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The Contribution of Exercise Haemodynamic Measurements by Signal-Morphology Impedance Cardiography in the Management of Cardiac Rehabilitation Patients

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in Sport Sciences, Motor Function, and Human Movement

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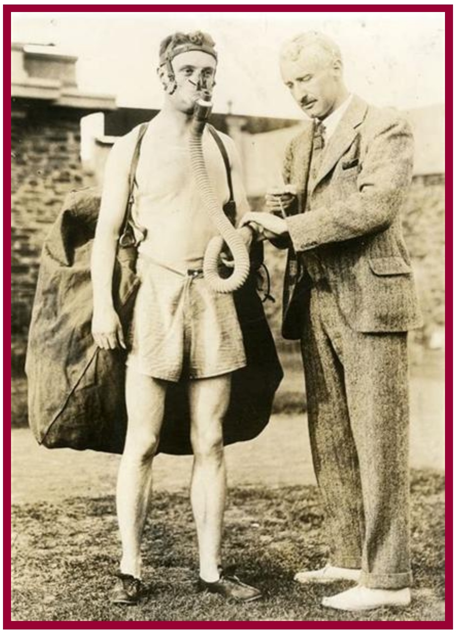
“Never give in, never give in,

never, never, never, never…”

Sir Winston Churchill, Harrow School, London area, October 29th, 1941



“(After the war will be over) …. there will remain the greater task of directing knowledge lastingly towards the purposes of peace and human good. In this task the scientists of the world, united by the bond of a single purpose which overrides all bounds of race and language, can play a leading and inspiring part.”

Sir Winston Churchill, letter to **Prof. Archibald V. Hill**, October 30th, 1943

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My family and colleagues were not thrilled about my decision to dedicate so much time and energy to a doctorate that was not considered necessary for my intellectual development or the growth of our business, especially given our limited resources and high demands. I am deeply grateful that my life partner, Céline Pillon, the mother of our two young children; my long-time business partner and friend, Benoît Bosquet; and all my family and colleagues graciously allowed me to take on this endeavor and discreetly supported me.

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Abstract

Cardiac Rehabilitation (CR) is one of the most effective interventions for secondary prevention of cardiovascular disease, yet its technological and methodological implementation remains heterogeneous worldwide. In many health systems, the limited use of advanced hemodynamic monitoring constrains individualized exercise prescription. Within this context, the present thesis aimed to integrate non-invasive impedance cardiography—specifically Signal Morphology Impedance Cardiography (SM-ICG) and its Contractility Index (CTi)—into the evaluation and optimization of exercise-based Comprehensive Cardiac Rehabilitation (CCR) programs.

Across four complementary studies involving 130 analyzable participants, SM-ICG was systematically applied during Cardiopulmonary Exercise Testing (CPET) to measure real-time changes in cardiac output ($\dot{Q}c$), Stroke Volume (SV), and CTi from rest to peak exercise. These parameters were compared with classical functional markers such as peak oxygen uptake ($\dot{V}O_2$peak) and peak power (Wpeak). The results demonstrated that CTi and its changes with training (ΔCTi) are reliable indicators of left-ventricular contractile adaptation and robust predictors of training responsiveness. Combining CTi-derived hemodynamic data with conventional metabolic indices enabled the identification of distinct physiological response phenotypes: central Responders (R) (improved $\dot{Q}c$ and SV), peripheral R (enhanced oxygen extraction and mechanical efficiency), and mixed R showing combined adaptations.

Two of the studies specifically confirmed the predictive and prescriptive potential of baseline CTi contractile profiles anticipated post-training improvement in $\dot{V}O_2$peak, while CTi itself emerged as a marker of clinical outcomes and a potential tool for the individualization of training intensity within CCR. Altogether, these findings reposition CCR within a precision-medicine framework, where hemodynamic profiling complements traditional functional evaluation to refine exercise prescription and improve clinical outcomes.

Keywords: cardiac rehabilitation; impedance cardiography; contractility index; responders; precision medicine.

List of Abbreviations

$(a–\bar{v})O_2$diff – Arteriovenous Oxygen Difference

ACSM – American College of Sports Medicine

ACEi – Angiotensin-Converting-Enzyme Inhibitor

AT – Anaerobic Threshold

ARB – Angiotensin Receptor Blocker

BMI – Body Mass Index

BSA – Body Surface Area

CaO_2 – Arterial Oxygen Content

CAD – Coronary Artery Disease

CDC – Centers for Disease Control

CR – Cardiac Rehabilitation

CCR – Comprehensive Cardiac Rehabilitation

CHF – Chronic Heart Failure

CI – Cardiac Index

COPD – Chronic Obstructive Pulmonary Disease

CPET – Cardiopulmonary Exercise Testing

CRT – Cardiac Resynchronization Therapy

CTi – Contractility Index

CVD – Cardiovascular Disease

CVP – Central Venous Pressure

CvO_2 – Mixed Venous Oxygen Content

DABP – Diastolic Arterial Blood Pressure

$\dot{D}$O2 – Diffusive component of oxygen transport

ECG -- Electrocardiographie

EDFR – End-Diastolic Filling Ratio

Ees – End-Systolic Elastance

EF – Ejection Fraction

ES – Effect Size

ESC – European Society of Cardiology

ESPVR – End-Systolic Pressure–Volume Relationship

FEO_2 – Expired Fraction of Oxygen

FECO$_2$ – Expired Fraction of Carbon Dioxide

FICO$_2$ – Inspired Fraction of Carbon Dioxide

FIO$_2$ – Inspired Fraction of Oxygen

FITT-VP – Frequency, Intensity, Time, Type, Volume, and Progression

FS – Fractional Shortening

GDMT – Guideline-Directed Medical Therapy

GLS – Global Longitudinal Strain

HF – Heart Failure

HFrEF – Heart Failure with Reduced Ejection Fraction

HIIT – High Intensity Interval Training

HR – Heart Rate

ICG – Impedance Cardiography

LBBB – Left Bundle Branch Block

LV – Left Ventricular

LVEF – Left Ventricular Ejection Fraction

LVESV – Left Ventricular End Systolic Volume

LDL – Low Density Lipoprotein

LVAD – Left Ventricular Assist Device

MABP – Mean Arterial Blood Pressure

MET – Metabolic Equivalent of Task

MICT – Moderate Intensity Continuous Training

6MWT – 6 Minutes Walking Test

NR – Non-Responder(s)

NYHA – New York Heart Association

OR – Odds Ratio

PET – Positron Emission Tomography

PETCO$_2$ – End-Tidal CO$_2$ Pressure

PRSW – Preload Recruitable Stroke Work

PV – Pressure–Volume

$\dot{Q}$c – Cardiac Output

$\dot{Q}$O$_2$ – Convective component of oxygen transport

R – Responder(s)

RER – Respiratory Exchange Ratio

SABP – Systolic Arterial Blood Pressure

SD – Standard Deviation

SM-ICG – Signal Morphology Impedance Cardiography

STE – Speckle-Tracking Echocardiography

SV – Stroke Volume

SVi – Stroke Volume index

SVR – Systemic Vascular Resistance

SVRi – Systemic Vascular Resistance index

TDI – Tissue Doppler Imaging

TEB – Thoracic Electrical Bioimpédance

TFC – Thoracic Fluid Content

$\dot{V}CO_2$ – Carbon Dioxide Output

$\dot{V}E$ – Minute Ventilation

$\dot{V}I$ – Inspired Ventilation

$\dot{V}O_2$– Oxygen Uptake

$\dot{V}O_2$peak – Peak Oxygen Uptake

$\Delta\dot{V}O_2$peak – Changes of maximal oxygen uptake value after CRR

VTI – Velocity-Time Integral

VT_1 – first aerobic threshold

$\frac{\dot{V}E}{\dot{V}CO2}$ slope – Ventilatory Efficiency

WBICG – Whole-Body Impedance Cardiography

WHO – World Health Organization

Wpeak – peak Workload

List of Illustrations

Illustration 1: A real life CCR environment 22
Illustration 2: Cardiorespiratory fitness at midlife and long-term mortality....23
Illustration 3: Implementation of the FITT-VP model....29
Illustration 4: Various CCR models and technology infiltration 31
Illustration 5: $\dot{V}O_2$peak vs $\dot{V}O_2$max....33
Illustration 6: $\dot{V}E$ / $\dot{V}CO2$ slopes and pathologies....34
Illustration 7: Determination of OUES 35
Illustration 8 : SV profiles vs. O_2 pulse profiles in HCM patients 38
Illustration 9: Various VT1 detection modalities 39
Illustration 10 : Professor Adolf Eugen Fick 42
Illustration 11: Strain improvement with CCR....49
Illustration 12: Positional impact of exercise ultrasound 50
Illustration 13: The first commercially available ICG device, BoMED NCCOM3, 1982 52
Illustration 14: Sports cardiac physiology on the field and the lab 58
Illustration 15: real life CPET SM-ICG test in CCR (courtesy of the patient) 66
Illustration 16: SM-ICG and CTi (its determination and abnormal profile) 68
Illustration 17: Real life CPET SM-ICG test in CCR (courtesy of the patient)....75
Illustration 18 : Electrode positions....78
Illustration 19: Electrode positions 78
Illustration 20: Calibration results 79
Illustration 21: Calibration signals 79
Illustration 22: Example of an exercise test screen shot 80
Illustration 23: Screen shot showing an improvement in CTi_reserve....81
Illustration 24: Characteristic CTi profiles....82
Illustration 25: Display of the S wave and O wave 83
Illustration 26: Pictures or the Corentin Celton and Leopold Bellan Rehabilitation Centers....85
Illustration 27: location of the Léopold Bellan rehabilitation center....85
Illustration 28: location of the Corentin Celton rehabilitation center....86
Illustration 29: Radar plot for Haemodynamic Parameters 94
Illustration 30: Flow Chart CTi decision tree in CCR....102
Illustration 31: The “Systemic Stress Test” 103
Illustration 32: SM-ICG, measuring and educating....109
Illustration 33: Presentation at the EAPC congress, Milan April 2025....126
Illustration 34: Presentation at the AACVPR congress, West Palm Beach, September 2025 129

List of Tables

Table 1: Population risk factors in the USA and France....18
Table 2 : Comparative Application of the FITT-VP Model in International CCR Programs....29
Table 3 : Clinical Intensity vs Technological Reliance in International CCR Models 31
Table 4: Key CPET Parameters in Comprehensive Cardiac Rehabilitation (CCR)....41
Table 5: SM-ICG clinical parameters 56
Table 6: Improving evaluations in CCR 71
Table 7: Baseline Demographic and Clinical Characteristics of the Analyzable Population 88
Table 8: Summary of Response Criteria Across the Four Thesis Studies 91
Table 9: Summary of the Four Thesis Studies 95

TABLE OF CONTENTS

***List of Abbreviations* 9**

***List of Illustrations* 12**

***List of Tables* 12**

***Introduction* 15**

***1. Part I: Review of the Literature* 21**

***1.1. CHAPTER 1: CARDIOPULMONARY PHYSIOLOGY IN REHABILITATION* 22**

- *1.1.1. Objectives and Benefits of CCR* 22
- *1.1.2. Current Practices in Cardiac Rehabilitation: A Comparative Overview* 25
- *1.1.3. The Use of Cardiopulmonary Exercise Testing in Cardiac Rehabilitation* 33
- *1.1.4. The Interest of Adding Direct Hemodynamic Measurements* 42
- *1.1.5. Going Deeper: the Components of Cardiac Output* 46

***1.2. CHAPTER 2: IMPEDANCE CARDIOGRAPHY* 51**

- *1.2.1. Introduction to Impedance Cardiography* 51
- *1.2.2. The Originality of Signal-Morphology Impedance Cardiography* 54
- *1.2.3. Exercise Applications of SM-ICG* 57
- *1.2.4. Summary and Outlook* 60

***1.3. CHAPTER 3: APPLICATION OF SM-ICG TECHNOLOGY TO CARDIAC REHABILITATION* 64**

- *1.3.1. State of the Art of Studies on ICG and SM-ICG in Rehabilitation* 64
- *1.3.2. Innovative Prospects with SM-ICG* 66

***2. Part II: Presentation of the Thesis Studies* 72**

***GENERAL OBJECTIVE OF THE THESIS STUDIES* 73**

***2.1. CHAPTER 4: METHODOLOGY OF THE THESIS* 75**

- *2.1.1. Cardiopulmonary Exercise Test* 75
- *2.1.2. Signal Morphology Impedance Cardiography* 76
- *2.1.3. Patient Populations and Training protocols* 84
- *2.1.4. Response Criteria and Statistical Methods* 89

***2.2. CHAPTER 5: RESULTS OF THE THESIS* 93**

- *2.2.1. Study 1 – Predictive Value of Baseline CTi Profile in a CVD Population* 93
- *2.2.2. Study 2 – Validation of CTi Predictive Role in CHF* 93
- *2.2.3. Study 3 – Mechanistic Evidence of Contractile Plasticity* 93
- *2.2.4. Study 4 – Hemodynamic Determinants of Response in HFrEF* 93

***2.3. CHAPTER 6: ANALYSIS OF THE THESIS STUDIES* 96**

2.3.1. Discussion *96*
2.3.2. Limitations of the Studies *97*
2.3.3. Perspective of the Thesis *101*
2.3.4. Future Perspectives and Research Directions for SM-ICG and CTi in Cardiac Rehabilitation and Beyond *106*

Conclusion* *112

Bibliography and Appendices* *115

Bibliography* *116
Peer-reviewed Publications (Reproduced in Full) *116*
General Bibliography *154*

Introduction

Cardiovascular Disease (CVD) remains the leading cause of mortality and morbidity worldwide, despite considerable advances in both pharmacological therapies and interventional strategies over recent decades. As emphasized by the World Health Organization (WHO), the increasing prevalence of sedentary lifestyles—now identified as the fourth leading global cause of death—has compounded the burden of chronic cardiovascular pathologies, particularly Chronic Heart Failure (CHF) and Coronary Artery Disease (CAD). The growing prevalence of chronic diseases in the United States, particularly diabetes and hypertension, constitutes a significant public health concern. According to recent data published by the Centers for Disease Control and Prevention (CDC): approximately 38.4 million Americans are currently living with diabetes, which equates to 11.6% of the population (CDC, 2023). Alarmingly, nearly 9 million individuals remain undiagnosed. Among adults aged 20 years and older, the prevalence rate now approaches 16%, a notable increase from the early 2000s. Prediabetes affects an additional 97.6 million adults, most of whom are unaware of their condition (CDC, 2023). In parallel, hypertension affects nearly half (49.4%) of all U.S. adults, with only one in four individuals managing to maintain adequate blood pressure control. Disparities across demographic groups remain prominent, with particularly elevated rates observed among Black Americans (CDC, FastStats). The silent nature of these conditions, often remaining undiagnosed or poorly controlled, contributes significantly to downstream health complications, particularly cardiovascular.

Contributing substantially to the burden of these diseases is the high prevalence of sedentary behavior (excessive sitting time) and physical inactivity (not meeting recommended activity levels). Sedentary behavior: defined as activities performed in a sitting posture with an energy expenditure ≤1.5 METs, has been independently associated with a wide range of adverse health outcomes, regardless of exercise levels (Lee et al., 2012). By contrast, physical inactivity refers to the failure to meet recommended levels of moderate-to-vigorous physical activity. While related, the two concepts are not interchangeable: an individual may exercise regularly yet spend most of the day sitting or remain on their feet all day.

It is estimated that nearly 25% of American adults report no leisure-time physical activity (CDC, Physical Activity Facts). According to the National Health Interview Survey (NHIS, 2022), less than 24% of adults meet the guidelines for both aerobic and muscle-strengthening activity. These behavioral patterns are strongly correlated with increased incidence of obesity, metabolic syndrome, insulin resistance, and vascular dysfunction. A sedentary lifestyle has been independently associated with a wide array of adverse outcomes (Lee et al., 2012). Prolonged physical inactivity contributes to systemic inflammation, impaired glucose metabolism, and elevated blood pressure. Individuals who are physically inactive face up to a 30% greater risk of developing type 2 diabetes and CVD compared to those who meet recommended activity levels (HHS, 2018). Furthermore, sedentary behavior has been linked to elevated mortality from all causes, including cancer and CVD (WHO, 2014). The long-term impact of physical inactivity extends well beyond clinical diagnoses and includes reduced functional status and quality of life. The long-term consequences of diabetes and hypertension are profound. Both conditions are strongly associated with increased risk of cardiovascular events, including myocardial infarction, stroke, and Heart Failure (HF), as well as chronic kidney disease and premature mortality (Mokdad et al., 2018, INSERM, 2017). From an economic standpoint, the cost burden is both immediate and long-ranging. In 2022 alone, the total cost attributable to diagnosed diabetes was estimated at $412.9 billion. This figure encompasses $306.6 billion in direct healthcare expenditures and $106.3 billion in indirect costs such as lost productivity and premature death (ADA, 2023). These costs are mirrored in the broader context of chronic disease, which accounts for 90% of the $4.5 trillion in annual healthcare expenditures in the United States (CDC, 2023). Without urgent coordinated intervention, these trajectories pose a substantial risk to the financial sustainability of public insurance systems such as Medicare and Medicaid, and to the country's finances as a whole.

Although the United States exhibits some of the most severe statistics regarding chronic diseases and lifestyle-related conditions, it is not alone in facing this escalating crisis. Many other nations, particularly those undergoing rapid urbanization and dietary westernization, are exhibiting parallel trends in the rising prevalence of diabetes, hypertension, sedentary behavior, and thus, CVD (WHO, 2023). For instance, France, historically perceived as a comparatively healthy nation, is now exhibiting trends that align increasingly with global patterns in chronic disease and physical inactivity. While the burden of conditions such as diabetes and hypertension remain somewhat lower than in the United States, national data reflect a steady rise in prevalence over the past two decades. Concurrently, the country is experiencing a pronounced decline in physical fitness, particularly among children and adolescents. According to Professor François Carré, cardiologist at CHRU Rennes (University Hospital of Rennes) and expert for the Fédération Française de Cardiologie, French adolescents have lost about 25% of their cardiorespiratory fitness over the past four decades, as shown by endurance test data collected since the 1970s (Carré, 2013; Fédération Française de Cardiologie, 2017). At the international level, Professor Grant Tomkinson's meta-analyses report a smaller but still significant decline—around 7–15% in youth fitness globally between 1981 and 2014 (Tomkinson et al., 2019). These changes underscore that no country is immune to the broader forces driving the global epidemic of noncommunicable diseases, and that timely public health intervention is as critical in France as it is elsewhere.

Table 1: Population risk factors in the USA and France

Risk Factor	United States	France	Comment
Obesity (BMI ≥ 30)	~42% of adults	~17% of adults	The US shows very high obesity prevalence; France remains lower but steadily increasing.
Overweight (BMI ≥ 25)	~74% of adults	~47% of adults	Both countries have a large overweight population, but the US is much higher.
Pre-diabetes	~38% of adults	~6–10% (varies by definition)	Massive reservoir of metabolic risk in the US; early identification improving in France.
Type 2 Diabetes	~11% of adults	~5% of adults	Prevalence in the US is roughly double compared to France.
Hypertension	~47% of adults	~30% of adults	Higher prevalence in the US; control rates remain suboptimal in both countries.
Smoking	~12% of adults	~25% of adults	Opposite pattern: smoking remains much more common in France.
Physical inactivity	~24% insufficiently active	~32% insufficiently active	France paradoxically more sedentary despite a "healthy lifestyle" reputation.
Hyperlipidemia	~12% uncontrolled LDL	~8–10% depending on age group	Statin use common in both; residual risk remains.

Because sedentary behavior and physical inactivity are major contributors to the development and progression of cardiovascular disease, Cardiac Rehabilitation (CR) has become a cornerstone of modern preventive cardiology. By offering structured exercise, education, and behavioral support, CR programs in general, and more specifically Comprehensive Cardiac Rehabilitation (CCR) programs, address not only secondary prevention following cardiovascular events, but also broader goals of risk reduction among individuals with chronic conditions or cardiovascular risk factors (Taylor et al., 2022). CCR evolved from conventional CR to address the full spectrum of cardiovascular recovery—physical, psychological, and behavioral. While early CR focused mainly on exercise and risk factor control, CCR integrates six core domains defined by WHO and the European Association of Preventive Cardiology: standardized assessment, supervised exercise, education, risk reduction, psychosocial support, and long-term follow-up. In this context, CCR has become a fundamental component of prevention, offering structured programs that integrate exercise training, education, and behavioral interventions aimed at reducing recurrence and improving functional outcomes (WHO, 2023; Piepoli et al., 2016). Beyond its well-documented benefits on survival and quality of life, CCR has demonstrated efficacy in improving exercise tolerance, decreasing hospital readmissions, and favorably modulating cardiovascular risk profiles (Anderson et al., 2016). Nevertheless, the heterogeneity in patient responses to CCR—particularly in terms of functional improvement as measured by Peak Oxygen uptake ($\dot{V}O_2$peak)—has raised critical questions about the need for more precise and individualized approaches. Notably, a significant subset of patients, termed "Non-Responders (NR)", exhibit minimal or no improvement in $\dot{V}O_2$peak or related clinical endpoints following participation in standard CCR programs (Savage et al., 2009; Mikkelsen et al., 2020). Identifying the physiological and hemodynamic determinants underlying this variability has thus emerged as a research and clinical priority.

Exercise capacity, and $\dot{V}O_2$peak in particular, reflects the integrated performance of cardiovascular, pulmonary, and muscular systems. However, traditional markers of cardiac function, such as Left Ventricular Ejection Fraction (LVEF), are often limited in their predictive power and do not account for dynamic responses to exertion. In this light, the concept of oxygen transport chain analysis—differentiating between central (cardiac output ($\dot{Q}c$) and convection ($\dot{Q}O_2$) and peripheral (arteriovenous oxygen difference ($(a–\bar{v})O_2$diff) and diffusion ($\dot{D}O_2$) components—has gained prominence as a framework for interpreting exercise intolerance and individual variability (Legendre et al., 2021; Girault et al., 2024). Within this framework, non-invasive tools capable of monitoring $\dot{Q}c$, Stroke Volume (SV), and myocardial contractility during exercise are increasingly valued for their clinical and prognostic utility.

Signal Morphology Impedance Cardiography (SM-ICG), and the PhysioFlow® system that uses its principle, have emerged as a novel and promising solution for real-time, non-invasive hemodynamic monitoring. Unlike conventional Impedance Cardiography (ICG), SM-ICG offers robust beat-to-beat tracking with enhanced resistance to motion and respiratory artifacts, making it feasible for use during dynamic exercise testing. While promising, the incorporation of SM-ICG monitoring into routine clinical care and multicenter rehabilitation trials remains limited. Standardization of measurement protocols, validation across diverse populations, and integration into clinical decision-making algorithms are key challenges for future research. Nevertheless, the convergence of technological innovation, growing interest in individualized medicine, and the pressing need to improve CCR outcomes provides a compelling rationale for the expanded use of SM-ICG in cardiovascular rehabilitation.

