“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY

DOCTORAL SCHOOL

MEDICINE

Management of patients affected by electrical storm

PhD THESIS SUMMARY

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SUMMARY

Abbreviations list

AC – arrhythmogenic cardiomyopathy
ACS – acute coronary syndrome
AHD – acute hemodynamic decompensation
ATP – antitachycardia pacing
BB – beta blocker
BCKDCR – chronic kidney disease
BrS – Brugada syndrome
BZ – border zone
CHD – congenital heart disease
CL – cycle length
CRT – cardiac resynchronization therapy
CS – cardiogenic shock
Cx – circumflex artery
DCM – dilated cardiomyopathy
DSC – sympathetic cardiac denervation
EKG – electrocardiogram
ES – electrical storm
ESC – European Society of Cardiology
ESx – extrastimuli
ETA – epidural thoracic anesthesia
GS – stellate ganglion
HCM – hypertrophic cardiomyopathy
HF – heart failure
HQ – quinidine
HR – hazard ratio
HTx – cardiac transplantation
ICD – implantable cardioverter defibrillator
ICM – ischemic cardiomyopathy
ISP – isoproterenol
LAD – left anterior descending artery
LM – left main artery
LV – left ventricle
LVEF – left ventricular ejection fraction
MI – myocardial infarction
MR – mitral regurgitation
MVT – monomorphic ventricular tachycardia
NICM – non-ischemic cardiomyopathy
NIPS – non-invasive programmed ventricular stimulation
NR-CTO – non-revascularized chronic total occlusion
PH – pulmonary hypertension
PVS – programmed ventricular stimulation
PVT – polymorphic ventricular tachycardia
RBM-20 – RNA-binding ribosomal protein 20
RCA – right coronary artery
RFA – radiofrequency ablation
RV – right ventricle
RVOT – right ventricular outflow tract
SCD – sudden cardiac death
TdP – torsades de pointes
ToF – Fallot tetralogy
VF – ventricular fibrillation
VT – ventricular tachycardia

LIST OF PUBLISHED PAPERS

In extenso papers published in ISI journals:

1. **Cojocaru C,** Năstasă A, Hîrceagă M, Iorgulescu C, Gondos V, Scărlătescu A, et al. The impact of previous VT substrate radiofrequency catheter ablation procedures for patients presenting with electrical storm. Kardiol Pol 2025; 83:605–614. **IF 3.8/2025, Q1 (first author)** (Chapter IX); https://doi.org/10.33963/v.phj.105096

2. **Cojocaru C,** Dorobanțu M, Vătășescu R. Pre-ablation and Post-ablation Factors Influencing the Prognosis of Patients with Electrical Storm Treated by Radiofrequency Catheter Ablation: An Update. Rev Cardiovasc Med. 2024 Dec 5;25(12):432. doi: 10.31083/j.rcm2512432. **IF 1.3/2024, Q3 (first author)** (Chapter I); https://doi.org/10.31083/j.rcm2512432

3. Vatasescu R, **Cojocaru C**, Gondos V, Iorgulescu C, Bogdan S, Onciul S, Berruezo A. MSA-VT Score for Assessment of Long-Term Prognosis after Electrical Storm Ablation. Biomedicines. 2024 Feb 22;12(3):493. **IF 3.9/2024, Q2 (corresponding author)** (Chapter VIII); https://doi.org/10.3390/biomedicines12030493

4. **Cojocaru C,** Deaconu S, Gondos V, Onciul S, Petre I, Gheorghe-Fronea O, Vătășescu R. Complex Substrate Leading to PVC-Mediated Systolic Dysfunction in addition to Sustained Monomorphic VT in Repaired Tetralogy of Fallot. Diagnostics (Basel). 2024 Jan 10;14(2):158. doi: 10.3390/diagnostics14020158. **IF 3/2024, Q1 (first author)** (Chapter II); https://doi.org/10.3390/diagnostics14020158

5. **Cojocaru C,** Nastasa A, Bogdan S, Iorgulescu C, Deaconu A, Onciul S, Vatasescu R. Non-revascularized chronic total occlusions impact on substrate and post-ablation results in drug-refractory electrical storm. Front Cardiovasc Med. 2023 Sep 21;10:1258373. **IF 2.8/2023, Q2 (first author)** (Chapter VII); https://doi.org/10.3389/fcvm.2023.1258373

6. Vătășescu R, **Cojocaru C,** Năstasă A, Popescu S, Iorgulescu C, Bogdan Ș, Gondoș V, Berruezo A. Monomorphic VT Non-Inducibility after Electrical Storm Ablation Reduces Mortality and Recurrences. J Clin Med. 2022 Jul 4;11(13):3887. **IF 2.8/2022, Q2 (first author equal contribution)** (Chapter VI); https://doi.org/10.3390/jcm11133887

7. **Cojocaru C,** Pupăză A, Iorgulescu C, Onciul S, Câlmâc L, Vătășescu R. Case Report: Pulmonary Vein Isolation as a Tailored Treatment for Recurrent Ventricular Tachycardia During Hemodialysis in a Patient With Right Coronary Artery Chronic Total

Occlusion. Front Cardiovasc Med. 2022 May 30;9:871386. **IF 3.6/2022, Q2 (first author)** (Chapter I); https://doi.org/10.3389/fcvm.2022.871386

CURRENT KNOWLEDGE

CHAPTER I – ELECTRICAL STORM – GENERAL INFORMATION

Electrical storm (ES) is a malignant arrhythmic complication defined by the occurrence of at least three episodes of sustained ventricular tachycardia (VT) within 24 hours, separated by a minimum 5-minute interval of baseline rhythm and requiring active intervention to suppress the arrhythmia (usually in the form of internal cardioverter defibrillator (ICD) appropriate therapies) [1]. Although arbitrarily and variably defined in previous documents, ES terminology has been recurringly used in studies to identify a subset of patients affected by frequent ventricular arrhythmic episodes which highly increase short-term mortality. However, there are numerous other clinical arrhythmic phenotypes that impact long-term prognosis: from incessant ventricular tachycardia (VT) defined by its persistence of over 12 hours and immediate (< 5 minutes) recurrence (despite successful transient termination by antitachycardia pacing (ATP) or shocks) and "clustered" VT (at least two episodes of sustained VT over an interval of three months) to isolated infrequent episodes of VT [1,2]. Data stemming from the OBSERVO-ICD registry shows that 4.7% of patients develop ES over a median interval of 39 months, especially driven by events in secondary prophylaxis ICD recipients (10.5%) in comparison to primary prophylaxis indications (3.9%) [3]. Irrespective of the cause of structural heart disease, development of ES is associated with severe acute and long-term clinical course due to increased risk of death, both due to arrhythmic-driven mortality and non-arrhythmic mortality associated with progressive heart failure (HF) and hemodynamic deterioration induced by recurrent arrhythmia and ICD shocks [1,2,4,5]. Hence, ES development induces a three-fold higher mortality and a five-fold higher risk of major adverse cardiovascular events (general mortality, cardiac transplantation (HTx), hospital admission for decompensated HF) [6].

CHAPTER II – ELECTRICAL STORM TREATMENT

ES management is highly complex and must involve the synergic use of multiple therapeutic strategies, starting with antiarrhythmic pharmacological agents (non-selective beta-blockers typically associated with intravenous amiodarone [7,8] or other medication guided by specific clinical scenarios, types of VTs and underlying etiologies: procainamide, sotalol,

lidocaine, quinidine, isoproterenol [1]) and optimization of ICD programming (to avoid unnecessary treatment and to increase efficiency of appropriate therapies) [1,4,9–12]).

Radiofrequency catheter ablation (RFA) has been shown to improve mortality and reduce the risk of VT recurrence in patients affected by drug-refractory ES and is now a class IB recommendation in the European Society of Cardiology (ESC) guidelines dedicated to ventricular arrhythmias and sudden cardiac death (SCD) management [1,13–16]. However, RFA results are influenced by multiple factors, such as patient characteristics (firstly related to the particularities of the arrhythmogenic substrate determined by the underlying etiology and secondly the severity of associated cardiovascular and non-cardiovascular comorbidities) and ablation-specific technical procedural aspects. In this regard, the optimal strategies to identify and eliminate the relevant substrate, the "gold-standard" procedural result and the most accurate programmed ventricular stimulation protocols (PVS) to identify residual arrhythmogenic sites are still under scrutiny. The lack of inducibility of sustained VT during PVS is regarded as proof of successful arrhythmogenic substrate elimination [17] and has been constantly associated with improved clinical outcomes in terms of mortality and VT recurrence risk[14,18–20].

Furthermore, other therapeutic strategies may aid in ES suppression and should be selectively considered: autonomic modulation [4] (in the form of stellate ganglion (GS) block, sympathetic cardiac denervation (DSC) or epidural thoracic anesthesia (ETA) [1,21,22]), sedation and advanced heart failure management based on temporary mechanical circulatory support (as rescue therapy in cardiopulmonary resuscitation for cardiac arrest induced by refractory malignant arrythmia or as prophylactic circulatory support during RFA in ES patients that are considered to exhibit a high risk of acute hemodynamic decompensation [23–26]).

PERSONAL CONTRIBUTION

CHAPTER III – HYPOTHESIS AND GENERAL OBJECTIVES

Development of ES significantly alters the clinical course of patients with structural heart disease and exponentially increases the risk of arrhythmic death or refractory HF [1,7]. RFA may abolish VT episodes and improve long-term mortality and risk of recurrences [1,7]. However, even if treated by RFA and managed correctly according to current guidelines [1,7], certain subsets of patients will still develop severe outcomes. Hence, we **hypothesize** that identifying novel patient-related characteristics (regarding arrhythmogenic substrate supplied by non-revascularized chronic total occlusions (NR-CTO) in post-myocardial infarction (MI)

patients or related to previous RFA attempts for VT substrate elimination) and procedural aspects (concerning the effect of more aggressive PVS protocols to enhance detection of residual arrhythmogenic substrate) can improve risk stratification and may be used in the future to aid clinical decisions.

