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A COMPARATIVE STUDY BETWEEN THE DYNAMIC ECG (HOLTER SYSTEM) FINDINGS OBTAINED BY QUORETECH'S QUOREONE SYSTEM WITH THOSE OBTAINED BY CARDIOS' CARDIOLIGHT RECORDER.

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Summary

SUMMARY OF CHANGES

Protocol		Amendment		
Version No.:	**Date**	**Amendment No.**	**Protocol Section**	**Summary of Changes (to/from)**
1.0	26-Oct-2020			N/A – First version
2.0	21-Jan-2021	1	2.5 Data Collection	Inclusion of the application of a questionnaire about the convenience of use and functions of QuoreOne.
3.0	10-Sep-2021	2	1.4.1 Primary Objective	Modification of the primary endpoint with a focus on detection of arrhythmias
3.0	10-Sep-2021	2	1.4.2 Secondary Objective	Addition of a secondary objective
3.0	10-Sep-2021	2	3. Methodology	Modification about same physicians evaluating both exams
3.0	10-Sep-2021	2	4.2 Primary Endpoint	Modification of the primary endpoint with a focus on arrhythmia detection
3.0	10-Sep-2021	2	4.3 Secondary Endpoints	Addition of secondary endpoints
3.0	10-Sep-2021	2	4.4 Exploratory Endpoints	Deletion of exploratory endpoints
3.0	10-Sep-2021	2	4.5 Sample calculation	Update of the sample calculation
4.0	25-Feb-2022	3	4.2 Primary Endpoint	Modification of the primary endpoint´s statistical analysis method
4.0	25-Feb-2022	3	4.3 Secondary Endpoints	Modification of the secondary endpoints' statistical analysis method

1. Study Design

1.1. Summary

There has been an important advance in the technology for capturing electrocardiographic signals by the Holder system in recent years. Among these advances, the following stand out: a) the miniaturization of devices; b) the possibility of capturing electrical signals by electrodes applied to the thorax without the need for cable intermediation with the recorder; c) the direct positioning of the recorder on the thoracic surface, allowing greater movement of the patient without the inconvenience of artifact records or interference in the signal line; d) possibility of transmitting electrocardiographic signals almost in real time over the computer network (internet), speeding up medical intervention in cases of high-risk arrhythmias or suspected clinical condition (syncope) being caused by such arrhythmias. No less important, it should be highlighted the speed of the preparation of the reports by the analysis software itself, which interprets the records and issues an initial report, with little or no interference from a technician or physician to edit the records. This is possible when neural networks, machine learning, and artificial intelligence are used to analyze those signals. The system in question is based on the capture of electrocardiographic recordings by Quoretech's *QuoreOne* recorder.

In order to reliably detect, electrocardiographic recordings obtained by *QuoreOne* should be compared with others already routinely used in clinical practice.

The objective of this study will be to analyze the data obtained by *QuoreOne* and compare it with those obtained by *Cardiolight* recorder analyzed by Cardios' software.

1.2. Introduction

The 24-hour ambulatory electrocardiogram, performed by the Holder system, is a procedure whose objective is to find the correlation between symptoms and possible changes in the electrocardiogram in order to establish a cause-effect relationship [1-5]. In practice, a digital recorder is connected to a cable with electrodes at its ends, which are then applied to the thoracic surface. The objective is for the electrical signal emitted by the heart to be captured and recorded in at least three channels that correspond to the electrocardiographic leads [6]. Once captured, the signals recorded on a digital card are transferred to a computer that, by means of specific software, performs the analysis and issues a result that includes the maximum, minimum and mean heart rates, in addition to the total number of atrial and ventricular ectopic heart beats, total tachycardias and ST segment alterations and T waves. The interpretation of the electrocardiographic recordings is then carried out by a specialized technical analyst who confirms the data or corrects the information that is in disagreement. The following result is confirmed by a physician[6].

Current systems are limited to this type of analysis, but they suffer from some limitations. These are of a technical nature related to signal capture, the dependence on electrode cables, which often limit the mobility of patients and is associated with greater risks of interference in the recording channels (50/60 Hz electrical network,

touching of clothing on the electrodes; electrode displacements, etc.)[1]. Depending on the intensity and duration of these alterations, there may be a need to repeat the examination.

With the advancement of technology, new signal capture systems have been developed. The possibility of applying the recorder directly to the thoracic surface eliminated the need for electrode cables. This fact not only improved the quality of the signs, but also allowed greater patient mobility, making the test better tolerated. The possibility of sending the recorded signals over the internet speeds up their interpretation. In addition, an analysis software previously trained by neural networks allows the editing of records more quickly by issuing a pre-report, facilitating the routine of the physician who will have less work to prepare the final report. With this approach, it is expected that the more exams the system analyzes, the better its performance should be, probably reaching almost the point of minimal medical interference in the final result.

In the study, which is now proposed to be carried out at the Cardiac Arrhythmias Outpatient Clinic of the Dante Pazzanese Institute of Cardiology (IDPC), Holter recordings will be performed in about 180 consecutive patients with the two systems simultaneously, the *QuoreOne* from Quoretech (system under test) and the *Cardiolight* from Cardios (conventional 24-hour Holter-system), a system that has been on the market for more than 30 years and is widely used in the country today. This approach will allow for the comparison of *QuoreOne*'s results with those of *Cardiolight*.