The overarching objectives of the thesis are:

- To investigate the physiological mechanisms underlying the response to CCR using advanced non-invasive hemodynamic monitoring and specifically SM-ICG.

- To contribute to a more refined, mechanistically informed, and personalized approach to exercise-based cardiovascular care.

1. Part I: Review of the Literature

1.1. CHAPTER 1: CARDIOPULMONARY PHYSIOLOGY IN REHABILITATION

1.1.1.Objectives and Benefits of CCR

1.1.1.1. Objectives of CCR

Illustration 1: A real life CCR environment

CCR is a multidimensional, evidence-based intervention aiming to restore and optimize patients' physical, psychological, and social functioning after a cardiac event or in the context of chronic heart disease. It extends far beyond supervised exercise, encompassing education, behavioral counseling, nutritional guidance, and psychosocial support. The overarching goal is to reduce the risk of recurrent cardiovascular events while enhancing long-term health and quality of life (Anderson et al., 2016; World Health Organization, 2023).

The physiological objectives of CCR focus on improving cardiovascular efficiency and exercise tolerance through structured, progressive training tailored to individual risk and capacity. By enhancing $\dot{V}O_2$peak, SV, and peripheral oxygen extraction, CCR seeks to reverse deconditioning and improve prognosis. Typical programs produce a 1–2 mL·kg^{-1}·min^{-1} increase in $\dot{V}O_2$peak —equivalent to a 10–15% improvement in aerobic capacity—which translates into lower mortality risk and improved daily functioning (Taylor et al., 2004).

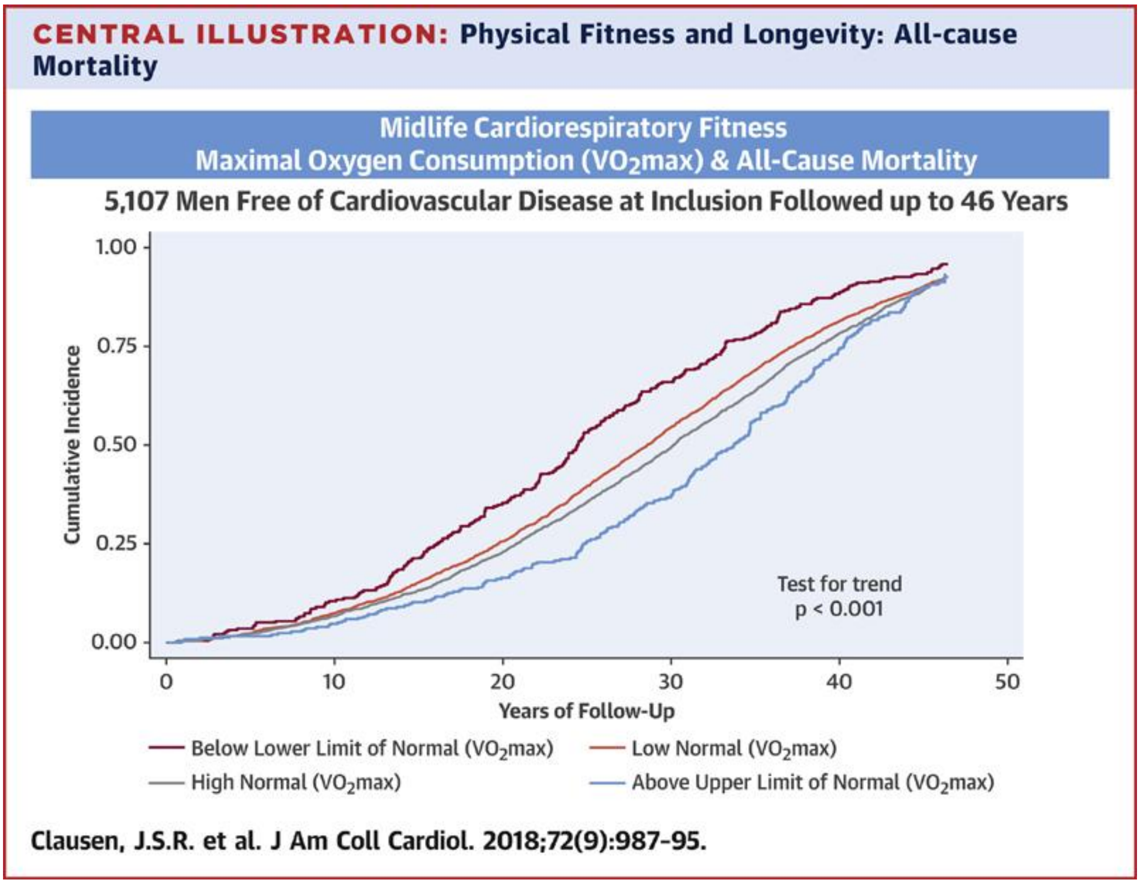


Illustration 2: Cardiorespiratory fitness at midlife and long-term mortality

Behavioral and educational objectives target the adoption of sustainable heart-healthy habits. These include smoking cessation, adherence to cardioprotective medication, balanced nutrition, and regular physical activity. Education modules, reinforced by self-management training, empower patients to take active responsibility for their recovery and long-term health maintenance. This educational component, central to both the WHO and European Society of Cardiology (ESC) frameworks, has demonstrated sustained effects on medication adherence and lifestyle modification (Blacher et al., 2024).

Psychosocial objectives address the emotional and cognitive dimensions of recovery. Depression and anxiety affect up to 30% of post–myocardial infarction patients, influencing both prognosis and adherence. CCR programs integrate counseling, cognitive behavioral therapy, and peer support, aiming to restore confidence, social engagement, and psychological resilience. These aspects directly contribute to improved quality of life and reduced hospital readmissions (Milani & Lavie, 2007; Clark et al., 2015).

Modern CCR also embraces technological and digital objectives. Tele-rehabilitation platforms extend access beyond hospital walls, supporting continuity of care and long-term engagement. The UK-based Reach-HF project has demonstrated that home-based, digitally guided rehabilitation can replicate many of the benefits of center-based programs while reaching a broader population (Dalal et al., 2019). Such innovations represent a paradigm shift toward hybrid models that integrate face-to-face supervision with remote follow-up.

Ultimately, the objectives of CCR are to restore patients to their highest possible level of health and autonomy—physically, psychologically, and socially—while equipping them with the tools and knowledge necessary to maintain those gains throughout life.

1.1.1.2. Benefits of Cardiac Rehabilitation

The benefits of CCR are well established across decades of clinical trials, registries, and meta-analyses. Participation in structured rehabilitation programs yields tangible improvements in survival, morbidity, exercise tolerance, and psychosocial outcomes. These benefits confirm the success of CCR in achieving its multidimensional objectives.

Mortality reduction remains one of the most significant benefits. Comprehensive meta-analyses have shown 20–30% decreases in both all-cause and cardiovascular mortality among participants (Anderson et al., 2016). French registry data echo these findings, with 25% lower mortality two years after acute coronary syndrome in CCR participants (Blacher et al., 2024).

Exercise tolerance and physical performance markedly improve. Typical gains of 1–3 Metabolic Equivalents of Task (METs) correspond to enhanced functional independence, reduced symptom burden, and improved capacity for daily living activities. Physiologically, these gains reflect improved $\dot{Q}c$, enhanced skeletal muscle oxygen extraction, and better ventilatory efficiency ($\frac{\dot{V}E}{\dot{V}CO2}$ slope). Repeated assessments using Cardiopulmonary Exercise Testing (CPET) quantify these changes objectively.

CCR also leads to substantial improvements in modifiable risk factors. Average reductions of 10–12 mmHg in Systolic Arterial Blood Pressure (SABP) and 15–25 mg/dL in Low-Density Lipoprotein (LDL) cholesterol are consistently reported, alongside improved glycemic control and body composition. Among patients with diabetes, mean glycated hemoglobin decreases by approximately 0.3–0.5%, reflecting enhanced metabolic regulation (Snowling et al., 2006). Such effects contribute directly to secondary prevention and reduced long-term cardiovascular risk.

Psychological and social benefits are equally profound. Reductions of 35–60% in depressive symptoms have been observed (Milani & Lavie, 2007; Clark et al., 2015). Enhanced mood, motivation, and social reintegration foster improved adherence to both physical activity and medical therapy. Patients report higher quality of life scores, greater sense of control, and improved coping mechanisms.

Participation in CCR also significantly reduces hospital readmissions. National and international data indicate up to 40% fewer readmissions within one year, translating into major cost savings and reduced healthcare burden (Clark et al., 2015; Blacher et al., 2024). Cost-effectiveness analyses consistently place CCR among the most efficient cardiovascular interventions, combining clinical benefit with economic sustainability.

Return-to-work rates provide another measure of CCR's societal value. Between 60% and 70% of patients resume professional activity within six months of completing CCR (Blacher et al., 2024), highlighting its role in restoring productive capacity and social participation.

Finally, the integration of digital follow-up tools such as Reach-HF extends these benefits over the long term. By maintaining patient engagement and promoting sustained activity, tele-rehabilitation solutions bridge the gap between intensive rehabilitation and lifelong maintenance. This continuity aligns with WHO's call for rehabilitation as a core health service, rather than a finite episode of care (World Health Organization, 2023).

In summary, CCR delivers comprehensive, measurable benefits that span physiological, psychological, and social domains. Its effectiveness is universally recognized, yet participation rates remain suboptimal—often below 40% of eligible patients in France (Blacher et al., 2024), and not all patients respond to CCR in the same way. Expanding access through hybrid, digitally supported models, introducing innovative and scalable technologies and reinforcing multidisciplinary collaboration public policy, funding and clinician engagement are key strategies to maximize the benefits of this essential intervention.

1.1.2.Current Practices in Cardiac Rehabilitation: A Comparative Overview

CCR has evolved from hospital-based convalescence to an evidence-driven continuum of care integrated into national health systems. Following the objectives and benefits detailed in Section 1.1, this chapter reviews how CCR is structured internationally, examining how various health systems translate its key components—exercise training, education, psychosocial support, and secondary prevention—into practice under differing clinical and economic conditions.

1.1.2.1. International Models of Cardiac Rehabilitation

The organization of CCR varies widely among nations, reflecting health-care financing, policy frameworks, and multidisciplinary workforce capacity. WHO's 2023 Package of Interventions for Rehabilitation outlines six foundational CCR domains—standardized assessment, progressive exercise, education, risk-factor control, psychosocial care, and long-term follow-up—now regarded as a global benchmark. Building on this framework, national CCR models align with these principles yet differ in duration, delivery mode, and technological sophistication.

France

France maintains one of the most structured CCR systems worldwide, supported by national health insurance. Programs begin soon after acute coronary syndrome, coronary artery bypass grafting, percutaneous coronary intervention, or hospitalization for HF. Inpatient programs typically last 3–4 weeks, with five supervised sessions per week integrating aerobic and resistance exercise, nutrition, risk-factor management, education, and psychosocial support.

To extend care beyond hospitals, France launched Walk Hop, a national tele-rehabilitation pilot authorized by the Ministry of Health (Télé-réadaptation cardiaque hors les murs). Among 310 participants, adherence averaged 81% and mean exercise power improved ≈15 W, demonstrating safety and feasibility (Walk Hop Consortium, 2024, Guy et al, 2021). UK-validated home-based programs such as Reach-HF (Dalal et al., 2019) have also inspired French adaptations for remote follow-up.

United States

In the United States, CCR is primarily outpatient and insurance-based. Since 2014, the Centers for Medicare & Medicaid Services (CMS) have expanded coverage to include stable CHF (LVEF ≤35%, NYHA II–IV) under National Coverage Determination NCD 20.10. Standard coverage authorizes up to 36 sessions over 12 weeks. Despite broader eligibility, national participation remains only ≈20–30% of eligible patients, according to updated Million Hearts data and Medicare analyses (Ritchey et al., 2021; Million Hearts, 2024). Barriers include copayments, geographic access, and referral gaps.

Recent policy extensions allow home-based and tele-CR reimbursement under Medicare's telehealth flexibilities, currently authorized through September 30, 2025. These remote models demonstrate similar safety and VO_2 gains compared with traditional center-based CCR.

United Kingdom

Within the National Health Service, CCR follows British Association for Cardiovascular Prevention and Rehabilitation guidelines. Programs last 6–12 weeks, combining supervised exercise, education, and behavioral support. Home-based tele-rehabilitation such as Reach-HF provides comparable outcomes and improved accessibility for patients unable to attend on-site sessions (Dalal et al., 2019).

Germany

Germany's insurance-funded inpatient model admits patients immediately after discharge for a 3-week residential program including daily supervised exercise, dietary advice, psychological counseling, and vocational reintegration (Gohlke et al., 2008). The model yields major short-term gains in exercise tolerance and risk-factor control but relies on costly inpatient infrastructure.

Japan

Japan's hospital-based CCR emphasizes safety and individualized monitoring. CPET and exercise echocardiography are routinely used to tailor prescriptions, particularly for heart-failure patients (Kikuchi et al., 2021). National initiatives led by the Japanese Circulation Society and Japanese Association of Cardiac Rehabilitation promote the scale-up of multidisciplinary CCR teams—cardiologists, rehabilitation specialists, nurses, physiotherapists, dietitians, and psychologists—to extend phase-II programs across more hospitals nationwide (JCS/JACR Guideline, 2021).

China

China's CCR network remains centered in tertiary hospitals, with limited reach in rural areas. Resource gaps and low awareness restrict participation, though multicenter trials demonstrate significant improvements in functional capacity and quality of life (Zhou et al., 2020). Mobile-health solutions are under evaluation to extend CCR beyond major urban centers.

Israel

Israel's Remote Cardiac Rehabilitation Program links patients to trained community coaches who supervise two sessions per week while wearable devices transmit physiological data to centralized databases (Nabutovsky et al., 2023). Participants average ≈183 minutes of aerobic activity weekly, achieving significant improvements in $\dot{V}O_2$-based capacity and adherence.

Sweden

Sweden has developed a predominantly outpatient, publicly funded CCR model that emphasizes long-term secondary prevention, patient autonomy, and sustained physical activity. Programs are integrated into the national healthcare system and typically initiated following acute coronary events, revascularization procedures, or hospitalization for heart failure. While inpatient rehabilitation exists in selected centers, the Swedish model is largely community-based and longitudinal, with a high prescription and participation rate (around 80%). (SWEDESHEART, Ekblom et al, 2022).

In university and regional hospitals, cardiopulmonary exercise testing (CPET) is frequently performed at program entry for risk stratification, safety assessment, and individualized exercise prescription, particularly in patients with complex cardiovascular profiles. However, repeated maximal CPET during follow-up is not systematic. Instead, baseline CPET is leveraged to guide training intensity over time, often using submaximal thresholds (e.g., first ventilatory threshold, VT_1) and heart-rate-based zones for ongoing supervision.

Exercise training typically consists of moderate-intensity aerobic activity, complemented by resistance training and structured education focused on lifestyle modification and long-term adherence. In this context, CPET-derived parameters that are robust under submaximal conditions—such as VT_1, ventilatory efficiency indices, and Oxygen Uptake Efficiency Slope (OUES)—are particularly well suited to monitoring functional adaptation and guiding progression. The Swedish approach thus places less emphasis on short-term gains in $\dot{V}O_2$peak and greater emphasis on sustainable functional capacity and cardiovascular risk reduction.

Digital tools and wearable heart-rate monitoring are increasingly incorporated to support continuity of care and patient engagement, reinforcing a hybrid model that combines high-quality physiological assessment at baseline with pragmatic, scalable follow-up strategies. This organization is consistent with WHO and the European Association of Preventive Cardiology (EAPC) recommendations advocating individualized assessment coupled with long-term participation rather than repeated high-intensity diagnostics alone.

The FITT-VP model (ACSM, 2021) is a structured framework used to design, prescribe, and progress exercise programs, including in cardiac rehabilitation. It specifies six key dimensions:

- Frequency – how often exercise is performed (sessions per week).
- Intensity – how hard the exercise is (e.g., %$\dot{V}O_2$peak, heart-rate zones, VT_1/VT_2).
- Time – duration of each exercise session.
- Type – modality of exercise (aerobic, resistance, interval, flexibility).
- Volume – total exercise dose (frequency × intensity × time).
- Progression – planned, individualized increases in exercise load over time.

In comprehensive cardiac rehabilitation, FITT-VP provides a common language to individualize exercise prescriptions, ensure safety, and monitor training progression while accommodating patient heterogeneity and clinical constraints.

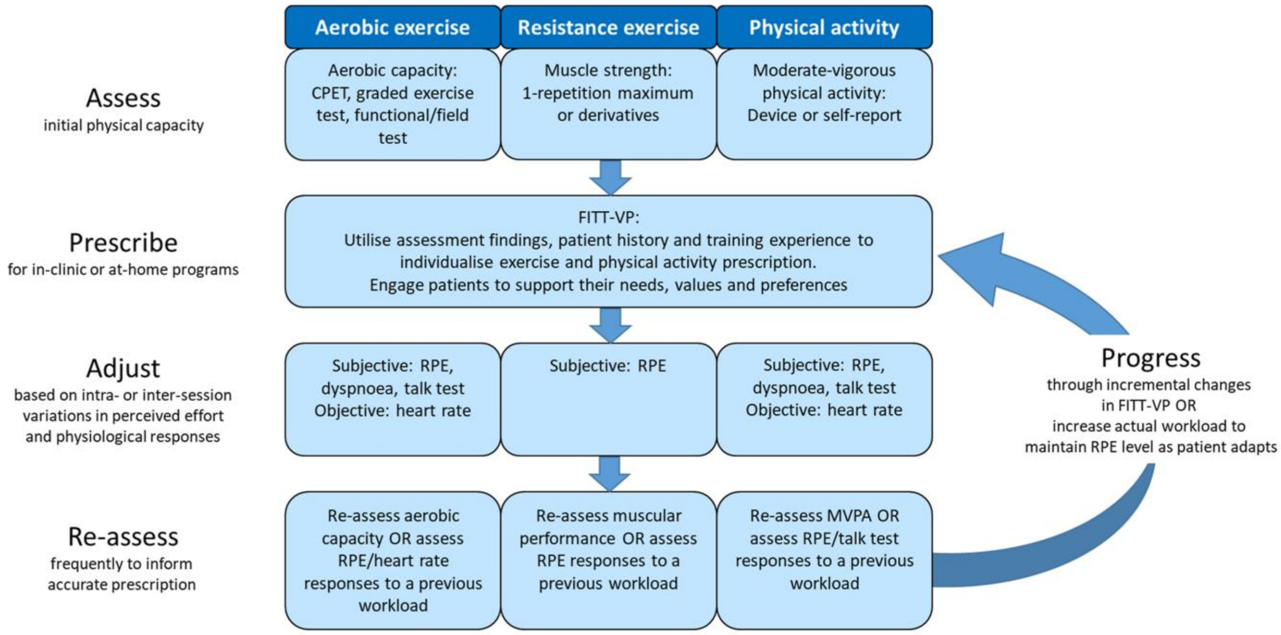


Illustration 3: Implementation of the FITT-VP model

Table 2 : Comparative Application of the FITT-VP Model in International CCR Programs

Country	Frequency	Intensity	Time	Type	Volume	Progression
France	3–5 sessions/week (hospital)	Moderate–high; CPET/echo supervised	30–60 min; 3–4 weeks	Aerobic + resistance + education + psychosocial	15–20 sessions/week	Structured progression; tele-rehab (Walk Hop, Reach-HF)
USA	2–3 sessions/week (outpatient)	Moderate; submaximal tests	≤36 sessions / 12 weeks	Aerobic, resistance, counseling	36 reimbursed sessions	Gradual; ACSM-based; coverage expanded 2014; tele-CR flex through 2025
UK	1–2 sessions/week + home	Low–moderate; field tests	6–12 weeks; 30–60 min	Aerobic, resistance, education, tele-health	8–16 sessions + home	Slow progression; hybrid engagement (Reach-HF)
Germany	Daily (5–6 days/week)	Moderate–high; CPET/echo guided	3 weeks inpatient	Aerobic, resistance, vocational, psychological	15–20 sessions/week × 3	Accelerated inpatient progression
Japan	2–3 sessions/week (hospital)	Low–moderate; safety focused; CPET used	8–12 weeks	Aerobic, resistance, education, nutrition	16–24 sessions	National scale-up of multidisciplinary teams

Country	Frequency	Intensity	Time	Type	Volume	Progression
Israel	2 sessions/week (gym) + home	Moderate; HR zones via wearables	Ongoing; ≈183 min/week	Aerobic focus; digital monitoring	Continuous	Adherence-oriented; lifelong participation
Sweden	2–3 sessions/week + home activity	Moderate; CPET-informed at entry; VT1/HR-zone guided	Long-term outpatient	Aerobic + resistance + educatio	Variable; emphasis on weekly activity targets	Individualized, adherence-focused; increasing digital support

1.1.2.2. Comparison and Key Takeaways

Although CCR frameworks share the same preventive objectives, their organization and intensity vary considerably. France and Germany prioritize inpatient rehabilitation with advanced diagnostics and high supervision. The U.S. and U.K. rely mainly on outpatient or community programs for scalability. Japan and China are hospital-based but differ in scope and reimbursement. Israel and Sweden represent a community-digital hybrid designed for long-term adherence.

Countries with hospital-based, CPET-guided CCR models (France, Germany, Japan) are more likely to integrate High Intensity Interval Training (HIIT), whereas systems prioritizing scalability, outpatient delivery, and long-term adherence (US, UK, Sweden, Israel, China) rely predominantly on continuous or moderate-intensity workloads.

Technological integration differs as well: CPET and exercise echocardiography are standard in France, Germany, and Japan, optional in China, and rarely routine in the U.S. and U.K. Israel and Sweden apply initial testing followed by wearable-based monitoring (Piepoli et al., 2010; Ades et al., 2017; Nabutovsky et al., 2023).

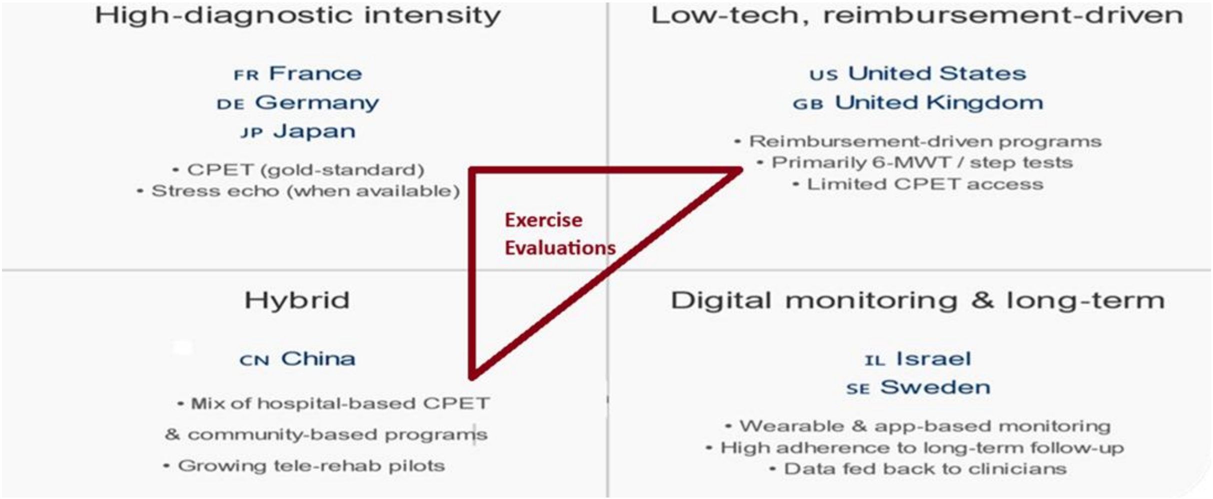


Illustration 4: Various CCR models and technology infiltration

Hybrid tele-rehab solutions such as Walk Hop (France) and Reach-HF (UK) illustrate scalable digital continuity (Dalal et al., 2019; Walk Hop Consortium, 2024). China and Israel demonstrate how mobile health and wearable technologies sustain adherence where resources are limited. Effective CCR depends on coordinated teams of physicians, physiotherapists, nurses, dietitians, and psychologists; digital tools increasingly complement these roles by facilitating monitoring and follow-up continuity (Ambrosetti et al., 2021).