Therefore, the **primary objectives of** this doctoral thesis were the following:

- To assess acute procedural results of RFA for ES as defined by a more aggressive PVS protocol based on 4-extrastimuli induction and to analyze the impact of procedural results on long-term all-cause mortality and the risk of recurrent sustained VT/VF episodes

- To assess substrate characteristics in the presence of NR-CTO in post-MI patients treated by RFA for ES and to analyze the influence of NR-CTO on long-term mortality and the risk of recurrent sustained VT episodes

- To develop a new multiparametric scoring algorithm to enhance prediction of mortality and sustained VT recurrence after ES ablation in comparison with previously published scoring algorithms and individual predictors

- To assess the impact of a previous RFA procedure for sustained VT episodes on procedural data and on long-term mortality and risk of recurrent sustained VT/VF episodes for patients requiring RFA for ES

CHAPTER IV – GENERAL RESEARCH METHODOLOGY

This is an ambispective cohort study conducted between January 2014 – June 2023 at the Clinical Electrophysiology Laboratory of the Cardiology Department of the Emergency Clinical Hospital of Bucharest which enrolled consecutive ES patients treated by substrate RFA, in agreement with current European definitions and indications [1,7]. The retrospective phase of the study was carried out between January 2014 – June 2021 and the prospective phase was conducted between June 2021 – June 2023. The inclusion and exclusion criteria and patient management and monitoring protocols were consistently and uniformly applied throughout both study phases. The inclusion criteria were: ES patients as defined by the ESC guidelines [1,7] in the presence of at least three episodes of sustained monomorphic VT with appropriate ICD therapies (either antitachycardia pacing (ATP) or shocks) or by external electrical shocks and/or intravenous antiarrhythmic medication, which were treated by RFA; a minimum age of eighteen years old; informed consent given for study inclusion. Any patient found to have a correctable reversible cause for ES development (acute coronary syndromes, adverse reactions to medication, electrolyte abnormalities, supraventricular arrhythmias inducing VTs) was

excluded from this study. Severe HF at admission was defined in the presence of class III or IV New York Heart Association symptoms at the moment of admission.

All patients were uniformly assessed prior to RFA based on ESC guidelines [7] and all clinical, electrocardiographic, imaging [27] and intraprocedural electrophysiological data (based on Boston Scientific Labsystem PRO EP Recording System v.2.7.0.16, CARTO-3™, Biosense Webster, Diamond Bar, California softwares) were collected for analysis. The procedural workflow is extensively detailed in the Chapter IV – General research methodology and the mapping/ablation strategy is summarized in Figure 4.1. [28].

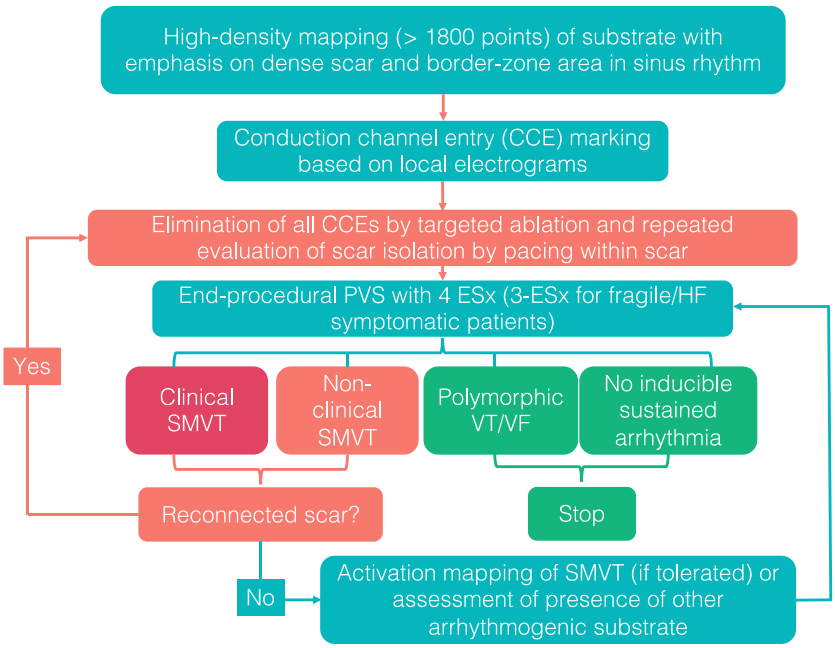

Figure 4.1. Electrical storm mapping and ablation strategy and workflow implemented in the Clinical Electrophysiology Laboratory in the Emergency Clinical Hospital of Bucharest, used with permission from the author (Prof. Dr. Radu Vătășescu). CCE = conduction channel entry, PVS = programmed ventricular stimulation, HF = heart failure, SMVT = sustained monomorphic ventricular tachycardia, VT = ventricular tachycardia, VF = ventricular fibrillation

Normal myocardium was defined by bipolar endocardial electrogram (EGM) voltages > 1.5 mV, LV unipolar EGM voltages > 8.3 mV, RV unipolar EGM voltages > 5.5 mV epicardial EGM voltages > 1 mV whereas dense scar was defined by < 0.5 mV EGM voltages and border zone areas by 0.5 – 1.5 mV EGM voltages. Procedural results were defined by the response to PVS at the end of RFA, at two distinct sites (medially and laterally) within the scar border zone (BZ) (as defined in methodology by local bipolar electrogram voltage of 0.5-1.5 mV), using at

least two baseline drive cycle lengths (CLs) and the progressive delivery of two, three and subsequently four extrastimuli (ESx) (at a minimum of 200 ms or until refractoriness). Less aggressive 3-ESx-based PVS protocols were selectively applied for patients deemed to be fragile or at risk for periprocedural hemodynamic deterioration. This response to PVS was either *dichotomically* defined (inducibility vs. non-inducibility of sustained monomorphic VT) or *specifically* defined (R1 = absolute non-inducibility – no arrhythmia was induced by PVS, R2 = residual inducibility only for polymorphic VT or ventricular fibrillation (VF), no inducibility for monomorphic VTs, R3 = inducibility for non-clinical monomorphic VTs, no inducibility for clinical monomorphic VT, R4 = persistent inducibility of clinical monomorphic VT). Clinical monomorphic VT was defined by a similar (± 20 bpm) rate to previous ICD-stored arrhythmic episodes or by similar QRS morphology based on 12-lead electrocardiogram recording (if available). The monitoring protocol was based on routine 6-month interval visits for ICD interrogation. The study center was telephonically notified with regard to patient death during the monitoring interval. If any patient became symptomatic (palpitations, syncope or ICD therapies), a prompt ICD interrogation visit was scheduled. All patients that were alive were scheduled for the ICD interrogation in June 2023.

All follow-up data was analyzed and reported in relation to the most recent RFA procedure (for patients with multiple interventions). All patients were monitored to detect the occurrence of the following events: death (irrespective of cause) and VT/VF recurrences (as defined by appropriate ICD therapy or by electrocardiogram/Holter tracings of a new sustained monomorphic VT episode for patients without ICDs).

SPSS version 23 (IBM Corp., Armonk, NY, US) software was used for statistical analysis and graphical representation of data was performed using Prism 9 version 10.3.1 (464) (GraphPad Software, LLC). The Kolmogorov-Smirnov test and Q-Q plots interpretation were used to assess normality of data distribution. Based on normality of distribution, continuous variables were expressed by either mean (standard deviation) or median (interquartile range) and compared using t test or Mann-Whitney U test. Categorical variables were compared using Chi-square or Fisher's Exact Test. Survival analysis was performed using Kaplan-Meier method and log-rank test. Cox hazards analyses were used to assess the association between the first occurrence of time-dependent outcome events (death and/or arrhythmic recurrence) and targeted predictors. The association of targeted predictors and effects (i.e. death and/or arrhythmic recurrence) was tested using univariable Cox regression analysis; variables with significant effect were subsequently included in multivariable models to test the independent prediction of the selected event. The accuracy of prediction of certain events by selected factors

was tested using ROC curves and the corresponding area under the curve (AUC) and DeLong's test. Optimal prediction cut-offs were interpreted using Youden's index. A 2-sided P-value <0.05 was considered statistically significant.

CHAPTER V – CHARACTERISTICS OF THE STUDY POPULATION

One hundred and one consecutive ES patients treated by RFA were included in the final analysis. General patient characteristics are extensively detailed in the thesis in Table 5.1 and specific data pertaining to each study is reported in each dedicated chapter. The cohort predominantly consisted of males (86.1%) with a mean age of 59.6 ± 12.8 years, 88.1% ICD recipients, 33.7% of subjects with at least one previous RFA procedure for monomorphic VT episodes (n = 12 [35.3%] fulfilling ES criteria at the time of RFA; n = 22 [64.7%] had undergone the previous RFA procedure in the study center, with a total number of RFA procedures of 141 with a median number of 1 (1-2) procedures per patient).

Concerning pre-RFA treatment, beta-blockers were prescribed in 82.2% of cases and amiodarone in 67.3% of patients. A median of 5 (3-11.5) appropriate ICD therapies were delivered prior to admission. Seventy-nine (78.2%) patients demonstrated left ventricular ejection fraction (LVEF) < 40% with a median LVEF of 30% (20-40). The most frequent cause of structural heart disease was MI (n = 64 [63.3%]), followed by idiopathic dilated cardiomyopathy (DCM) (n = 11 [10.89%]).

The median duration of RFA procedures was 185 (146-246.5) minutes. The rate of end-procedural residual monomorphic VT inducibility was 31.7% as assessed by 4-ESx PVS protocol in the majority of cases (n = 67 [66.3%]). Autonomic modulation was performed in 3.9% of patients by stellate ganglion (GS) blockade and surgical sympathetic cardiac denervation (DSC) in 1.9% of cases. Post-RFA treatment consisted of beta-blockers in 86.1% of cases and amiodarone in 71.3% of patients. The median follow-up interval was 32.8 (10-68) months.

A total of thirty-one (30.7%) patients died during follow-up and thirty-six (35.6%) patients developed VT/VF recurrences during follow-up.

CHAPTER VI – FIRST STUDY. VENTRICULAR TACHYCARDIA NON-INDUCIBILITY AFTER ELECTRICAL STORM ABLATION REDUCES MORTALITY AND RECURRENCES

6.1. Introduction

Complete elimination by RFA of relevant arrhythmogenic substrate may abolish VT episodes in ES patients and therefore improve clinical outcomes [14,18]. However, the optimal PVS protocol to assess the presence of residual substrate is still under debate. Non-inducibility of sustained monomorphic VT at 3-ESx-based final PVS is currently regarded as the "gold-standard" endpoint after VT ablation [14,17,18]. We sought to assess the impact of 4-ESx based PVS protocols on acute RFA results and long-term prognosis in ES patients.

6.2. Material and methods

Study protocols and statistical analysis methodology have been extensively detailed in Chapter IV. The primary endpoint was defined by the occurrence of any of death (irrespective of cause) or VT/VF recurrence during follow-up interval. The secondary endpoints were defined by death (irrespective of cause) or VT/VF recurrence respectively (as separate endpoints) during follow-up interval.

The *specific objectives* of this study were:

1. To assess the acute procedural results of RFA in ES patients as evaluated by a 4-ESx-based PVS protocol (3-ESx-based PVS exclusively used only for fragile or decompensated HF patients)

2. To analyze the occurrence of secondary endpoints (all-cause mortality and VT/VF recurrences separately) during follow-up after RFA for ES in relation to acute procedural results

3. To assess if the acute procedural results can accurately predict the occurrence of the primary endpoint during follow-up in ES patients treated by RFA

6.3. Results

Sixty-seven (66.3%) patients were evaluated by 4-ESx-based PVS protocol out of which thirteen (19.4%) demonstrated residual sustained monomorphic VT inducibility. Figure 6.1. depicts the distribution of PVS protocols (A) and specifically defined RFA results (B) and dichotomically defined RFA results (C). Figure 6.2. shows the Kaplan-Meier survival analysis evaluating all-cause mortality (A) and VT/VF recurrences (B) during follow-up after RFA for ES in relation to specifically defined RFA results (A and B respectively) and in relation to dichotomically defined RFA results (C and D respectively).