1.3. Hypothesis

The initial hypothesis in this study is that the electrocardiographic recordings obtained by the two systems are comparable, thus validating the information obtained by *QuoreOne*. Therefore, the study will test the hypothesis of comparability of the *QuoreOne* system in relation to the conventional Holter system.

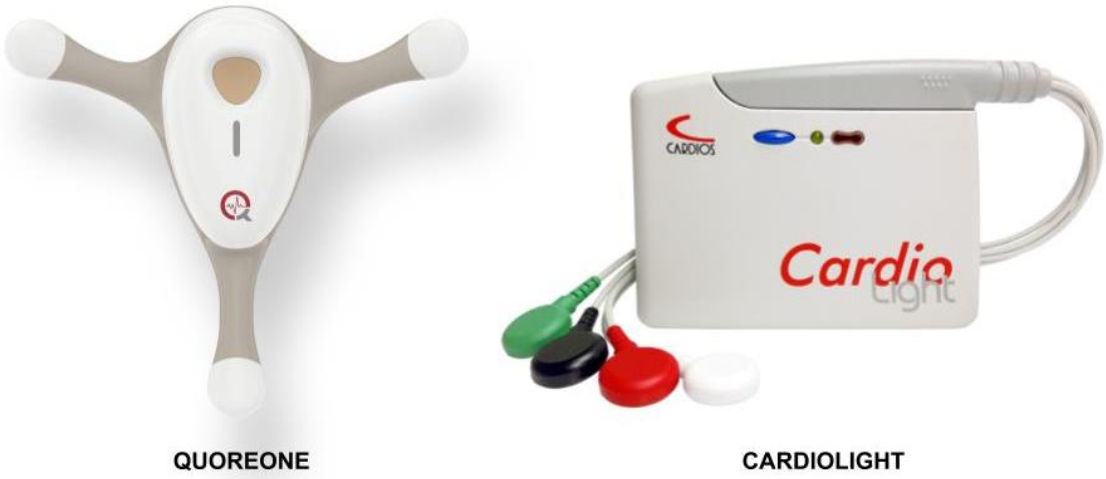

Figure 1 – Holter, Quoreone (Quoretech) and Cardiolight (Cardios) recorders that will be used in this study.

1.4. Objectives

1.4.1. Primary Objective:

To assess whether the detection of arrhythmias by *QuoreOne* is comparable to *Cardiolight*. Detection of the following arrhythmias will be compared: atrial fibrillation or atrial flutter, supraventricular tachycardia, ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation; atrioventricular block and pauses.

1.4.2 Secondary Objective

Compare the 24-hour electrocardiographic recordings detected by both systems. The following will be included in the analysis: a) maximum, minimum and mean heart rates; b) total atrial and ventricular ectopic heart beats; c) episodes of supraventricular tachycardia, ventricular tachycardia, and pauses. In addition to these variables, the duration of the examination and the convenience of using both systems should also be compared.

2. Materials and methods

2.1. Sample

It will consist of data from Holter recordings to be performed on patients from the Electrophysiology and Cardiac Arrhythmias outpatient clinic of the Medical Section of Electrophysiology of IDPC. The sample size calculation foresees the inclusion of a minimum of 182 patients with complete data from both exams.

2.2.Inclusion Criteria

- Patients aged ≥ 18 years, with indication for continuous 24-hour electrocardiographic monitoring by 24-hour Holter at the IDPC outpatient clinic, and who agree to participate in the study by signing the free and informed consent form (ICF).

2.3. Exclusion Criteria

- Patients who do not sign the informed consent form will be excluded.

2.4. Holter Device

The Holter-type cardiac monitor is a portable ambulatory electrocardiography device. It aims to monitor the electrical activity of the heart over a prolonged period, usually twenty-four hours.

For this study, the *Cardiolight* recorder from the company Cardios, the predominant equipment in the medical practice of the IDPC, and the *QuoreOne* recorder, from Quoretech, will be used, which will be submitted to comparison.

2.5. Data Collection

All exams will be performed at IDPC, the exams performed with the Cardiolight equipment will be stored both in the original file (.xcm) and in the final version of the report (.pdf). The exams performed with the QuoreOne equipment will be saved directly on the online report platform and in the final version of the report (.pdf). These files will be exported to an external hard drive and sent for tabbing. If there has been a report of symptoms by the patient, this data will be included in both files to establish the relationship between the complaint and any alteration in the electrocardiogram. The parameters will be analyzed with anonymized data from the participants.

After the Holter devices are removed, the participant will be asked to answer a questionnaire about the convenience of use and functions of the *QuoreOne* device.

3. Methodology

The exams performed by the conventional system (*Cardiolight,* Cardios) and by the *QuoreOne* system will be analyzed and the reports released by physicians from the Electrophysiology Section of the IDPC. These tests will be implemented at the same time in the same patient and for the same duration. The physicians evaluating the results of one method will be the same as the physicians evaluating the results obtained by the other method, but these will be blinded to the patients' data, making it impossible to identify that the tests being evaluated are from the same patient.