Table 3 : Clinical Intensity vs Technological Reliance in International CCR Models

Country	Clinical Intensity	Technological Reliance	Dominant Setting	Emerging Trend
France	High (inpatient supervision)	High (CPET, echo, tele-rehab)	Hospital	Hybrid digital follow-up (Walk Hop)
Germany	High	High (CPET, structured protocols)	Inpatient rehab	Efficiency optimization
USA	Moderate	Moderate (tele-CR coverage to 2025)	Outpatient	Home-based expansion post-CMS 2014
UK	Moderate	Moderate (tele-health, limited CPET)	Community / NHS	Hybrid continuity (Reach-HF)
Japan	Moderate–High	High (CPET standard, multidisciplinary scale-up)	Hospital	Nationwide phase-II expansion
China	Variable	Moderate (CPET tertiary only)	Tertiary hospitals	Digital scale-up to rural areas
Israel	Moderate	High (wearables, apps, data integration)	Community	Fully remote long-term model
Sweden	Moderate	Moderate (wearables, apps, data integration)	Community	Remote long-term model

Despite structural differences, international CCR models are converging toward hybrid systems balancing diagnostic precision with scalability. Advanced testing (CPET and exercise echocardiography) informs individualized training, while digital monitoring maintains engagement and safety. This trend embodies WHO’s vision of CCR as a continuous health service rather than a time-limited episode.

The following chapters (1.3 and 1.4) will examine in greater depth the clinical and technological determinants underlying these international variations, focusing on CPET and exercise hemodynamics as objective tools for evaluating and optimizing cardiac performance within CCR programs.

1.1.3. The Use of Cardiopulmonary Exercise Testing in Cardiac Rehabilitation

1.1.3.1. Applications in Cardiac Rehabilitation

CPET has become a cornerstone of contemporary CCR. Unlike resting evaluations, CPET captures the integrative responses of the cardiovascular, pulmonary, and muscular systems under graded exercise stress, thereby providing a multidimensional profile of exercise tolerance. This makes CPET uniquely suited to risk stratification, individualized exercise prescription, and longitudinal monitoring in CCR programs. Key physiological markers—including $\dot{V}O_2$peak, oxygen pulse, $\frac{\dot{V}E}{\dot{V}CO2}$ slope, and OUES — are recognized prognostic tools that inform both clinical and training decisions (Guazzi et al., 2005; Arena et al., 2007; Mezzani et al., 2009; Herdy et al., 2016).

Assessment of Cardiorespiratory Fitness

$\dot{V}O_2$peak is the clinical standard for quantifying cardiorespiratory fitness and a powerful predictor of cardiovascular and all-cause mortality (Guazzi et al., 2005). Although $\dot{V}O_2$max represents the theoretical maximal capacity, $\dot{V}O_2$peak is the clinically relevant and reproducible parameter in patients with CVD.

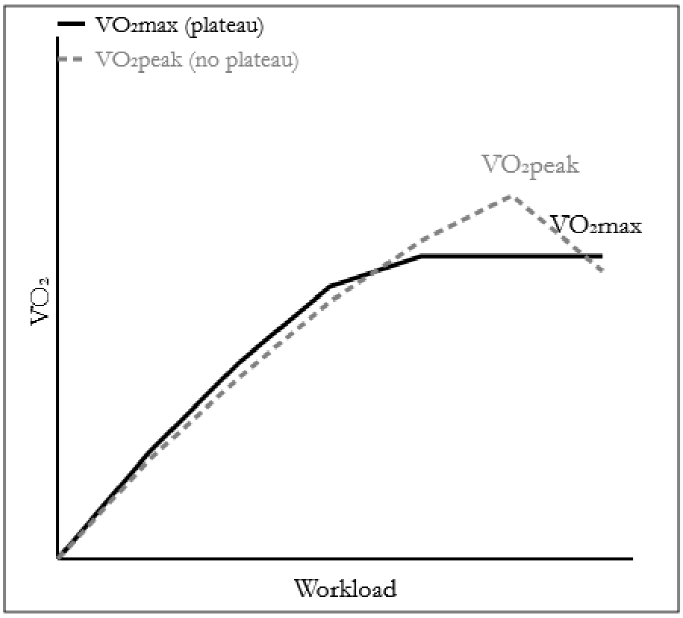


Illustration 5: $\dot{V}O_2$peak vs $\dot{V}O_2$max

Increases in $\dot{V}O_2$peak after CCR reflect central adaptations (improved $\dot{Q}c$ and SV) and peripheral adaptations (enhanced mitochondrial density, capillary perfusion, and oxygen extraction). Oxygen pulse ($\dot{V}O_2$/HR), a non-invasive surrogate of SV derived from the Fick principle, adds insight into cardiac performance. A progressive oxygen-pulse trajectory indicates adequate ventricular response, whereas a plateau or decline suggests contractile impairment, ischemia, or chronotropic incompetence (Arena et al., 2007).

The $\frac{\dot{V}E}{\dot{V}CO2}$ slope reflects the coupling of ventilation to perfusion. Elevated slopes (>34) predict poor outcomes in HF and may indicate pulmonary hypertension, increased dead space, or impaired ventilation–perfusion matching (Mezzani et al., 2009). Additional variables such as the VT_1—the ventilatory correlate of the Anaerobic Threshold (AT)—ventilatory reserve, Respiratory-Exchange Ratio (RER), and end-tidal CO_2 pressure ($PETCO_2$) deepen interpretation by distinguishing central, pulmonary, and peripheral limitations.

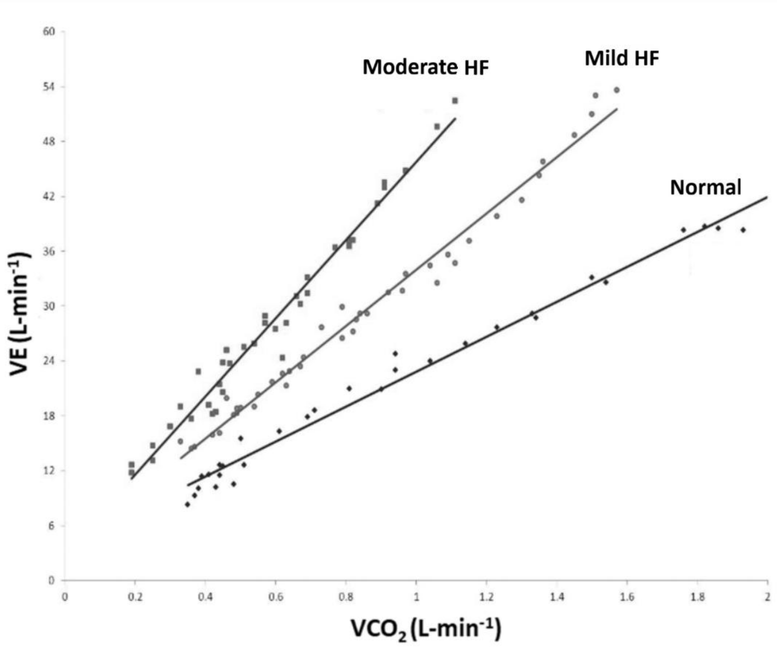
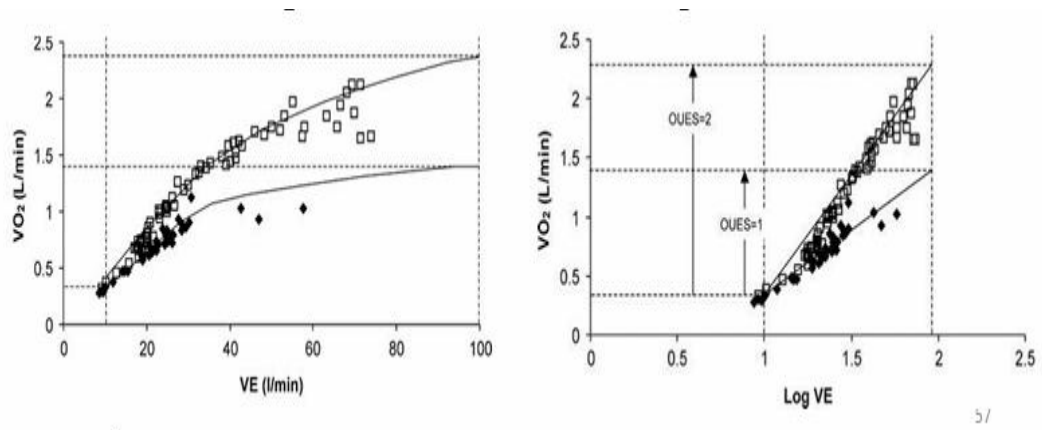


Illustration 6: $\frac{\dot{V}E}{\dot{V}CO2}$ *slopes and pathologies*

The OUES, defined as the linear relationship between $\dot{V}O_2$ and the logarithm of $\dot{V}E$ during incremental exercise, has emerged as a robust submaximal index of cardiorespiratory efficiency. Unlike $\dot{V}O_2$peak, OUES can be reliably derived without achieving maximal effort, making it particularly valuable in CCR populations characterized by early fatigue, chronotropic limitation, motivational constraints, or safety-driven test termination.



(Davies et al. Eur. Heart J. 2004)

Illustration 7: Determination of OUES

In CCR patients, OUES provides an integrative assessment of cardiopulmonary function that reflects the combined efficiency of pulmonary ventilation, circulatory transport, and peripheral oxygen utilization. Multiple studies have demonstrated that OUES correlates strongly with $\dot{V}O_2$ peak across a wide range of cardiac conditions, including coronary artery disease and heart failure, while maintaining superior reproducibility under submaximal conditions (Baba et al., 1996; Arena et al., 2006).

This characteristic is particularly relevant in CCR settings where:

- Maximal CPET is contraindicated or impractical,
- Exercise tests are terminated early due to symptoms, ECG abnormalities, or abnormal blood pressure responses,
- Baseline evaluations are performed shortly after acute cardiac events or surgical interventions.

Importantly, OUES has been shown to retain prognostic value independent of $\dot{V}O_2$peak, predicting mortality and hospitalization in heart failure populations (Arena et al., 2006; Hollenberg & Tager, 2000). As such, OUES complements traditional CPET metrics by providing a risk-sensitive marker of global efficiency, even when maximal indices are unavailable or unreliable.

Monitoring of Therapy Progression

Serial CPET enables objective monitoring of CCR progress. Improvements in $\dot{V}O_2$peak and VT_1 indicate enhanced global exercise tolerance; rising oxygen-pulse values suggest gains in SV or peripheral extraction; and a more favorable $\frac{\dot{V}E}{\dot{V}CO2}$ slope may signal improved pulmonary hemodynamics or reduced sympathetic drive. These changes support precise adjustment of exercise prescriptions and early recognition of plateaus or maladaptations. Serial improvements in CPET parameters during CCR predict fewer readmissions and improved survival (Arena et al., 2008; Mikkelsen et al., 2020; Baccanelli et al., 2023).

During CCR follow-up, changes in OUES offer insight into training-induced adaptations that may not be fully captured by $\dot{V}O_2$peak alone. Improvements in OUES reflect enhanced ventilatory efficiency and improved coupling between ventilation and oxygen uptake, potentially driven by:

- Reduced ventilatory demand for a given metabolic load,
- Improved hemodynamic responses and pulmonary perfusion,
- Favorable autonomic and peripheral adaptations.

Several studies report that OUES improves after structured exercise training in cardiac patients, even when gains in $\dot{V}O_2$peak are modest or absent, suggesting sensitivity to submaximal functional improvements that are highly relevant to daily activities (Mourot et al., 2004; Guazzi et al., 2009). This makes OUES particularly useful for identifying *partial responders* to CCR and for documenting clinically meaningful progress in frail or high-risk patients.

Detection of Exercise-Induced Ischemia

Although CPET provides no direct imaging, characteristic physiological patterns can suggest ischemia: a blunted or falling oxygen-pulse trajectory, excessive heart-rate acceleration, delayed VT_1, and low $\dot{V}O_2$peak despite preserved ventilatory reserve (Keteyian et al., 2010). These findings prompt further evaluation with stress echocardiography or nuclear perfusion imaging. In selected patients—particularly those with equivocal functional tests, atypical symptoms, or low-to-intermediate pretest probability—coronary computed tomography angiography (CCTA) may also be considered to non-invasively assess coronary anatomy and exclude significant obstructive disease, thereby complementing functional ischemia testing.

Evaluation of Pulmonary Pressures and Right-Ventricular Function

A steep $\frac{\dot{V}E}{\dot{V}CO2}$ slope, low $PETCO_2$, or early ventilatory overshoot indicates elevated pulmonary pressures or right-ventricular dysfunction. Such markers are valuable in HF with preserved Ejection Fraction (HFpEF) and combined cardio-pulmonary disorders, where CPET complements echocardiography and invasive hemodynamics (Guazzi et al., 2011).

Assessment of Diastolic Dysfunction

In HFpEF, exercise intolerance often results from limited preload reserve and rising filling pressures. CPET helps differentiate this from deconditioning or pulmonary disease. Typical findings include reduced $\dot{V}O_2$peak with preserved oxygen pulse, delayed VT_1, and an elevated $\frac{\dot{V}E}{\dot{V}CO2}$ slope—features suggestive of exercise-induced diastolic limitation (Borlaug et al., 2010).

1.1.3.2. Limitations of CPET in Rehabilitation

Limitations of Surrogate Indices

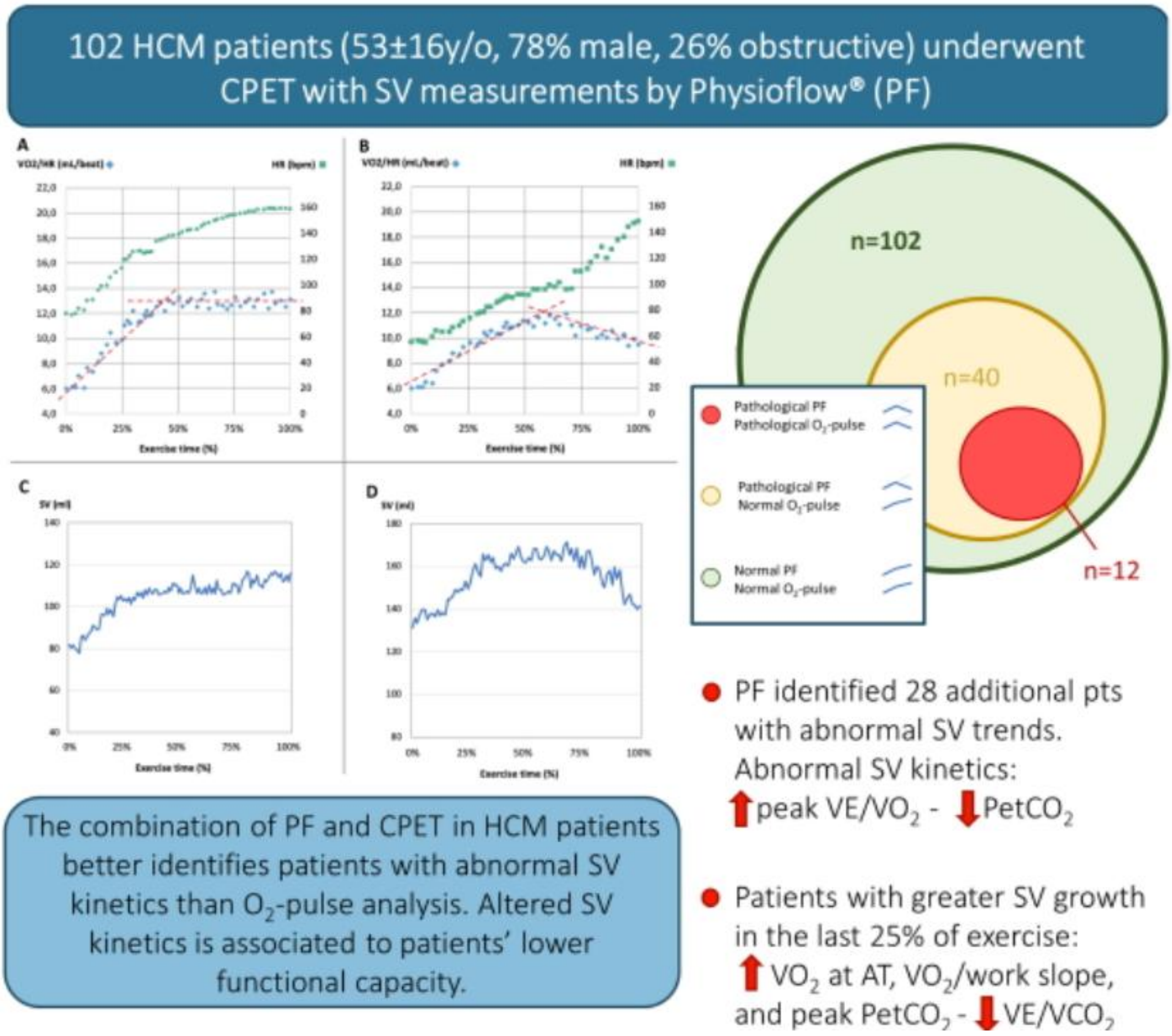
Oxygen pulse ($\dot{V}O_2$/HR) is frequently interpreted as a surrogate of SV via the Fick principle

$\dot{V}O_2 = \dot{Q}c \times (a–\bar{v})O_2diff$; $\dot{Q}c = SV \times HR \rightarrow \dot{V}O_2/HR = SV \times (a–\bar{v})O_2diff$.

This relationship assumes a stable $(a–\bar{v})O_2$diff, valid mainly at steady-state submaximal exercise in healthy individuals (Åstrand, 1976). During incremental exercise—and particularly in cardiac or pulmonary disease— $(a–\bar{v})O_2$diff is not constant, so oxygen pulse represents a composite rather than a pure index of SV (Tovar et al., 2023).

Clinical and pharmacological factors further complicate interpretation: oxygen-pulse plateaus may reflect chronotropic incompetence, ischemia, or autonomic dysfunction; β-blockers blunt HR and oxygen-pulse kinetics independently of SV (Forton et al., 2022; Wernhart et al., 2023). Peripheral limitations, such as impaired oxygen extraction or advanced deconditioning, can also distort oxygen-pulse patterns.

Recent evidence presented at the ESC Preventive Cardiology Congress (2025) in patients with hypertrophic cardiomyopathy (HCM) demonstrated that reliance on oxygen-pulse patterns alone underestimates abnormal SV kinetics compared with direct stroke-volume monitoring. Patients with pathological SV trajectories exhibited higher $\frac{\dot{V}E}{\dot{V}CO2}$ slopes, lower $PETCO_2$, and reduced $\dot{V}O_2$peak, whereas those maintaining late-exercise SV growth displayed more favorable CPET profiles. These findings highlight the limitation of oxygen-pulse-only interpretation and underscore the need for integrative, multimodal evaluation (European Society of Preventive Cardiology, 2023).



102 HCM patients (53±16y/o, 78% male, 26% obstructive) underwent CPET with SV measurements by Physioflow® (PF)

- PF identified 28 additional pts with abnormal SV trends. Abnormal SV kinetics: ↑peak VE/VO_2 - ↓$PetCO_2$
- Patients with greater SV growth in the last 25% of exercise: ↑VO_2 at AT, VO_2/work slope, and peak $PetCO_2$ - ↓VE/VCO_2

The combination of PF and CPET in HCM patients better identifies patients with abnormal SV kinetics than O_2-pulse analysis. Altered SV kinetics is associated to patients' lower functional capacity.

Illustration 8 : SV profiles vs. O_2 pulse profiles in HCM patients

(https://esc365.escardio.org/preventive-cardiology/sessions/14150)

1.1.3.3. Challenges in VT_1, $\frac{\dot{V}E}{\dot{V}CO2}$ *slope, and OUES Determination*

Precise VT_1 determination is essential for training-intensity prescription but can be ambiguous in HFpEF, chronotropic incompetence, or under β-blockade, where ventilatory and metabolic responses are blunted. Technical factors (mask leaks, irregular breathing, noise) further obscure identification. Even small VT_1 errors can shift target workloads by 10–15 % $\dot{V}O_2$, leading to under- or over-training (Mezzani et al., 2009). Complementary methods such as ventilatory equivalent ($\dot{V}E/\dot{V}O_2$ nadir) or end tidal gas ($PETO_2$ inflection) are often recommended to cross-validate VT_1 and improve reliability.

