

ABSTRACT OF THE DOCTORAL THESIS

**Assessing the correlation between advanced
electrocardiographic predictors of sudden cardiac
death and the complexity of coronary lesions**

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Introduction

Cardiovascular diseases are the most important cause of death globally. By clinical presentation, 25% of cardiovascular deaths occur as sudden cardiac death (SCD), and as etiology, 50% of cardiovascular deaths are due to ischemic heart disease (IHD). Furthermore, 80% of SCDs are due to IHD. Therefore, patients with IHD most frequently die from SCD, and patients who suffer SCD most frequently have IHD. Numerous electrocardiographic (ECG) predictors of SCDs have been investigated. The importance of ECG predictors stems from the fact that tachycardia and/or ventricular fibrillation (VT/VF) is the initiating event in approximately 85% of SCD cases. The aim of this thesis was (1) to study the pathophysiological basis of ECG predictors, (2) to develop and validate tools for measuring some ECG predictors, (3) to identify new ECG parameters with predictive value on SCD, (4) to study the correlation between ECG predictors of SCD and coronary lesion complexity and (5) to study the impact of coronary lesion complexity on all-cause and cardiovascular death.

Objective

In order to achieve these goals, five studies were performed whose objectives were:

Study I – Identification of advanced electrocardiographic predictors of sudden cardiac death in Brugada syndrome – The objective was to study ECG parameters at rest and during ajmaline testing in both Brugada syndrome (BrS) and control patients. The utility of ECG parameters in risk stratification of SCD in patients with and without ventricular arrhythmic events was studied.

Study II – Modulation of electrocardiographic predictors of sudden cardiac death by pulmonary vein ablation in the treatment of atrial fibrillation – The objective was to study the pathophysiology and modulation of the autonomic nervous system reflected by ECG parameters during pulmonary vein ablation.

Study III – Evaluation of the correlation between advanced electrocardiographic predictors of sudden cardiac death and the complexity of coronary lesions – The objective was to study the actual correlation between ECG parameters of the SCD and the complexity of coronary lesions as reflected by the SYNTAX score.

Study IV – Fibromuscular coronary dysplasia - a rare non-atherosclerotic etiology of coronary lesions that can be associated with sudden cardiac death - The objective was to illustrate the importance of non-atherosclerotic coronary lesions in the etiology of SCD through a clinical case (young patient who suffered cardiac arrest by VF successfully resuscitated).

Study V – Impact of coronary lesion complexity on 3-year cardiovascular and all-cause death in a prospective PCI registry - a comparison of machine learning and classical clinical scores - Objective was to study the impact of coronary lesion complexity on all-cause death cause and cardiovascular cause. The performance of different scores in predicting death at 3 years was compared such as – anatomical scores (SYNTAX score), clinical scores (GRACE score, ACEF), combined clinical and anatomical scores (SYNTAX II score) as well as a prediction model based on machine learning.

General methodology

Study I – A total of 308 patients with BrS and a control group of 100 patients testing negative for BrS to ajmaline were included. **Study II** – A total of 92 patients who underwent the initial cryoablation procedure for paroxysmal atrial fibrillation (AF) and 3D mapping for AF recurrence were included. **Study III** – A total of 874 patients were included of whom 523 (59.8%) had coronary heart disease and 47 (5.3%) died at 3-year follow-up. **Study IV** – We illustrated the case of a young patient with coronary fibromuscular dysplasia with cardiac arrest via VF resuscitated at the age of 14 years. **Study V** – A number of 2242 patients were included. Death at 3 years was present in 336 (14.9%) patients, of which 272 (80.9%) were of cardiovascular cause.

Results

Study I – Identification of advanced electrocardiographic predictors of sudden cardiac death in Brugada syndrome – The main results of this study can be summarized as follows: (1) ajmaline challenge induces in control and BrS patients an increase in sympathetic tone and a reduction in vagal tone reflected by heart rate variability (HRV) parameters, respectively a decrease in the baroreflex response shown by heart rate turbulence (HRT), while the increase in microvolt T alternans (mTWA) was observed only in patients with BrS; (2) patients with BrS and VT/VF at 5 years had more pronounced changes during ajmaline testing, such as longer QRS complex duration, lower LF power,

lower TS value, and higher maximum mTWA value compared with patients with BrS and without VT/VF; (3) LF power and peak mTWA during ajmaline testing were independent predictors of 5-year VT/VF occurrence in multivariate analysis; (4) in a combined prediction model, LF power and maximum mTWA significantly improved Sieira score prediction with a final AUC-ROC of 0.846.

Study II – Modulation of electrocardiographic predictors of sudden cardiac death by pulmonary vein (PV) ablation in the treatment of atrial fibrillation – The main results of this study are: (1) parasympathetic tone is increased in patients with reconnected VP compared to patients without reconnected VP, (2) markers of vagal tone are affected proportionally to the number of VPs reconnected, (3) among parameters reflecting parasympathetic tone, CD, SDNNI and absolute power of VLF are specific for VP reconnection, especially of the right veins. Ablation of the right VP produces complete cardiac denervation evidenced by both HRV parameters and electrical stimulation of the vagus nerve, most likely due to denervation of the right anterior ganglion plexus which is the main and final relay of the autonomic nervous system to the sinus node.

