
Efficacy of High Intensity Interval Training vs Moderate Intensity and Continuous Training on Autonomic Nervous System modulations in Chronic Heart Failure.

HRVFIT 2 - Study

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UPDATE OF THE PROTOCOL

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Protocol Signature

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Clinical Routine Care Study

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Table of contents

Abbreviations List.....	7
Scientific Background.....	8
Chronic Heart Failure : definition and epidemiology.....	8
Chronic Heart Failure and the autonomic nervous system	8
Effects of exercise training on the autonomic nervous system in CHF.....	10
Hypothesis.....	10
Objectives.....	11
Routine medical examination	12
Cardiopulmonary Exercise Test.....	12
24-h Holter ECG recording	12
Echocardiography	12
Endothelial Function	13
Blood Sample Analysis	13
Rehabilitation Program: MICE and HIIT training mode.....	13
Primary and secondary endpoints	14
Primary endpoint	14
Secondary Endpoint	14
Design of the study	15
Randomization	15
Eligibility criteria (inclusion / exclusion)	15
Recruitment	15
Expected fallout	16
Statistics	17
Sample Size	17
Statistical analyses	17
Research Calendar	18
Specific terms of monitoring.....	19
Rules for stopping research	19
The final stop rules.....	19
Research Monitoring Committee.....	20
Ethical and regulatory compliance.....	21
References	22

Abbreviations List

ANS : autonomic nervous system

CHF : chronic heart failure

HIIT : high intensity interval exercise training

HR : heart rate

HRR : heart rate recovery

HRV : heart rate variability

MAP : maximal aerobic power

MICE : moderate intensity and continuous exercise training

RMSSD : root mean square successive difference of heart rate

SDNN : Standard Deviation of Normal-Normal interbeat interval

VO2 max : maximal oxygen consumption

Scientific Background

Chronic Heart Failure : definition and epidemiology

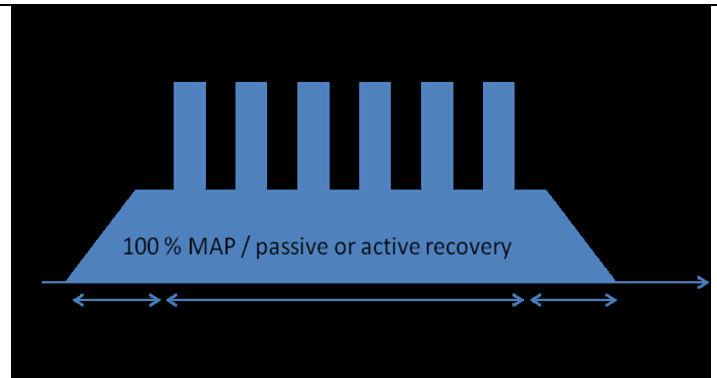
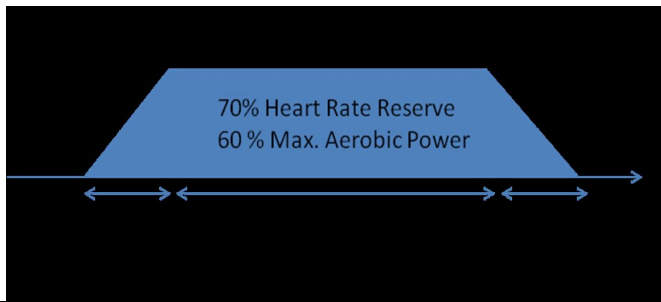
Chronic Heart Failure (CHF) is defined as a structural or functional abnormalities of the heart leading to insufficient oxygen supply to the tissues. The prevalence is estimated between 2 and 3% in Europe by the European Society of Cardiology and increases sharply with age from 75 years [1]. Despite a significant reduction in mortality between 2000 and 2010, CHF remains a common cause of death, especially among the elderly [2]. In France, the mortality rate is 60% in the five years following diagnosis [2] and up to 40% of CHF patients die within one year of their first hospitalization [3].

