The MUSIC Database: Sudden Cardiac Death in Heart Failure Patients

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Abstract

The MUSIC study is a prospective, multicenter study designed with the aim of developing prognostic models for sudden cardiac and total mortality in mild-to-moderate chronic heart failure (CHF). The database, now made available at Physionet, includes a total of 992 consecutive patients with symptomatic CHF corresponding to New York Heart Association (NYHA) classes II and III. All patients had a 24-hour, 3-lead Holter ECG recorded at enrollment, plus available demographic and relevant clinical data. Primary outcomes were cardiac death, either sudden cardiac death (SCD) or pump failure death (PFD) at the end of the 4-year follow-up.

1. Introduction

The MUSIC database was collected as a part of the MUSIC study (*"MUerte Súbita en Insuficiencia Cardiaca"* - Sudden Cardiac Death in Heart Failure), a multicenter, prospective and longitudinal study conducted by the specialized heart failure (HF) clinics from eight Spanish University Hospitals [1]. The aim of the study was the design of prognostic models for cardiac and sudden cardiac mortality in ambulatory chronic heart failure (CHF) patients. The study started in April 2003, and patients' enrollment and data collection were extended until December 2004. All patients were followed up on an outpatient basis every 6 months, for a median of 44 months.

The database includes a total of 992 consecutive patients with symptomatic CHF corresponding to New York Heart Association (NYHA) classes II and III [1]. All patients had a 24-hour, 3-lead Holter ECG performed at enrollment. A high-resolution, 20-min ECG, chest X-ray, echocardiography, and blood laboratory parameters were also collected. Primary outcomes were cardiac death, either sudden cardiac death (SCD) or pump failure death (PFD) at the end of the follow-up. It is now made available to the scientific community on Physionet resource.

2. Data Acquisition

Data for demographic and clinical characteristics, radiographic, echocardiographic and laboratory variables, as well as medications were collected at the time of enrolment. Collection of clinical data for this population was reported in previous studies [1, 2].

Holter ECG signals were acquired by using SpiderView records (ELA Medical, Sorin Group, Paris, France) and two or three orthogonal leads (X, Y, Z), sampled at 200 Hz with amplitude resolution of 10 μV, were available for each subject. Two examples of 10-s ECG traces from a patient in sinus rhythm and another with permanent atrial fibrillation are shown in Fig. 1. Before the Holter acquisition while resting in supine position, a 20-min high-resolution ECG sampled at 1000 Hz was also recorded. Out of the 992 patients, both clinical and ECG Holter data were available for only 936 patients. High-resolution ECGs were available for a sub-cohort of 691 patients, while the most significant automatic ECG measures from the comercial equipment are available for the entire population.

A follow-up period was conducted for a median of 44 months (until November 2008), including periodic visits every 6 months. At the end of the follow-up period, the study group included 94 SCDs, 111 deaths due to a different cardiac origin (PFD), 20 cardiac transplantations, 61 non-cardiac deaths, and 695 survivors. There were 11 patients lost during follow-up. SCD was defined as: (i) a witnessed death occurring within 60 min from the onset of new symptoms unless a cause other than cardiac was ob-

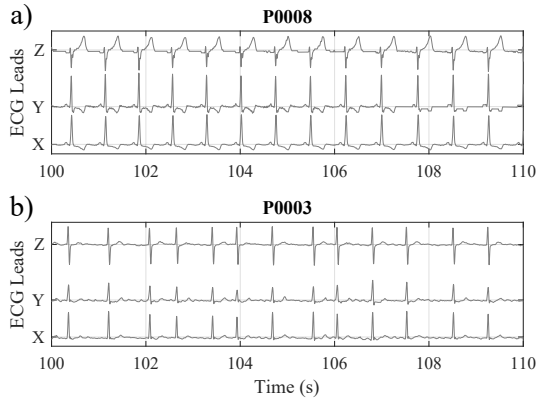

Figure 1: Example of two 10-s traces from ECG Holters. Orthogonal leads X, Y and Z from a patient in a) sinus rhythm, and b) permanent atrial fibrillation.

vious; (ii) an unwitnessed death (<24h) in the absence of preexisting progressive circulatory failure or other causes of death; or (iii) a death during attempted resuscitation. PFD was defined as death occurring in a hospital as a result of refractory progressive end-stage heart failure [1].

Institutional investigator's committees approved the study protocol and all patients gave written informed consent.