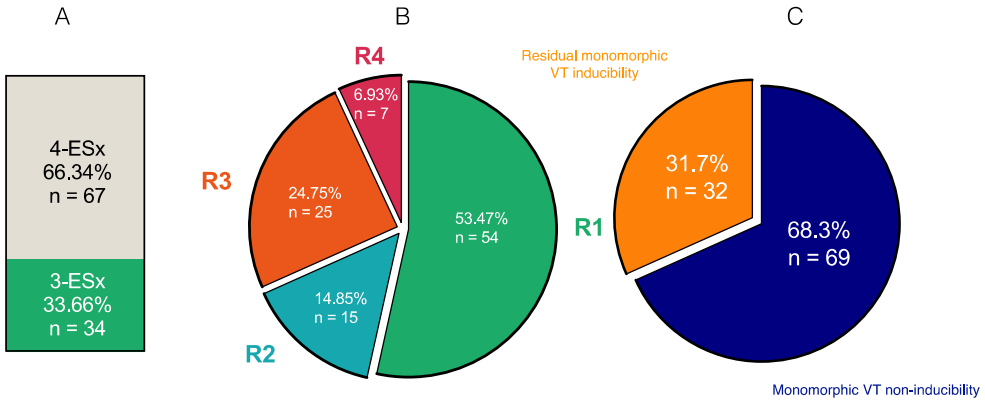

Figure 6.1. A = PVS protocols used for end-procedural ventricular arrhythmia inducibility, B = Distribution of specifically defined procedural results (R1-R4, detailed definitions in Chapter IV), C = Distribution of dichotomotically defined procedural results. PVS = programmed ventricular stimulation, ESx = extrastimuli, VT = ventricular tachycardia

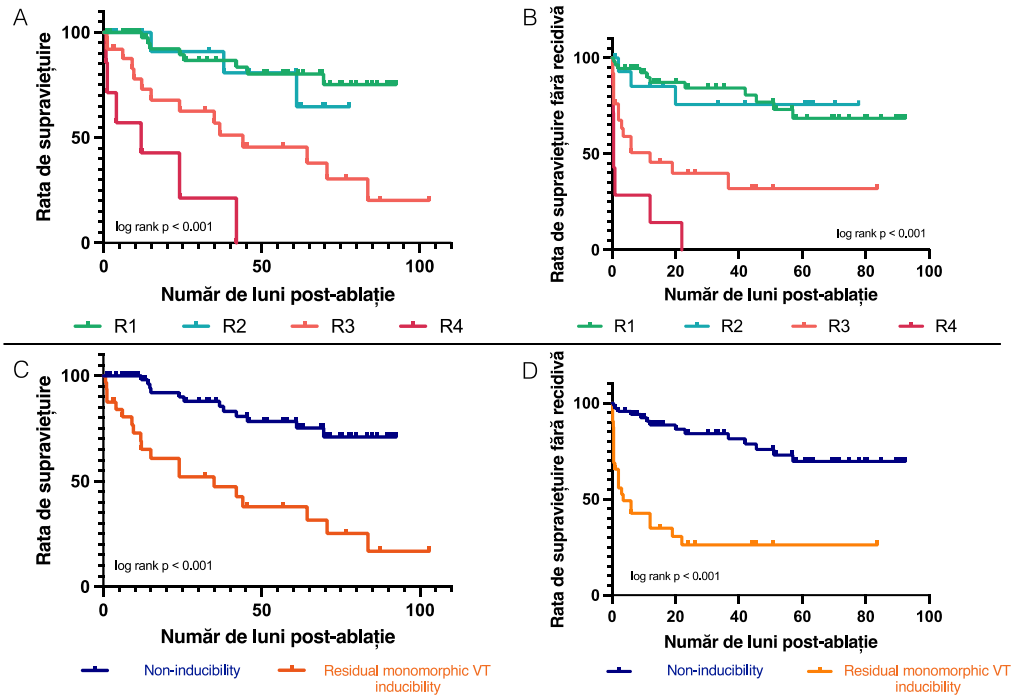

Figure 6.2. Kaplan-Meier survival analysis regarding A (all-cause mortality stratified by specifically defined acute procedural results), B (VT/VF recurrences stratified by specifically defined acute procedural results), C (all-cause mortality stratified by dichotomically defined acute procedural result), D (VT/VF recurrences stratified by dichotomically defined acute procedural results). VT = ventricular tachycardia, VF = ventricular fibrillation

Thirty-one (30.7%) patients died during follow-up, more frequently in the presence of residual monomorphic VT inducibility (nineteen [59.4%] vs. twelve [17.4% of patients without residual monomorphic VT inducibility], $p < 0.001$).

Thirty-six (35.6%) patients developed VT/VF recurrences, more frequently in the presence of residual monomorphic VT inducibility at PVS (fourteen [20.3%] vs. twenty-two [8.8% of patients without residual monomorphic VT inducibility], $p < 0.001$).

The primary endpoint was observed during follow-up in forty-seven (46.5%) patients, more frequently in the presence of residual monomorphic VT inducibility at PVS (twenty-seven [84.4%] vs. twenty [29%], $p < 0.001$). In patients with residual monomorphic VT inducibility demonstrated by 4-ESx PVS, the primary endpoint was observed during follow-up in 69.2% of patients (nine cases), whereas the rate all-cause mortality was 53.8% (seven cases) and the rate of VT/VF recurrences was 61.5% (eight cases). There was no difference regarding the primary endpoint ($p = 0.051$), all-cause mortality ($p = 0.59$) or VT/VF recurrences ($p = 0.46$) in patients with residual monomorphic VT inducibility demonstrated at 4-ESx PVS vs. 3-ESx PVS.

Eight predictors for the occurrence of the primary endpoint during follow-up were identified in Cox univariate regression analysis: chronic kidney disease (CKD) (HR 2.536, CI 95% [1.140-5.641], $p = 0.022$), severe HF at admission (HR 2.534, 95% CI [1.361-4.717], $p = 0.003$), pre-ablation amiodarone (HR 2.841, CI 95% [1.396-5.783], $p = 0.004$), post-ablation amiodarone (HR 2.190, CI 95% [1.018-4.710], $p = 0.045$), residual monomorphic VT inducibility at PVS (HR 4.070, CI 95% [2.266-7.308]), atrial fibrillation (AF) at admission (HR 1.528, CI 95% [1.052-2.218], $p = 0.026$) and left ventricular ejection fraction (LVEF) (HR 0.963, CI 95% [0.937-0.989], $p = 0.006$). Furthermore, residual monomorphic VT inducibility at PVS predicted VT/VF recurrences during follow-up in univariable Cox regression analysis (HR 6.54, CI 95% [3.26-13.1], $p < 0.001$). Due to the limited number of events during follow-up ($n = 47$, [46.5%]), four factor-based multivariable prediction models were tested including residual monomorphic VT inducibility at PVS and three other predictors extracted from univariable analysis.

Table 6.1. Multivariable Cox regression analysis models based on residual monomorphic VT inducibility and three other factors to predict the occurrence of the primary endpoint during follow-up. LVEF =left ventricular ejection fraction, VT = ventricular tachycardia, HR = hazard ratio, CI = confidence interval, CKD = chronic kidney disease

Variable	HR (95% CI)	p
Model 1		

Residual monomorphic VT inducibility	3.596 (1.930-6.699)	< 0.001
LVEF	0.981 (0.953-1.011)	0.217
CKD	3.378 (1.454-7.847)	0.005
Preablation amiodarone	1.975 (0.932-4.184)	0.076
Model 2		
Residual monomorphic VT inducibility	3.954 (2.053-7.617)	< 0.001
LVEF	0.975 (0.946-1.004)	0.095
CKD	3.288 (1.417-7.626)	0.006
Postablation amiodarone	0.952 (0.383-2.365)	0.916
Model 3		
Residual monomorphic VT inducibility	3.330 (1.813-6.118)	< 0.001
LVEF	0.994 (0.961-1.028)	0.738
Severe HF at admission	1.797 (0.852-3.792)	0.124
Preablation amiodarone	1.94 (0.897-4.199)	0.92
Model 4		
Residual monomorphic VT inducibility	3.643 (1.883-7.046)	< 0.001
LVEF	0.987 (0.954-1.020)	0.433
Severe HF at admission	1.848 (0.871-3.922)	0.11
Postablation amiodarone	0.975 (0.393-2.418)	0.956
Model 5		
Residual monomorphic VT inducibility	3.208 (1.758-5.851)	< 0.001
LVEF	0.976 (0.947-1.007)	0.127
Age	1.033 (1.004-1.062)	0.026
Preablation amiodarone	1.751 (0.823-3.723)	0.146
Model 6		
Residual monomorphic VT inducibility	3.834 (2.012-7.303)	< 0.001
LVEF	0.967 (0.939-0.997)	0.03
Age	1.038 (1.009-1.069)	0.011
Postablation amiodarone	0.682 (0.28-1.661)	0.4

6.4. Discussions

In summary, our study demonstrated the following [19]:

1. Monomorphic VT non-inducibility was obtained in 68.3% of cases and a more aggressive 4-ESx-based PVS protocol can identify residual monomorphic VTs which were not previously evident at 3-ESx-based testing.

The rate of monomorphic VT non-inducibility 68.3% is consistent with previously published evidence, even in the context of more aggressive 4-ESx-based PVS protocol which was applied in the majority of cases [14,18]. Importantly, the 4-ESx-based PVS uncovered thirteen patients (19.2%) with residually monomorphic VT morphologies that had not been accurately identified at 3-ESx testing. Whether this finding translates into clinical outcomes is still under research, yet the superior sensitivity of the fourth extrastimulus-based detection of residual substrate has already been suggested by other previous papers [29,30] Arrhythmias exclusively identified by the fourth extrastimulus are faster, require electrical shocks more frequently, but seem to have a similar risk of future recurrence as those identified by 3-ESx [30].

In this sense, our data shows that the rate of VT/VF recurrence for patients with residual monomorphic VT inducibility declared by 3-ESx protocols (73.7% recurrences) is equivalent to the rate observed after positive 4-ESx testing (61.5%, $p = 0.46$).

2. Patients who achieve monomorphic VT non-inducibility after RFA for ES demonstrate lower rates of all-cause mortality and VT/VF recurrences in comparison to those with residual end-procedural inducibility.