It is estimated that nearly half of the deaths related to the pathology are due to rhythm disorders leading to sudden cardiac death. The role of the autonomic nervous system (ANS) and in particular the imbalance of the sympatho-vagal balance is recognized as a main factor in the occurrence of a number of rhythm disorders that can lead to sudden cardiac death [4].

Chronic Heart Failure and the autonomic nervous system

The activation of the orthosympathetic nervous system is constantly found in CHF [5]. The Holter-ECG-24h and heart rate variability (HRV) allows non-invasive analysis of ANS activity and abnormalities. With CHF, the HRV index as SDNN, rMSSD, HFnu%, are decreased and indicate alteration of the ANS [6]. Several studies have shown that in cardiovascular diseases, the HRV parameters were prognostic markers of mortality [7]. In both healthy subjects and CHF, studies show that regular exercise improves HRV by increasing vagal tone and decreasing sympathetic nervous system activity [6, 8, 9]. In CHF, exercise training is a non-pharmacological treatment and improves symptoms, quality of life, physical fitness and has a favorable impact on morbi-mortality [10]. The ESC/AHA recommend moderate-intensity and continuous-exercise training sessions (MICE) [11, 12]. However, recent data suggest that high intensity interval training (HIIT) is superior to MICE to improve quality of life, maximal oxygen uptake (VO₂max) and cardiac remodeling of CHF patients [13]. Our team has also study high-intensity exercises on different parameters in these patients with interesting results [14-18]. The two exercise training mode is illustrated by the figure 1.

Figure 1 : exercise training mode of MICE or HIIT



The following table illustrated this new mode of training and is from the latest ESC guideline [12].

Table 4 Main characteristics of each form of training (calisthenic/gradual mobilization, endurance, interval, strength, and respiratory)

	Gradual mobilization – Calisthenic training	Continuous endurance training	Interval endurance training	Resistance/strength training	Respiratory training
Variables of interest		VO ₂ peak, VE/VCO ₂ slope, VAT, peak SBP, peak HR pre- and post-training programme Peak SBP and peak HR pre- and post-training sessions	VO ₂ peak, VE/VCO ₂ slope, VAT, peak SBP, peak HR pre- and post-training programme Peak SBP and peak HR pre- and post-training sessions	Muscle mass (hypertrophy)	PI _{max} : sensation or respiratory work during exercise according to Borg RPE scale
How to start	Can be started as soon as the patient is mobilized Increase in exercise intensity according to RPE	Initial stage: intensity at low level (e.g. 40–50% VO ₂ peak) until an exercise duration of 10–15 min is achieved. Exercise duration and frequency of training is increased according to symptoms and clinical status	Low intensity: It is recommended to start low and go slow [for the very deconditioned] e.g. start with alternation of shorter (10 s) bout of lower intensity exercise workload (50% of peak capacity) and longer recovery period (80 s) for 5–10 min	Intensity: <30% 1-RM Repetitions: 5–10 Frequency: 2–3 training sessions per week, 1–3 circuits during each session	
Progression of training		Initial stage: primary aim is to increase gradually the intensity (50 to >60 to >70% of VO ₂ peak); the secondary aim is to increase sessions duration to 15–20 min, up to 30 min Maintenance stage: usually begins after 3–6 months	High intensity: When well tolerated, first the duration of the bout of the strain (10–30 s) with shortening the recovery (80–60 s) phase, and therefore increasing the intensity (60–100%). The training session should last 15 up to 30 min Then the training frequency and duration per session are increased	Intensity: 30–50% 1-RM RPE 12–13 Repetitions: 15–25 Frequency: 2–3 training sessions per week, 1 circuits during each session	
Optimal ET intensity target	RPE < 15	RPE < 15	RPE < 15	Intensity: 40–60% 1-RM RPE < 15 Repetitions: 8–15 Frequency: 2–3 training sessions per week, 1 circuits during each session	RPE < 15
Exercise capacity		Improved Exercise tolerance (exercise time, VO ₂ peak, maximal workload), VE/VCO ₂ Rate–pressure product at VAT Submaximal exercise capacity (6 m walking test).	Improved Exercise tolerance (exercise time, VO ₂ peak, watts) Submaximal exercise capacity (6 m walking test)	Improved Exercise tolerance (exercise time, VO ₂ peak, maximal workload) and work economy (VO ₂ /WR) Submaximal exercise capacity (6 m walking test)	Improved Exercise tolerance (exercise time, VO ₂ peak, watts) Submaximal exercise capacity (6 m walking test) Ventilatory capacity

