NeuroArrhythmias Area Registry of AIAC (NAARA) Syncope-Asystole Latency Time in Tilt Table Test (SALT-TILT) study

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Summary

1. SYNOPSIS

Title	NeuroArrhythmias Area Registry of AIAC (NAARA) Syncope-Asystole Latency Time in Tilt Table Test (SALT-TILT) study
Background	Syncope is a common presenting condition. Pacemaker implantation can significantly reduce syncope recurrence in reflex syncope. Still, despite accurate selection, a substantial part of the patients treated with pacemaker suffers of syncope recurrence. It is thought that an accentuated vasodepressive component could hinder the effective pacing in patients by disallowing adeguate cerebral perfusion during the reflex, relativizing the anti-bradycardia function of the pacemaker to prevent syncope.
Objectives	The aim of this study is to compare the Syncope Asystole Latency time (SALT) using Video Tilt Table Testing (VTTT) to assess the time intercourse between the effective transitory loss of evoked by VTTT and the asystole recorded on ECG during the test in patients eligible for invasive treatment. To date, it is not known if there is a connection between the time when a patient faints to the occurrence of asystole in the ECG and its reversibility when treated with a pacemaker. Thus, patients with syncope recurrence despite optimal guideline – directed therapy will be compared to patients without recurrence to explore the existence of a potential SALT cut-off.
Endpoints	<u>Primary:</u> • Syncope – asystole latency time (SALT) in patients with syncope recurrence despite guideline-directed invasive treatment <u>Secondary</u>: • Recurrence of syncope in patients treated with different pacemaker configurations (DDD-CLS, DDD-RDR, DDDrr) and Neurocardioablation • Recurrences of syncope in treated patients selected by loop recorder, Carotid Sinus Massage and VTTT
Sample size	Prospective, observational study with first analysis when 68 patients reached 12 months of follow up
Design	Prospective, observational, multicenter study Patients with severe syncope presentation and guideline-directed workup and treatment are followed up for 24 months

Inclusion criteria	• Patients with severe reflex syncope and eligible for invasive treatment strategies according to the ESC Guidelines for pacing 2021[6]
Exclusion criteria	• Other condition which explains syncope cause other than reflex syncope • Structural heart disease (valvular, ischaemic, cardiomyopathies) • Pregnancy
Institution	Ospedale centrale di Bolzano- Cardiologia Via Lorenz Böhler, 5, 39100 Bolzano BZ
Investigators	**Principal Investigator** Dr. Marco Tomaino Ospedale centrale di Bolzano- Cardiologia Via Lorenz Böhler, 5, 39100 Bolzano BZ Tel: Email: marco.tomaino@sabes.it **Co-Investigators** Unterhuber Dr. Matthias Sette Dr.ssa Antonella Marcheselli Dr. Andrea Di Maggio Dr.ssa Debora Attena Dr. Emilio Gallo Dr. Antonio
Time schedule	• Start 10/2023 • First analysis (64 patients, 12 months FU) 11.2025

2. SCIENTIFIC BACKGROUND

Syncope is a common leading affection and is responsible for 1-3% [1-2] of the presentations in emergency departments and up to 3% of inpatient admissions. The phenomenon of syncope poses often a diagnostic and therapeutic challenge for the attending physician and is often misdiagnosed or underdiagnosed. After an accurate evaluation, patients can be treated with pacemaker implantation when the syncope cause is a cardioinhibition with documented asystole during the syncopal event according to the current ESC Guidelines for pacing 2021 [6]. When accurately selected, patients benefit from pacemaker therapy with a significant reduction of syncope recurrence in the follow up. However, a substantial portion of the patients (approx. 25%) experience recurrence of syncope despite optimal pacemaker therapy[3,4]. The underlying mechanism is not well understood and object of the current study.

3. Definitions

- **Syncope:** Transient Loss of Consciousness due to a cerebral hypoperfusion characterized by a rapid onset, short duration and spontaneous and complete recovery of the affected person.

4. PRIMARY OBJECTIVE

The main goal of the study is to evaluate the time elapsed between the T-LOC during Video Tilt Table Testing and the asystole at the ECG using a national registry and to assess its predictive value in patients undergoing invasive treatment. The hypothesis is that a vasodepressive component could lessen the effect of pacing in a patient, leading to cerebral hypoperfusion and syncope despite maintaining a stable rhythm.

5 METHODS

5.1 Design and trial population

- Prospective, multi-center observational study with 2 year follow-up of patients eligible for invasive treatment of reflex syncope.