The observed rates of all-cause mortality were three-fold higher (59.4% vs. 17.4%) and of VT/VF recurrences and two-fold higher (20.3% vs. 8.8%) during follow-up, in the presence of residual monomorphic VT inducibility, with early divergence of survival curves after RFA. The worse outcomes of ES patients with suboptimal RFA results have been previously demonstrated [14,18]. Patients with absolute non-inducibility have the best prognosis and display no significant differences in terms of all-cause mortality and VT/VF recurrences compared to those that only develop polymorphic VT or VF at PVS (but no monomorphic VTs). Hence, the specificity of polymorphic VT induction to predict subsequent cardiovascular events is limited. The risk of arrhythmic sudden death or cardiac arrest of coronary artery disease patients displaying non-sustained episodes of monomorphic VT that were tested by PVS and only developed VF (and no sustained monomorphic arrhythmia) was equivalent to those with no ventricular arrhythmia induced by PVS [31].

However, persistent inducibility of "clinical" monomorphic VT leads to the most severe outcomes in terms of mortality and VT/VF recurrences. In this specific subgroup, six of seven patients died and all seven developed VT/VF recurrences during follow-up in our study.

3. Residual inducibility of sustained monomorphic VT after ES ablation independently predicts the occurrence of the primary endpoint (death *or* VT/VF recurrence) during follow-up in all the evaluated prediction models.

We identified four distinct types of factors that predicted events (death or VT/VF recurrences) during follow-up by univariable Cox regression: clinical (age, CKD, severe HF at admission), electrophysiological (AF at admission, residual inducibility for monomorphic VT), imaging (LVEF) and pharmacological (preablation or postablation amiodarone). Residual inducibility for sustained monomorphic VT was the strongest predictor for events during follow-up, providing a three-fold higher risk of death *or* VT/VF recurrences (highest of all factors). The limited number of events observed during follow-up (forty-seven deaths/VT/VF recurrences) restricted our analysis to four factors-based models. Residual sustained monomorphic VT inducibility at PVS independently predicted negative outcomes during follow-up irrespective of the evaluated model. Residual arrhythmic inducibility is a marker of persistent arrhythmogenic substrate after RFA that may cause subsequent arrhythmic ventricular recurrences (which are known to increase both arrhythmic and non-arrhythmic HF-driven mortality due to progressive hemodynamic deterioration and recurrent shocks) [32].

Study limitations

1. Single-center study with a limited study population (n = 101) with retrospective collection of data during the initial phase of the study (January 2014 June 2021); we only reported all-cause mortality rates (irrespective of specific arrhythmic or non-arrhythmic causes) due to the lack of detailed information regarding the mechanism of death

2. Study sample particular characteristics – higher rate of amiodarone prescription compared to previous observational studies (67.3% preablation/71.3% postablation) which may impact the long-term clinical course [32–34]

3. 4-ESx-based PVS could only be applied for 66.7% of cases, which may influence acute procedural results and subsequent prognosis analysis stratified by RFA results; there were thirty-four patients tested by 3-ESx PVS - nineteen (55.9%) demonstrated residual monomorphic VT inducibility (and therefore 4-ESx testing would have been redundant) and fifteen (44.1%) were considered non-inducible solely by 3-ESx PVS due to severe frailty; however the majority of ES ablation studies include a minority of up to 10% of cases which PVS was deferred due to severe intraprocedural symptoms or risk of hemodynamic decompensation [14]

6.5. Conclusions

Non-inducibility for sustained monomorphic VT was achieved by RFA in 68.3% of ES patients and independently predicted a favorable long-term prognosis after ablation. Aggressive 4-ESx-based PVS may further uncover residual arrhythmogenic substrate in up to one in five patients only tested by 3-ESx-based protocols.

CHAPTER VII – SECOND STUDY. NON-REVASCULARIZED CHRONIC TOTAL OCCLUSIONS MODIFY ARRHYTHMOGENIC SUBSTRATE AND LONG-TERM RESULTS IN ELECTRICAL STORM PATIENTS TREATED BY RADIOFREQUENCY ABLATION

7.1. Introduction

Non-revascularized chronic total coronary occlusions (NR-CTO) are invasively diagnosed in up to 20% of post-MI patients [35,36] and are associated with incremental risk for death and appropriate ICD therapies (in both primary and secondary prophylaxis indications) [37–40]. There is limited evidence concerning the impact of NR-CTOs on RFA efficiency for monomorphic VT [41–43], especially in the specific setting of ES which has been marginally represented in previous studies. This study sought to evaluate the impact of NR-CTOs on acute procedural results and long-term outcomes of post-MI ES patients undergoing RFA.

7.2. Material and methods

Study protocols and statistical analysis methodology are extensively detailed in Chapter IV. The specific patient selection methodology is summarized in Figure 7.1.; only patients with a history of MI were included. Patients without invasive coronary angiography < 6 months prior to RFA, patients that underwent coronary revascularization (either interventional or surgical) during the follow-up interval and patients developing ES as a complication of acute coronary syndrome were excluded from this study. Atherosclerotic coronary stenoses > 70% (as defined angiographically by interventional cardiologists) in the left anterior descending artery (LAD), right coronary artery (RCA) or the circumflex artery (Cx) and > 50% in the left main (LM) were considered to be potentially significant lesions. NR-CTOs defined by the interventional cardiologist (irrespective of Rentrop collateralisation) which only affected main coronary arteries (LM, RCA, LAD or Cx) were considered. The primary endpoint was defined by the occurrence of any of death (irrespective of cause) or VT/VF recurrence during follow-up interval. The secondary endpoints were defined by death (irrespective of cause) or VT/VF recurrence respectively during follow-up interval.

The *specific objectives* of this study were:

- To assess substrate differences in terms of distribution of dense scar and border zone area in the presence of NR-CTOs in ES patients treated by RFA

- To evaluate the impact of NR-CTOs on acute procedural results of RFA in ES patients

- To analyze the impact of NR-CTOs on survival free of the primary endpoint (all-cause mortality or VT/VF recurrences) and secondary endpoints (all-cause mortality and VT/VF recurrences separately) during follow-up after RFA in ES patients

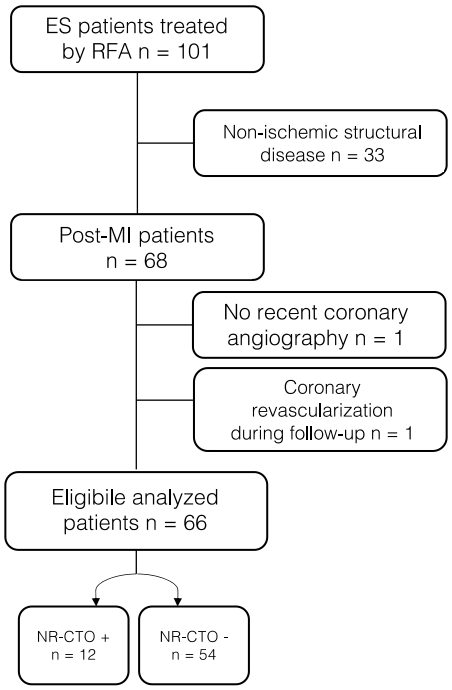

Figure 7.1. Flowchart detailing the selection process of the final study population. RFA = radiofrequency ablation, ES = electrical storm, NR-CTO = non-revascularized chronic total occlusion, MI = myocardial infarction

7.3. Results

Sixty-six patients were included for this analysis. There were no significant differences between NR-CTO + and NR-CTO – subgroups, with the exception of coronary artery bypass surgery (CABG) history (more frequent in NR-CTO + 41.7% vs. 9.3%, p = 0.005). NR-CTOs most frequently affected the RCA (75% of NR-CTO + subgroup). One NR-CTO was documented in seven patients and two NR-CTOs in five patients in the NR-CTO + subgroup. The border zone area percentage was higher in the NR-CTO + subgroup (72.2% [62.8-76.5]) compared to NR-CTO – subgroup (52.5% [39.8-73.4], p = 0.018). Sustained monomorphic VT was more frequently inducible at PVS in the NR-CTO + subgroup (50% vs. NR-CTO – subgroup 22.2%, p = 0.05). The NR-CTO + subgroup demonstrated longer hospitalization intervals (10 days [3-26] vs. NR-CTO – subgroup 5.5 days [4-7.75], p = 0.05).

Over a median monitoring interval of 25 (7.7 – 62.1) months, eighteen (27.3%) deaths and nineteen (28.8%) VT/VF recurrences were observed. Deaths were more frequent in the NR-CTO + subgroup – nine patients (75%) vs. NR-CTO – subgroup nine patients (16.7%), p < 0.001. VT/VF recurrences were more frequent in the NR-CTO + subgroup – seven (58.3%) vs

NR-CTO – subgroup twelve patients (22.2%) p = 0.012. The Kaplan-Meier survival analysis in Figure 7.2. shows that the NR-CTO + subgroup demonstrated worse survival in terms of primary endpoint occurrence (log rank p = 0.05) and in both secondary endpoints (all-cause mortality log rank p < 0.001 and VT/VF recurrences log rank p = 0.03) during follow-up interval.

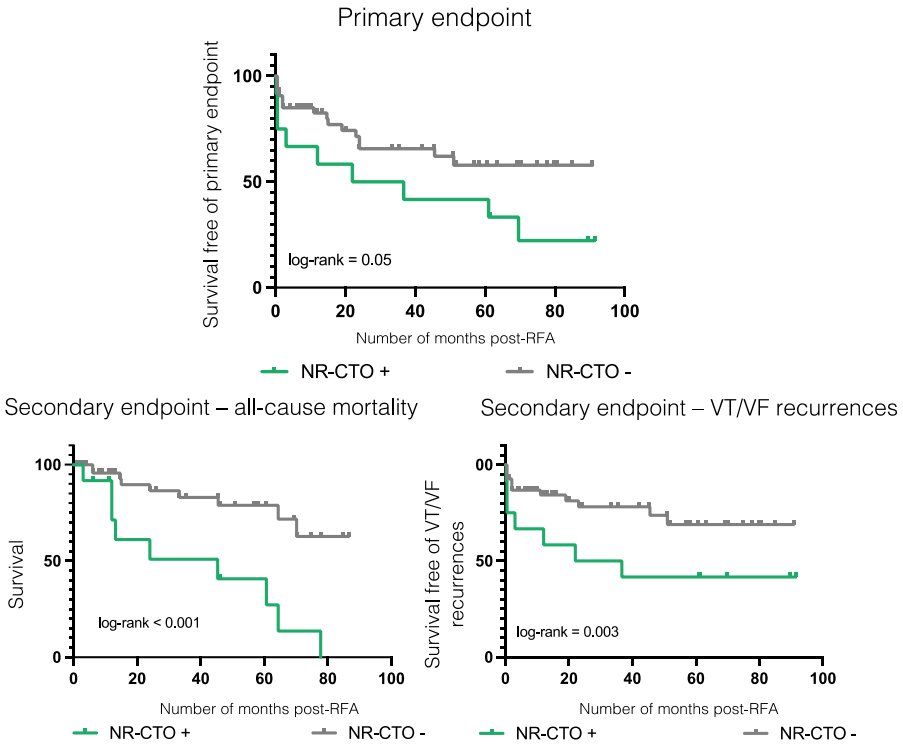

Figure 7.2. Kaplan Meier survival curves evaluating primary endpoint occurrence (all-cause mortality or VT/VF recurrences) during follow-up (above) and secondary endpoints occurrence (all-cause mortality and VT/VF recurrences separately) during follow-up (bottom). NR-CTO = non-revascularized chronic total occlusion, VT = ventricular tachycardia, VF = ventricular fibrillation