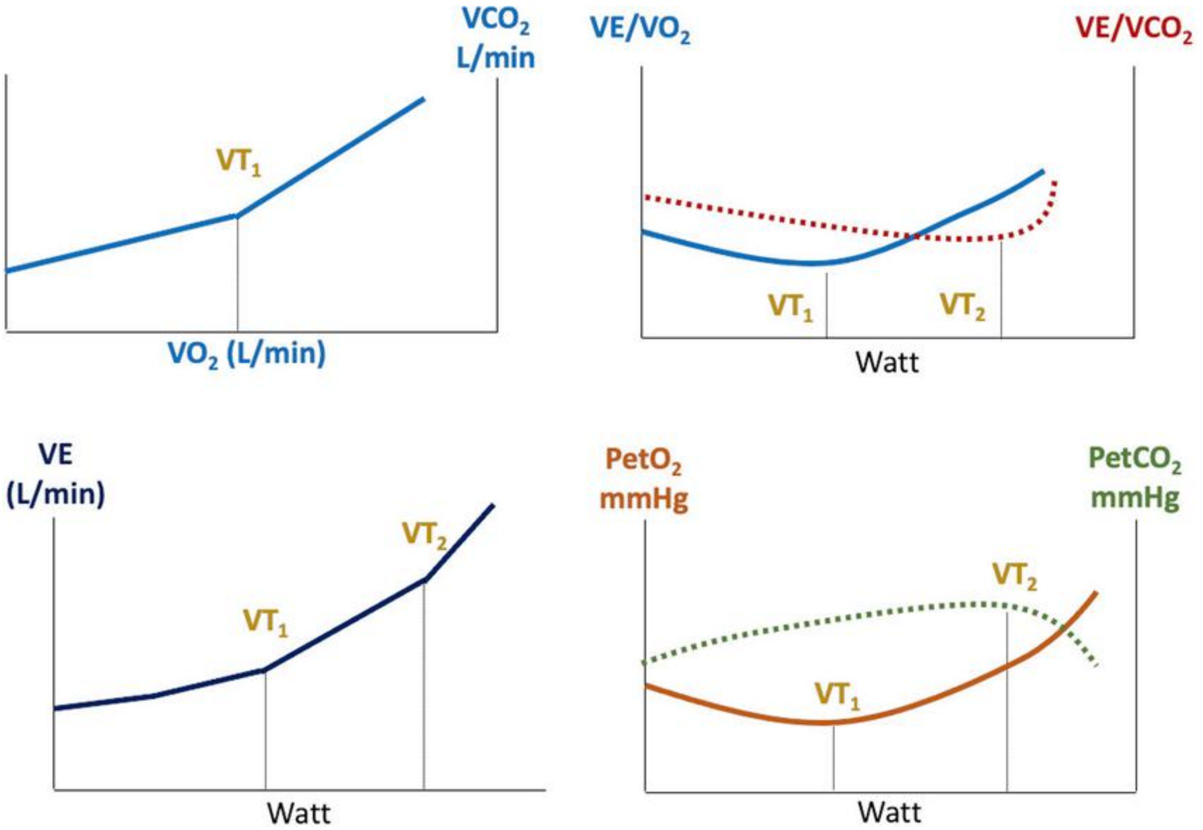


Illustration 9: Various VT1 detection modalities

The $\frac{\dot{V}E}{\dot{V}CO2}$ slope, though prognostically strong, lacks specificity: elevations may arise from chemosensitivity, metabolic acidosis, ventilatory mechanics, or pulmonary disease rather than central hemodynamic dysfunction.

Despite its advantages, OUES should be interpreted with caution in CCR. Its calculation depends on the ventilatory range achieved during testing, and values may vary depending on whether the full exercise test or truncated data segments are used. Additionally, OUES does not localize the primary limiting factor (central vs. peripheral vs. pulmonary) and therefore should not replace integrative interpretation alongside $\dot{V}O_2$ kinetics, oxygen pulse, $\frac{\dot{V}E}{\dot{V}CO2}$ slope, and hemodynamic markers.

1.1.3.4. Psychosocial and Interpretive Barriers

Anxiety, low motivation, or discomfort with the CPET mask may affect test performance. They are particularly common in older patients and in those with respiratory comorbidities, which can systematically reduce test validity. CPET interpretation requires expertise; inter-observer variability remains a limitation. Structured operator training and multidisciplinary review reduce these discrepancies.

1.1.3.5. Practical and Logistical Constraints

CPET demands specialized equipment, calibration, and trained personnel, which limit availability. Institutional variability in protocol design also affects reproducibility. Frailty, orthopedic limitations, or neuromuscular disease may preclude maximal exertion, yielding submaximal tests that require cautious interpretation (Balady et al., 2010).

In Summary, CPET provides a unique, integrated evaluation of cardiovascular, pulmonary, and muscular function during exercise. It guides risk stratification, personalizes exercise prescription, and objectively monitors therapeutic progress. However, indices such as oxygen pulse and $\frac{\dot{V}E}{\dot{V}CO2}$ slope cannot isolate specific hemodynamic mechanisms and must be interpreted within the broader physiological and clinical context. Practical limitations and operator variability further constrain routine use.

These limitations do not diminish CPET's value but underscore that its findings should be complemented by direct hemodynamic measures and imaging modalities to achieve mechanistic precision and guide truly personalized rehabilitation strategies.

Table 4: Key CPET Parameters in Comprehensive Cardiac Rehabilitation (CCR)

Parameter	**Physiological Meaning**	**Interest for Patient Evaluation (Baseline)**	**Interest for Monitoring CCR Progression / Outcomes**	**Main Limitations**
$\dot{V}O_2$peak	Maximal integrated capacity of cardiovascular, pulmonary, and muscular systems	Gold standard for cardiorespiratory fitness; strong prognostic marker for mortality and hospitalization; reflects global disease severity	Quantifies overall training response; clinically meaningful improvements associated with better outcomes	Requires maximal effort; often limited by symptoms, motivation, or safety criteria; insensitive to submaximal adaptations
$\dot{V}O_2$ at VT_1	Aerobic efficiency and sustainable exercise capacity	Reflects functional capacity relevant to daily activities; less effort-dependent than $\dot{V}O_2$peak	Sensitive marker of endurance adaptations; useful for exercise prescription and functional improvement tracking	VT_1 identification can be method-dependent and operator-sensitive
O_2 pulse ($\dot{V}O_2$/HR)	Surrogate of stroke volume × peripheral O_2 extraction	Provides insight into cardiac performance and contractile reserve; plateau or decline suggests ischemia or dysfunction	Increase suggests improved stroke volume and/or peripheral extraction	Indirect measure; influenced by chronotropic response and peripheral adaptations
$\dot{V}O_2$/$\dot{V}CO_2$ slope	Ventilatory efficiency and V/Q matching	Strong prognostic marker, especially in heart failure; reflects pulmonary vascular load and autonomic imbalance	Improvements may indicate better pulmonary hemodynamics or reduced sympathetic drive	Less sensitive to peripheral muscular adaptations; may change little with training
OUES	Global efficiency of oxygen uptake relative to ventilation	Robust submaximal index; valuable when maximal effort is not achieved; retains prognostic value	Sensitive to submaximal training adaptations; useful in frail or partially responsive patients	Does not localize limiting system; influenced by ventilatory range achieved
RER (peak)	Degree of metabolic stress and effort	Assesses test maximality and patient engagement	Confirms comparability of serial tests	Not a fitness marker; limited standalone physiological value
$PETCO_2$ (rest, exercise, peak)	Pulmonary perfusion and ventilatory control	Low values suggest impaired cardiac output or pulmonary vascular disease	Increase during exercise may reflect improved perfusion and ventilatory efficiency	Influenced by breathing pattern and pulmonary disease

1.1.4. The Interest of Adding Direct Hemodynamic Measurements

1.1.4.1. Fick's Law

Illustration 10 : Professor Adolf Eugen Fick

Fick's principle, formulated by Adolf Eugen Fick in 1870, is a cornerstone of cardiovascular and exercise physiology. It provides the quantitative framework for relating oxygen consumption ($\dot{V}O_2$) to systemic blood flow ($\dot{Q}c$) and the $(a–\bar{v})O_2$diff ($CaO_2 - CvO_2$). Expressed in its simplest form:

$$\dot{V}O_2 = \dot{Q}c \times (\mathbf{CaO_2 - CvO_2})$$

Here, $\dot{V}O_2$represents oxygen uptake, $\dot{Q}c$ is cardiac output, CaO_2 is arterial oxygen content, and CvO_2 is mixed venous oxygen content (Fick, 1870). This relationship underlies the measurement of $\dot{Q}c$ and remains fundamental to CPET. Physiologically, systemic oxygen delivery depends on both convective transport ($\dot{Q}O_2$) and peripheral diffusive/utilization processes ($\dot{D}O_2$). Clinically, impairments in any component— SV/Heart Rate (HR) responses, hemoglobin concentration/oxygenation, or tissue extraction—can limit $\dot{V}O_2$ (Wasserman et al., 2012).

Limitations of the Fick principle largely stem from simplifying assumptions. First, it treats the organism as a single well-mixed compartment, implying homogeneity of perfusion and oxygen extraction across tissues. In reality, regional disparities in muscle blood flow, capillary recruitment, and mitochondrial function can cause global $\dot{V}O_2$ calculations to obscure important local constraints (Wagner, 1996). Second, precise measurement of CvO_2 requires pulmonary artery catheterization, limiting routine applicability; non-invasive substitutes introduce variance. Third, the classic form does not explicitly incorporate diffusion limitations within the lung or muscle that may cap oxygen transfer at high metabolic rates or in disease states such as HF and Chronic Obstructive Pulmonary Disease (COPD) (Wagner, 2000). More recently, Wagner (2010) provided a comprehensive systems model of O_2 transport that integrates convective and diffusive components, showing how multiple factors interact to limit $\dot{V}O_2$peak.

Haldane's transformation complements Fick's framework by leveraging nitrogen conservation to relate inspired and expired volumes. It enables calculation of $\dot{V}O_2$ from expired ventilation and gas fractions without measuring inspired flow directly (Haldane, 1892). In practice, metabolic systems compute $\dot{V}O_2$ and $\dot{V}CO_2$ using the Haldane relation:

$$\dot{V}I = \dot{V}E \times (1 - FEO_2 - FECO_2) \,/\, (1 - FIO_2 - FICO_2)$$

$$\approx\ \dot{V}E \times (1 - FEO_2 - FECO_2) \,/\, (1 - FIO_2)$$

$$\dot{V}O_2 = \dot{V}I \times FIO_2 - \dot{V}E \times FEO_2$$

$$\dot{V}CO_2 = \dot{V}E \times FECO_2 - \dot{V}I \times FICO_2\ \approx\ \dot{V}E \times FECO_2$$

where $\dot{V}$I and $\dot{V}$E are inspired and expired minute ventilations; FIO_2, $FICO_2$ and FEO_2, $FECO_2$ are inspired and expired fractions of oxygen and carbon dioxide, respectively. Assuming inspired $CO_2 \approx 0$ simplifies the expressions commonly used by metabolic carts. Combined with Fick's principle, these relations permit an integrated, non-invasive characterization of circulatory-ventilatory-metabolic responses during exercise (Beaver et al., 1986; Wasserman et al., 2012).

Taken together, Fick's law and Haldane's transformation provide complementary tools: the former quantifies the balance between convective delivery and tissue extraction, while the latter ensures accurate gas-exchange calculations from expired measurements.

The physiologic frameworks provided by Fick's principle and Haldane's transformation are not only of historical interest but also of direct contemporary relevance. By quantifying the interplay between central convective delivery and peripheral oxygen utilization, they establish the analytical basis upon which CPET rests. In turn, CPET has become a cornerstone of cardiac rehabilitation, where $\dot{V}O_2$peak, $\frac{\dot{V}E}{\dot{V}CO2}$ slope, and oxygen pulse serve as clinically validated predictors of prognosis and therapeutic response. Bridging theory and practice, the application of these principles within cardiac rehabilitation allows the design, monitoring, and optimization of exercise programs, aligning mechanistic physiology with the applied goals of improving survival, functional capacity, and quality of life in patients with CVD.

1.1.4.2. *Applications in Cardiac Rehabilitation*

The application of Fick's principle to cardiac rehabilitation provides a rigorous physiological framework for understanding both the determinants of exercise capacity and the mechanisms underlying inter-individual variability in training response. In patients with CAD or CHF, $\dot{V}O_2$peak measured by CPET is one of the strongest predictors of survival and rehospitalization risk (Wasserman et al., 2012; Arena et al., 2007). Because $\dot{V}O_2$ is the product of $\dot{Q}c$ and (a–$\bar{v}$)O_2diff, improvements in either convective transport or peripheral extraction can mediate exercise-induced gains in $\dot{V}O_2$peak.

CCR programs leverage this duality. Aerobic training enhances SV and chronotropic competence, thereby augmenting $\dot{Q}$c, while peripheral adaptations such as increased capillary density, mitochondrial biogenesis, and enhanced muscle oxidative enzyme activity improve tissue O_2 extraction. This bidirectional framework, rooted in Fick's principle, underscores why both central and peripheral mechanisms must be addressed to optimize CCR outcomes (Hambrecht et al., 2000; Haykowsky et al., 2013).

Haldane's transformation further amplifies the clinical utility of Fick's principle in CCR by enabling non-invasive determination of $\dot{V}O_2$ and $\dot{V}CO_2$ from expired gases. This innovation made CPET feasible in routine practice, allowing reproducible assessment of exercise tolerance, $\frac{\dot{V}E}{\dot{V}CO2}$ slope, and the anaerobic threshold (Beaver et al., 1986). These variables provide integrative markers of cardiovascular, pulmonary, and metabolic function. In rehabilitation settings, they allow precise tailoring of exercise prescriptions and objective monitoring of patient progress.

Beyond diagnostic profiling, CPET-derived Fick variables have prognostic implications. For example, impaired O_2 pulse ($\dot{V}O_2$/HR), a surrogate of SV, is associated with poor outcomes in HF and can improve with training (Myers et al., 2002). Similarly, a flattened $\dot{V}O_2$/work rate slope indicates limited peripheral extraction capacity, guiding interventions to address skeletal muscle deconditioning (Duscha et al., 1999). By systematically quantifying central and peripheral limitations, the Fick–Haldane framework offers mechanistic insights into why some patients are "Responders (R)" while others fail to improve with CCR.

In recent years, non-invasive hemodynamic monitoring systems (such as ICG) have extended the clinical application of Fick's law during exercise. These tools enable direct measurement of $\dot{Q}c$ responses and contractility indices, complementing CPET gas exchange data to provide a comprehensive picture of circulatory adjustment to training (Myers et al., 2022). The integration of these modalities aligns with current WHO and European Society of Cardiology recommendations, which emphasize individualized, physiology-based CCR programs (World Health Organization, 2023; Piepoli et al., 2016).

Thus, Fick's principle and Haldane's transformation forms the physiological and methodological bedrock of modern cardiac rehabilitation. They enable precise quantification of exercise tolerance, guide patient-specific exercise prescriptions, and clarify the mechanisms of functional improvement. As CCR evolves toward hybrid and digital models, these classical concepts continue to provide irreplaceable insight into the fundamental question: how do central and peripheral systems interact to restore cardiovascular health through exercise?

A recent clinical contribution further illustrates the relevance of combining Fick's principle and Haldane's transformation in cardiac rehabilitation. At the Journées Nationales du GERS-P 2025 in Rennes, Leprêtre and colleagues presented a retrospective analysis of 40 HF patients with reduced EF (HFrEF < 40%) undergoing 20 sessions of exercise-based CCR (Leprêtre et al., 2025).

Their key objective was to determine whether ventilatory parameters derived from gas exchange, via the Haldane transformation, could explain differential patient responses in $\dot{V}O_2$peak. Consistent with established R definitions (>6% increase in $\dot{V}O_2$peak), 67.5% of patients improved significantly, showing parallel gains in $\dot{V}O_2$peak, power output, HR and O_2 pulse. Importantly, R also exhibited marked improvements in $\frac{\dot{V}E}{\dot{V}CO2}$ slope and breathing pattern (tidal volume, respiratory frequency).

The authors concluded that ventilatory adaptations—particularly improvements in tidal volume and $\frac{\dot{V}E}{\dot{V}CO2}$ slope —may be central explanatory factors of training response, complementing convective and diffusive (muscle oxygen extraction) components of the Fick framework. These findings strengthen the case for integrating ventilatory and hemodynamic analysis into CCR evaluation, providing a mechanistic bridge between classical physiology and clinical outcome prediction.

Having explored the integrative frameworks of Fick's law and Haldane's transformation and their application to cardiac rehabilitation, we now turn to the fundamental determinants of $\dot{Q}c$. A deeper analysis of preload, contractility, and afterload provides essential insight into how central hemodynamic adjustments condition exercise tolerance and training response.

1.1.5. Going Deeper: the Components of Cardiac Output

$\dot{Q}c$, defined as the volume of blood ejected by the heart per minute, is the product of SV and HR. While Fick's principle provides the overarching framework, understanding the determinants of SV requires a deeper analysis of three central physiological variables: preload, contractility, and afterload. These components are intimately interrelated and their balance largely determines cardiovascular performance at rest and during exercise (Guyton & Hall, 2020; Pinsky, 2018).

1.1.5.1. Preload, Contractility, Afterload

Preload refers to the end-diastolic stretch of the ventricular myocardium, often approximated clinically by end-diastolic volume or central venous pressure. The Frank–Starling mechanism describes how increased preload augments SV through length-dependent activation of sarcomeres (Katz, 2002). In cardiac rehabilitation, preload reserve may be limited in HF patients due to diastolic dysfunction or elevated filling pressures, thereby constraining the capacity to increase SV with exercise.

Contractility reflects the intrinsic capacity of the myocardium to generate force independent of preload and afterload. Traditionally measured invasively by maximal dP/dt, it can also be assessed via echocardiographic indices (e.g., strain imaging) or ICG-derived parameters (Kass & Beyar, 2021). Exercise training has been shown to improve contractile reserve in selected populations, suggesting that this component contributes to the variability in CCR responsiveness (Myers et al., 2022).

Afterload denotes the resistance the ventricle must overcome to eject blood, commonly related to Systemic Vascular Resistance (SVR) and arterial elastance. Elevated afterload reduces SV for a given preload and contractility. Pharmacological interventions (e.g., ACE inhibitors, vasodilators) and exercise-induced vascular adaptations both modulate afterload. Improved arterial compliance with aerobic training constitutes one mechanism by which CCR enhances cardiac efficiency (Green et al., 2017).

Taken together, preload, contractility, and afterload act as determinants of SV, and thus $\dot{Q}c$. Their dynamic interaction underlies the variability of exercise tolerance and training response. For this reason, detailed assessment of these components has direct clinical implications in tailoring cardiac rehabilitation programs.

Among the determinants of SV, contractility occupies a unique position. Unlike preload and afterload, which reflect external loading conditions, contractility embodies the intrinsic performance of the myocardium itself. Because of its central importance and its methodological challenges, it warrants a dedicated focus before turning to the tools available for its measurement

1.1.5.2. Focus : The Concept of Contractility

Among the determinants of SV, contractility occupies a distinct place. Whereas preload and afterload reflect external loading conditions imposed on the ventricle, contractility refers to the intrinsic capacity of the myocardium to develop force and shorten, independent of changes in preload and afterload. Conceptually, it embodies the inotropic state of the heart, determined by the properties of the cardiac myocytes, excitation–contraction coupling, and intracellular calcium handling (Suga, 1979; Katz, 2002).

At the cellular level, contractility depends on calcium influx through L-type calcium channels, release from the sarcoplasmic reticulum, and the sensitivity of the contractile proteins to calcium. Sympathetic stimulation and circulating catecholamines increase contractility by enhancing calcium cycling and myofilament sensitivity, whereas pathological states such as HF reduce contractile reserve through alterations in β-adrenergic signaling, sarcoplasmic reticulum function, and mitochondrial energetics (Bers, 2002; Kass & Beyar, 2021).

From a clinical perspective, contractility is not directly measurable, but is inferred from surrogate indices. This limitation stems from the fact that ventricular pressure and volume are simultaneously influenced by preload, afterload, and HR. The ideal descriptor of contractility should therefore isolate intrinsic myocardial performance, independent of loading conditions. This challenge has motivated the development of load-independent indices such as the End-Systolic Pressure–Volume Relationship (ESPVR) and Preload Recruitable Stroke Work (PRSW), which are considered gold standards in invasive physiology (Suga & Sagawa, 1974; Kass & Beyar, 2021).

Contractility assumes particular importance in cardiac rehabilitation, as impaired inotropic reserve is a central feature of HF and other cardiovascular pathologies. Understanding the physiological basis of contractility, its regulation, and its limitations provides the foundation for appreciating how exercise training can improve myocardial performance and, ultimately, patient outcomes. This conceptual focus thus paves the way for the subsequent discussion of conventional and novel methods for measuring contractility.

1.1.5.3. Conventional Measures of Contractility (Invasive and Echocardiographic)

Historically, invasive Pressure–Volume (PV) loop analysis has been considered the gold standard for assessing myocardial contractility. By introducing high-fidelity conductance catheters into the ventricle, investigators can derive beat-to-beat relations between pressure and volume, allowing precise quantification of ventricular mechanics.

The ESPVR is central to this approach. Its slope, termed End-Systolic Elastance (Ees), reflects the contractile state of the myocardium largely independent of loading conditions. Because ESPVR shifts in response to inotropic stimulation or myocardial depression, it has been regarded as a nearly load-independent marker of intrinsic systolic function (Suga & Sagawa, 1974).

Other derived indices include PRSW, which describes the linear relation between stroke work and end-diastolic volume, and has shown relative independence from loading conditions. Additionally, dP/dtmax, the maximal rate of ventricular pressure rise during isovolumetric contraction, has long been used as a surrogate of contractility. However, dP/dtmax is strongly affected by preload, afterload, and HR, limiting its specificity (Kass & Beyar, 2021). Though physiologically rigorous, invasive measures are seldom applied outside of research laboratories or highly selected interventional settings. The requirement for catheterization, specialized equipment, and advanced expertise, together with patient risk, renders them impractical for routine cardiac rehabilitation assessment.

Echocardiography has become the most accessible and widely applied non-invasive tool for assessing cardiac function, offering practical alternatives to invasive PV analysis. The most traditional indices are LVEF and Fractional Shortening (FS). Both are simple to calculate and widely understood, yet they remain highly load-dependent. An increase in afterload can reduce EF without any change in intrinsic contractility, whereas volume status fluctuations may produce misleading improvements.

In recent decades, technological advances have expanded the echocardiographic toolbox. Tissue Doppler Imaging (TDI) allows measurement of myocardial velocities (systolic S' wave), while Speckle-Tracking Echocardiography (STE) provides quantitative analysis of myocardial deformation. The most widely adopted STE parameter is Global Longitudinal Strain (GLS), which measures the percentage shortening of longitudinal myocardial fibers during systole. GLS is more sensitive than EF in detecting early systolic dysfunction and has demonstrated superior prognostic value across ischemic and non-ischemic cardiomyopathies (Smiseth et al., 2016).

In the context of cardiac rehabilitation, GLS has been linked to training outcomes. Smart et al. (2006) reported that patients with more favorable baseline strain patterns experienced greater improvements in $\dot{V}O_2$peak following exercise training, suggesting that GLS may reflect the myocardial substrate for adaptability. Furthermore, studies in HFpEF (Murray et al., 2012; Sugita et al., 2020) confirmed GLS as a robust predictor of outcomes, highlighting its clinical relevance beyond reduced-EF populations. There is also preliminary evidence that strain parameters may improve with training, suggesting a potential role as biomarkers of CCR-induced myocardial remodeling.