3. Data Files

Clinical and demographic information, radiographic, echocardiographic, laboratory variables and medication are summarized in an Excel file (*subject-info.xlsx*). Each category of variables is grouped by color, including:

- Demographic and clinical variables: age, gender, body mass index, blood pressure, NYHA, hypertension, heart failure etiology, diabetes, prior implantable device, etc.
- Radiographic variables: cardiothoracic ratio and signs of pulmonary venous hypertension.
- Echocadiographic variables: Left ventricular ejection fraction, left atrial size, end-diastolic and end-sistolic diameters, mitral flow pattern and mitral insufficiency, etc.
- Laboratory variables: Haemoglobin, HDL, LDL, glucose, potassium, sodium, troponin, creatinine, TSH, etc.
- ECG variables: rhythm (sinus rhythm, atrial fibrillation and flutter or pacemaker), PR and QT intervals, QRS duration, presence of Q waves (necrosis).
- Holter variables: rhythm (sinus rhythm (651), atrial fibrillation (171) and flutter (2) or pacemaker (105)), mean heart rate, number of ventricular premature beats, ventricular extrasystoles and tachycardia, etc.
- Medications: Digoxin, beta-blockers, statins, diuretics, amiodarone, anticoagulants, calcium blockers, etc.

The spreadsheet is completed with the date of enrollment and exit of the study, together with mortality codes. The codification of categorical variables are described on the second spreadsheet, in the same file.

Each recording in the database comprises a data file, named *PXXXX.dat*, containing the ECG signal, and the corresponding header *PXXXX.hea*, with information about the recording format. Similarly, each high-resolution, 12-lead, short ECG recording comprises the data files *PXXXX_H.dat*, containing the ECG signal, and the corresponding *PXXXX_H.hea*, with the header information. The full filename list of the 936 records is available in the file *RECORDS.txt*.

4. Clinical Applications

CHF patients are subject to arrhythmia-related SCD and heart failure events. The final scope of the MUSIC study was the design of prognostic models for cardiac mortality in CHF. Several clinical trials and reviews have shown the efficacy of implantable cardioverter defibrillators (ICD) for primary prevention of SCD [3]. According to current guidelines, indications for ICD therapy mainly include left ventricular ejection fraction (LVEF) $\leq$35%, previous myocardial infarction, and NYHA classes II or III. Therefore, many patients may be eligible for ICD therapy, however, the actual cost-effectiveness for ICD implantation remains low, and it is not clear if the benefits of ICD extend equally to clinically significant subgroups.

There have been several studies involving the MUSIC study up to date, serving as a valuable resource for developing and evaluating a wide range of prognostic ECG-derived biomarkers, focused on quantifying ventricular repolarization heterogeneity and autonomic function throughout heart rate variability (HRV) and other biomarkers, the most relevant summarized below:

- Repolarization dynamics, i.e., the QT-interval adaptation to changes in heart rate, has been assessed in terms of the QT/RR and T-peak-to-end/RR slopes, and resulted to be associated to both, total mortality and SCD [4, 5].
- Long-term averaging of T-wave alternans (TWA) activity, an index of ventricular repolarization instability measured automatically from Holter ECGs, was for the first time proposed and evaluated its prognostic value in the MUSIC study. The index of average alternans (IAA) was a strong, independent predictor of SCD [6, 7].
- The T-wave morphology restitution (TMR) index represents another novel electrocardiogram marker that measures morphological changes in the T-wave as a response to heart rate variations, and whose clinical value was evaluated for the first time in MUSIC study. TMR specifically predicted SCD with no association with PFD [8, 9].

Additionally, the results derived from MUSIC database are completed by studies on the assessment of the autonomic nervous system using heart rate information:

- New developed non-linear segmented symbolic dynam-

Table 1: Summary of the association of ECG-derived variables with cardiac death endpoints in the sinus rhythm cohort.

	Sudden Cardiac Death		**Pump Failure Death**		**Total mortaily**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**	**Hazard ratio (95% CI)**	**p-value**
QT/RR slope [4]	NS		NA		**1.59 (1.09,2.3)**	**0.016**
$\Delta\alpha^{T_{pe}}$ [5]	**2.676 (1.52,4.70)**	**0.001**	**2.068 (1.24,3.46)**	**0.006**	NA	
IAA [6, 7]	**2.386 (1.39,4.09)**	**0.002**	NS		**1.62 (1.15,2.29)**	**0.006**
TMR [8]	**2.929 (1.59,5.45)**	**0.001**	NS		NA	
TS [12]	**1.91 (1.05,3.46)**	**0.033**	**3.24 (1.65,6.33)**	**<0.001**	**2.10 (1.41,3.12)**	**<0.001**
TO [12]	NS		**1.74 (1.02,2.98)**	**0.042**	**1.52 (1.07,2.16)**	**0.019**
PDR [14]	**2.001 (1.13,3.55)**	**0.018**	NS		**1.636 (1.10,2.43)**	**0.014**