Only the presence of NR-CTO (HR [95% CI], 4 (1.5-10.1), p = 0.003), residual sustained monomorphic VT inducibility at PVS (HR [95% CI], 4.7 [1.8-12.2], p = 0.001) and VT/VF recurrences (HR [95% CI], 5.2 [2.03-13.6], p = 0.001) predicted all-cause mortality during follow-up in univariable Cox regression analysis. Only the presence of NR-CTO (HR 3.2, CI 95% [1.2-8.4], p = 0.01) and VT/VF recurrences during follow-up (HR 3.1, CI 95% [1.01-10.5], p = 0.05) independently predicted all-cause mortality in the multivariable Cox model, whereas residual sustained monomorphic VT inducibility at PVS did not (HR 2.2, CI 95% [0.6-7.4], p = 0.18). The presence of NR-CTO (HR 1.6, CI 95% [0.6-4.5], p = 0.31) and severe HF at admission (HR 2.1, CI 95% [0.8-5.4], p = 0.12) did not predict VT/VF recurrences in the

multivariable model, whereas residually inducible monomorphic VT at PVS (HR 8.3, CI 95% (2.9-23.8), $p < 0.001$) did.

7.4. Discussions

In summary, our study demonstrated the following [44]

1. The presence of a NR-CTO in ES patients is associated with a higher percentage of the border zone area within the scar and higher rates of residual inducibility for sustained monomorphic VT after RFA.

In our study, the contribution to the total scar area of the arrhythmogenic BZ area was more prominent, even if no differences in total scar surface were found when comparing the NR-CTO + and NR-CTO – subgroups. In this sense, Di Marco *et al* [41] demonstrated that post-MI scars are more complex and extensive in patients with NR-CTOs in terms of both dense scar and BZ area dimensions. Contrast magnetic resonance imaging studies have demonstrated that NR-CTO-supplied territories most frequently display residual viability and < 50% transmurality [45]. Hence, revascularization has been shown to provide electrophysiological benefits in these territories, by dynamically reducing the area of the BZ and increasing local EGM voltages [46]. Furthermore, NR-CTOs are known to induce dynamic recurrent episodes of myocardial ischemia that may serve as a ventricular arrhythmogenic mechanism [47]. We hypothesize this is why the observed risk of ES development is two-fold higher in the presence of NR-CTOs in ICD recipients [48] and this may explain the higher residual monomorphic VT inducibility at PVS in our study.

Even if based on a limited sample analysis, patients with NR-CTOs in our cohort demonstrated approximately two-fold higher residual monomorphic VT inducibility when tested by similar PVS protocols after RFA. In contrast, existing evidence suggests that efficient arrhythmogenic substrate elimination by RFA is not influenced by the presence of NR-CTOs [41–43]. However, this may be influenced by patient selection (ES patients have only been marginally represented in previous studies) and PVS strategies (mostly based on 3-ESx testing [42,43], which may underestimate residually inducible VT morphologies compared to more aggressive protocols).

2. ES patients demonstrate worse survival in terms of both primary endpoint and secondary endpoints (all-cause mortality and VT/VF recurrences separately) occurrence after RFA in the presence of NR-CTOs.

The NR-CTO + subgroup demonstrated significantly higher mortality rates both early (two of twelve patients died during the first 30 days after RFA compared to none in the NR-CTO – subgroup) and late after RFA (four out of twelve died compared to two out of fifty-four

in the NR-CTO – subgroup). The rate of VT/VF recurrence was higher (75% over a median interval of 25 months) in the presence of NR-CTOs and most recurrences (up to two thirds) manifested over the first 30 days after ablation. This has already been demonstrated in ICD recipients in the presence of NR-CTOs, both in primary and secondary prevention settings [37–40,49]. The number of NR-CTOs has also been associated with incremental arrhythmic risk[37]. Van Dongen *et al* [39] suggests that the pro-arrhythmic effect is not influenced by the quality of lesion collateralization and revascularization may reduce the number of appropriate ICD therapies to those observed in patients with no NR-CTOs. Similarly, the VACTO PCI study has shown that percutaneous revascularization of NR-CTOs leads to better outcomes in terms of ventricular arrhythmia and mortality compared to optimal medical therapy [50].

The impact of NR-CTOs on patient outcomes after RFA for monomorphic VTs is still under research and is currently characterized by limited conflicting evidence [41–43]. Di Marco *et al*[41] has indicated a higher risk of ventricular arrhythmia recurrence (however equivalent mortality), whereas Lurz *et al* [42] showed a higher risk of death during follow-up which was not associated with a higher rate of VT/VF recurrence after RFA. Furthermore, the latter study identified an apparently paradoxical effect: the rate of VT/VF recurrence was higher if the chronic total occlusions were treated by revascularization compared to those remaining under optimal medical therapy (52 % vs. 31%, p = 0.002). This observation requires further investigation as it contradicts existing evidence from the VACTO-PCI study which supported the mortality and antiarrhythmic benefit of NR-CTOs revascularization [50].

3. The presence of NR-CTO only independently predicted all-cause mortality but not VT/VF recurrences during follow-up after RFA in ES patients. VT/VF recurrences were only predicted by residual monomorphic VT inducibility at PVS.

Our study sought to explain the differences observed in terms of mortality and VT/VF recurrences after RFA ablation in the presence of NR-CTOs. The risk of death was increased by 3.2-fold by NR-CTOs irrespective of residual monomorphic VT inducibility at PVS after RFA. This may be explained by the direct contribution of NR-CTOs to progressive HF and pump failure which justifies therapeutic interventions in view of the VACTO PCI study [50]. We observed that residual monomorphic VT inducibility does no longer independently predict mortality if the model includes VT/VF recurrences during follow-up (which we consider is the actual mechanism through which acute procedural results influence long-term mortality). In contrast, NR-CTO does not independently predict VT/VF recurrences if the model includes procedural results. This may suggest that the long-term recurrences in NR-CTO patients are determined by the suboptimal result of ablation and the inability to adequately eliminate

substrate (and not the coronary lesion itself). This has been thoroughly evaluated as residual monomorphic VT inducibility was the central VT/VF recurrence predictor in every observational study dedicated to VT ablation [14,18,32].

In conclusion, after ES ablation in post-MI patients, there are two main contributors to mortality: firstly, the presence of NR-CTOs that can induce persistent myocardial ischemia and progressive HF and secondly, VT/VF recurrences which drive arrhythmic death and progressive pump failure due to frequent VTs and ICD discharges.

Study limitations

1. Single-center study with a limited study population (n = 66 post-MI ES patients) with retrospective collection of data during the initial phase of the study (January 2014 June 2021); we only reported all-cause mortality rates (irrespective of specific arrhythmic or non-arrhythmic causes) due to the lack of detailed information regarding the mechanism of death.

2. Data regarding Rentrop collateralization and myocardial viability assessment were limited and not included in the analysis.

3. Data regarding chronic coronary syndrome pharmacological therapy were limited and may influence outcomes in post-MI patients.

7.5. Conclusions

The presence of NR-CTOs in post-MI ES patients treated by RFA was associated with a higher contribution of the BZ area to the scar. The rate of residual monomorphic VT inducibility was higher and long-term outcomes in terms of all-cause mortality and VT/VF recurrences were worse.

CHAPTER VIII – THIRD STUDY. MSA-VT SCORE: A NOVEL SCORING ALGORITHM TO ASSESS LONG-TERM PROGNOSIS IN ELECTRICAL STORM TREATED BY RADIOFREQUENCY ABLATION

8.1. Introduction

Mortality due to progressive HF and pump failure after ES episodes is very high during the first year after ES development, even if initially stabilized by RFA [6,51]. This is why long-term risk stratification is critical in ES [13,14,18,52,53] and scoring algorithms have attempted to anticipate prognosis and the risk of procedural complications during VT ablation to identify high-risk patients (I-VT, MORTALITIES-VA,PAINESD, RIVA [25,54–56]**)**. This study sought to develop a new scoring algorithm to stratify the risk of death and VT/VF recurrences specifically after ES ablation.

8.2. Material and methods

The PAINESD, RIVA and I-VT scores were calculated accordingly as previously published [25,55,56]. Each factor for the MSA-VT scoring algorithm was selected through univariable Cox regression and the coefficient attributed to each predictor was obtained by rounding the value of HR to the next integer. The MSA-VT score was calculated as a sum of the factors' coefficients (5 points were attributed for residually inducible monomorphic VT, 3 points for severe HF at admission, 4 points for moderate/severe mitral regurgitation (MR), 4 points for AF at admission). Internal validation was performed on a randomized sample of 75% of the study population.

The *specific objectives* of this study were:

- To develop a novel scoring multivariable-based algorithm to predict the risk of death after RFA for ES patients

- To assess the accuracy of prediction of death by the novel scoring algorithm in comparison to previously published scores and known individual predictors for mortality after ES ablation

8.3. Results

Survivors were younger (median age 59 vs. 68 years), less affected by severe HF (20% vs 48.4%) or AF at admission (5.7% vs. 29%), demonstrated moderate-to-severe mitral regurgitation less frequently (21.7% vs 61.2%) and were less frequently prescribed postablation amiodarone (64.3% vs. 81%). Deceased patients had undergone longer procedures (median time 200 vs. 176 min, $p = 0.013$), required epicardial ablation more frequently (35.5% vs 14.3%, $p = 0.01$), with more significant BZ area (70.7% vs 51.9%, $p = 0.03$) and demonstrated a higher

rate of residual monomorphic VT inducibility (61.3% vs. 18.6%, p < 0.001), a higher rate of VT/VF recurrences (64.5% vs 22.9%, p < 0.001) compared to survivors.

Age (HR 1.06 CI 95% [1.02-1.1], p = 0.001), severe HF at admission (HR 3.2, CI 95% [1.5-6.2], p = 0.002), preablation amiodarone (HR 2.4, CI 95% [1.05-5.7], p = 0.038), and post-ablation amiodarone (HR 2.9, [1.03-8.5], p = 0.042) significantly predicted death in univariable Cox regression. Residual inducibility of monomorphic VT provided a 4.9-fold higher risk of death (CI 95% [2.3-10.2], p < 0.001). Each score RIVA (p = 0.015), PAINESD (p = 0.006) and I-VT (p = 0.001) significantly predicted death during follow-up. The detailed regression analysis is included in the thesis. The following points were attributed based on HR values: 5 points for residual monomorphic VT inducibility, 4 points for moderate-to-severe MR, 4 points for AF at admission and 3 points of severe HF at admission.