5.2 Endpoints and safety

5.2.1 Primary endpoint

- Syncope to asystole latency time (SALT) and its prognostic value regarding freedom of syncope recurrence after pacemaker implantation

5.2.2 Secondary endpoints

- Recurrence of syncope in patients treated with different pacemaker configurations (DDD-CLS, DDD-RDR, DDDrr) and Neurocardioablation
- Recurrences of syncope in treated patients selected by CSM or loop recorder and negative or positive vasodepressive VTTT

5.2.3 Adverse events

- Acute: any major procedure-related adverse cardiac events or pacemaker-related complications

Follow-up: 24 months

- Assessment of all cardiac events leading to hospitalization or change of treatment strategy
- Recurrence of syncope

.3 Inclusion and exclusion criteria

- ***Inclusion criteria***

- Patients eligible for invasive treatment according to the ESC Guidelines for pacing 2021
- Written informed consent

5.3.2 Exclusion criteria

- Other condition which explains syncope cause other than reflex syncope
- Structural heart disease (valvular, ischaemic, cardiomyopathies)
- Pregnancy
- Patient denial to be recorded on video during tilt table test

5.3.3 Inclusion process

The inclusion of patients should happen at any time when a patient is guided to the doctor's attention for syncope. All patients with reflex syncope eligible for an invasive treatment according to the ESC Guidelines for pacing 2021 should be included. If after guideline-directed implantable loop recorder insertion no cardioinhibition has been made, the patient

is included automatically in the registry. Informed consent must be obtained and can be withdrawn at any time. In case of consent withdrawal, the collected data will be removed from the database.

5.4 Monitoring

5.4.1 Hemodynamic parameters

Systolic and diastolic arterial blood pressure (SBP/DBP) as well as heart rate must be measured in all patients according to the ESC Guidelines.

5.4.2 Other parameters and data assessed

Baseline data: comorbidities are assessed (diabetes mellitus, renal failure, valve disease, hyperthyroidisms etc.) and echocardiography performed to assess eligibility and to exclude other causes of syncope.

Medication received, i.e., current antihypertensive medication.

Laboratory parameters: serum creatinine (Crea), potassium (K), thyroid-stimulating hormone (TSH), blood count (BC - leucocytes, erythrocytes, hemoglobin, thrombocytes) have to be documented according to the standard of care protocols.

Electrocardiogram (12-lead): All patients have to undergo at least one 12-lead Electrocardiogram in the context of syncope-workup according to the ESC Guidelines for pacing 2021.

Procedural data: Invasive treatment (pacemaker implantation and/or neurocardioablation) must be documented with pacemaker modus (e.g. DDD), and procedure data has to be documented according to the local standard of care protocol.

Complications: proactive assessment of possible complications related to pacemaker implantation or neurocardioablation (any physician on the ward as well as investigators).

5.4.3 Parameters assessment upon follow-up

Study assessments	**Baseline***	**post**	**at dis-charge**	**12M** (phone call or clinical esamination)	**24M** (phone call or clinical esamination)
Consent Process	X				
Inclusion/ Exclusion	X				
Medical and Cardiovascular History	X			X	X
Medications	X		X		
Physical Assessment and Office Blood Pressure	X		X		
12-Lead ECG	X				
Serum creatinine[1)]	X				
Estimated GFR[1)]	X				
Blood sample	X				
Adverse Event		X	X	X	X
Withdrawal/ Termination		X	X	X	X

5.4.4 Video Tilt Table Test procedure

The Video-Tilt-Table-Test set-up uses a personal computer (PC) to capture screen video data from a non-invasive-beat-to-beat (NIBTB) hemodynamic blood pressure (BP) device, combined with video recording of a patient. Using this technique, TTT can be performed with any routine protocol with the addition of video information of the patient enabling the physician to review the images and to assess the exact moment of T-LOC of the patient in concomitance to the ECG tracing. This novel technique does not pose new risks or novel interventions and does not affect the patient.

5.4.4 Pacemaker implantation for reflex syncope

Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope. Establishing a relationship between symptoms and bradycardia should be the goal of the clinical evaluation of patients with syncope and a normal baseline ECG. The efficacy of pacing depends on the clinical setting. In patients with reflex syncope, cardiac pacing should be considered in severe forms of reflex syncope with frequent recurrences associated with a high risk of injury. Therefore, the ESC guidelines suggest to implant a pacemaker in these individuals selected by carotid sinus massage, tilt table testing and / or loop recorder in class IA.

Pacemaker implantation is a procedure commonly used to treat bradycardia episodes, consisting in the insertion of pacing leads into the heart chambers, connected to a generator with a microcomputer which is inserted under the skin in the subclavian region.