4. Statistical analysis

4.1.Descriptive Analysis

Data will be collected regarding demographic variables, underlying diseases, use of medications, and medical indication for Holter monitoring. Categorical variables will be presented with counts and percentages. Quantitative variables will be presented as means and standard deviations if normal distribution and as medians and interquartile ranges if non-Gaussian distribution. The Kolmogorov-Smirnov test will be used to evaluate the normality of the distributions of quantitative variables.

4.2. Primary Endpoint

To compare the detection of arrhythmias between the two methods mentioned with regard to the set of the following arrhythmias: a) atrial fibrillation or atrial flutter; b) supraventricular tachycardia (≥ 3 beats); c) ventricular tachycardia (≥ 3 beats); d) polymorphic ventricular tachycardia or ventricular fibrillation; e) atrioventricular block (2nd degree Mobitz AVB I and II, 2:1 AVB and total AVB); and f) pauses (≥ 2.5 seconds). The comparison between the two methods will be evaluated by the accuracy of *QuoreOne* compared to the conventional system, in addition to the other diagnostic statistics: sensitivity, specificity, positive and negative predictive values will also be presented always followed by 95% confidence intervals.

4.3. Secondary Endpoints

- Comparison of the detection of each type of arrhythmia between the two devices

- Comparison of the duration of the examination between the two devices;
- Comparison of mean, minimum, and maximum heart rate captured between the two devices;
- Comparison of the total atrial ectopic heart beats captured between the two devices;
- Comparison of total ventricular ectopic heart beats captured between the two devices;
- Comparison of total episodes of supraventricular tachycardia, ventricular tachycardia, and pauses between the two devices;
- Evaluate the convenience of using the two registration systems.

The individual categorical secondary endpoints (detection of each type of arrhythmia) will also be evaluated by diagnostic statistics (accuracy, sensitivity, specificity, positive and negative predictive values) with respective 95% confidence intervals.

The continuous secondary endpoints (mean, minimum and maximum heart rate, total atrial and ventricular ectopic heart beats, total episodes of supraventricular tachycardia, ventricular tachycardia and pauses) will be described by Bland-Altman plots accompanied by Lin and Pearson correlation coefficients.

Lists with the patient's reports will be made to evaluate the convenience of the systems. The Chi-square test or Fisher's exact test will be used to evaluate the

proportion of patients who report greater comfort (comfort of the device) with *Quoreone* versus *Cardiolight*.

4.4. Sample size calculation

The sample size calculation of the study was established assuming the hypothesis of comparability of the *QuoreOne* device in relation to the conventional device. Considering data from a previous study,[7] a two-tailed alpha of 5% and a power of 80% for the primary endpoint, the study will need to include a minimum of 182 patients with valid and complete measures of the 24-hour records by both methods.

5. Ethical Aspects

5.1. About Informed Consent Form (ICF)

When recordings are made, all patients must sign an informed consent form.

6. Study personnel and Organiztions Involved

6.1.Study personnel

Dr. Bruno Pereira Valdigem – Cardiologist of the Dante Pazzanese Institute of Cardiology (IDPC).

Dr. Dalmo Antonio Ribeiro Moreira – Cardiologist of the Medical Section of Electrophysiology at the Dante Pazzanese Institute of Cardiology (IDPC).

Dr Otávio Berwanger – Director of the Academic Research Organization of Hospital Israelita Albert Einstein

Dr. Karla Espírito Santo – Cardiologist and Researcher at the Academic Research Organization of Hospital Israelita Albert Einstein

Dr Remo Holanda de Mendonça Furtado – Cardiologist and Researcher at the Academic Research Organization of Hospital Israelita Albert Einstein

Lucas Damiani – Statistitician at the Academic Research Organization of Hospital Israelita Albert Einstein

Silvia Lamas – Biostatistician of the Academic Research Organization of Hospital Israelita Albert Einstein

Ronaldo Soares – Manager of the Academic Research Organization of Hospital Israelita Albert Einstein

Luciana Piano – Regulatory Affairs Manager of the Academic Research Organization of Hospital Israelita Albert Einstein

6.2. Organizations

Instituto Dante Pazzanese de Cardiologia (IDPC).

ARO of Hospital Israelita Albert Einstein – Responsible for support in protocol design, data analysis and operational and regulatory support.

Quoretech S.A. – Innovation and technology company in health and cardiac monitoring.

7. Schedule

Activities	2021											2022			
	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr-Aug
Data collection*	x	x	*	*	*	*	x	x	x	x					
Data cleaning and preparation of reports											x	x	x		
Data analysis														x	
Results presentation														-	x

*Recruitment paused due to the COVID-19 pandemic.

8. Budget

The company Quoretech will bear the costs involved in conducting the study.

9. Statement of Conflicts of Interest and Funding

This study proposal is funded by Quoretech S.A. – a company of innovation and technology in health and cardiac monitoring (homepage: www.quore.tech e-Mail: contato@quore.tech).

10. Bibliography

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