Figure 8.1. summarizes receiver operating characteristic (ROC) curves analysis regarding comparative prediction of death by MSA-VT, RIVA, PAINESD and I-VT scores. The MSA-VT score demonstrated best predictive value with AUC 0.848 (p = 0.04), whereas PAINESD (AUC 0.623, p = 0.06, sensitivity 41.9%, specificity 76.8% for 18 points cut-off), RIVA (AUC 0.691, p = 0.057, sensitivity 58.1%, specificity 71% for 13.5 points cut-off) and I-VT (AUC 0.558, p = 0.069, sensitivity 32.3%, specificity 92.8% for 3.55 points cut-off) did not accurately predict death during follow-up. An optimal cut-off threshold of 3 points for MSA-VT was identified which was associated with 93.5% sensitivity and 62.3% specificity. Patients with MSA-VT scores ≥ 3 points demonstrated higher all-cause mortality compared to MSA-VT < 3 during follow-up (log rank p = 0.001).

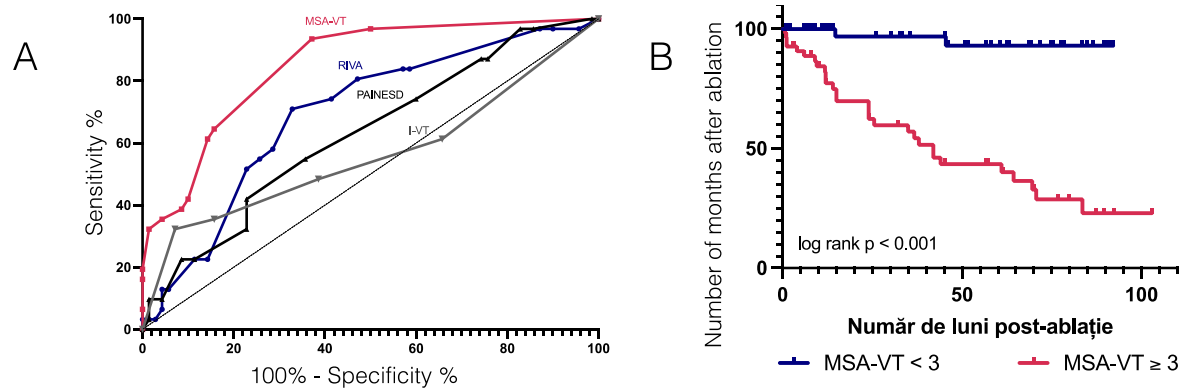

Figure 8.1. A. ROC curves analysis regarding prediction of death during follow-up by MSA-VT and previously published scores (RIVA, PAINESD, I-VT) [25,55,56]. *B. Kaplan-Meier survival analysis regarding all-cause mortality in patients with MSA-VT scores ≥ 3 points and MSA-VT < 3. ROC = receiver operating characteristics curve*

MSA-VT score accurately predicted early 30-days post-ablation mortality AUC 0.866 (CI 95%, 0.77-0.95), $p < 0.001$ and VT/VF recurrences during follow-up with good AUC value 0.715 (CI 95%, 0.6-0.82), $p < 0.001$. Internal validation was performed using a randomized 75% sample that showed consistent prediction accuracy with AUC 0.821 (CI 95% 0.72-0.91), $p < 0.001$. Figure 8.2. demonstrates that prediction of death during follow-up through MSA-VT score is superior based on ROC curve analysis compared to individual factors. LVEF did not provide accurate prediction of death during follow-up AUC 0.396 ($p = 0.097$).

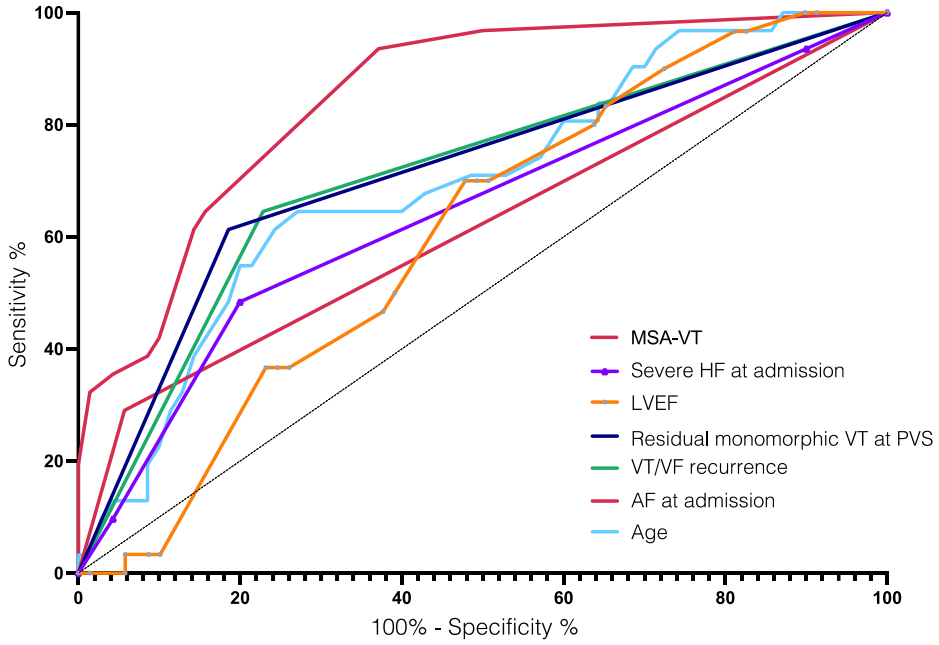

Figure 8.2. ROC curve analysis to evaluate prediction of death during follow-up by MSA-VT score and individual factors. HF = heart failure, LVEF = left ventricular ejection fraction, VT = ventricular tachycardia, VF = ventricular fibrillation, AF = atrial fibrillation, PVS = programmed ventricular stimulation

8.4. Discussions

In summary, our study demonstrated the following [57]:

1. In this cohort, prediction of death using a multivariable scoring algorithm (based on residual monomorphic VT inducibility, severe HF at admission, AF at admission and moderate-to-severe MR) was more accurate compared to prediction based on individual factors.

The multiparametric MSA-VT score provided higher prediction accuracy for death during follow-up in comparison to single-factor-based prediction. Two factors implemented in the MSA-VT score were previously included in other algorithms (residual monomorphic VT inducibility in the post-ablation version of I-VT and severe HF at admission in PAINESD and

modified RIVA score [25,55,56,58]) and have been thoroughly validated as negative outcome predictors by previous large scale observational studies [14,18,59]. The presence of at least one factor was associated high mortality rates after ablation (51.7% for severe HF at admission and 59.4% for residual inducibility) and if both were present, up to 71.4% of patients died during follow-up.

In contrast, the presence of AF at admission and of moderate-to-severe mitral regurgitation have not been previously assessed as predictors for death after ES ablation. AF is known to double the risk of death and appropriate ICD therapies in meta-analysis data and may itself represent a trigger for VT episodes [60–62]. The deleterious effect of moderate-to-severe MR is well established in HF patients, inducing a 7.53-fold higher risk of death and a rate of 46.1% mortality over two years of follow-up in the COAPT trial [63,64]. Unexpectedly, our data did not confirm LVEF as a predictor of mortality (which may result from transiently aggravated LVEF due to VTs and shocks which underestimates baseline systolic function).

Hence, severely symptomatic HF patients with AF at admission and significant MR that obtain suboptimal results during ES ablation have the most unfavorable prognosis which may in turn justify early referral and candidacy for mechanical circulatory support and advanced HF therapies (HTx or long-term ventricular assist devices) rather than pursue antiarrhythmic strategies.

2. In this cohort, prediction of death using the MSA-VT score was more accurate in comparison to prediction based on RIVA, PAINESD and the post-procedural version of I-VT scores.

ES patients have only been marginally represented in the published studies that have previously validated the aforementioned scoring algorithms. This study sought to develop an algorithm exclusively in ES patients.

MSA-VT provided superior accuracy for prediction of death during follow-up compared to PAINESD score. This score [23,25,26] was developed to correctly identify candidacy for prophylactic mechanical circulatory support before VT ablation to avoid periprocedural acute hemodynamic decompensation (AHD). Diabetic elderly post-MI patients exhibiting severe symptomatic systolic dysfunction were at highest risk in view of this algorithm. However, subsequent attempts to externally validate the PAINESD score were inconsistent and contradictory [65–68]. One of the most important observations of Stojadinovic *et al* [68] (which also reflects our center's experience) is that avoidance of VT induction and activation mapping substantially reduces the risk of AHD. In this sense, having based our study protocol on mapping and ablation in baseline sinus or pacing rhythm (and avoiding VT induction), we did

not detect any case of AHD in this cohort, even if 41.6% of patients were classified as high-risk by PAINESD score.

The RIVA score was developed to predict VT ablation-related complications and in-hospital mortality [56]. The modified version of this score (mRIVA) [58] improved prediction accuracy by including age and severe HF symptoms at admission. In our cohort, this score demonstrated the second-best value of AUC (0.691), however without statistical significance for death during follow-up prediction ($p = 0.057$). Furthermore, RIVA did not predict VT/VF recurrences. The aforementioned scores are used in different moments in relation to the RFA procedure. PAINESD, RIVA/mRVA and I-VT are based on preprocedural parameters, whereas MSA-VT and the post-procedural version of I-VT include ablations results. The post-procedural version of I-VT assesses the risk of mortality based on systolic dysfunction LVEF < 30%, residual inducibility at PVS, ES setting and the presence of diabetes mellitus and age > 80 years. The post-procedural I-VT score did not accurately predict death or VT/VF recurrences in our analysis.

In summary, we identified an optimal cut-off threshold of 3 points for MSA-VT score to predict mortality after ES ablation. This shows that any ES patient undergoing RFA that demonstrates at least one of the following factors: moderate-to-severe MR, residual VT inducibility, severe HF or AF at admission must be closely monitored for adverse events after ablation. In contrast, stable patients with no recent HF decompensation, in sinus rhythm, with no significant MR that obtain optimal results at ablation are most likely to have a favorable long-term outcome. However, the MSA-VT score requires external validation on larger multicenter cohorts to confirm these initial observations.

Study limitations

1. Single-center study with a limited study population (101 consecutive ES patients); all previous scoring algorithms were validated in larger cohorts - 175-193 patients (for MORTALITIES-VA and PAINESD) and 1251-1417 patients (for I-VT and RIVA [25,54–56]); ES patients were however marginally represented in these previous studies (10-35%); our analysis did not include the MORTALITIES-VA [54] score as limited data was available concerning ongoing treatment with renin-angiotensin-aldosterone modulators and previous oncological comorbidities.