NS: No significant; NA: Not available.

ics (SSD) method was investigated for the suitability for risk stratification in the sub-cohort of patients with ischemic cardiomyopathy (ICM) in comparison to other HRV indices from time and frequency domain, non-linear dynamics, and clinical markers. The results suggested that the SSD enhances considerably risk stratification in ICM patients [10]. Moreover, short-term analysis of 30 min may provide at least a comparable risk stratification power in ICM in comparison to a 24-h analysis period [11].

- The standard heart rate turbulence (HRT) parameters, turbulence onset (TO) and slope (TS), as well as HRT categories, were also assessed for predicting total mortality and sudden death in MUSIC, showing that HRT is a potent risk predictor for both heart failure and arrhythmic death in patients with NYHA class II and III [12, 13].
- Sympathetic modulation of ventricular repolarization, assessed by periodic repolarization dynamics (PRD), which quantifies low-frequency oscillations in the T wave vector of the ECG, was shown to be an univariate predictor of SCD. Nonetheless, the combination of PRD with other ECG-based indices, such as TS and the IAA, improved SCD prediction. PRD could only predict PFD when combined with TS [14].
- Restricting the analyses to the preserved LVEF (>35%) subcohort, in which risk stratification performance remains particularly challenging, traditional electrocardiographic variables, including HRV, HRT, and repolarization dynamics were evaluated through Holter monitoring. Assessing a combination of standard deviation of all normal-to-normal RR intervals, TS, and QT/RR parameters can predict increased total mortality and SCD risk in patients with CHF and LVEF>35% [2].
- Finally, risk models combining ECG markers and clinical variables to specifically assess the risk of SCD and PFD have been developed. Results showed that factors such as gender, NYHA class, LVEF, IAA, T-peak-to-end restitution, and TMR had significant prognostic impacts for SCD. For PFD, diabetes, NYHA class, T-peak-to-end restitution, and TS were significant predictors, concluding the study that integrating ECG markers capturing proarrhythmic and pump failure mechanisms with standard clinical variables enhances the accuracy of predicting adverse outcomes in CHF patients [15]. SCD probability curves for the combined model are shown in Fig. 2.

All cited studies have been restricted to the sinus rhythm cohort since the highly irregular ventricular response and the presence of f-waves during atrial fibrillation had limited the analysis of ECG signals in this particular condition. However, the MUSIC study has served as a proof of concept for the development of new signal processing techniques to overcome this limitation, allowing the assessment of ventricular repolarization instability through long-term beat averaging [16], or using a multilead strategy based on periodic component analysis (πCA) before QT delineation [17], showing the prognostic value of the index of ventricular repolarization variation (Hazard ratios > 2.6 for the proposed indices) in [16] and a prolonged QT adaptation time lag associated with a high risk for SCD and PFD (Hazard ratios of 3.49 and 2.40, respectively) in [17]. On the other hand, studies based on high-resolution ECGs revealed that reduced atrial fibrillatory rate (AFR) was associated with an increased risk of death because of heart failure progression [18] and reduced irregularity of RR intervals during AF was an independent predictor of all-cause mortality, SCD and PFD [19].

5. Contributors

Patients in the MUSIC study were recruited thanks to the following Spanish Hospitals: Arrixaca Hospital (Murcia), Gran Canaria Insular Hospital (Las Palmas), Gregorio Marañón Hospital (Madrid), Joan XXIII Hospital (Tarragona), Santiago de Compostela University Hospital (Santiago de Compostela), Sant Pau Hospital (Barcelona), Son Dureta Hospital (Mallorca), and Valme Hospital (Sevilla).

6. Conclusion

The publication of MUSIC database on Physionet aims to the development and validation of novel algorithms,

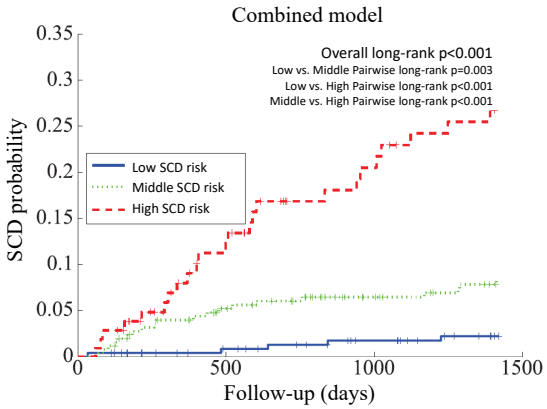

Figure 2: SCD probability curves for the low-, medium- and high-risk groups according to a combined model based on clinical and ECG markers proposed in [15].

