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# **DOCTORAL THESIS**

**THE SIGNIFICANCE OF SYSTEMATIC FOLLOW-UP  
THROUGH STRESS TEST IN PATIENTS WITH CARDIAC  
RESYNCHRONISATION THERAPY**

## **A B S T R A C T**

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**Keywords:** cardiac resynchronisation therapy, exercise test, heart rate recovery index, responders, non-responders

## INTRODUCTION

Heart failure is one of the leading health problems, both in our country and worldwide, due to the vast number of patients known or newly diagnosed with this condition and the devastating impact on life expectancy. Heart failure causes significant repercussions, both socially and economically, with a substantial impact on cardiovascular morbidity and mortality, despite scientific and technological advances in recent years. Furthermore, patients with heart failure represent an economic "burden" on the health system due to many hospitalisations for the decompensation of heart failure, becoming a problem of interest to health policies in Romania. Due to these aspects, it is mandatory to have innovative treatment strategies that will improve the symptoms of HF, increase the quality of life and reduce hospitalisations for heart failure.

Research in this study was based on the hypothesis that patients with heart failure who have a prolonged heart rate recovery rate after exercise associate decreased exercise tolerance and an advanced degree of heart failure. Therefore, we assume that the exercise test can be practical and applicable to the study by analysing the ratio between the time of acceleration and deceleration of the heart rate. Thus, a simple and easy-to-understand tool can be developed for the rapid assessment of patients with cardiac resynchronisation therapy.

This paper aims to evaluate the significance of a systematic follow-up by performing the cardiovascular exercise test in patients with cardiac resynchronisation therapy and analysing the association between HRR (heart rate recovery) - heart rate recovery parameter, a parameter derived from the exercise test, and the response to cardiac resynchronisation therapy.

We hope that this research work will be a starting point for the widespread use of exercise tests and the inclusion of this non-invasive investigation in future guidelines for cardiac resynchronisation therapy.

## **GENERAL PART**

In the theoretical part, we will present the existing data in the literature, which support the benefits of cardiac resynchronisation therapy in patients with heart failure, data related to stimulation modes, more precisely, evidence supporting biventricular stimulation and LV-only stimulation. In addition, data on the effects of exercise in patients with heart failure and indications for performing the exercise test in patients with heart failure and cardiac resynchronisation therapy are also detailed in the first part of this doctoral thesis.

Existing data to present have shown that CRT is the standard interventional treatment in patients with heart failure, having beneficial effects on cardiovascular morbidity and mortality. Cardiac resynchronisation therapy (CRT) can be performed either by implanting three-chamber devices, being the standard interventional treatment in patients with heart failure or by univentricular LV-only pacing. This technique is increasingly accepted as non-inferior to biventricular stimulation but not yet routinely used in daily clinical practice. To date, there are few small studies in the literature to support cardiac resynchronisation therapy without RV probes.

## **SPECIAL PART**

The special part of this thesis aims to demonstrate the importance of systematic follow-up by using the exercise test in patients with cardiac resynchronisation therapy. The special part also includes a chapter for a new parameter derived from the exercise test, the heart rate recovery index (HRRI), and its implications for cardiac resynchronisation therapy.

The patients included in the analysis were hospitalised at the Institute of Cardiovascular Diseases from Timisoara between 2011-2019. According to the guidelines at the time, patients who had an indication for cardiac resynchronisation therapy underwent a pacemaker implant, either three-chamber devices or dual-chamber RA / LV devices. In addition, to define the response to cardiac

resynchronisation therapy, all patients benefited from a complete clinical and echocardiographic evaluation, according to the existing recommendations in the literature and additional assessment, through the exercise test, intending to increase the number of non-responders.

## **STUDY OBJECTIVES**

The primary objectives of this research thesis were:

- Evaluation of cardiac resynchronisation therapy efficacy in patients implanted with triple-chamber pacemakers and RA / LV dual-chamber pacemakers.
- To introduce the cardiovascular exercise test as a routine investigation, with an essential role in the monitoring and follow-up of patients who have undergone cardiac resynchronisation therapy.
- To validate the new parameter, HRRI, to define the response to cardiac resynchronisation therapy in association with classical, clinical and electrocardiographic criteria.

The secondary objectives of the thesis were:

- To identify the ideal parameters for optimising implantable cardiac devices, both in the short and long term, to increase the rate of responders.
- To propose new research topics and directions in the future.

### **Criteria for including patients in the study:**

The study population included patients with an indication for cardiac resynchronisation therapy, according to the recommendations of the ESC guideline for cardiac pacing from 2013. In the study were included patients with:

- NYHA II-IV heart failure,
- Left ventricular ejection fraction  $\leq 35\%$  ,
- QRS complex duration  $\geq 130$  ms,

- Optimal drug treatment applied for a period of at least three months before cardiac resynchronisation therapy

**Exclusion criteria:**

The following patients were excluded from the study:

- Acute coronary syndrome in the last three months,
- Permanent atrial fibrillation,
- Severe comorbidities (e.g. renal, pulmonary, hepatic, cerebral, or end-stage neoplasms),
- Non-cardiac diseases that limit physical activity (e.g. orthopaedic conditions)

## RESULTS

Initially, we selected 122 patients admitted to the clinic with heart failure and met the eligibility criteria required for inclusion in the study. From the initial group of patients, 13 (10.65%) were excluded from the study (from statistical analysis), either due to the impossibility of performing the exercise test (for example, orthopaedic conditions, patients with symptoms of decompensated heart failure) or due to lack of consistent data (for example, if patients were absent at more than three follow-up visits). The final group consisted of 109 patients, 74 men, with a mean age of  $63.32 \pm 9.8$  years.