2. This study requires external validation in larger multicentric cohorts to confirm our initial observations; however, internal validation using a randomized 75% sample was performed and MSA-VT maintained accurate prediction of death during follow-up.

8.5. Conclusions

In this cohort, the novel MSA-VT score predicted death and VT/VF recurrences in ES patients undergoing RFA more accurately compared to individual separate factors and compared to previously published scoring algorithms (PAINESD, I-VT and RIVA).

CHAPTER IX – FOURTH STUDY. THE IMPACT OF PREVIOUS VENTRICULAR TACHYCARDIA RADIOFREQUENCY CATHETER ABLATION PROCEDURES FOR PATIENTS PRESENTING WITH ELECTRICAL STORM

9.1. Introduction

One in three patients undergoing VT ablation will develop recurrences (determined by residual or newly-developed substrate) that increase long-term mortality [32]. Hence, the role of repeated RFA is expanding and under research. Limited observational evidence suggests that the mortality benefit of the index RFA for ES patients may be obtained by redo procedures, as long as no recurrences occur during follow-up [69–73]. ES patients have only represented 30-60% of cases included in previous studies that evaluated the role of redo RFA. This study sought to assess procedural differences and long-term prognosis of ES patients undergoing repeated ablations.

9.2. Material and methods

The following subgroups were specifically defined for this analysis:

- *"Single-RFA"* subgroup – ES patients with no other previous VT substrate ablation
- *"Repeat-RFA"* subgroup– ES patients with a history of least one procedure VT substrate ablation prior to study enrollment and current ES ablation

The *specific objectives* of this study were:

- **To assess differences in patient and procedural characteristics in single-RFA versus repeat-RFA subgroups**
- **To compare all-cause mortality and VT/VF recurrences during the first year after ES ablation in single-RFA versus repeat-RFA subgroups**

9.3. Results

There were no significant differences between single-RFA (n = 67 patients) and repeat-RFA subgroups (n = 34 patients) with the following exceptions: post-MI patients were more frequent in the single-RFA subgroup (73.1% vs. 52.9%, p = 0.04) and moderate-to-severe MR was more frequent in the repeat-RFA subgroup (48.5% vs. 25.4%, p = 0.02). In the repeat-RFA subgroup, the previous RFA had been performed for ES in twelve (35.3%) patients and for isolated VT episodes in twenty-two cases (64.7%). In the repeat-RFA subgroup, there were twenty-eight cases (82.3%) with a total of 2 procedures (including the study enrollment RFA), five (14.7%) with 3 procedures and one (2.9%) with 4 procedures.

In the repeat-RFA subgroup, only twelve (35.3%) patients had obtained non-inducibility for monomorphic VT at their previous procedure. The median interval from the last RFA was

3.5 (1-24) months. Out of the eight (23.5%) patients with residual inducibility for the clinical monomorphic VT at the previous procedure, seven repeated the ablation during the same hospitalization. The median interval from the previous RFA was significantly influenced (p = 0.001) by the previous procedure's result: absolute non-inducibility (R1) 24 (7.5-51) months vs. residual inducibility for non-clinical monomorphic VT (R3) 3 (1-4.5) months vs. residual inducibility for clinical monomorphic VT 0.75 (0.5-1) months. Epicardial ablation had been performed for only four (11.8%) patients from the repeat-RFA subgroup.

The rates of non-inducibility for monomorphic VT were similar in the single-RFA and repeat-RFA subgroups (53.7% vs. 55.9%, p = 0.99).

In the repeat-RFA subgroup, endoepicardial ablation was more frequently required (32.4% vs. 14.9%, p = 0.04) and more frequent non-vascular complications were observed (17.6% vs 4.5%, p = 0.027). These were mostly represented by pericardial effusions n = 4 (11.7%) in the repeat-RFA subgroup vs. n = 1 (1.5%, p = 0.02) in the single-RFA subgroup which were managed conservatively. One patient (2.9%) from the repeat-RFA subgroup developed periprocedural acute coronary spasm which remitted after intravenous nitroglycerine infusion and one (2.9%) developed periprocedural transient ischemic cerebral event. There were no such complications in the single-RFA subgroup. One patient (1.5%) from the single-RFA subgroup developed brachial artery thromboembolism during RFA which required emergency thrombectomy.

The median interval of follow-up was 32.8 (10-68) months. Thirty-one (30.7%) patients died during follow-up, similarly distributed between repeat-RFA n = 21 (31.3%) and single-RFA n = 10 (29.4%, p = 0.99) subgroups. Thirty-six (35.6%) patients developed VT/VF recurrences, similarly distributed between repeat-RFA n = 13 (38.2%) and single-RFA n = 23 (34.3%, p 0.82). In the repeat-RFA subgroup, out of the twenty-one patients that did not develop VT/VF recurrences, only three (14.3%) died during follow-up compared to seven out of thirteen (53.8%) that died after developing VT/VF recurrences. There were no differences in mortality in relation to VT/VF recurrence (p = 0.87) in the single-RFA subgroup.

Over the first year post-RFA, there were thirty-seven events (deaths and VT/VF recurrences), as follows: ten (9.9%) deaths and twenty-seven (26.7%) VT/VF recurrences. Survival analysis (Figure 9.1.) did not demonstrate any differences in terms of all-cause mortality and VT/VF recurrences respectively over the first year post-RFA when comparing single-RFA and repeat-RFA subgroups. The only independent predictor for the combined outcome over the first year after ablation was residual inducibility for monomorphic VT at PVS with HR 8.8 (95% CI 3.6-21.2), p = 0.001. Furthermore, survival analysis (Figure 9.2.)

demonstrates there is no difference in mortality or VT/VF recurrences (separately) over the first year after ablation between single-RFA and repeated-RFA subgroups when stratified by residual monomorphic VT inducibility at PVS (pairwise comparison for death in non-inducible cases log rank p = 0.49 and for residually inducible log rank p = 0.53 and pairwise comparison for VT/VF recurrences in non-inducible cases log rank p = 0.84 and for residually inducible log rank p = 0.75), by etiology (post-MI vs. non-ischemic etiologies) and LVEF subgroup (LVEF > 40% vs. LVEF ≤ 40% - Figure 9.2. and thesis for detailed analysis).

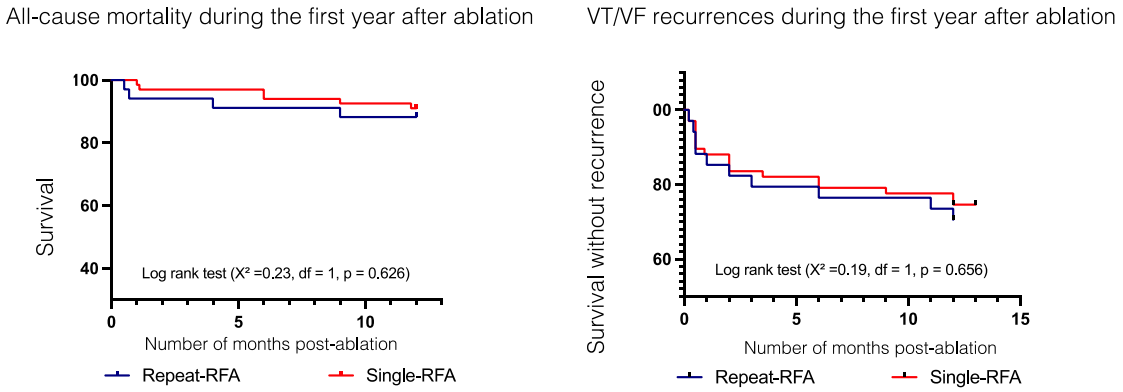

Figure 9.1. Survival analysis comparing all-cause mortality and VT/VF recurrences during the first year after ES ablation in the repeat-RFA vs. single-RFA subgroups. RFA = radiofrequency catheter ablation

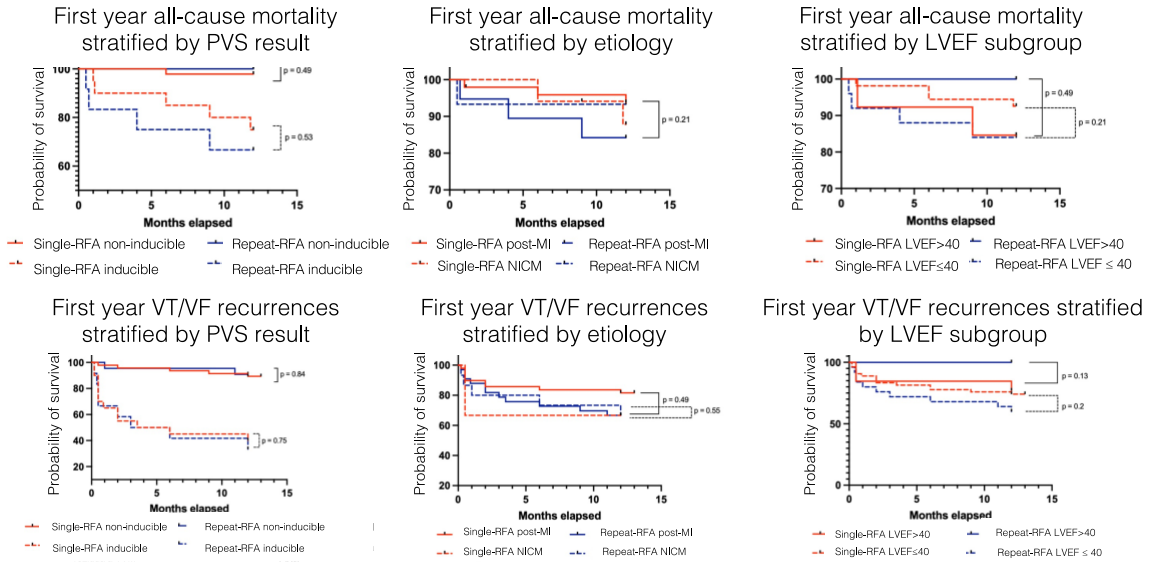

Figure 9.2. Survival analysis comparing all-cause mortality and VT/VF recurrences during the first year after ES ablation stratified by PVS result, etiology and LVEF subgroup. RFA = radiofrequency ablation, VT = ventricular tachycardia, VF = ventricular fibrillation, LVEF =

left ventricular ejection fraction, PVS = programmed ventricular stimulation, MI = myocardial infarction, NICM = non-ischemic cardiomyopathy

Repeat-RFA status did not predict death (HR 1.36 [CI 95% 0.38-4.84], p = 0.628) or VT/VF recurrences 1.19 [CI 95% 0.54-2.601], p = 0.66) during the first year after ablation. Furthermore, in the repeat-RFA subgroup, all patients that obtained sustained monomorphic VT non-inducibility remained alive during the first year after ablation, whereas three of twelve (33.3%) with residually inducible monomorphic VT died (p = 0.011). VT/VF recurrences during the first year after ablation were more frequent in patients with residual sustained monomorphic VT inducibility in comparison to those without (66.7% vs. 9.1%, p.= 0.001).