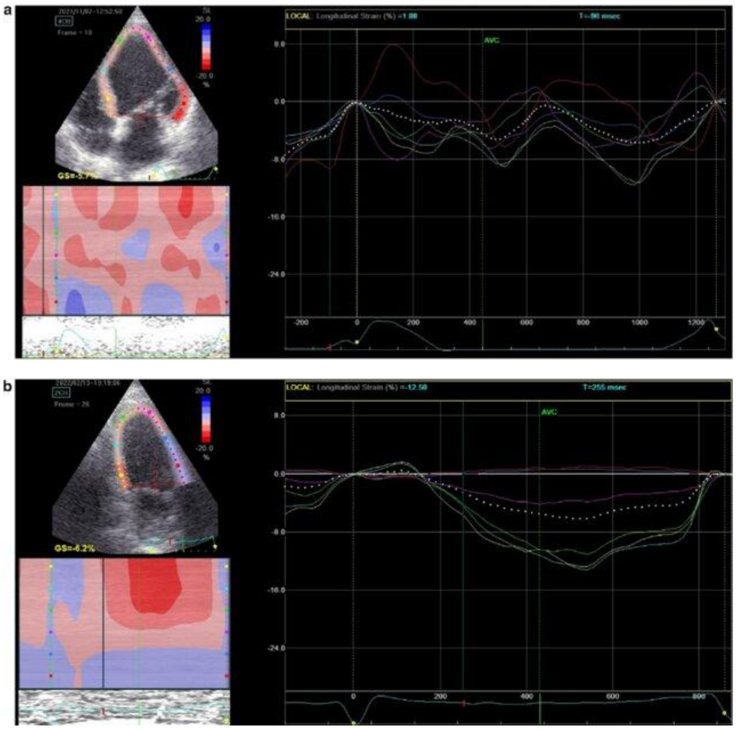


Illustration 11: Strain improvement with CCR

Echocardiography also allows evaluation of contractile reserve, defined as the ability of the heart to enhance contractile function under stress. Stress can be induced pharmacologically (e.g., dobutamine) or by dynamic exercise protocols. Stress echocardiography provides insights into myocardial adaptability and viability that resting measurements cannot capture.

Kirsch et al. (2023) applied exercise echocardiography, using the stress/rest ratio of LV elastance (SABP peak /LVESV peak) / (SABP rest / LVESV rest) to evaluate contractile reserve non-invasively (LVESV being Left Ventricular End Systolic Volume). Patients with reduced reserve exhibited lower exercise tolerance and worse prognosis, even when EF was preserved. These results emphasize that blunted contractile reserve may underlie exercise intolerance and explain variability in CCR responsiveness. Thus, stress imaging has potential value in stratifying patients and tailoring rehabilitation strategies.

Despite their diagnostic and prognostic power, advanced echocardiographic assessments remain impractical in the daily workflow of cardiac rehabilitation. They require costly equipment, significant operator training, high inter- and intra-observer variability, positional effect, and considerable patient cooperation. As a result, echocardiographic measures of contractility—particularly strain imaging and stress testing—are rarely used systematically in CCR worldwide (Ambrosetti et al., 2021). Instead, CCR programs typically rely on simpler functional assessments, such as exercise testing, which, while less precise physiologically, are more feasible and scalable.

Illustration 12: Positional impact of exercise ultrasound

The limitations of invasive and echocardiographic approaches—ranging from invasiveness to cost, operator dependency, and limited reproducibility—highlight the need for alternative methods in rehabilitation contexts. ICG has emerged as such a candidate: a non-invasive, operator-independent, and continuous monitoring tool capable of providing dynamic insights into contractility and $\dot{Q}c$ during exercise. The next chapter will explore its physiological basis, validation, and clinical applications in cardiac rehabilitation.

1.2. CHAPTER 2: IMPEDANCE CARDIOGRAPHY

"It is a source of regret that the measurement of flow is so much more difficult than the measurement of pressure. This has led to an undue interest in the blood pressure manometer. Most organs, however, require flow rather than pressure."

— Jarisch A., Kreisslauffragen. Dtsch Med Wochenschr, 1928;54:1213

1.2.1. Introduction to Impedance Cardiography

1.2.1.1. Scientific and Technical Principles

ICG, also referred to as Thoracic Electrical Bioimpedance (TEB), represents a non-invasive modality for assessing central hemodynamic parameters through the measurement of electrical impedance variations across the thorax. These impedance fluctuations correlate with volumetric and velocity changes in thoracic blood flow, particularly within the aorta, as modulated by the cardiac cycle. The methodology employs surface electrodes strategically positioned along the neck and thorax to transmit a high-frequency, low-amplitude alternating current and detect its resultant voltage shifts. As blood volume dynamically shifts during systole and diastole, the resulting impedance changes provide indirect yet quantifiable markers of cardiovascular function.

SV estimation via ICG is derived from the dynamic changes in thoracic impedance during ventricular ejection. The classical Kubicek equation (Kubicek et al., 1966) provided the first quantitative relationship linking these impedance variations to volumetric blood flow. In this model, SV is proportional to blood resistivity (ϱ), the square of the thoracic segment length (L^2), and the maximal rate of change of the impedance waveform ($(dZ/dt)_{max}$), and inversely proportional to the square of the baseline thoracic impedance (Z_0^2). The product is then multiplied by the left ventricular ejection time (LVET), representing the duration of systolic outflow.

$$SV = \varrho \times (L^2 / Z_0^2) \times (dZ/dt)_{max} \times LVET$$

where ϱ is blood resistivity, L is thoracic length, Z_0 is baseline impedance, $(dZ/dt)_{max}$ is the maximum rate of change of impedance, and LVET is the left ventricular ejection time. In the Sramek–Bernstein modification, C represents a calibration constant incorporating thoracic geometry and individual body habitus, allowing for improved reproducibility and cross-patient comparison

$$SV = C \times ((dZ/dt)_{max} / Z_0) \times LVET$$

Contemporary ICG systems integrate advanced digital signal processing techniques to enhance artifact suppression, respiratory noise filtration, and beat-to-beat accuracy. These features allow for operator-independent measurements suitable for bedside use, ambulatory monitoring, and even dynamic assessments during exercise. Such versatility positions ICG as an accessible alternative to invasive hemodynamic modalities, particularly in scenarios requiring repeated or continuous monitoring.

1.2.1.2. Historical Background and Technological Developments

The conceptual underpinnings of impedance-based physiological monitoring date back to the mid-20th century. One of the earliest studies originated from Moscow, led by Kedrov (1948), who attempted to quantify the assessment of central and peripheral circulation using electrometrical methods. This pioneering work laid the groundwork for subsequent developments in noninvasive cardiovascular monitoring.

In the late 1960s, researchers such as Lababidi and Kubicek established the mathematical and technical framework for measuring $\dot{Q}c$ through thoracic impedance analysis, marking the formal genesis of ICG. Early ICG systems were hindered by analog design limitations, bulkiness, and susceptibility to motion artifacts, restricting their use to controlled laboratory environments. The miniaturization of electronics and the rise of digital signal processing in the 1990s enabled more compact and reliable systems, suitable for real-time clinical application.

Illustration 13: The first commercially available ICG device, BoMED NCCOM3, 1982

In parallel with thoracic approaches, the late 1990s and early 2000s witnessed the emergence of Whole-Body Impedance Cardiography (WBICG) (Kööbi et al., 1997a; 1997b). This technique extended the classical ICG principle beyond the thorax by introducing multiple current-injection and voltage-sensing sites distributed over the limbs and trunk. By capturing impedance variations across the entire circulatory loop, WBICG enabled estimation of total $\dot{Q}c$, SVR, and body-fluid shifts rather than focusing solely on central aortic flow. Although promising in its capacity to represent global hemodynamics, WBICG required careful electrode standardization and was more susceptible to peripheral vascular artifacts. For these reasons, its clinical use remained limited, but conceptually it paved the way for more comprehensive, whole-system impedance assessments.

The 2000s saw the emergence of phase-based bioreactance systems (such as the NICOM® system) and SM-ICG, such as PhysioFlow®, the latter allowing accurate flow assessment even during exercise. These innovations enhanced motion tolerance, reduced baseline dependence (Z_0), and facilitated broader adoption in both research and clinical practice.

1.2.1.3. Validation and Limitations

The validity of ICG has been rigorously evaluated against reference standards such as thermodilution and Doppler echocardiography. Correlation coefficients for $\dot{Q}c$ typically range between 0.70 and 0.90, depending on population and testing conditions. Beyond absolute accuracy, reproducibility and sensitivity in tracking hemodynamic changes are essential performance metrics for clinical reliability.

However, several limitations persist. Anatomical and physiological variables—including obesity, pleural effusions, and pulmonary diseases—can distort the signal. Motion artifacts and variations in electrode placement remain key sources of measurement variability, although modern HD-ICG and SM-ICG systems employ advanced filtering to mitigate such interference.

Contemporary consensus guidelines from the AHA and ESC recommend ICG as an adjunctive tool in HF management, hypertension phenotyping, and exercise evaluation (Yancy et al., 2013; Guazzi et al., 2016).

Despite its clinical value, conventional ICG remains limited by baseline dependence and motion sensitivity. SM-ICG addresses these issues by analyzing the waveform's shape rather than its absolute amplitude, enabling more robust, beat-to-beat evaluation of cardiac performance during dynamic conditions.

1.2.2. The Originality of Signal-Morphology Impedance Cardiography

1.2.2.1. Origin of the Concept

The concept of SM-ICG originated in France during the mid-1980s from the work of Dr Jean Bour, a cardiologist leading a hospital unit of internal medicine and CVD. His objective was to create a non-invasive method for continuous hemodynamic monitoring at rest and during exercise. Early studies were empirical, focusing on categorizing impedance waveforms from a large patient cohort with diverse physiological and pathological profiles. This database enabled the identification of reproducible patterns linking the morphology of the impedance signal to SV and contractility, without dependence on baseline impedance (Z_0). In 1993, Dr Bour patented this morphological approach, which was subsequently validated in French university hospitals, notably Strasbourg, Rennes, and Angers. These investigations confirmed the potential of morphology-based indices to estimate $\dot{Q}c$ and contractile function non-invasively. Industrial development followed with the creation of Manatec Biomedical in 1995, marking the transition from prototype systems to medical-grade devices, while academic collaborations continued to refine the methodology.

1.2.2.2. Methodological Innovation

Unlike conventional ICG, SM-ICG relies on signal morphology rather than amplitude or baseline impedance. A high-frequency, low-amplitude current is injected through outer electrodes, while inner electrodes record voltage changes. These signals are processed using an adaptive high-definition filter (HD-Z™) that minimizes respiratory and motion artifacts. Each cardiac cycle is identified, validated, and aligned to a reference beat, ensuring reproducible morphology tracking.

A resting calibration phase establishes a proportionality constant between impedance variations and hemodynamic flow parameters. Stroke volume index (SV_i) is estimated from the morphological characteristics of each beat according to:

$$SV_i = k \times [(dZ/dt)_{max} / (Zmax - Zmin)] \times W(TFIT_i)$$

where k is a calibration constant, $(dZ/dt)_{max}$ is the maximal derivative of the impedance curve, (Zmax – Zmin) is the impedance amplitude during systole, and $W(TFIT_i)$ is a weighting function derived from the Thoracic Flow Inversion Time (TFIT).

$$TFIT = t_1 / (t_1 + t_2)$$

where t_1 and t_2 represent the acceleration and deceleration phases of systolic flow, respectively. TFIT thus reflects the relative duration of forward flow and is sensitive to contractile dynamics and afterload.

$$CTi = (dZ/dt)_{max}$$

The CTi expresses the maximal impedance slope normalized around 100 (cutoff between depressed LV contractility and resting normal values), providing a dimensionless indicator of ventricular contractile performance. This morphology-based index is less affected by thoracic geometry and better suited to detect dynamic variations during exercise or stress. SM-ICG also provides $\dot{Q}c$ ($\dot{Q}c$ = SV × HR), cardiac index (CI = $\dot{Q}c$ / BSA), End-Diastolic Filling Ratio (EDFR) (LV preload response indicator), and SVR, offering a comprehensive view of central hemodynamics and ventricular-arterial coupling.

Although SM-ICG is fully non-invasive, it remains a direct hemodynamic technique in physiological terms. The recorded impedance waveform represents a real-time electrical analog of the pulsatile blood flow within the thoracic cavity—predominantly reflecting left-ventricular ejection. It does not rely on derived surrogates (such as blood-temperature dilution curves, pulse-contour modeling, or pressure-based algorithms) nor on mathematical substitutions like the so-called "direct" Fick calculation, which in practice estimates rather than measures $\dot{Q}c$.

In this respect, SM-ICG is conceptually closer to the Velocity-Time Integral (VTI) obtained by Doppler echocardiography, as it reflects the instantaneous flow profile throughout systole. However, it is not constrained by geometric assumptions such as aortic root diameter measurement, nor by the operator variability inherent to ultrasound imaging. This explains why morphology-based impedance tracing can provide reliable and reproducible beat-to-beat information, even during exercise or motion, and across patients with different body habitus.

Table 5: SM-ICG clinical parameters

Directly derived from the signals	**Calculated**	**Estimated**	**User entered (or interfaced with automatic monitors)**	**Combined**
HR (Heart Rate)	SV (Stroke Volume)	LV-EF (Left Ventricular Ejection Fraction)	Systolic and Diastolic Blood Arterial Blood Pressure)	SVR/SVRi (Systemic Vascular Resistance/index)
CTI (Contractility index)	$\dot{Q}c$ (Cardiac Output)	LV-EDV (Left Ventricular End Diastolic Volume)	CVP (Central Venous Pressure)	LCWi (Left Cardiac Work index)
SVi (Stroke Volume index)	CI (Cardiac Index)	LVET (Left Ventricular Ejection Time)	PCWP (Pulmonary capillary Wedge Pressure)	
EDFR Early Diastolic Filling Ratio)	Aortic Stiffness			
TFi/TFC (Thoracic Fluid index/Content)	Aortic Distensibility			
	Aortic Resistance			

1.2.2.3. Validation of SM-ICG

The clinical credibility of SM-ICG has been established through an extensive body of validation research. According to a 2024 compendium of studies, the PhysioFlow® system has been evaluated in over 40 peer-reviewed investigations encompassing a wide range of clinical scenarios and physiological conditions. These studies focus on three primary domains: accuracy, reproducibility, and physiological sensitivity. In terms of accuracy, the original validation studies by Charloux et al. (2000) and Richard et al. (2001) demonstrated strong concordance between SM-ICG-derived $\dot{Q}c$ and that obtained via the gold-standard direct Fick method. Subsequent investigations confirmed these findings in pediatric and adult populations. Mean percentage errors were consistently within ±30%, which is the threshold for clinical acceptability as defined by Critchley and Critchley (1999). Bias values and limits of agreement were found to be comparable to those reported for standard hemodynamic measurement techniques.

Regarding reproducibility, several studies reported coefficients of variation for SV and $\dot{Q}c$ below 5%, even under dynamic conditions such as exercise or pharmacological challenge (Legendre et. al., 2019, Filaire et. al., 2025). This high degree of intra-subject and inter-session consistency underscores the robustness of the morphology-based approach. The sensitivity of SM-ICG to physiological perturbations has also been well documented. Extensive research demonstrated the system's capacity to detect incremental changes in preload, afterload, and contractility during both pharmacological interventions and physical exertion. These findings validate the utility of SM-ICG in monitoring therapeutic efficacy and physiological adaptation. In summary, SM-ICG as implemented in the PhysioFlow® system provides accurate, reproducible, and physiologically responsive hemodynamic data. Its innovative reliance on waveform morphology and advanced signal processing distinguishes it from classical impedance techniques and positions it as a valuable tool for modern, non-invasive cardiovascular monitoring.

The strong methodological and clinical validation of SM-ICG across diverse populations provides the foundation for its use in dynamic physiological investigations. Its ability to deliver reliable, beat-to-beat hemodynamic data during incremental and constant-load exercise allows for precise characterization of cardiovascular responses in both health and disease. The following section outlines the principal exercise applications of SM-ICG, emphasizing its role in sports physiology, pulmonary and cardiac medicine, and, more specifically, its integration into cardiac rehabilitation research and practice.

1.2.3. Exercise Applications of SM-ICG

Over the past two decades, Signal-Morphology Impedance Cardiography (SM-ICG) has evolved from a research tool into a versatile clinical technology with demonstrated applications across a wide range of physiological and pathological contexts. According to the 2024 PhysioFlow Clinical Studies Reference Guide (https://physioflow.com/rsc/physioflow_clinical_studies_2024.pdf) and the recent 2024–2025 compilation of clinical data (to be formally added to the guide), over 220 peer-reviewed publications have employed SM-ICG or PhysioFlow® systems in domains including sports physiology, cardiology, pulmonary and metabolic disease, hypertension, congenital and valvular disorders, pediatric cardiology, intensive care, anesthesia, and obstetrics. This extensive literature demonstrates both the technological robustness and clinical versatility of morphology-based impedance analysis in dynamic, real-world conditions.

1.2.3.1. Applications in Sports Physiology

Illustration 14: Sports cardiac physiology on the field and the lab

In sports and exercise physiology, SM-ICG enables continuous, beat-to-beat measurement of $\dot{Q}c$ and SV during dynamic activity. Unlike classical methods requiring gas exchange or imaging, it allows real-time evaluation of cardiovascular responses under field or laboratory conditions.

The ability to measure SV and $\dot{Q}c$ non-invasively provides a window into one of the most important physiological systems governing endurance: oxygen transport. As described by the Fick equation, maximal oxygen uptake depends on both oxygen delivery and extraction. The cardiovascular circulation—through its central components of HR, SV, and blood flow distribution—represents a main determinant of oxygen transport, and thus a key performance-limiting factor, particularly in endurance sports.

Several investigations have confirmed that SM-ICG can quantify these determinants with sufficient precision to track training adaptation. Leprêtre et al. (2005) showed that endurance-trained cyclists exhibit higher exercise SV, lower HR, and greater cardiac efficiency compared with less-trained individuals. Le Meur et al. (2013) demonstrated that SM-ICG detects paradoxical reductions in SV and CI during periods of functional overreaching in triathletes—despite unchanged external workload—highlighting its diagnostic sensitivity to subclinical fatigue or maladaptation.

Finally, as the athletic population ages, SM-ICG offers potential for detecting changes in cardiac performance associated with age-related remodeling and emerging cardiovascular pathologies such as hypertrophic cardiomyopathy, which may alter diastolic filling and exercise tolerance even in previously trained individuals.

1.2.3.2. Applications in Pulmonary Disease

SM-ICG has contributed substantially to the characterization of dynamic cardiovascular constraints in chronic respiratory disorders, where exercise limitation frequently reflects combined ventilatory and circulatory impairment.

In Chronic Obstructive Pulmonary Disease (COPD), comparative validation studies have strengthened confidence in SM-ICG-derived measurements during exercise. Charloux et al. (2000) demonstrated good agreement between SM-ICG-derived $\dot{Q}$c and the direct Fick method across exercise intensities. Louvaris et al. (2019) further confirmed acceptable concordance between PhysioFlow-derived $\dot{Q}$c and dye-dilution measurements in COPD patients during exercise, supporting the feasibility of dynamic assessment even in hyperinflated lungs.

Earlier work by Bougault et al. (2005) reported limited agreement between SM-ICG and reference methods (direct Fick) during maximal or intermittent exercise in COPD. However, this study employed a questionable protocol (no steady state exercise, indispensable for Fick measurements), which likely contributed to the observed discrepancies.

In Pulmonary Arterial Hypertension (PAH), Ferreira et al. (2012) demonstrated the feasibility of SM-ICG during incremental CPET, highlighting its ability to track dynamic $\dot{Q}$c responses under progressive stress. Dupuis et al. (2018) showed good agreement between PhysioFlow-derived $\dot{Q}$c and invasive reference methods in pulmonary hypertension. Although Panagiotou et al. (2017) reported insufficient agreement in PAH, methodological and technical constraints—particularly related to early device hardware—likely influenced these findings.

More recently, post-acute sequelae of SARS-CoV-2 infection have extended the relevance of SM-ICG. Nascimento et al. (2025) demonstrated altered exercise hemodynamics characterized by impaired CTi responses despite preserved resting function, highlighting the sensitivity of CTi as a marker of dynamic myocardial performance.

Collectively, contemporary comparative studies support the reliability of SM-ICG-derived hemodynamic profiling during exercise in pulmonary disease. Across COPD, pulmonary hypertension, and post-COVID syndromes, SM-ICG identifies impaired SV reserve, altered $\dot{Q}$c kinetics, and abnormal contractile adaptation (CTi) without requiring invasive catheterization.

1.2.3.3. Applications in Cardiology

In cardiology, SM-ICG complements exercise Electrocardiography (ECG) and echocardiography by providing direct, continuous measurements of $\dot{Q}c$ and vascular resistance. Myers et al. (2019) showed that SM-ICG-derived CI and oxygen pulse independently predict prognosis in CHF. Findings from the PhysioFlow Clinical Studies Compilation (2024) extend to multiple disease domains, for instance:

- Ischemic heart disease: impaired stroke-volume augmentation and reduced cardiac reserve during exercise (Dupuis et al., 2000)

- Heart failure (HFrEF and HFpEF): chronotropic incompetence, autonomic dysregulation, and central hemodynamic insufficiency (Franzoni et al., 2024).

- Hypertension: exaggerated SVR and blood-pressure responses to effort (Kurpaska et al., Clin Exp Hypertens 2019; Kurpaska et al., Hypertens Res 2019; PhysioFlow Clinical Studies Guide).

- Congenital and valvular disease: compensatory stroke-volume dynamics and residual functional capacity (Legendre et al., 2017).

These observations reveal hemodynamic abnormalities that may elude resting echocardiography or standard ECG-based testing, while supporting longitudinal follow-up of functional recovery or treatment effects in outpatient and rehabilitation contexts.

In summary, SM-ICG enhances the resolution and relevance of cardiovascular evaluation during exercise. Its real-time, operator-independent capabilities facilitate precision medicine approaches in sports science, respiratory care, and cardiovascular medicine, among other fields, broadening the utility of exercise testing in clinical and research contexts.

1.2.4. Summary and Outlook

The evolution from classical ICG to signal-morphology impedance cardiography (SM-ICG) marks a decisive step in the clinical translation of non-invasive hemodynamic monitoring. Early ICG systems, based on the Kubicek model, were limited by baseline drift, motion artefacts, and dependency on absolute signal amplitude. By contrast, SM-ICG focuses on waveform morphology, allowing accurate and reproducible measurements of $\dot{Q}c$ and derived indices even under dynamic conditions. The integration of high-definition filtering (HD-Z™) and morphology-based calibration has transformed a research technique into a clinically credible, operator-independent modality suitable for continuous use during exercise or stress testing.

As discussed in Section 2.1, the theoretical framework of SM-ICG allows simultaneous assessment of $\dot{Q}c$, SV, SVR, and contractility through parameters such as the CTi and the EDFR. These variables provide unique insight into continuous ventricular–arterial coupling and preload–afterload dynamics with a temporal resolution that can generally not be achieved even with invasive catheterization.

Validation work summarized in Section 2.2 demonstrates that SM-ICG achieves accuracy and reproducibility comparable to gold-standard reference methods such as the direct Fick and dye-dilution techniques, while maintaining high sensitivity to physiological variation. This robustness has encouraged its integration across both clinical and applied physiological contexts.

Building on this foundation, SM-ICG has proven clinical value that extends beyond hemodynamic quantification alone. The key clinical benefits, derived from more than 220 peer-reviewed studies compiled in the PhysioFlow Clinical Studies Reference Guide (2024) and summarized by Bour (2023), can be grouped as follows:

1. Early and sensitive detection of cardiovascular abnormalities. SM-ICG enables detection of hemodynamic dysfunctions that may remain undiagnosed with conventional tests such as ECG, stress echocardiography, or metabolic carts—particularly in patients with HF, pulmonary hypertension, or unexplained exertional dyspnea.

