern the potential, possible placebo effect of device implantation, in this case of ILR. This is a delicate point at which we have to pay particular attention. As mentioned before,

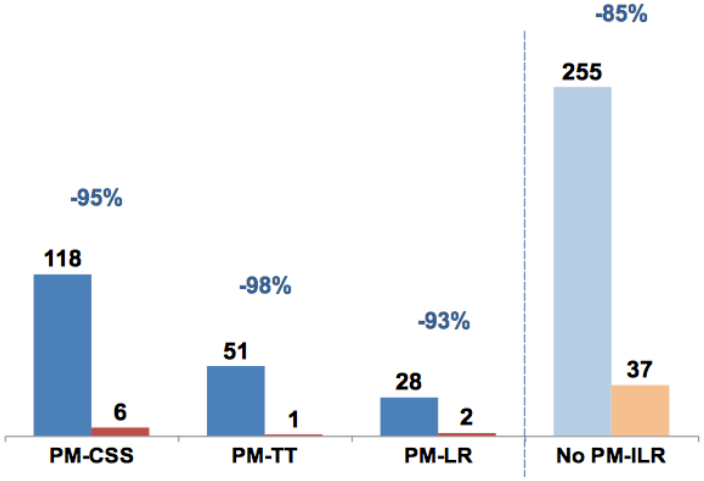

Figure A:

starting from the "cyclicity" characterising the NMS, what we need is only the opportunity to follow the patient for a very long period (decades); if we take in count the high number of syncope – free survival already Sheldon and Rose[12] had observed in 2001, where by following a group of patients with severe quality of life reduction by neurally mediated syncope a big part (40-60%) of the patients had not had any recurrence in 2 years of follow up. The patients were not implanted and had similar recurrence rates to our implanted patients. We are not mistaken affirming that we would have obtained a higher number of recurrences of syncope in the ILR group (control group) if we had monitored our patients for a longer and longer period. The suspect is that actually what we call possible placebo effect in observing relatively limited samples in size and time is simply the statistical "regression to the mean". It is the phaenomenon which occurs when natural events are followed up for a too short period of time or in a too little sample size, not allowing the observed event to occur spontaneously within statistical expectation of the mean.

After these considerations and according to the findings of the scientific literature and our study, we can affirm that the ILR mantains its important diagnostic role, related to the capacity to focus on the electrocardiographic detection at the moment of the clinical loss of counsciousness. Controversial is its potential placebo effect, considering the fact that, according to the natural history of NMS, we should monitor patients for a very long period, activity that is not necessary considering the benign condition of this form. For this reason it will be difficult to discriminate between a potential placebo effect of ILR and the statistical "regression to the mean".

Conclusions

The high rate of undiagnosed syncopes despite ILR implantation are most probably attributable to a combination of regression to the mean with not enough long FU- time and the main feature of syncope itself: the cyclicity of syncope.

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