9.4. Discussions

In summary, our study demonstrated the following [74]:

1. For patients undergoing RFA for ES, a preexisting history of substrate ablation for VT is more frequently associated with non-ischemic structural heart disease, with a higher rate of moderate-to-severe mitral regurgitation and a more frequent need for endoepicardial ablation leading to a higher rate of periprocedural complications.

The role of repeated RFA targeting monomorphic VTs has been marginally evaluated in observational studies [69–73]. Patients that require redo VT ablations are more frequently admitted in ES scenarios [69,70]. Thus, our study is the first to exclusively assess redo VT ablations in ES patients, as previous papers have only had a rate of 38.2-60% ES patients included [69]. The previously reported patient characteristics were consistent with our observations: redo procedures are more frequently performed in cases of non-ischemic cardiomyopathies and therefore require more frequent endoepicardial ablation [69]. The rationale of actively searching and elimination epicardial substrate in patients that develop recurrences after RFA has been demonstrated (even in post-MI patients with subepicardially extending scars) [71,73]. Tzou *et al* [69] showed that up to 40.1% of redo ablations involve epicardial targets. Consequently, (consistent with published data [69]) more frequent non-vascular procedural complications related to pericardial effusions were observed in this subgroup.

Although the two subgroups showed similar LVEF, the repeat-RFA subgroup demonstrated more moderate-to-severe MR. Unexpectedly, there were no increments in total scar area (or its components) in redo procedures. Importantly, the repeat-RFA subgroup demonstrated similar rates of procedural success (i.e. lack of inducibility of monomorphic VTs at PVS) when compared to single-RFA patients, which reflects published experience in post-

MI patients [71]. However, the largest analyzed cohort that assessed the role of redo VT ablation showed that the rate of residual inducibility of monomorphic VT was significantly higher compared to initial ablation cases (41.8%% vs. 32.9%, $p < 0.001$).

Additionally, preablation amiodarone may influence procedural success and was significantly more frequently prescribed in our cohort compared to published data (68.7% versus 55% in [69]). Amiodarone is known to facilitate acute procedural success, although it can "hide" relevant arrhythmogenic substrate from PVS which may be responsible for future recurrences [75].

2. Patients requiring redo VT ablation procedures demonstrate similar one-year survival in terms of all-cause mortality and VT/VF recurrences compared to patients undergoing their first ablation at the time of ES.

The overall rates of all-cause mortality (30.7%) and VT/VF recurrences (35.6%) observed in our study were high, but consistent with previously published data [14,15,18]. The main conclusion is that patients that required redo VT ablation at the moment of ES did not show increased risk for adverse events (death or recurrences) during the first year after RFA when compared to those undergoing first-time ablation at the moment of ES, irrespective of LVEF, etiology and residual inducibility for monomorphic VT. Conversely, Tzou *et al*'s analysis [69] of the most numerous redo VT ablations cohort showed that clinical outcomes were in fact more severe in patients with multiple procedures with one exception: redo procedures obtained similar long-term mortality as index procedures only as long as no recurrences developed during follow-up. This is why repeating VT ablation may improve outcomes only if the procedure completely eliminates arrhythmogenic substrate that may serve as a basis for future recurrences. Our data shows that 53.8% of patients undergoing redo procedures that developed recurrences died during follow-up and the most important factor that increases the risk of recurrences is residual monomorphic VT inducibility, whereas a "redo scenario" itself did not independently predict death or recurrences. Interestingly, Yokokawa *et al* [76] showed that recurrences are potentially caused by residual substrate not eliminated during the initial RFA, by newly-formed substrate related to radiofrequency lesions or to disease progression or even by substrate pertaining to distinct anatomical sites which was not previously targeted. In this sense, routine testing by PVS at the end of the VT ablation or non-invasively ICD-based testing prior to discharge [19,30,77,78] may identify residually inducible patients that can benefit from early redo procedures (considering recurrences are known to increase mortality [32]). In our cohort, patients with persistently inducible clinical monomorphic VTs at final intraprocedural

PVS required redo ablation after a median interval of three weeks (seven out of eight patients during the same hospitalization).

Study limitations

1. Ablation protocol variability – 35.2% of patients underwent the previous VT ablation procedure in other centers which may influence results and long-term outcomes due to different ablation strategies and experience; however, we found no differences in long-term outcomes attributed to previous procedures performed in other ablation centers in comparison to those exclusively performed in the study center

9.5. Conclusions

Patients requiring redo VT substrate ablation at the time of ES demonstrated similar rates of acute procedural success as those undergoing their first VT ablation, despite more frequent non-ischemic etiology, more frequent epicardial ablation and more pericardial effusions. One-year survival in terms of all-cause mortality and VT/VF recurrences were similar in patients with redo procedures and those undergoing the first VT ablation at the moment of ES.

CHAPTER X – CONCLUSIONS. PERSONAL CONTRIBUTIONS

10.1. Final conclusions

Testing the presence of residual arrhythmogenic substrate after radiofrequency ablation for electrical storm using a more aggressive programmed ventricular stimulation protocol based on the delivery of four extrastimuli demonstrated the following:

1. Monomorphic VT non-inducibility was obtained in 68.3% of cases and a more aggressive 4-ESx-based PVS protocol can identify residual monomorphic VTs which were not previously evident at 3-ESx-based testing.

2. Patients who achieve monomorphic VT non-inducibility after RFA for ES demonstrate lower rates of all-cause mortality and VT/VF recurrences in comparison to those with residual end-procedural inducibility.

3. Residual inducibility of sustained monomorphic VT after ES ablation independently predicts the occurrence of the primary endpoint (death *or* VT/VF recurrence) during follow-up in all the evaluated prediction models.

Identifying the presence of non-revascularized chronic total occlusions in post-myocardial infarction patients affected by electrical storm is important because:

4. The presence of a NR-CTO in ES patients is associated with a higher percentage of the border zone area within the scar and higher rates of residual inducibility for sustained monomorphic VT after RFA.

5. ES patients demonstrate worse survival in terms of both primary endpoint and secondary endpoints (all-cause mortality and VT/VF recurrences separately) occurrence after RFA in the presence of NR-CTOs.

6. The presence of NR-CTO only independently predicted all-cause mortality but not VT/VF recurrences during follow-up after RFA in ES patients. VT/VF recurrences were only predicted by residual monomorphic VT inducibility at PVS.

Novel multivariable scoring algorithms may enhance the accuracy of long-term risk assessment in electrical storm patients in terms of mortality and recurrences. A novel MSA-VT score was developed during this research and the following were demonstrated:

7. In this cohort, prediction of death using a multivariable scoring algorithm (based on residual monomorphic VT inducibility, severe HF at admission, AF at admission and moderate-to-severe MR) was more accurate compared to prediction based on individual factors.

8. In this cohort, prediction of death using the MSA-VT score was more accurate in comparison to prediction based on RIVA, PAINESD and the post-procedural version of I-VT scores.

Survivors of ventricular tachycardia may develop subsequent recurrences after an initial ablation, even in the form of electrical storm, that mandate redo ablations. Our research showed that:

9. For patients undergoing RFA for ES, a preexisting history of substrate ablation for VT is more frequently associated with non-ischemic structural heart disease, with a higher rate of moderate-to-severe mitral regurgitation and a more frequent need for endoepicardial ablation leading to a higher rate of periprocedural complications.

10. Patients requiring redo VT ablation procedures demonstrate similar one-year survival in terms of all-cause mortality and VT/VF recurrences compared to patients undergoing their first ablation at the time of ES.

10.2. Personal contributions and future research directions

- The second study of thesis is the first research to evaluate the impact of NR-CTO in patients undergoing VT ablation exclusively in ES scenarios. This was motivated by the high incidence of monomorphic VT episodes in post-MI patient populations in which NR-CTOs are frequently encountered (up to 20% of cases) [35,36]. In contrast to previous studies that have analyzed the role of NR-CTOs in the broader context of VT ablations, our study is the first to show that in ES patients, NR-CTOs are associated with a higher contribution of the BZ area to the total scar area and lower acute procedural success rates. Notwithstanding, residual monomorphic VT inducibility remains the central factor that influences the risk of future recurrences (which appears not to be directly influenced by NR-CTOs). The risk of death however is independently predicted by NR-CTOs. In this sense, this research adds valuable evidence for electrical storm management and all the specific objectives of this study were met.

NR-CTO revascularization is unfeasible in the acute settings of ES and is not currently supported by evidence. Whether stabilization of ES should be followed by revascularization of NR-CTO to reduce the subsequent risk of death or recurrences should be answered by future research. Evidence to support the decision for revascularization is conflicting in this regard as Lurz *et al* [42] even reported a proarrhythmic effect of NR-CTO treatment in VT patients, despite the potential antiarrhythmic and survival benefit initially demonstrated in VACTO PCI [50]. This is why we plan to assess the effect on border-zone area characteristics and long-term clinical outcomes of elective NR-CTO revascularization in ES stabilized patients.

- The **MSA-VT score** is a novel multiparametric algorithm that seeks to improve detection of patients at high risk for unfavorable clinical course after ES ablation and was developed during our research. Mortality was more accurately predicted after ES ablation by the MSA-VT score compared to previously published scores and individual traditional risk factors for negative outcomes. All of the specific objectives of this study were met. However, due to the limited number of patients included in this initial analysis, we **further plan** to extend this research by externally validating this algorithm larger multicentric ES patient cohorts. Unexpectedly, LVEF was not able to predict long-term outcomes in our dataset. In our experience, ES patients frequently display aggravated systolic dysfunction at the moment of admission due to frequent VT episodes and recurrent shocks. Hence, survivors of ES may demonstrate significant recovery of contractility (which may explain why evaluating systolic function at the moment of admission may be biased and may underestimate potential LVEF achievable after VT suppression). We seek to **further investigate** our initial clinical observations in this regard by monitoring the extent of LVEF recovery after ES suppression and its effect on post-ablation outcomes (which has not been yet formally evaluated, to our knowledge).

- This thesis is the first to assess the role of redo VT ablations exclusively for patients presenting in ES scenarios and compare results and long-term outcomes to those of initial procedures performed at the time of ES. The specific objectives of this study were met. Our data shows that redo procedures are similarly efficient as initial procedures in obtaining monomorphic VT non-inducibility and patients demonstrate similar long-term clinical course, irrespective of etiology, ablation result and LVEF subgroup. This supports the positive effect of repeating RFA procedures in ES scenarios for patients with a history of VT substrate ablation.

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