Effects of exercise training on the autonomic nervous system in CHF

Several studies have shown a reduction of the sympathetic activity measured by microneurography (MSNA) after an exercise training program in heart failure [19, 20]. This is also found on other ANS parameters such as the Heart Rate Variability that is improving [6, 9]. Catecholamines also tends to decrease with aerobic activity [21]. This improvement in vegetative balance is associated with an improvement in the different vegetative reflexes involved in the regulation of cardiovascular ANS. Thus, the abnormalities noted on the baroreflex, the chemoreflex, the ergoreflex and the central control are all potentially improved by repeated aerobic exercise [22, 23]. Thus the sympathetic stimulation induced during the exercise is followed by a period of increase in vagal tone, explaining the benefit on the rhythmic profil . To our knowledge there is no study comparing the effects on the ANS of MICE training versus HIIT training in CHF.

Hypothesis

Our team recently used an intermittent exercise protocol that has been optimized in CHF patients [24] in order to induce a strong cardiovascular and muscular stimulus while ensuring safety and comfort of the patient (30 seconds at 100% of peak power alternate with 30 sec of passive recovery). In 18 CHF patients, we showed that a single intermittent exercise session increases parasympathetic tone (high frequency index in normalized units HFnu%) and significantly decreases premature ventricular contraction within the 24h of the exercise, compared to a single session of MICE [16]. These results appear promising and suggest that stimuli associated with intense intermittent exercise and passive recovery, as opposed to continuous-type exercise of moderate intensity, would be more effective to increase sympatho-vagal balance and arrhythmias. Nevertheless, the effects of a several weeks of an HIIT program on explanatory parameters of sudden death (SNA activity, arrhythmias, cardiac function) have never been studied in CHF patients. We therefore hypothesize that HIIT is superior to MICE for 1/ increasing parasympathetic activity measured by HRV, 2 / the cardiorespiratory fitness. In addition, we also hypothesize that there is a link between improved physical capacity and vagal tone and decreased arrhythmias.

Objectives

Main objective:

To compare, in patients with chronic heart failure, the efficacy of 4-weeks exercise training programs (MICE vs HIIT) on the evolution of the spectral high frequency (HF) component of HRV.

Secondary Objectives:

To compare, in patients with heart failure, the effectiveness of 4-weeks exercise training programs (MICE vs HIIT) on:

- The temporal and spectral component of HRV
- The number and nature of arrhythmias
- Diastolic and systolic functions measured by echocardiography
- The maximum oxygen consumption (VO₂max)
- Arterial vasomotricity
- biomarkers measurements (BNP, catecholamines)

Routine medical examination

All the evaluations of this research are part of the patient follow-up classically performed in a cardiovascular rehabilitation center. Thus, for this study, the current care evaluated will include: an ECG-24h holter, a maximal cardiopulmonary exercise test, an echocardiography, a blood sample test, an endothelial function analysis (Endopath system). The exams will be done at the inclusion (J0), after 4 weeks of rehabilitation (S4).

Cardiopulmonary Exercise Test

CPET will be performed according to current guidelines for CHF patients [12]. A continuous progressive exercise protocol will be performed on a cycle ergometer (Ergoline 800S, Ergoline, Bitz, Germany). A 2-min warm-up at 20 W ; and the power will be increased by 10 W/min until exhaustion [12]. Peak power output (PPO) is define as the power output reached at the last fully completed stage. All subjects will be encouraged to provide a maximal effort. Oxygen ($\dot{V}O_2$) and carbon dioxide (CO_2) were registered by a breath by breath analysis (PowerCube, Ganshorn Electronic Medizin, Germany). Heart rate, blood pressure, and rating of perceived exertion (RPE) using the Borg scale (level 6 to 20) will be recorded before the test and at 2-min intervals during exercise and recovery. Electrocardiographic activity will be continuously monitored using a 12-lead ECG (GE Healthcare Marquette) and will be recorded throughout the test and during the 6-min passive recovery after the test.