Study III – Evaluation of the correlation between advanced electrocardiographic predictors of sudden cardiac death and the complexity of coronary lesions – The main results of this study are: (1) regarding HRV parameters, although coronary patients achieved lower maximum heart rate, achieved lower METs and exerted less effort due to positivity of the stress test, sympathetic activation was higher in coronary patients; HRV parameters were predictive of coronary heart disease and death from any cause at 3 years; (2) similarly, mTWA parameters were predictive of coronary heart disease, but not of death from any cause at 3 years; (3) HRV parameters showed the highest sympathetic activation and mTWA parameters had the highest values in patients with left main or LAD injury, correlated with the number of vessels with significant injury, and correlated with the SYNTAX score.

Study IV – Coronary fibromuscular dysplasia – a rare non-atherosclerotic etiology of coronary lesions that can be associated with sudden cardiac death – We illustrated the case of a young patient with coronary fibromuscular dysplasia, a type of non-atherosclerotic and non-inflammatory coronary lesion. The first manifestation of the disease was at the age of 14 through acute coronary syndrome complicated with cardiac arrest by VF resuscitated with probable success by spontaneous dissection of the right coronary artery. Progression was rapid to ischemic dilated cardiomyopathy through severe tricarotary lesions by the age of 22 years. The patient was started on medical treatment for heart failure and percutaneous myocardial revascularization was performed. Follow-up at 2 years revealed a relatively good evolution with improvement in LV systolic and diastolic function, and coronary anatomy was stable.

Study V – Impact of coronary lesion complexity on 3-year cardiovascular and all-cause death in a prospective PCI registry – a comparison of machine learning and classical clinical scores – Anatomical scores reflecting coronary lesion complexity such as SYNTAX score, residual SYNTAX score or the SYNTAX revascularization index were significantly outperformed by scores combining clinical and anatomical parameters such as the SYNTAX II score or the clinical SYNTAX score in predicting death at 3 years. Also, the combined scores performed similarly to clinical scores such as ACEF score, GRACE score, and TIMI score in predicting 3-year death. Furthermore, the machine learning model that included 140 clinical and anatomical parameters significantly outperformed all conventional clinical or anatomical scores such as GRACE, ACEF, SYNTAX II 2020 or TIMI score in predicting short- and long-term mortality of any cause and cardiovascular cause in a prospective PCI registry.

Conclusions

In the first study, ajmaline testing produced an increase in sympathetic tone and a reduction in vagal tone in both BrS patients and control patients. This effect of ajmaline has not been described before and may be a class effect of sodium channel blockers. BrS patients showed an increase in the expression of mTWA during ajmaline administration when compared to baseline, whereas control patients did not show a change in mTWA during ajmaline administration. Heart rate variability, heart rate turbulence, and mTWA were found to be parameters with important prognostic value for SCD and ventricular arrhythmias at 5 years in patients with BrS. Patients with arrhythmic events had greater sympathetic activation and mTWA expression.

In the second study, PV ablation produces important modulation of the autonomic nervous system, particularly parasympathetic tone, by concomitant ablation of intramural ganglion plexuses. The right anterior ganglion plexus represents the final and common parasympathetic relay to the sinus node and lies near the right superior pulmonary vein. Ablation of the right PVs, especially the right superior, produces complete cardiac vagal denervation, as reflected

by HRV parameters and direct extracardiac vagus nerve stimulation. This observation contributes to the understanding of the physiology of the autonomic nervous system.

In the third study, heart rate variability parameters are more specific to death at 3 years, while vectorcardiographic parameters and mTWA are more specific to coronary artery disease. There is a moderate correlation between the complexity of coronary artery disease as reflected by the SYNTAX score and several ECG parameters such as mTWA in orthogonal leads during exercise, deceleration capacity during exercise, ST-elevation in standard leads during exercise, or Q-wave duration in the lower leads and the T wave area in the resting precordial leads.

In the fourth study, we presented a case of fibromuscular coronary dysplasia, a type of non-atherosclerotic and non-inflammatory coronary lesion in which the onset of the disease was at a young age by aborted cardiac arrest. This case shows us the importance of documenting the coronary anatomy regardless of age in patients with arrhythmic events and without an obvious cause, preferably by coronary angiography at the expense of coronary angioCT which may not reveal particularities such as spontaneous coronary dissection.

In the fifth study, scores combining coronary anatomy with clinical parameters such as the SYNTAX II score or the clinical SYNTAX score, as well as clinical scores such as the GRACE or ACEF score had a higher predictive power for 3-year death than strictly anatomical scores. Thus, clinical parameters have a greater impact than the complexity of coronary lesions in long-term survival. However, the machine learning model had the highest predictive power compared to previous scores. The machine learning model identified the presence of lesion in the proximal segment of the anterior descending artery as the coronary anatomy parameter of greatest importance.