The mean follow-up period was 36 months (range 12-60 months). Patients were evaluated periodically by performing a thorough, objective examination, paraclinical investigations (ECG, echocardiography and routine blood work, exercise test) through one-day hospitalisation, except for patients with decompensated heart failure.

In the following, we will present the data related to the new parameter introduced and studied, HRRI, in responding versus non-responding patients (table 1) and echocardiographic data with a role in characterising the response to pre-implant and post-implant CRT (Table 2).

**Table 1. Comparative analysis of exercise test parameters in the group of responding versus non-responding patients**

Parameters	Responder (N=98)	Non-responder (N=11)	p-value
METs	$6.43 \pm 1.2$	$6.04 \pm 1.0$	0.3
W	$111.16 \pm 32.6$	$102.27 \pm 23.5$	0.4
Resting HR	$67.55 \pm 10.2$	$63.64 \pm 7.2$	0.2
Maximal HR	$100.55 \pm 21.8$	$88.90 \pm 10.7$	0.09
Acceleration time (AT)	$303.66 \pm 125.9$	$303.7 \pm 96.9$	0.9
Deceleration time (DT)	$125.86 \pm 77.4$	$241.68 \pm 116.6$	<0.001
HRRI=AT/DT	$3.16 \pm 2.0$	$1.4 \pm 0.5$	0.007

HRRI, the new parameter studied, was statistically significantly higher in responding versus non-responding patients ( $3.16 \pm 2$  versus  $1.4 \pm 0.5$ ,  $p < 0.001$ ; Fig. 17, Table 1 ).



**Table 2. Comparative analysis of echocardiographic parameters before and after cardiac resynchronisation therapy**

	Before CRT	After CRT	<i>p</i> -value
LVEF (%)	26 ± 5.8	35 ± 8.7	<0.001
LVESV (ml)	176 ± 72	145 ± 73	<0.001
LVEDV (ml)	240 ± 90	217 ± 89	<0.001
LVEDD (cm)	6.4 ± 0.95	6.1 ± 1.1	<0.001

All patients reported an improvement in symptoms and signs of heart failure, and amelioration in NYHA functional class by at least one degree was declared in all responding patients from the study (89.9%). In addition, a significant improvement in echocardiographic parameters accompanied the process of reverse remodelling of the LV level.

Patients received medical treatment based on current recommendations and adjusted to their hemodynamic status (BP, HR, creatinine clearance).

An essential aspect of this thesis is the increase in the number of patients responding to CRT through careful and regular post-implant monitoring, repeated optimisation of both short-term and long-term cardiac devices and periodic optimisation of medication after performing stress tests.

## CONCLUSIONS

The study aimed to evaluate the significance of systematic follow-up by cardiovascular exercise test in patients who received cardiac resynchronisation therapy, in NYHA II-IV functional class, with LVEF  $\leq 35\%$  and QRS complex duration  $\geq 130$  ms, on optimal drug treatment for a period of at least three months before performing the CRT. We also introduced a new parameter derived from the exercise test, HRRI and its involvement in defining the response to CRT. The conclusions of this research thesis are the following:

1. Heart failure, in this case, the one with impaired LV systolic function, is an absolute peak of mortality and morbidity in countries with high-performing medical systems, at least as aggressive as that represented by neoplastic diseases. Nevertheless, despite innovative medication, modern procedures, the mortality of these patients remains very high.
2. CRT is currently a proven effective and feasible method in patients with heart failure with impaired systolic function, sinus rhythm, and QRS complex over 130 ms.
3. It is not so much the implant technique, or the chosen solution - biventricular pacing or RA / LV fusion pacing would make it difficult to control patients' hemodynamic status at high vital risk, but rather to optimise the criteria for resynchronisation and increase the number of responders among implanted patients.
4. HRRI is a new tool in analysing the cardiovascular exercise test and can be routinely introduced in evaluating patients to define the optimal response to CRT. Optimising the functioning of cardiac devices and medication can be improved using the new parameter studied, HRRI.
5. HRRI involves an entirely non-invasive, available, easy to reproduce and standardise approach and cheap and accessible to any cardiology team endowed with an appreciable routine.

6. Of course, the other aspects of complete evaluation cannot be neglected - clinical, electrocardiographic, echocardiographic, but this new parameter greatly simplifies and standardises the follow-up protocol for patients with HF with reduced systolic function and CRT therapy.
7. There were no complications related to three-chamber or dual-chamber pacemakers (e.g. pacemaker malfunctions or infections).
8. Optimal parameters for optimising both short-term and long-term cardiac devices have been identified to allow adequate pacing to increase the percentage of patients responding to CRT.
9. Moreover, HRRI also indicates the adaptation to the effort of the resynchronised patient in an attempt to increase not only the lifespan (identification of the risk of sudden arrhythmic death) but also the quality of life, for which classical parameters such as LVEF and chamber diameters are not sufficiently eloquent.
10. Quality of life is a desideratum and a proof of performance from a nowadays team and medical system, at least as appreciated as the increase of life expectancy.