24-h Holter ECG recording

24-h ECG monitoring will be performed at baseline and at the end of the stay using a two-lead 24-h Holter ECG system (Spiderview, ELA medical, France). Patients will be requested to avoid any exercise, caffeinated beverages, and smoking during the 24 h of recording. An experienced technician blinded to randomization will analyse the recordings (Synescope, ELA medical, France).

Echocardiography

Echocardiography will be performed using a phased-array transducer (Vivid T8, GE Healthcare). Three cine loops from the three standard apical planes (four-chamber, two-chamber and long-axis) as well as short-axis (basal, mid-papillary and apical) will be recorded in gray scale harmonic mode and tissue Doppler mode. B-mode recordings will be done with an average of 53 frames/s and tissue Doppler with 154 frames/s. Measurements will be done in accordance with recommended procedures of the European Association of Cardiovascular Imaging. LV volumes and ejection fraction (EF) will be calculated from apical recordings by modified biplane Simpson's method. Left ventricle inflow velocity was measured by pulsed Doppler with the sample volume at the tips level of mitral valves. Measurements will included early diastolic filling (E) and late diastolic filling (A). Stroke volume (SV) and cardiac output (CO) were calculated by Doppler flow measurement in the LV outflow tract (LVOT). Tissue Doppler recordings of the

mitral annulus will be obtained from the septal and lateral points in four-chamber and in the anterior and inferior points in two chamber views. Peak annulus velocity in systole (S'), early diastole (e') and late diastole (A') will be measured as average of the four points.

Endothelial Function

Reactive hyperemia index (RHI), a surrogate of endothelial function, will be assessed using the EndoPAT 2000 device (Itamar Medical, Israel) and an automated algorithm provided with the accompanying software (v3.1.2) according to the manufacturer's instructions. Briefly, patients will be in a supine position for a minimum of 20 min before measurement in a quiet, temperature-controlled (21–24 °C) room with dimmed lights. Each recording will consist of 5 min baseline measurement, 5 min occlusion measurement, and 5 min post-occlusion measurement (hyperemic period). Occlusion of the brachial artery involved the non-dominant upper arm. The natural logarithmic scaled RHI (LnRHI) will be calculated from the ratio between the digital pulse volume during RH and at baseline [25].

Blood Sample Analysis

Measurements will include: NT-pro-BNP (electrochemiluminescence immunoassay) and both epinephrine and norepinephrine plasma levels (HPLC).

Rehabilitation Program: MICE and HIIT training mode

The rehabilitation program focus on controlling cardiovascular risk factors, diet monitoring, therapeutic education sessions and psychological support when needed. In our clinical center, the RP last 3 hours per day, 5 days per week during 3.5 weeks. The daily activity training include a cycling endurance training (HIIT or MICT), a 30-min of gymnastics or muscle strengthening (3 series of 15 repetitions at 50% of 1-repetition maximum test in chest press, leg press, pull over, low row, leg extension) and 45-min outside walking sessions. Each session will be monitored by a physiotherapist and was supervised by a cardiologist.

The HIIT consist of two sets of 8-min intervals at 100% of peak power output (PPO) [24, 26]. Each interval set is composed of repeated bouts of 30 s at 100% of PPO interspersed by 30 s of passive recovery in the seated position. Four minutes of passive recovery are allowed between the two sets. The MICT training consist of cycling 30 minutes at 60% of peak power output. Each mode of training start with 5 minutes of warm up and finish with 5 minutes of cool down at 30% of PPO.

Primary and secondary endpoints

Primary endpoint

Evolution between day 0 (D0) and Week 4 (W4), of the High Frequency component of HRV measured during the night time period and expressed in normalized units (%): HF nu%.