Study workflow

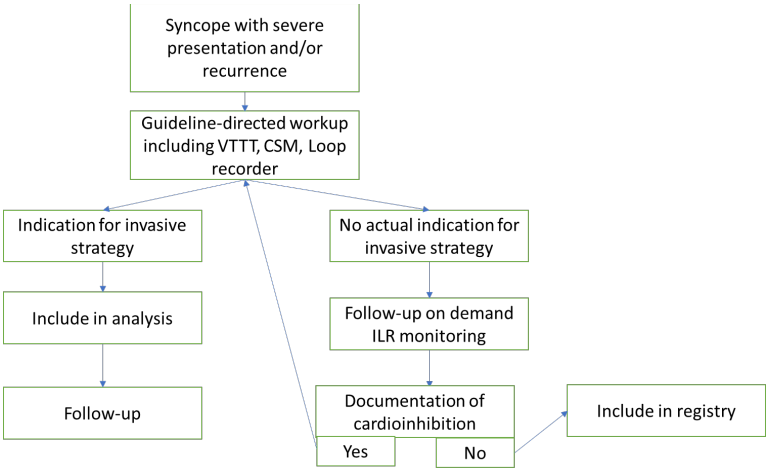

Figure: Flow chart of the study. VTTT: Video Tilt Table Test, CSM: Carotid Sinus Massage, ILR: Implantable Loop Recorder.

5.5 Follow-up

All patients are followed at 12 and 24 months after the index visit.

6. STATISTICS

6.1 Statistical Analysis

Normality of data distribution is tested with the Shapiro–Wilk test. Normally distributed continuous variables will be tested using Student's *t*-test or
if non-normally distributed medians with interquartile range. Mann–Whitney *U* test will be used for non-normally distributed data, while Fisher's exact test will be used for dichotomous variables. Receiver Operating Curves plotted to discover potential ideal cut-offs and Kaplan–Meier estimates will be used to estimate hazard ratios.

6.2 Sample size

Since the explored syncope-to-asystole time has never been assessed before, power calculations to estimate the needed sample size are not easily feasible. However, the combination of Video-assisted Tilt Testing and precise ECG tracing during syncope allows for very precise syncope-to-asystole time measurements. Therefore, assuming values of -5 seconds to 5 seconds of syncope-to-asystole time seems reasonable. Starting from a 25% recurrence rate in pacemaker-treated cohorts [3,4], allowing a 95% minimum acceptable probability of preventing Type I errors and 80% power and a standard deviation of $\pm$10s, 16 patients with recurrences are needed. Thus, 16 patients with recurrences +48 patients without recurrences should suffice to be hypothesis generating. Therefore, a first analysis will be carried out at the reach of 64 included patients.

7. ORGANISATORY

7.1 Investigating center

Südtiroler Sanitätsbetrieb - Azienda Sanitaria dell'Alto Adige
Lorenz Böhler-Straße 5 39100 Bozen - Via Lorenz Böhler 5 39100 Bolzano
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Sekretariat/Segreteria (Hauptgebäude/Padiglione Centrale) 0471908335

7.2 Clinical Investigation

Principal Investigator
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Sette Dr.ssa Antonella
Marcheselli Dr. Andrea
Di Maggio Dr.ssa Debora
Attena Dr. Emilio
Gallo Dr. Antonio

The investigators have a clear track record of designing, conducting and analyzing clinical trials and fulfill the required standards.

Participating physicians
All physicians working at the cardiac care unit as well as all electrophysiologists trained adequately to pursue syncope work-up.

Time schedule

- Start 10/2023

8. ETHICAL ASPECTS

8.1 General aspects and risk-benefit relationship

The trial is conducted according to:

- Requirements of GCP (Good Clinical Practice)
- And according to principle of the Declaration of Helsinki.

As pacemaker implantation strategy is a standard treatment option the risk- benefit ratio can be considered as positive. Furthermore, the treatment is in line with the current guidelines and does not introduce new treatment options to the syncope work-up.

8.2 Informed Consent

After screening for eligibility, patients are thoroughly and comprehensively informed about all aspects of the study, specific potential complications and potential disadvantages. In particular, the patient will be assured that consenting for participation in the study can be withdrawn at any time. Further, the refusal of participation will not have any influence on further treatment of the patient. Appropriate consenting includes signing of the attached consent form by both the patient and consenting physician (attached).

8.3 Documentation of the data assessed

All clinical data, results of diagnostic tests and procedures and patients' consent forms are archived within the Case Reporting Forms. The content of the Case Reporting Forms should be consistent with patient's clinical notes. All patients' data will be anonymized and electronically saved. No patients' names, birthdate, or initials will be used. All data will be used only for the purpose of the study and will be accessible only for the investigators. Data will be treated according to the legal requirements concerning the confidential medical communication. Data will be kept for 10 years after study completion.

8.4 Adverse events

Adverse events will be assessed and documented in the patient's clinical notes at any time and in the case reporting for at the follow-ups.

8.5 Ethic commission

The protocol and patients' consent form will be submitted for approval to the local ethics committee of the University of Bozen. All relevant changes to the protocol have to be approved by the ethics committee.

8.6 Insurance

Concerning the general procedural risk, the individual patients are insured in the the context of the stay in hospital by the hospital operator.

10. SIGNATURE

Protocol approved.

Bolzano, 14/07/2023

Dr. Marco Tomaino, Dr. Matthias Unterhuber,

11. LITERATURE

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