techniques, and tools for ECG analysis and its interpretation, but also of innovative clinical applications aimed at improving patient care and outcomes. The growing population of patients with mild-to-moderate CHF raises the need for better risk stratification of these patients who might benefit the most from primary prevention of mortality. MUSIC database comprises a collection of Holter ECGs completed by significant clinical data and follow-up information, including mortality endpoints. In conclusion, it represents a valuable piece of data for the development of prognostic models and novel ECG methodologies aimed at improving this risk stratification in heart failure.

Acknowledgements

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References

[1] Vázquez R, et al. The MUSIC risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. Eur Heart J 2009;30:1088 - 1096.

[2] Cygankiewicz I, et al. Risk stratification of mortality in patients with heart failure and left ventricular ejection fraction >35%. Am J Cardiol. 103:1003-1010, 2009.

[3] Earley A, et al. Effectiveness of implantable cardioverter defibrillators for primary prevention of sudden cardiac death in subgroups a systematic review. Ann Intern Med. 160(2):111-21, 2014.

[4] Cygankiewicz I, et al. Prognostic value of QT/RR slope in predicting mortality in patients with congestive heart failure. J Cardiovasc Electrophysiol. 19(10):1066-72, 2018.

[5] Ramírez J, et al. QT/RR and T-peak-to-end/RR curvatures and slopes in chronic heart failure: Relation to sudden cardiac death, J Electrocardiol, 47:842–848, 2014.

[6] Monasterio V, et al. Average T-wave alternans activity in ambulatory ECG records predicts sudden cardiac death in patients with chronic heart failure. Heart Rhythm, 9(3):383-389, 2012.

[7] Martín-Yebra A, et al. Post-ventricular premature contraction phase correction improves the predictive value of average T-wave alternans in ambulatory ECG recordings. IEEE Trans Biomed Eng. 65(3):635-644, 2018.

[8] Ramirez J, et al. T-wave Morphology Restitution Predicts Sudden Cardiac Death in Patients with Chronic Heart Failure. JAHA. 6:e005310;1-12, 2017.

[9] Palmieri F, et al. Weighted Time Warping Improves T-wave Morphology Markers Clinical Significance, IEEE Trans Biomed Eng. 69(9):2787-2796, 2022.

[10] Voss A, et al. Segmented Symbolic Dynamics for Risk Stratification in Patients with Ischemic Heart Failure. Cardiovascular Engineering and Technology Volume 1:290–298, 2010.

[11] Voss A, et al, Short-term vs. long-term heart rate variability in ischemic cardiomyopathy risk stratification. Front Physiol,4;363:1-15, 2013.

[12] Cygankiewicz I, et al. Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients. Heart Rhythm. 5(8):1095-1102, 2008.

[13] Martínez JP, et al. Detection performance and risk stratification using a model-based shape index characterizing heart rate turbulence. Ann Biomed Eng, 38(10):3173-3184, 2010.

[14] Palacios S, et al. Periodic Repolarization Dynamics as Predictor of Risk for Sudden Cardiac Death in Chronic Heart Failure Patients. Sci Rep, 11:20546, 2021.

[15] Ramírez J, et al. Sudden cardiac death and pump failure death prediction in chronic heart failure by combining ECG and clinical markers in an integrated risk model. PLOS ONE, 12(10):e0186152;1-15, 2017.

[16] Martín-Yebra A, et al. Quantification of Ventricular Repolarization Variation for Sudden Cardiac Death Risk Stratification in Atrial Fibrillation. IEEE J Biomed Health Inform. 23(3):1049-1057, 2019.

[17] Martín-Yebra A, Sörnmo L, Laguna P. QT interval Adaptation to Heart Rate Changes in Atrial Fibrillation as a Predictor of Sudden Cardiac Death. IEEE Trans Biomed Eng. 69(10):3109-3118, 2022.

[18] Platonov P, et al. Low atrial fibrillatory rate is associated with poor out come in patients with mild to moderate heart failure. Circ Arrhythm Electrophysiol, 5: 77–83, 2012.

[19] Cygankiewicz I, et al. Reduced Irregularity of Ventricular Response During Atrial Fibrillation and Long-term Outcome in Patients With Heart Failure. Am J Cardiol, 116(7):1071-5, 2015.

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