Secondary Endpoint

The analysis will also focus on the evolution of the following variables:

Variables extracted from the analysis of the HRV (Holter-ECG 24h)

Heart Rate rest (beats per minute - bpm)

LF, HF (milliseconds², standard units)

VLF (milliseconds²)

Total Spectral Power (milliseconds²)

SDNN (milliseconds)

rMSSD (milliseconds)

LF / HF ratio

Number and nature of arrhythmias

Variables of echocardiography

Size of the cardiac cavities (diameter (mm), surface (cm²), volume (ml.m²))

LV systolic function (Ejection fraction (%), parietal thickness (mm))

Filling LV (E / A, E / e', Ap-Am (ms), E / Vp)

Systolic function of RV (shortening fraction (%), S'wave (cm.s), systolic excursion of tricuspid ring (mm))

Variables of the cardiopulmonary exercise test

Maximum oxygen consumption (VO₂pic (ml.min))

Maximum heart rate (bpm)

Heart rate after 1 minute, 2 minutes and 3 minutes of passive recovery

Oxygen pulse (ml.min.batt)

Slope VE / VCO₂

Maximum aerobic power (watts)

Variables of endothelial function

Reactive Hyperemia Index (RHI)

Variables of the blood test

Blood glucose (mmol.L); HbA1c (%)

Adrenaline, norepinephrine (ng.L)

NT pro BNP (ng.L)

Design of the study

Prospective / randomized study in 2 parallel groups (1:1): arm 1 (MICE) and arm 2 (HIIT).

Randomization

The randomization to assign each patient to one of the 2 groups will be done just after the verification of the eligibility criteria and the collection of the sign consent of participation of the patient. The numbers of the 2 groups (arm 1: MICE / arm 2: HIIT) are balanced with a 1: 1 ratio

Eligibility criteria (inclusion / exclusion)

Inclusion

Inclusion criteria will be stable CHF with NYHA functional class from I to III, stable left ventricular ejection fraction (LVEF) < 45% over at least 6 months, stable optimal medical therapy including a beta-blocker and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARB) for at least 6 weeks and ability to perform a maximal CPET.

Exclusion

Exclusion criteria will be any relative or absolute contraindications to exercise training according to current recommendations [12], fixed-rate pacemaker with HR limits set lower than exercise training target HR, major cardiovascular event or procedure within the 3 months preceding enrolment, chronic atrial fibrillation, heart failure secondary to significant uncorrected primary valve disease (except for mitral regurgitation secondary to left ventricular dysfunction), and heart failure secondary to congenital heart disease or obstructive cardiomyopathy.

Patients eligible for the study must not have participated in biomedical research within 30 days of the start of this research and will not be able to participate in another research at the same time.

Recruitment

The recruitment of CHF patients will be done only at the Clinic of Saint-Orens, during the first day of consultation and only by investigators avowed by the Ethical Committee. After verification of the eligibility criteria, the cardiologist will explain to the patient the research and propose to participate. He will then give him the information notice. The expected duration of the inclusion period is 1 year.

Expected fallout

If HIIT is more interesting to improve ANS activity, arrhythmias, cardiac function and cardiorespiratory fitness (all are parameters of sudden cardiac death), then the optimization and the prescription of this type of exercise training would be important. That would demonstrate the great interest and the feasibility of an intense exercise training program specific to chronic heart failure patients. This prescription could later be transposable at home for a long term period of practice. Thus this study will open the field to other research perspectives in particular in terms of longer-term impact on the mortality that remains to be evaluated.

Statistics

Sample Size

The primary outcome measure is the change of High Frequency power in normalized units (HFnu) measure at night as a surrogate of cardiac parasympathetic modulation. Based on our first study [16], we hypothesise that HIIT mode will induce a ~11% change in HFnu compare to MICT training mode. With a mean value of the main criteria (HFnu %) of 31.5%, a standard deviation of 3%, a statistical power (1- β) to 90% and a α risk set to 0.05 in bilateral hypothesis, 16 patient per group must be recruited.