2. Improved diagnostic precision and personalization. By distinguishing central (cardiac) from peripheral (vascular or muscular) limitations, SM-ICG clarifies the dominant physiological deficit and supports individualized therapeutic strategies—pharmacological, pacing-related, or rehabilitative.

3. Enhanced prognostic assessment. When combined with CPET, SM-ICG improves prediction of post-test decompensation and long-term outcomes in CHF, outperforming ECG or VO_2-based evaluation alone.

4. Guidance for differential diagnosis. SM-ICG assists in evaluating complex presentations such as

dyspnea of uncertain origin, NR to cardiac rehabilitation, or post-COVID cardiovascular sequelae, by quantifying SV and contractility responses under physiological stress.

5. Optimization of rehabilitation and training. By revealing whether $\dot{Q}c$ limitation, contractility impairment, or excessive vascular resistance constrains performance, SM-ICG enables precise exercise prescription and objective tracking of functional recovery.

6. Reduction of invasive testing. SM-ICG offers a non-invasive alternative to pulmonary artery catheterization for routine follow-up or screening, reserving invasive diagnostics for ambiguous or severe cases.

7. Safety, reproducibility, and practicality. The method's non-invasive, rapid, and cost-effective nature favors its adoption in serial testing, tele-rehabilitation, and decentralized care, where continuity of physiological monitoring is essential.

Through these advantages, SM-ICG fosters a more integrative understanding of cardiovascular physiology, bridging the gap between research-grade hemodynamic insight and everyday clinical decision-making. Its capacity to capture real-time circulatory trajectories at rest and during exertion supports precision medicine approaches, from individualized training prescriptions to early detection of maladaptive responses and remote patient management.

Looking ahead, the potential of SM-ICG lies in its convergence with digital health ecosystems—including AI-based signal analysis, automated pattern recognition, and wearable monitoring—to deliver continuous, personalized cardiovascular profiling. This evolution positions SM-ICG as both a scientific instrument and a clinical enabler, facilitating a transition from episodic testing toward adaptive, data-driven care.

Ultimately, the progressive adoption of SM-ICG across clinical disciplines—from sports medicine to HF management—reflects a paradigm shift: from static, snapshot evaluations to dynamic, patient-centered assessment of cardiovascular function. This evolution embodies the promise of non-invasive hemodynamic monitoring as both a scientific and clinical tool, fostering safer, more efficient, and more personalized cardiovascular care.

The next chapter will focus on how these methodological and clinical foundations translate into practical therapeutic use. It will examine how SM-ICG can enhance patient stratification, refine training intensity targets, and predict functional recovery.

1.3. CHAPTER 3: APPLICATION OF SM-ICG TECHNOLOGY TO CARDIAC REHABILITATION

Building on the technological foundations outlined in the previous chapter, this chapter explores the application of signal-morphology impedance cardiography (SM-ICG) within the specific context of CCR. Rehabilitation represents a unique testing ground for hemodynamic monitoring: it combines structured exercise with clinical supervision and aims to optimize both safety and functional improvement. Traditional assessment methods, such as echocardiography or invasive hemodynamic measurements, are either impractical or unsuitable for repeated use in this setting. By contrast, SM-ICG offers a non-invasive, continuous, and exercise-compatible tool for tracking $\dot{Q}c$, SV, and contractility. This makes it particularly valuable for understanding patient heterogeneity, personalizing exercise prescriptions, and improving prognostic evaluation in real-world rehabilitation programs.

1.3.1. State of the Art of Studies on ICG and SM-ICG in Rehabilitation

1.3.1.1. Key Applications and Findings in CCR

Early applications of conventional ICG in CCR demonstrated its potential to non-invasively capture central hemodynamic responses to structured exercise. Belardinelli et al. (2005) reported that a six-month CCR program in CAD patients was associated with significant increases in $\dot{V}O_2$peak, SV, and $(a–\bar{v})O_2$diff. These results suggested that ICG could document both central and peripheral adaptations to training. Similarly, Wang et al. (2022) examined patients undergoing early Phase I rehabilitation after acute coronary syndrome or HF, and found improvements in $\dot{Q}c$, SV, and SVR with exercise therapy. These findings reinforced the feasibility of ICG for guiding and monitoring early rehabilitation interventions.

Other studies extended these observations to more challenging populations. For example, Celik et al. (2013) used the BioZ ICG platform in patients with Heart Failure with preserved Ejection Fraction (HFpEF), reporting improved SV response and enhanced heart-rate recovery. These data suggested that ICG could provide longitudinal evidence of improved cardiovascular performance in patients in whom standard markers of adaptation are less sensitive.

Additional work using conventional ICG provided further insight but also revealed key methodological constraints. Butterfield et al. (2008) evaluated the effects of exercise training in patients with stable CHF using thoracic ICG and observed improvements in SV and reductions in B-type natriuretic peptide concentrations. Similarly, Gielerak et al. (2011) studied HF patients enrolled in a rehabilitation program and found modest reductions in Thoracic Fluid Content (TFC) and pre-ejection period without significant changes in SV or $\dot{Q}c$. Together, these studies illustrated the potential of classical ICG for monitoring central hemodynamic changes while underscoring its inherent restriction to resting conditions.

More recently, technological advances have allowed the emergence of signal-morphology impedance cardiography (SM-ICG), which addresses the limitations of conventional ICG by employing waveform pattern analysis and reference-beat alignment. This innovation has enabled the reliable assessment of beat-to-beat SV, $\dot{Q}c$, and SVR during dynamic exercise. In Gayda et al. (2012), SM-ICG was used to compare hemodynamic responses to HIIT versus moderate continuous exercise in CHF patients, revealing greater increases in SV and $\dot{Q}c$ with interval training. Legendre et al. (2021) further demonstrated the ability of SM-ICG to distinguish whether improvements in $\dot{V}O_2$peak reflected central or peripheral mechanisms, thus enabling refined phenotyping of patient responses. Other investigations have highlighted the prognostic and diagnostic potential of SM-ICG. Kirsch et al. (2024) identified R versus NR phenotypes in HFrEF patients, showing that improvements in peak $\dot{Q}c$ and SV correlated with favorable outcomes. Girault et al. (2024), working in coronary heart disease, found that ventilatory and peripheral factors predominated over central adaptations, suggesting disease-specific mechanisms of benefit. Taken together, these studies underscore the added value of SM-ICG for capturing individual patterns of adaptation and guiding more personalized CCR strategies.

1.3.1.2. Limitations in CCR

Despite these encouraging findings, conventional ICG faced several limitations that restricted its broader integration into CCR practice. Signal quality was highly susceptible to motion artifacts, especially during moderate-to-vigorous exercise, reducing reliability under precisely the conditions where monitoring would be most informative. The method was also operator-dependent: variability in electrode placement, skin impedance, and patient anatomy introduced significant inter- and intra-observer variability. Furthermore, signal-to-noise ratios were particularly poor in obese patients or in those with rapid breathing patterns.

These technical limitations—particularly the inability to obtain reliable data during physical exertion—were exemplified by the studies of Butterfield et al. (2008) and Gielerak et al. (2011), that yielded limited results. Their findings highlighted both the physiological relevance and the practical shortcomings of conventional ICG. The development of SM-ICG, incorporating morphology-based signal analysis and real-time artifact suppression, directly addressed these challenges, enabling continuous assessment of cardiac performance under exercise conditions.

Yet, while the ability to measure SV and $\dot{Q}c$ continuously during exercise represents an undeniable step forward, these global measures do not capture the complexity of cardiovascular adaptation. SV is determined by the interaction of preload, afterload, and myocardial contractility, each of which may be differentially altered in patients with CVD and may respond differently to training. The potential of SM-ICG lies not only in refining the measurement of SV and CO but also in dissecting their components, and in particular in quantifying contractile function during exercise. This shift from global indices to mechanistic insights offers a pathway toward more precise phenotyping of rehabilitation responses and sets the stage for the discussion in the following section.

1.3.2. Innovative Prospects with SM-ICG

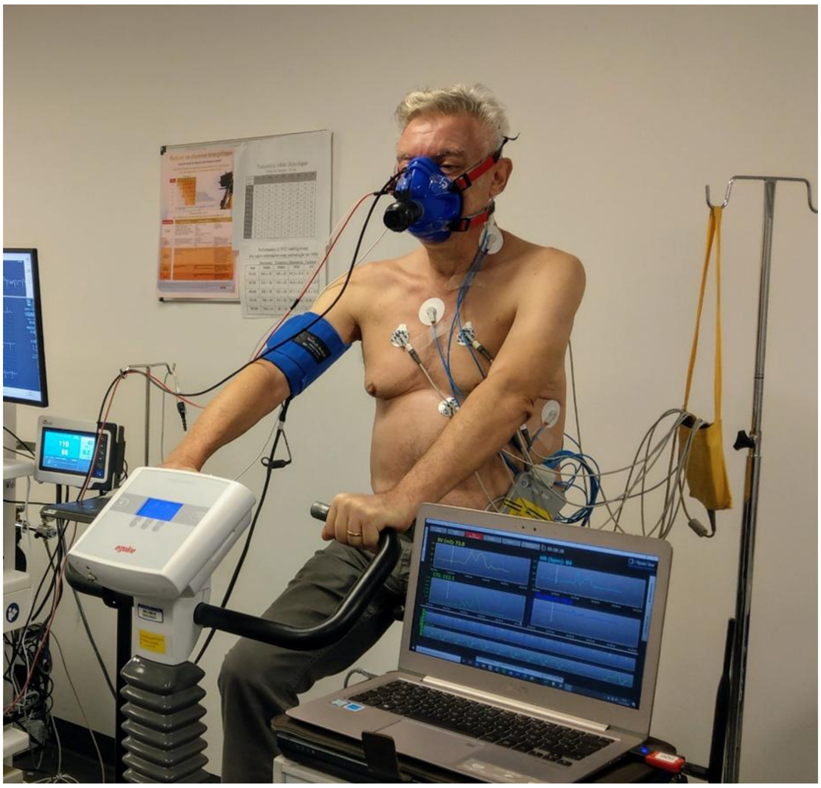


Illustration 15: real life CPET SM-ICG test in CCR (courtesy of the patient)

1.3.2.1. Description of the CTi and the CTi profiles

SM-ICG provides a practical, non-invasive approach to assessing myocardial contractility during exercise via the CTi. CTi is derived from the maximum rate of change of the impedance waveform during systole (dZ/dt_{max}), labelled $d(HD\text{-}Z^{TM})/dt_{max}$ by the designers of the technology, to account for the stabilizing effect of the HD-Z^{TM} filter. Physiologically, dZ/dt_{max} aligns with the early systolic acceleration of aortic flow—i.e., the time derivative of flow/velocity (dV/dt) — a parameter long recognized as a sensitive marker of ventricular contractile performance in invasive and non-invasive studies (Tomlin et al., 1975; Mehta et al., 1986; Bedotto et al., 1989; Pérez et al., 2021). Accordingly, CTi provides beat-to-beat information reflecting the rapidity with which the ventricle accelerates forward flow at the onset of ejection.

With SM-ICG, dZ/dt_{max} values are acquired on a beat-to-beat basis and displayed as five-second averaged CTi trend curves. This enables two complementary readings. First, CTi can be treated as a quantitative value that is sensitive to therapeutic interventions (e.g., exercise training, pharmacological therapy, device optimization); tracking CTi longitudinally provides an objective way to monitor intervention-related changes in contractile function. Second, CTi can be interpreted as a dynamic profile throughout exercise, capturing how contractility adapts across workloads.

A normal CTi profile shows a rapid rise early in exercise followed by a slower rise or plateau at higher intensities, consistent with physiological contractile reserve. Abnormal CTi profiles can be categorized as: (i) an altered profile, characterized by an inversion or relapse of the slope that occurs before the recovery phase; and (ii) a compromised profile, defined by the absence of any increase (flat slope) or an immediate decline (negative slope) from exercise onset. Such patterns indicate impaired contractile reserve and may herald reduced trainability during rehabilitation.

By distinguishing between normal and abnormal CTi profiles and by following absolute CTi values over time, SM-ICG enables patient stratification that goes beyond global indices such as SV and $\dot{Q}c$. Clinically, this dual perspective—value and profile—supports individualized exercise prescriptions and helps evaluate the efficacy of targeted interventions in cardiac rehabilitation.

[redacted]

Illustration 16: SM-ICG and CTi (its determination and abnormal profile)

1.3.2.2. Potential applications in Cardiac Rehabilitation

The CTi, derived from SM-ICG, represents a practical tool for evaluating left ventricular inotropy under dynamic conditions. Because CTi can be obtained continuously and non-invasively during exercise, it overcomes the limitations of imaging-based methods, which are resource-intensive, operator-dependent, and not readily applicable in rehabilitation environments. CTi integrates seamlessly into CPET or structured exercise sessions, providing real-time insight into contractile performance during stress. This methodological accessibility makes it well suited for both clinical and research applications.

Myers et al. (2019) demonstrated the prognostic relevance of CTi in a large heart-failure cohort, showing that it provided incremental value beyond classical CPET indices such as $\dot{V}O_2$peak and $\frac{\dot{V}E}{\dot{V}CO2}$ slope. CTi independently predicted mortality and refined risk classification, including in patients with preserved or mildly reduced EF. These findings support CTi as a clinically useful, non-invasive index of myocardial performance and training responsiveness.

Integrating CTi into cardiac rehabilitation protocols offers several advantages:

- Mechanistic insight – quantifying inotropy dynamically during exercise enriches interpretation of $\dot{V}O_2$peak and delineates central versus peripheral adaptations.

- Risk stratification – abnormal CTi profiles can identify patients with limited inotropic reserve, supporting tailored interventions.

- Monitoring adaptation – repeatable CTi assessment enables longitudinal tracking of contractile improvements during rehabilitation.

- Scalability – CTi can be applied in multicenter or resource-limited environments without advanced imaging.

By bridging cardiac physiology and clinical rehabilitation, exercise CTi contributes to a more individualized and precise model of cardiac rehabilitation, grounded in real-time hemodynamic evidence.

1.3.2.3. Specific Considerations Regarding the 6-Minute Walk Test in Cardiac Rehabilitation

When CPET is unavailable, the 6MWT is widely recommended as a practical alternative for assessing functional capacity in CCR. The test is simple, inexpensive, and well validated for submaximal evaluation of exercise tolerance in CHF and other cardiovascular conditions. However, it also presents limitations. Performance can be strongly influenced by non-cardiovascular factors such as motivation, mood, and depression—as demonstrated in HF populations where depressed patients consistently achieve shorter walking distances despite comparable physiological capacity (Xiong et al., 2012; Zhu et al., 2023). Moreover, the 6MWT does not capture the dynamic hemodynamic adjustments that underpin functional improvement.

In this context, integrating SM-ICG during the 6MWT provides a valuable complement. Studies have shown that real-time measures of SV, $\dot{Q}c$, and contractility obtained during the 6MWT are feasible, reproducible, and clinically informative in diverse populations, including CHF (Franzoni et al., 2024), pulmonary hypertension (Tonelli et al., 2013), and post-stroke rehabilitation (Liu et al., 2020; 2021; 2022). By adding continuous central hemodynamic data, SM-ICG enhances the interpretability of the 6MWT beyond walking distance, offering insight into circulatory efficiency and cardiac reserve.

Nonetheless, the 6MWT is not a controlled, incremental test, which makes interpretation of CTi profiles, thresholds, or maximal values (CTi_{max}) more challenging than during CPET. Despite this, SM-ICG integration into 6MWT protocols can yield valuable mechanistic insight, particularly in patients unable to perform maximal testing, thereby bridging functional evaluation with central hemodynamic assessment in everyday rehabilitation practice.

1.3.2.4. Summary and Outlook (Transition to the Thesis Studies)

CCR has traditionally relied on functional outcome measures such as $\dot{V}O_2$peak and $\frac{\dot{V}E}{\dot{V}CO2}$ slope. While these indices remain valuable, they provide limited insight into the central hemodynamic mechanisms underlying interindividual differences in training response. Over the past decades, ICG has introduced the possibility of monitoring $\dot{Q}c$, SV, and SVR in a noninvasive manner during exercise, thereby contributing to the physiological evaluation of CCR. Conventional ICG systems, however, were constrained by motion artifacts, operator dependency, and limited reproducibility, which curtailed their widespread adoption in rehabilitation settings.

The advent of signal-morphology impedance cardiography (SM-ICG) represents a conceptual shift. By incorporating morphological analysis and beat-to-beat tracking, SM-ICG enables robust hemodynamic monitoring under dynamic exercise conditions. Beyond global measures of SV and $\dot{Q}c$, the introduction of the CTi provides an opportunity to quantify myocardial inotropy in real time. Importantly, CTi can be considered both as a quantitative value, sensitive to therapeutic interventions, and as a dynamic profile, whose trajectory during exercise allows for patient stratification. These complementary perspectives position CTi as a potentially powerful tool for tailoring rehabilitation strategies.

Emerging evidence supports the clinical utility of SM-ICG in distinguishing phenotypes of response, identifying patients with limited contractile reserve, and tracking longitudinal adaptations to exercise training. Such applications move the field toward precision rehabilitation, where interventions are adapted to the patient's central physiological profile rather than applied uniformly across heterogeneous populations. In this sense, SM-ICG does not replace established techniques such as CPET or echocardiography; rather, it complements them by providing continuous, accessible, and mechanistically informative data within the everyday setting of CCR programs.

Table 6: Improving evaluations in CCR

Current Evaluations in CCR	**With SM-ICG (Enhanced Assessment?)**
$\dot{V}O_{2}$peak, VT1	Continuous stroke volume (SV)
Heart rate (HR) response	CTi (contractility index)
Blood pressure (BP) response	Cardiac index (CI), systemic vascular resistance (SVR)
No continuous SV / CTi	Detailed haemodynamic profiles & reserves
Limited mechanistic insight, surrogates	Real-time exercise haemodynamics

Looking ahead, integrating SM-ICG into routine rehabilitation practice raises important questions about feasibility, standardization, and professional boundaries between specialties. Nonetheless, the technology's portability, ease of use, seamless combination with exercise ECG, and capacity for multicenter application highlight its potential as a scalable solution for individualized assessment. These attributes make it particularly attractive in contexts where resources are constrained but the need for efficient risk stratification and personalized training is increasing.

In summary, the progression from conventional ICG to SM-ICG and the development of CTi mark a transition from descriptive to mechanistic cardiovascular monitoring in CCR. By enabling dynamic assessment of myocardial contractility during exercise, SM-ICG provides new opportunities to refine patient evaluation and intervention design. The following sections of this thesis build directly on these concepts, examining the application of SM-ICG-derived CTi profiles and trends in CCR and exploring their value for predicting, explaining, and potentially optimizing patient outcomes.

2. Part II: Presentation of the Thesis Studies

GENERAL OBJECTIVE OF THE THESIS STUDIES

Building on the theoretical framework developed in Part I, Part II of this dissertation is devoted to the empirical application of SM-ICG within CCR. Specifically, this section examines the clinical and physiological relevance of SM-ICG–derived myocardial contractility assessment, with a particular focus on the CTi and its dynamic behavior during exercise.

The overarching objective of the four studies presented in this part is to determine whether exercise CTi profiles and training-induced CTi adaptations provide actionable information beyond conventional CPET metrics. More precisely, the studies aim to evaluate the value of CTi for (i) predicting individual responsiveness to CCR, (ii) explaining interindividual heterogeneity in functional adaptation, and (iii) informing more personalized and physiologically grounded rehabilitation strategies.

The first study investigates whether baseline CTi profiles obtained during an entry CPET—reflecting the myocardial contractile response to incremental exercise—are associated with subsequent improvements in cardiorespiratory fitness following CCR. By distinguishing physiological from abnormal contractile patterns at program entry, this study explores the potential of CTi profiling as an early stratification tool for identifying patients more or less likely to benefit from exercise-based rehabilitation.

The second study focuses on patients with chronic heart failure, examining the relationship between training-induced changes in CTi and changes in functional capacity. This work addresses whether improvements in myocardial contractility contribute meaningfully to exercise tolerance gains in a population traditionally considered limited by central cardiac dysfunction, and whether CTi dynamics provide mechanistic insight beyond changes in $\dot{V}O_2$peak alone.

The third study extends this analysis by comparing responders and non-responders to CCR, with particular emphasis on CTi reserve and its evolution over time. The objective is to determine whether CTi-based indices can discriminate between adaptive and maladaptive training responses, thereby helping to clarify why patients with similar baseline characteristics may exhibit markedly different rehabilitation outcomes.

Finally, the fourth study adopts an integrative perspective, combining CTi with CPET-derived and SM-ICG-derived hemodynamic variables to characterize multidimensional response patterns to CCR. This approach aims to situate myocardial contractility within the broader framework of central and peripheral adaptations, and to assess whether CTi contributes independently to the physiological phenotype of rehabilitation response.

Taken together, these four studies seek to move beyond a purely descriptive use of SM-ICG by evaluating its predictive, explanatory, and potentially decision-support value in cardiac rehabilitation. By focusing on dynamic myocardial function rather than static resting measurements, Part II explores whether SM-ICG—and CTi in particular—can support a more mechanistically informed and individualized approach to CCR, aligned with contemporary principles of precision cardiovascular medicine.

2.1. CHAPTER 4: METHODOLOGY OF THE THESIS

Building on the physiological and technological foundations established in the preceding chapters, the present thesis proceeds to the methodological framework that underpins the original investigations. Chapter 3 highlighted the potential of SM-ICG, and in particular the CTi, as a promising tool for exploring central hemodynamic responses during cardiac rehabilitation. To rigorously evaluate this hypothesis, it was necessary to design and implement a comprehensive methodological approach that combined advanced hemodynamic monitoring with standardized rehabilitation protocols and validated outcome measures.

This chapter details the methodological choices that guided the thesis work, including study design, patient selection, instrumentation, data acquisition procedures, and statistical analyses. Particular attention is devoted to the integration of SM-ICG into exercise testing, the definition and classification of CTi profiles, and the criteria used to distinguish R from NR in rehabilitation programs. By systematically presenting these methodological elements, this chapter provides the foundation for interpreting the results and discussion that follow.