Statistical analyses

Data will be summarized by mean \pm standard deviation (SD) for continuous variables; percentages and frequencies for categorical ones. Shapiro-Wilk and Bartlett tests will be used to assess normality and equality of variance among variables analysed, respectively. Baseline inclusion characteristics will be compared between groups using one-way ANOVA or Mann-Whitney non-parametric test for quantitative variables. Changes within groups (difference between post and pre training values) will be analysed using a paired t-test for normally distributed data or paired Wilcoxon signed-rank test for non-normally distributed data. To analyse the differences between HIIT and MICT groups, repeated ANOVA analysis will be carried out estimating time effect (post vs pre), group effect (HIIT vs MICT) and the interaction time x group. P value <0.05 will be considered as significant. Correlation between parameters will be analyzed using the Pearson Correlation Test or Spearman's Rank Correlation Test, depending on the nature of the conditional distribution and the shape of the relation.

Research Calendar

Provisional schedule

Beginning of inclusions: June 2015

Duration of the inclusion period: 1 year

Duration of participation of each patient: 7 months (4 weeks in rehabilitation centre)

Total duration of the research: 3 years

Summary table of patient follow-up

	Pre-inclusion D- 1 à D- 2	Inclusion D 0 +/- 2 days	Week 4 +/- 3 days
eligibility criteria	✓		
Patient information of the research	✓		
Collection of sign informed consent		✓	
Randomization		✓	
Clinical Exam ¹ (Nurse)		✓	✓
Holter ECG-24h (nurse)		✓	✓
Endothelial function (nurse)		✓	✓
Biological assessment 2 (nurse)		✓	✓
Echocardiography (cardiologist)		✓	✓
Cardiopulmonary exercise test (cardiologist)		✓	✓

¹Clinical examination: measurement of: height, weight, analysis of body composition by impedance, measurement of waist circumference and resting blood pressure.

²Biological assessment: lipid balance, glycemic, adrenaline, norepinephrine, NT-pro-BNP, beta hCG for women(D0).

Specific terms of monitoring

In addition to the usual medical care of the patient, a Supervisory Committee will ensure the proper conduct of research, the safety of proposed programs. , Any adverse effects caused by physical exercise training (muscle pain cramp, fatigue of the patient), change of drug treatment, compliance with the protocol will be noted in the medical file. In case of fatigue of a patient or for medical or paramedical reason, the exercise training intensity may be reduced or even removed. In this case, any changes to the exercise training program will be documented in the medical file.

Rules for stopping research

The rules for temporary cessation of the participation of a person in research or part or all of the research:

- 1) Anyone is free to temporarily stop participating in the research at any time.
- 2) Anyone can ask to temporarily interrupt their participation due to side effects of physical activity (pain, muscle fatigue ...).
- 3) Anyone may be temporarily unavailable for personal reasons.
- 4) A person who has not missed more than 3 consecutive sessions on the 4 weeks of the rehabilitation program can maintain their participation in the research if they wish.
- 5) The Supervisory Committee has the possibility to stop the search

The final stop rules:

- 1) Anyone is free to permanently stop his participation in research at any time without having to give reason.
- 2) Anyone with an incapacitating health problem that prohibits the practice of a physical activity will be excluded from research by decision of the investigator who will inform the coordinator, the rehabilitation team and the research manager.

There are no plans to replace people who permanently stop the search. The data will be excluded from the statistical analysis. A temporary or permanent stop of the research will be automatically documented in the medical file.

Research Monitoring Committee

Research Monitoring Committee is composed of:

SENARD Jean-Michel (PU-PH, scientific manager)

RICHARD Lisa (Cardiologist, investigator)

LABRUNEE Marc (PH, Scientific Officer)

PATHAK Atul (Cardiologist, Scientific Officer)

GUIRAUD Thibaut (PhD, Deputy Director of Clinique Saint Orens, project leader)

BESNIER Florent (Teacher in Adapted Physical Activities, PhD student, coordinator of the project)

The Research Monitoring Committee will meet 3 times: before the start of the research for the implementation visit, once 10 patients are included in the study, and at the end of the last end-of-study visit of the last patient. The Supervisory Committee ensures the smooth running of the research.

Ethical and regulatory compliance

Exams and methods used in this research are part of the routine care as defined by Law No. 2004-806 of 9 August 2004 (Article L1121-1, 2^o paragraph and Article R1121-3 of the Public Health Code). This study is a Clinical Routine Care Study

The instigator, the coordinator, and the investigators who drive and supervise the research undertake that this research is carried out in accordance with the law n° 2004-806 of August 9th, 2004, as well as in line with **Good Clinical Practice and the Declaration of Helsinki** (Ethical Principles for Medical Research Involving Humans, Tokyo 2004).

The research will be conducted in accordance with this protocol. Except in emergency situations requiring the implementation of specific therapeutic acts.

This research received the favourable opinion of the **Committee for the Protection of Persons** (ethical committee) (CPP) Sud-Ouest and Outremer II on May 6, 2015. This research is covered by the liability insurance of La Clinique Saint Orens.

The data recorded during this research are in accordance with the law n° 78-17 of January 6, 1978 relating to data, files and freedoms modified by the law 2004-801 of August 6, 2004. The Saint Orens Clinic will send a request for an opinion to the Advisory Committee on the Treatment of Information in the Field of Health Research (CCTIRS) and a request of authorization to the National Information Commissioner's Office / French Data Protection Authority (CNIL).

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INFORMED CONSENT FORM

**Efficacy of High Intensity Interval Training vs Moderate Intensity and Continuous Training on Autonomic Nervous System modulations in Chronic Heart Failure.
HRVFIT 2 - Study**

I, the undersigned (last name, first name), certify that I have read and understood The Informed Consent.

I had the opportunity to ask all the questions that I wanted to the investigator who explained to me the nature, the objectives, the potential risks and the constraints related to my participation in this clinical care research.

Before taking part in this research, I benefited from medical examinations whose results were communicated to me and allow me to participate.

I know the opportunity to interrupt my participation in this research at any time without having to justify my decision and I will do my best to inform the doctor who follows me in the research. This will not naturally call into question the quality of subsequent care.

I have been assured that the decisions that are required for my health will be made at all times, in accordance with the current state of medical knowledge.

I have noted that this research is conducted in accordance with Articles L1121-1 and following of the Public Health Code, relating to the protection of persons who are suitable for biomedical research and in accordance with Good Clinical Practice.

I became aware that this research received the favourable opinion of the Ethical Research Committee on May 6, 2015 and the authorization of the French National Agency for Medicines and Health Products Safety (ANSM) on January 29, 2015 and was the subject of a statement to the National Information Commissioner's Office / French Data Protection Authority (CNIL).

The research is a current care research according to the Ethical Research Committee, which means that there is no additional risk related to the study, the insurance is that of the Clinic responsible for care (Article L. 1142 -2).

I agree that only persons who collaborate in this research or who are mandated by the instigator, as well as Health Authorities, have access to information in the strictest respect of confidentiality.

I have received, in accordance with the provisions of the law relating to data, files and freedoms, I have a right of access and rectification. I also have the right to oppose the transmission of data covered by professional secrecy that may be used in the context of this research and to be processed. These rights are exercised with my doctor in the context of this research and who knows my identity.

My consent does not relieve the investigator and the research manager of their responsibilities to me. I retain all rights guaranteed by law.

The overall results of the research are communicated to me directly, if I wish, in accordance with the law of 4 March 2002 on the rights of the sick and the quality of the health system.

Having had sufficient time for reflection before making my decision, I freely and voluntarily agree to participate in the HRVFIT2 research.

I can at any time ask additional information to the doctor who offered me to participate in this research.

Done at : date :

Done at : date :

Patient's signature:

Doctor's signature:

- 1st sheet (original): to be kept apart by the investigator for 30 years in a secure lockable place
- 2nd sheet: to give to the patient after signatures
- 3rd leaflet: to be stored in the patient's file