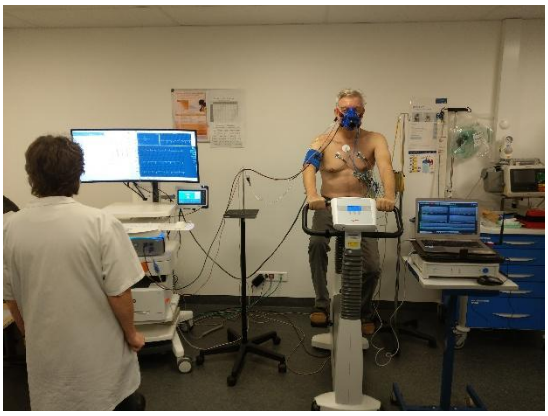


Illustration 17: Real life CPET SM-ICG test in CCR (courtesy of the patient)

2.1.1. Cardiopulmonary Exercise Test

CPET was conducted using electronically braked cycle ergometers under standardized environmental conditions. Participants performed the test in a seated or upright position depending on the equipment used—either a Sanabike 1.01 (SDS Excellence, Schiller, Switzerland) or an ERGOLINE 900 (Schiller Medical SAS, France). Prior to the incremental phase, subjects underwent a 3-minute period of rest followed by a 3-minute warm-up at a constant workload of 20 watts. Subsequently, a ramp protocol was implemented, increasing workload by 10 watts per minute until volitional exhaustion or the occurrence of clinical termination criteria such as RER > 1.05, inability to sustain cycling cadence, fatigue, dyspnea, abnormal electrocardiographic changes, or aberrant blood pressure responses.

Throughout the test, heart rate was recorded on a beat-to-beat basis via electrocardiography, while Systolic (SABP) and Diastolic Arterial Blood Pressures (DABP) were measured at one-minute intervals and at peak exertion. Respiratory gas exchange variables, including $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), respiratory frequency, tidal volume, and $\dot{V}E$, were measured breath-by-breath using automated gas analyzers: CPX Vyntus (Vyvaire Medical GmbH, Germany) and Quark-CPET (Cosmed, Rome, Italy). These data were averaged over 15-second or 5-second intervals, respectively, with ectopic values excluded via software-based filtering.

Cardiorespiratory performance indices such as $\dot{V}O_2$peak, $\frac{\dot{V}E}{\dot{V}CO2}$ slope, and Wpeak were derived following established guidelines. The VT_1 was determined using the V-slope method (Beaver), identifying the inflection point on the $\dot{V}CO_2$ versus $\dot{V}O_2$ curve indicative of the transition from aerobic to anaerobic metabolism. Equipment setup, including seat and handlebar positioning, was personalized for each participant, and cycling cadence was maintained at a consistent 60 revolutions per minute to ensure protocol fidelity and reproducibility.

2.1.2.Signal Morphology Impedance Cardiography

2.1.2.1. Cardiac hemodynamics during CPET

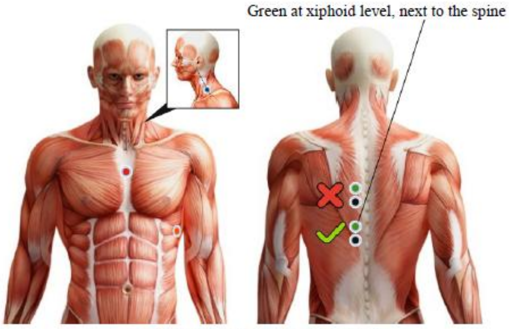
$\dot{Q}c$, SV, CTi and other values were determined during the entry and final CPET by morphological analysis of the beat-to-beat cardiac impedance signal using an advanced transthoracic impedance cardiograph, a technology called SM-ICG (PhysioFlow®, PF-05 Lab1, Manatec Biomedical, Macheren, France). The PhysioFlow® software used was version 2.8.0, up to date at the time of data collection, and the electrodes were those marketed by the manufacturer (PhysioFlow® PF50, subsequently replaced by the PhysioFlow® HTFS50PF model).

Throughout the study, all teams were instructed to adhere strictly to the manufacturer's user guide to ensure the highest possible recording quality during PhysioFlow® sessions. The consistency in technique across centers was critical to maintaining signal fidelity during both resting and exercise conditions.

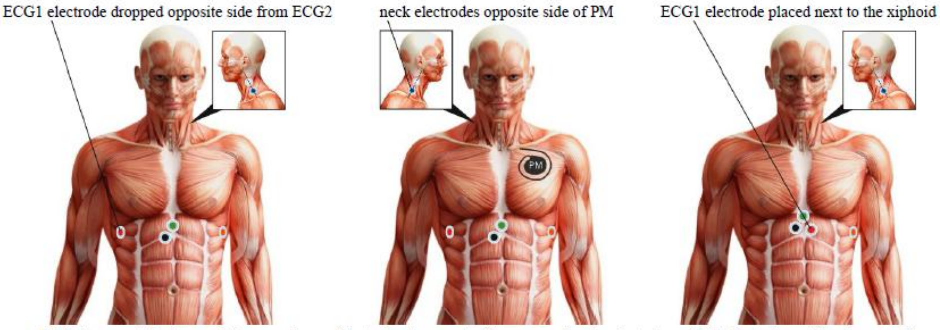
Prior to electrode application, skin preparation was systematically performed. This included shaving the area when needed using a surgical razor and gentle abrasion with some special abrasive gel (Nuprep® , Weaver and Company, Aurora, CO, USA). until a pinkish appearance was achieved. This procedure aimed to minimize impedance and secure optimal contact. Only PhysioFlow® PF50 electrodes were utilized, after being confirmed to be within their expiry date and stored under recommended conditions. Alternative brands were found to compromise data quality due to higher gel impedance and suboptimal packaging formats. Conventional ECG electrodes are typically distributed in bulk packaging—often in bags of 30 units or more—which, once opened, expose unused electrodes to air. This exposure leads to progressive gel desiccation within hours, significantly impairing their conductivity and rendering them unsuitable for ICG. In contrast, PhysioFlow® PF50 electrodes are individually packaged in sealed sets of six, corresponding precisely to the number required for one recording session. This design minimizes the risk of degradation and ensures optimal signal acquisition during each test

Electrodes were always connected to the patient cable before being placed on the body. The six electrodes were applied in a standardized configuration involving the neck, sternum, lateral rib cage, and paraspinal region near the xiphoid process. In cases where subjects exhibited wide QRS complexes, pronounced T-waves, or had implanted pacemakers, minor positional adjustments were made to minimize signal distortion. As the recommended electrode positioning did not conflict with the placement of stress ECG leads, particular attention was given to the neck impedance electrodes, as the straps of the $\dot{V}O_2$ face mask could come into contact with the upper electrode head and potentially disrupt signal acquisition.

Standard electrode position (rest)



Standard electrode position (Exercise)



ECG placement (red orange) in case of a wide QRS

Electrode placement with a pacemaker implanted

ECG electrode position in case of big T-Wave (double counting of HR)

Illustration 19: Electrode positions

To enhance adhesion and reduce motion-related artifacts, the gel portion of each electrode was first pressed against the prepared skin surface before securing the foam backing. Care was taken to avoid creating wrinkles or air bubbles. Particular attention was given to the placement of neck electrodes, which were prone to detachment due to perspiration and head movement. A relaxed neck posture was maintained throughout application to better simulate exercise conditions.

As the system was used during exertion, stabilization methods were employed, including the use of the recommended medical adhesive tape (Nexcare Transpore®)

During the data acquisition phase, all teams operated the PhysioFlow® software in accordance with manufacturer guidelines. This began with accurate entry of patient demographic information, including anthropometric variables such as height, weight, and age. Measurement settings (e.g., resting condition, averaging time) were selected.

Calibration of the PhysioFlow® device was conducted at rest prior to the onset of monitoring, and whenever feasible, in the same position intended for data acquisition (e.g., seated on the cyclo-ergometer). This practice ensured that baseline hemodynamic data aligned with subsequent recordings. Calibration was based on 30 consecutive heartbeats and required high signal stability, as visualized via the signal stability indicator. Operators were instructed to proceed with calibration only after confirming acceptable ECG and impedance waveforms.

Signal quality was continuously assessed using real-time visual feedback. In cases of suboptimal signal or artifact, electrode repositioning or skin preparation was repeated.

Following calibration, blood pressure values were either manually entered or automatically retrieved, and the operator validated the process before initiating monitoring. In the rare occurrences where calibration signals quality was poor or metrics clearly fell outside acceptable thresholds, the procedure was repeated until acceptable values were obtained.

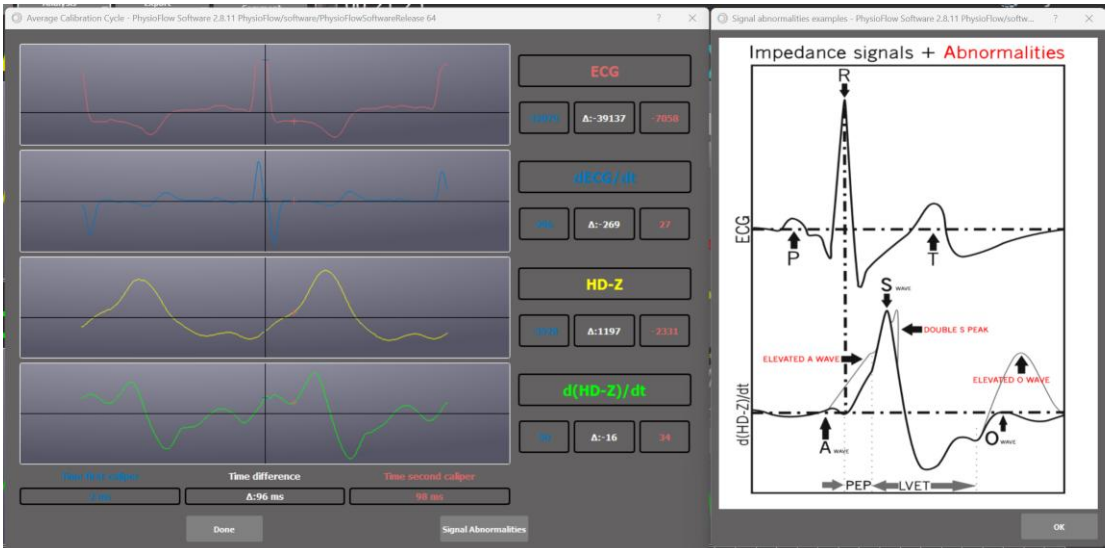

Calibration result - PhysioFlow Software 2.8.11 PhysioFlow/software/PhysioFlowSoftwareRelease 64

Calibration Result

🟥 High
🟩 Normal
🟨 Low

SV (ml)	SVi (ml/m²)	HR (bpm)	CO (l/min)	CI (l/min/m²)	SABP (mmHg)	DABP (mmHg)	MABP (mmHg)	CTI ()	EDFR (%)	SVRi (dyn.s/cm5.m²)
134.2	65	90	8.7	4.2	140	90	105	400	67	2483
72.2	35	50	5.2	2.5	100	60	70	100	0	1337
59.5	28.8	97	5.8	2.8	81	60	70	129.7	64.5	1801

Illustration 20: Calibration results


Average Calibration Cycle - PhysioFlow Software 2.8.11 PhysioFlow/software/PhysioFlowSoftwareRelease 64

ECG Δ:-39137 -7058
dECG/dt Δ:-269 27
HD-Z Δ:1197 -2331
d(HD-Z)/dt Δ:-16 34
Time difference Δ:96 ms
Time second caliper 98 ms

Signal abnormalities examples - PhysioFlow Software 2.8.11 PhysioFlow/softw...

Illustration 21: Calibration signals

After signal processing, which included a sophisticated and proprietary built-in noise reduction filter called HD-Z™, the heart signals were analyzed beat by beat and the results were averaged over 5 s. This method of measuring exercise hemodynamics has been described above (chapter 2.2.2) and has been validated for accuracy, reproducibility and sensitivity, including at maximal exercise.

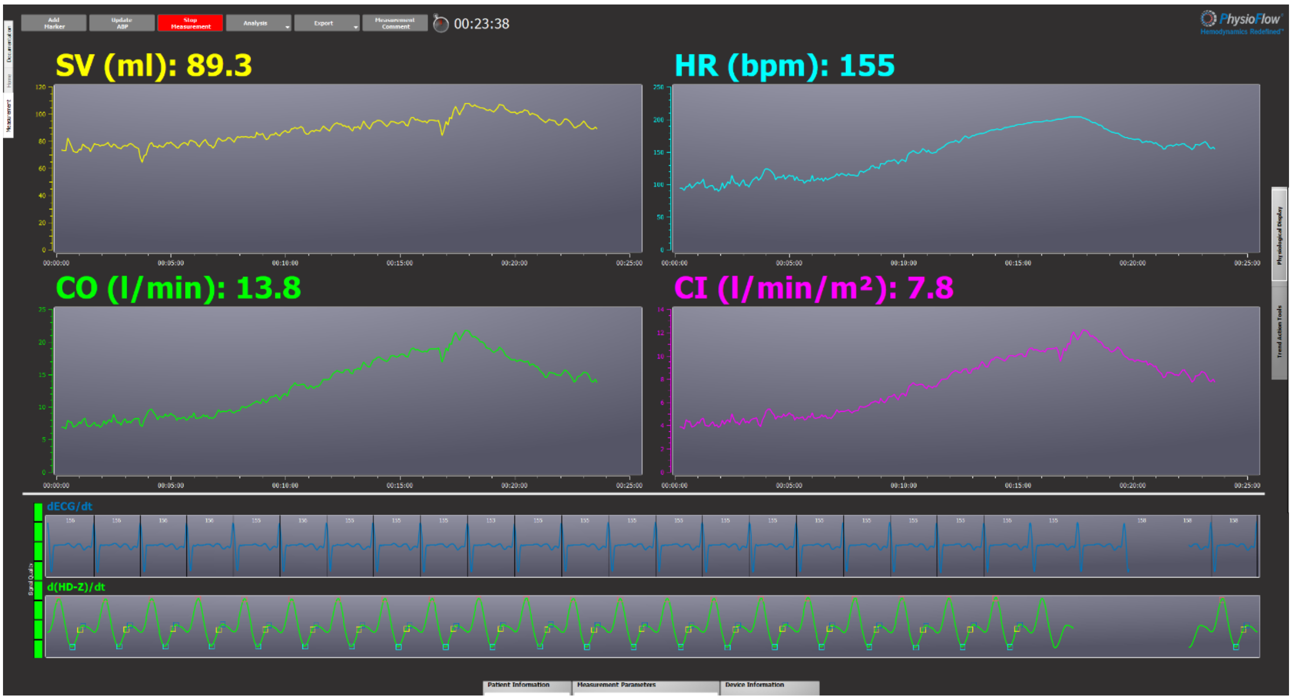


Illustration 22: Example of an exercise test screen shot

2.1.2.2. Contractility and contractility reserve measurements with SM-ICG (3rd and 4th study)

The dZ/dt maximum rate of change of the impedance waveform (dZ/dt_(max)), also called the peak of the first mathematical derivative of the impedance waveform during systole by the PhysioFlow® manufacturer, is a representation of the maximum ejection flow velocity during systole (dV/dt). It is a well-known parameter in ICG [29]. The dZ/dt_(max) values were recorded during each cardiac cycle and graphically represented by the software as trend curves averaged over five seconds under the name CTi (Figure 1). The PhysioFlow® software allows manual scrolling of these trend curves to evaluate slopes and averages over selected portions. This easy-to-use function is useful for determining averages and slopes. Attention was paid to applying it to stable, non-artefactual portions of the trendlines, especially at max exercise, and readings were confirmed by a second operator, not expert in SM-ICG, but who was trained to use the software. Average CTi values were recorded at rest before the exercise test started (CTi_rest) and at maximum exercise before recovery (CTi_max). Both CTi_max and the increase in CTi from rest to max (CTi_reserve) are analyzed here.

Note that the manufacturer chose to display CTi as a numerical scale around a cutoff value set at 100 at rest, rather than with a unit. This threshold is considered the lower limit of normal CTi at rest based on past clinical experience. Its strong predictive value for risk was established in a study involving over 1,200 HF patients (Myers et al., 2019, see above 1.3.2.2.).

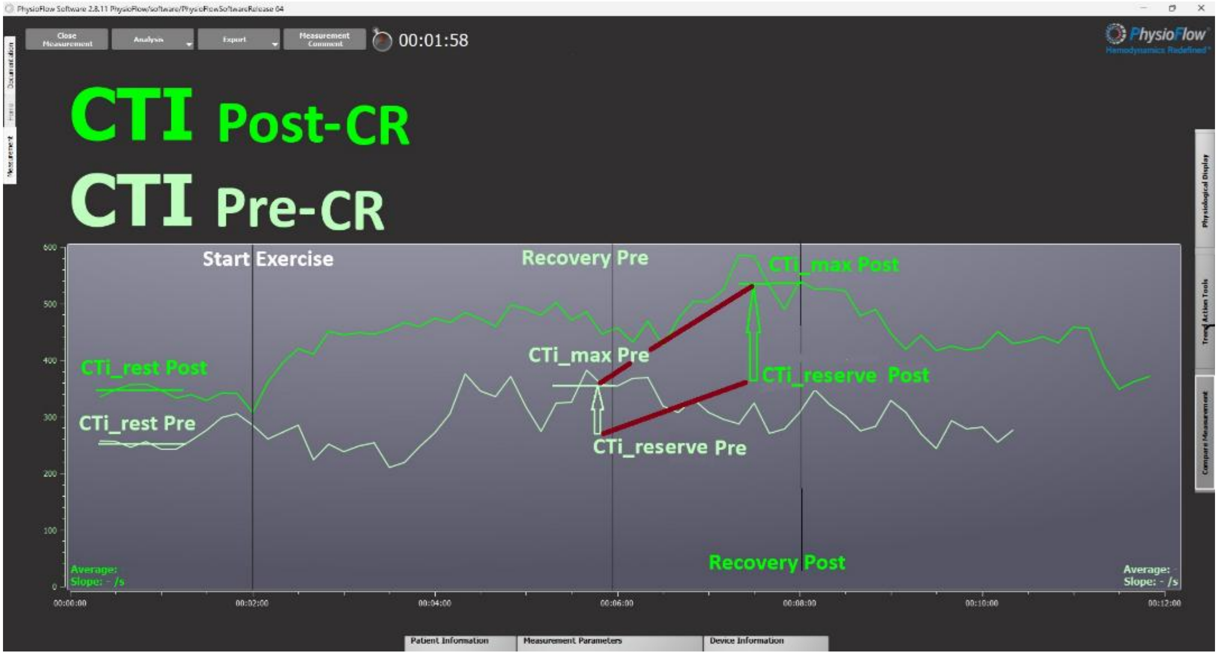


Illustration 23: Screen shot showing an improvement in CTi_reserve

2.1.2.3. CTi profiles during CPET (1st and 2nd study)

The maximal rate of change of the impedance waveform (dZ/dt max), computed as the peak of the first mathematical derivative over time of the impedance waveform during systole (also called d(HD-Z)/dt max by the manufacturer of PhysioFlow®), is a representation of the maximum ejection flow velocity during systole (dV/dt). It is a well-known parameter in ICG (Rubal et al, 1981). The dZ/dt_{max} values are recorded during each cardiac cycle and graphically represented by the software in the form of trend curves averaged over 5 s under the name CTi (Fig. 1). A normal contractility profile during exercise is characterized by a rapid increase in CTi followed by a slower increase or plateau. This pattern has been described previously using other methods to assess myocardial contractility in healthy subjects (Warburton et al., 2002). The PhysioFlow® software allows manual scrolling of portions of these trend curves to evaluate a slope and average over the selected portion. This function is useful for determining slope changes and, in particular, the possible CTi slope inversion that can occur for at least one minute prior to the recovery phase of the exercise test (negative slope after the positive slope observed at the start of exercise). This change in slope (altered CTi profile) appears to be a sign of an abnormal response to exercise of the ejection flow provided by left ventricular function. Sometimes the CTi does not increase during exercise (slope is zero or close to zero) or even collapses at the beginning of exercise (negative slope), which seems to be a sign of deteriorated left ventricular function (compromised CTi profile) (see illustration below). The normal CTi profile defined a first subgroup of patients, whereas the altered and compromised CTi profiles defined a second subgroup of patients (abnormal CTi profile). In order to minimize operator bias, the CTi profiles' analysis was conducted by two independent operators. In case of disagreement, a third operator would intervene. Both analyses were conducted in a blinded manner.

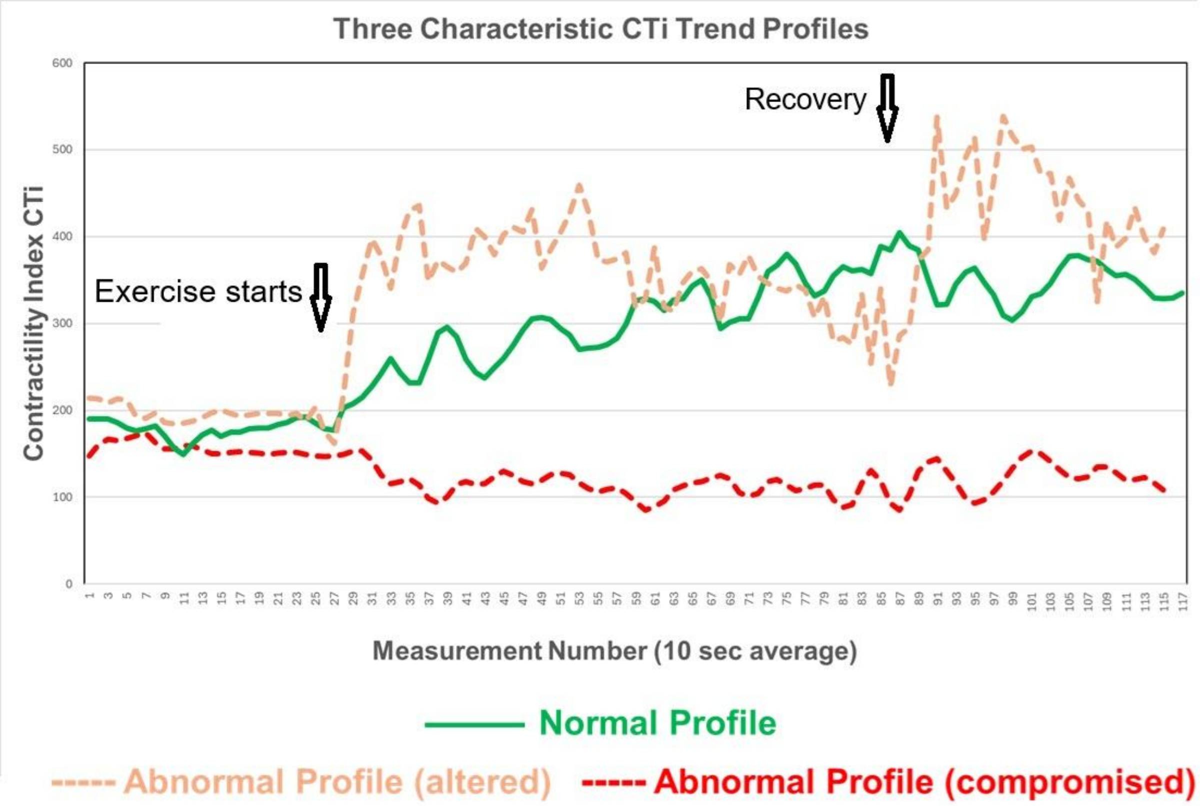


Illustration 24: Characteristic CTi profiles

2.1.2.4. Left ventricular preload assessment with SM-ICG (4th study)

The EDFR is a noninvasive hemodynamic parameter that reflects early ventricular filling. It is not the same as the E/A ratio in Doppler echocardiography, though both are related to diastolic function and LV preload. In SM-ICG, the EDFR is the ratio of the early filling peak velocity (O-wave) to the systolic peak velocity (S-wave), expressed as a percentage: EDFR = O/S*100. According to the manufacturer, a high EDFR (>67%) is usually associated with excessive LV preload according to the Frank-Starling law. There have been no formal comparative studies with ultrasound or invasive catheterization (e.g., pulmonary capillary wedge pressure), as the approaches to LV preload are too different. However, this parameter has been successfully studied in patients with CVD, stroke, spinal cord injury and unstable dialytic patients.

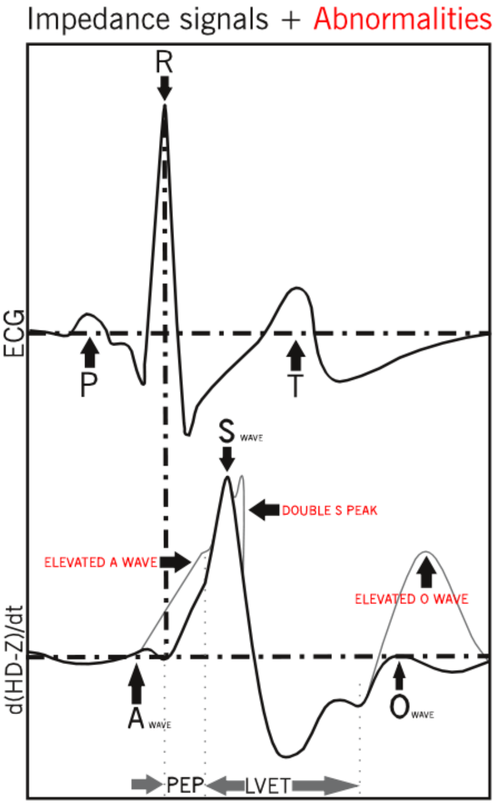


Illustration 25: Display of the S wave and O wave

Note: d(HD-Z)/dt is the dZ/dt signal filtered using the proprietary HD-Z^{TM} technology

2.1.2.5. Left ventricular afterload assessment with SM-ICG (4th study)

SVR (expressed in dyn·s·cm^{-5}) is the most accepted surrogate for LV afterload in ICG.

$$\text{SVR} = \frac{(MABP - CVP) \times 80}{\dot{Q}c}$$

where MABP is Mean Arterial Blood Pressure (in mmHg) and CVP, Central Venous Pressure, expressed in mmHg.

It is preferable to use SVRi (where CI is used instead of $\dot{Q}c$) rather than SVR to avoid interference from body size in the estimation of LV afterload. SVRi has been widely used at rest, but also in exercising HF patients.

CVP is usually measured invasively, but the PhysioFlow® software approximates it at 7 mmHg. This approximation is considered acceptable at rest in CHF patients, but it can double during maximum exercise in those patients. Following previously published studies on HF, we recalculated SVRi during maximal exercise by approximating CVP at rest to 6.4 mmHg and during exercise to 17.4 mmHg.

At rest, MABP was calculated using the conventional formula:

$$\text{MABP} = \frac{1}{3} \times \text{SABP} + \frac{2}{3} \times \text{DABP}$$

During maximal exercise, we chose to account for the reduction in diastolic time compared to systolic time using a formula described elsewhere (Morane et. al.1995, Rogers et. al. 2015):

$$\text{SVR\_max} = [\text{SABP\_max} + 0.01e^{(4.14 - \frac{40.74}{\text{HR}_{max}})})] \times \frac{(\text{SABP\_max} - \text{SABP\_max}) - \text{CVP\_max}}{\text{CI\_max}}$$

Where SABP and DABP are expressed in mmHg.

2.1.3. Patient Populations and Training protocols

2.1.3.1. Patient Populations

The analyses presented in this thesis are based on two independent, center-based clinical databases constituted at two distinct cardiac rehabilitation centers in France. These databases were not specifically created for the purposes of this doctoral work, but resulted from routine clinical activity and institutional research initiatives conducted at each center. Both datasets were subsequently made available to the author for secondary analysis within the framework of this thesis.

Illustration 26: Pictures or the Corentin Celton and Leopold Bellan Rehabilitation Centers

In both centers, data collection was performed prospectively as part of standard comprehensive cardiac rehabilitation (CCR) programs integrating cardiopulmonary exercise testing (CPET) combined with signal-morphology impedance cardiography (SM-ICG). The collection and secondary use of these data were approved by the appropriate French ethics committees (CPP/CCPPRB), and all patients provided written informed consent authorizing the use of their anonymized clinical and physiological data for research purposes, in accordance with the Declaration of Helsinki and applicable French regulations.

First Database: Léopold Bellan Prevention and Rehabilitation Center

Illustration 27: location of the Léopold Bellan rehabilitation center

The first database was constituted at the Léopold Bellan Prevention and Rehabilitation Center (Tracy-le-Mont, Oise) between March 2019 and March 2020. Data from this center were used in the first and third studies of the thesis. From the initial database, 58 consecutive patients were included based on the availability of both a baseline and a post-rehabilitation CPET incorporating SM-ICG-derived hemodynamic measurements.

Eligibility criteria reflected routine clinical indications for CCR and were aligned with national recommendations issued by the Société Française de Cardiologie. Patients were included if they completed the full CCR program and both CPET assessments. Exclusion criteria were those commonly applied in clinical practice for safety reasons and were not specific to this research work.

This cohort predominantly comprised patients with coronary artery disease (CAD) or high cardiovascular risk, including individuals with multivessel coronary disease and prior revascularization procedures (percutaneous coronary intervention and/or coronary artery bypass grafting). A smaller subset included patients with chronic heart failure or prior valvular surgery. Among the 54 patients with recent echocardiographic data, mean left ventricular ejection fraction (LVEF) was approximately 54%, indicating a predominance of preserved systolic function. Seven patients had mildly reduced LVEF (41–49%), and five had reduced LVEF (≤40%). Follow-up echocardiographic data after CCR were available in 30 patients. Of the 58 patients included, 57 had analyzable SM-ICG recordings, with one dataset excluded due to signal loss near peak exercise.

Second Database: Corentin Celton Hospital Rehabilitation Center

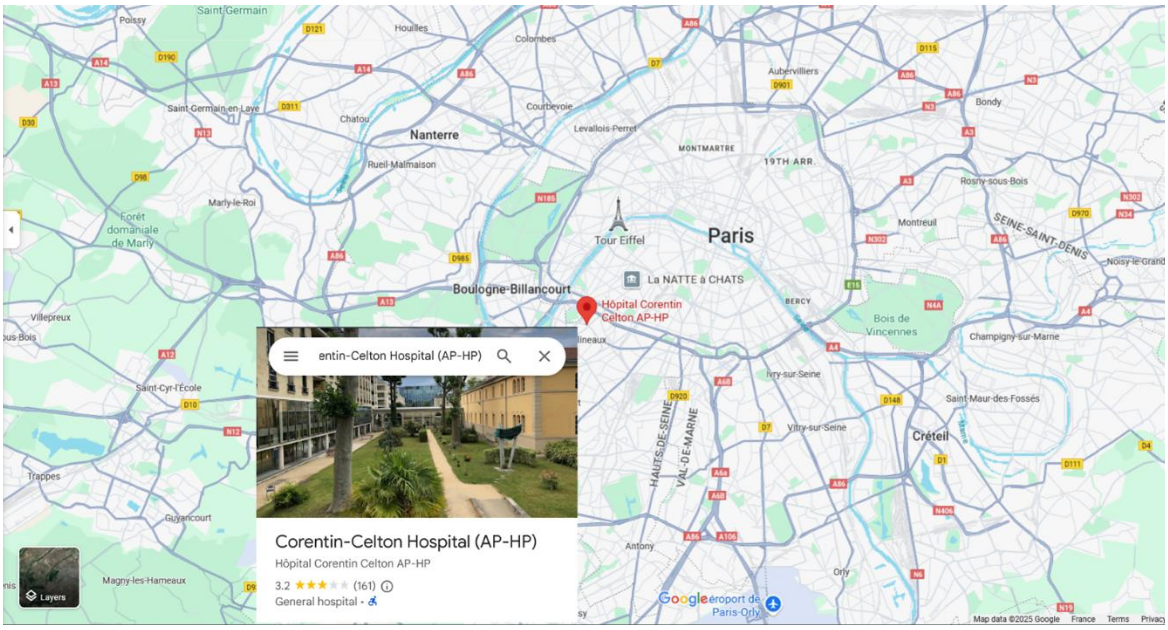


Illustration 28: location of the Corentin Celton rehabilitation center

The second database was constituted at the Corentin Celton Hospital Rehabilitation Center (Issy-les-Moulineaux, Paris area) between June 2017 and December 2019 and was used in the second and fourth studies of the thesis. This database initially included 99 patients referred for CCR with a primary diagnosis of chronic heart failure.

Inclusion criteria were predefined at the institutional level and included patients aged 18–85 years, clinically stable, and classified as New York Heart Association (NYHA) functional class II to IIIb. Exclusion criteria were designed to ensure patient safety and data quality and included recent acute coronary syndromes, valvular disease requiring surgery, severe pulmonary disease, significant hypotension or anemia, inability to perform exercise testing, or inadequate signal quality for CPET or SM-ICG analysis.

All patients underwent a standardized cardiovascular evaluation including laboratory testing (BNP, renal function, glycaemia, lipid profile), resting transthoracic echocardiography, and CPET combined with SM-ICG. Among the 99 patients initially included, 73 had complete and stable datasets suitable for analysis; 26 patients were excluded due to incomplete CPET data or unstable SM-ICG signals.

This cohort was largely homogeneous and consisted predominantly of patients with heart failure with reduced ejection fraction (HFrEF). Among the 72 patients with echocardiographic assessment, mean LVEF was 28.8 ± 8.0%. Only two patients were classified as having mildly reduced LVEF, and none had preserved ejection fraction.

Rationale for Group Construction

Together, these two databases provided complementary patient populations enabling the exploration of SM-ICG-derived hemodynamic responses across distinct clinical contexts. The first and third studies focused on a heterogeneous population dominated by CAD and preserved systolic function, whereas the second and fourth studies examined a more homogeneous HFrEF cohort. This structure allowed the present work to assess both the generalizability and the pathology-specific relevance of SM-ICG-derived contractility indices within CCR.

Analyzed Patient Population (n = 57+73 = 130)

Table 7: Baseline Demographic and Clinical Characteristics of the Analyzable Population

Variable	Mean ± SD or n (%)	Comments
Age (years)	63.8 ± 10.9	Combined cohorts (CVD + CHF)
Sex (male)	117 (90 %)	13 women total (2 in CVD, 11 in CHF)
BMI (kg·m^{-2})	27.6 ± 4.0	All cohorts
Underlying diagnosis	HF (HfrEF ± CAD): 65 % Coronary disease without HF: 35 %	Databases 1–3 (CVD) and 2–4 (CHF); overlap in ischemic HF cases
LVEF (%)	43 ± 10	Adjusted for overlap between CVD and CHF
NYHA class II–III	42 (58 %)	CHF subgroup only
Hypertension	81 (62 %)	All cohorts
Diabetes mellitus	31 (24 %)	All cohorts
Dyslipidemia	69 (53 %)	All cohorts
Current smoker	17 (13 %)	All cohorts
Beta-blockers	74 (57 %)	≈80 % in CVD, <30 % in CHF
ACEi / ARB	66 (51 %)	CHF predominant
Statins	72 (55 %)	Mostly in CVD cohort

Note: Databases 1–3 and 2–4 are distinct, but several participants in the 'CVD' database also presented stable HF (mostly ischemic etiology). Percentages refer to database origin rather than mutually exclusive pathology.

2.1.3.2. Training Protocols

The present studies implemented standardized and homogeneous exercise training protocols, consistent with the national recommendations for cardiovascular rehabilitation issued by the *Société Française de Cardiologie* (2012). These protocols reflect contemporary clinical practice in French inpatient cardiac rehabilitation and were designed to balance safety, physiological effectiveness, and feasibility across heterogeneous patient populations.

The exercise intervention followed a multidisciplinary regimen combining endurance, resistance, and balance/stretching exercises. All sessions were supervised by physiotherapists under the clinical oversight of a cardiologist. Endurance training was performed on a cycle ergometer, scheduled five times per week for 30 minutes per session over a three- to four-week period. Each session included a standardized five-minute warm-up and five-minute cool-down. The weekly program alternated between Moderate-Intensity Continuous Training (MICT) and High-Intensity Interval Training (HIIT) modalities. Continuous sessions were initially prescribed at an intensity corresponding to VT_1, ensuring a sustainable workload aligned with daily functional capacity.

HIIT sessions consisted of one-minute exercise bouts performed at 85–90% of VO_2peak, interspersed with three- to four-minute active recovery periods below VT_1. HIIT is increasingly recognized as a safe and effective modality in clinically stable cardiac patients when delivered under professional supervision and following appropriate risk stratification. Importantly, while HIIT has been shown to elicit greater improvements in VO_2peak compared with MICT, its implementation in standard cardiac rehabilitation remains complementary rather than exclusive, particularly in programs primarily oriented toward moderate-intensity training. In this context, HIIT was integrated in a pragmatic and progressive manner, allowing patients to benefit from higher-intensity stimuli without compromising safety or adherence.

Exercise intensity was progressively adjusted every two to three sessions by increasing workload by 5–10 watts, guided by Borg's perceived exertion scale (target range: 12–14) and clinical tolerance. Resistance training was performed three times per week for 30 minutes per session and focused on bodyweight exercises targeting both upper and lower limb muscle groups. In addition, participants engaged in balance and flexibility training sessions lasting 30 minutes, five times per week.

All training modalities were conducted under continuous supervision, including ECG monitoring, blood pressure measurements, and systematic assessment of perceived exertion. Training loads were re-evaluated every two weeks based on clinical status and repeat submaximal testing, allowing individualized progression and progressive overload tailored to patient adaptation.

Overall, by combining MICT and HIIT within a supervised, multidisciplinary framework, and by aligning with national recommendations, the adopted protocols ensured high levels of safety while allowing exposure to physiologically meaningful intensity domains. This hybrid approach reflects current evidence suggesting that both continuous and interval training can be effectively integrated in cardiac rehabilitation, depending on patient profile, clinical stability, and program objectives.

2.1.4.Response Criteria and Statistical Methods

2.1.4.1. Response Criteria: Definitions, Rationale, and Methodological Validity

In clinical exercise physiology and CCR, defining what constitutes a response to exercise-based interventions remains a core methodological challenge. Accurate classification of R and NR affects program evaluation, adaptive prescription, and mechanistic interpretation. While $\dot{V}O_2$peak is a standard index with strong prognostic value, the choice of threshold and the use of complementary indicators vary across studies.

Traditional $\dot{V}O_2$peak Thresholds

The decision to consider a rate of increase in $\dot{V}O_2$peak greater than 5% as a qualifying response to training can be controversial. Some studies have chosen higher rates, in the order of +10%, which may be very clinically significant and also closer to a statistical median (Mroué et al., 2023; Legendre et al., 2021). However, using this criterion, only half of the study population would have been R compared to 70% using the +5% criterion. Other studies have defined a +0% threshold for a positive CCR response (Little et al., 2022) (78% of patients had a positive response to CCR in this particular study). We believe that a 5% criterion remains a good compromise: it is a "real" improvement (beyond technical and physiological variability) and is also clinically relevant for these patient groups and not based on a purely statistical approach. It should be noted that in our group of patients, the average response in terms of changes of maximal oxygen uptake value after CRR ($\Delta\dot{V}O_2$peak) (+13.6 ± 22.9%) is consistent with the expected range of improvement observed in comparable studies (from +8.5% to +16.0%) (Prescott et al., 2020; Snoek et al., 2021).

Hybrid and Composite Criteria

Single-criterion schemes can miss relevant adaptations—especially in patients who improve via peripheral mechanisms (mechanical efficiency or $(a\text{–}\bar{v})O_2$diff) with limited central gains. Hybrid definitions therefore combine central and peripheral markers. For example, Schmid et al. (2013) proposed a composite endpoint: ≥ 5% increase in $\dot{V}O_2$peak and/or ≥ 10% increase in Wpeak and/or ≥ 5% decrease in $\frac{\dot{V}E}{\dot{V}CO2}$ slope, acknowledging multidimensional improvement.

Hybrid 1 MET Criterion Used in the Present Thesis

In the final study of this thesis, we adopted a pragmatic 1 MET hybrid criterion: $\Delta\dot{V}O_2\text{peak} \geq 3.5$ $\text{mL·min}^{-1}\text{·kg}^{-1}$ and/or $\Delta\text{Wpeak} \geq 24$ W. This integrates aerobic capacity and mechanical performance, recognizing that older or heart-failure patients may increase power without large $\dot{V}O_2$peak changes. Importantly, a 1 MET increase in cardiorespiratory fitness is associated with an ≈ 12% reduction in mortality risk, and even +25% in severe HFrEF (Keteyan et. al. 2008). This criterion yielded a balanced distribution (NR = 41; R = 32) in a physiologically heterogeneous cohort. Notably, eight patients would have been labeled NR by $\dot{V}O_2$peak alone despite Wpeak gains up to 43 W—consistent with peripheral improvements (blood-flow redistribution, pedaling efficiency).

Physiological Interpretation and Clinical Use

- Central R: parallel increases in $\dot{V}O_2$peak, SV, and $\dot{Q}c$.
- Peripheral R: improved mechanical efficiency of $(a\text{–}\bar{v})O_2$diff with modest $\dot{V}O_2$peak change.

- Mixed R: combined central/peripheral adjustments modulated by baseline status, therapy, and comorbidities.

Integrating hemodynamic indices (e.g., SV reserve, CTi_reserve from SM-ICG) alongside $\dot{V}O_2$peak and Wpeak refines response phenotyping and guides personalized training targets.

Table 8: Summary of Response Criteria Across the Four Thesis Studies

Study	Population	Core Outcome(s)	Response Threshold	Notes
Study 1	CVD (heterogeneous)	$\dot{V}O_2$peak	R = $\Delta\dot{V}O_2$peak ≥ 5%	Threshold exceeds CPET CV (<4%); clinically meaningful
Study 2	CHF (predominantly HFrEF)	$\dot{V}O_2$peak	R = $\Delta\dot{V}O_2$peak ≥ 5%	Aligned with Study 1
Study 3	CVD (abstract)	$\dot{V}O_2$peak	R = $\Delta\dot{V}O_2$peak ≥ 5%	Methodological coherence with Studies 1–2
Study 4	CHF (predominantly HFrEF)	$\dot{V}O_2$peak and Wpeak (hybrid)	R = $\Delta\dot{V}O_2$peak ≥ 3.5 $mL\cdot min^{-1}\cdot kg^{-1}$ and/or ΔWpeak ≥ 24 W (≈ 1 MET)	Balanced split: NR = 41; R = 32. Eight would be NR by $\dot{V}O_2$ alone despite up to +43 W in Wpeak

Statistical Methods

“I only believe in statistics that I doctored myself.” apocryphally attributed to W. Churchill.

Statistical analyses for all studies were conducted using JASP (version 0.17.1 for Apple Silicon, JASP Team, VU Amsterdam, The Netherlands). All results are expressed as mean ± Standard Deviation (SD). Prior to inferential testing, data normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was verified using Levene’s test. Depending on the outcome of these preliminary analyses, comparisons of key variables such as changes in $\dot{V}O_2$peak ($\Delta\dot{V}O_2$peak) between groups were evaluated using either the independent samples Student’s t-test, the Welsh test or the Mann-Whitney U test.

To assess the relationships between the CTi and CPET responses, multivariate logistic regression analyses were conducted. These models were adjusted for several potential confounding variables including age, sex, baseline $\dot{V}O_2$peak, LVEF, and duration of CCR. Variables with a significance level of $p < 0.10$ in univariate analyses were retained as covariates in adjusted models. The primary dependent variable was the CTi response to CPET. Odds Ratios (OR) and 95% confidence intervals were computed to quantify associations.

Additionally, the second study incorporated an evaluation of Effect Sizes (ES) to determine the practical significance of the findings, independent of sample size. Cohen's d was calculated, with ES values interpreted as small (0.2–0.4), medium (0.5–0.8), or large (>0.8). Given the non-normal distribution and unequal variance in some data subsets, non-parametric methods were applied, including the Mann-Whitney U test for independent samples and Spearman correlation analysis to explore associations between CTi_max and both $\dot{V}O_2$peak and LVEF.

To control the inflation of Type I error due to multiple hypothesis testing, the Bonferroni correction was employed in the fourth study. The conventional significance level ($p = 0.05$) was adjusted by dividing it by the number of independent comparisons (two), thereby establishing a more stringent criterion for statistical significance ($p = 0.025$).

This rigorous statistical approach ensures robust, reproducible insights into the relationship between myocardial contractility and functional performance following cardiac rehabilitation.

2.2. CHAPTER 5: RESULTS OF THE THESIS

This chapter summarizes the findings of four complementary studies exploring the prognostic and mechanistic role of the CTi, measured through SM-ICG, in CCR. Together, they demonstrate how myocardial contractile performance and its adaptability (CTi_reserve) influence the heterogeneity of training response in CVD and HF populations.

2.2.1. Study 1 – Predictive Value of Baseline CTi Profile in a CVD Population

In 72 patients with stable CVD (mainly CAD), baseline CTi profile obtained during the initial CPET was categorized as normal or abnormal. After CCR, 85.7 % of patients with normal CTi achieved ≥ 5 % $\Delta\dot{V}O_2$peak vs 44 % with abnormal CTi. Logistic regression confirmed predictive value (OR 8.7; $p = 0.009$). Thus, a preserved CTi response indicates higher adaptive potential and could serve as a practical predictor of CCR success.

2.2.2. Study 2 – Validation of CTi Predictive Role in CHF

In 65 patients with chronic HF (LVEF 29 ± 8 %), 78 % with normal CTi responded (≥ 5 % $\Delta\dot{V}O_2$peak) vs 64 % with abnormal CTi. R showed higher $\Delta\dot{V}O_2$peak (28 ± 30 % vs 14 ± 19 %, $p < 0.01$). Logistic regression: OR 3.3. Predictive power declined compared to Study 1, likely due to limited cardiac reserve, but CTi remained independently associated with outcome.

2.2.3. Study 3 – Mechanistic Evidence of Contractile Plasticity

In 58 cardiac patients (mean age 50 ± 10 years), 42 completed pre/post CR CPET + SM-ICG. Of 25 patients with abnormal CTi, 16 responded to CCR. R: + 70.22 ± 55.38 % CTi_reserve; NR: − 12.03 ± 24.92 % ($p = 0.007$). This highlights contractile plasticity—the heart's ability to regain contractile reserve through training.

2.2.4. Study 4 – Hemodynamic Determinants of Response in HFrEF

In 73 HFrEF patients (LVEF 28.8 ± 8.0 %), R were defined by ≥ 3.5 $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ $\Delta\dot{V}O_2$peak peak and/or ≥ 24 W ΔWpeak (1 MET). 32 R (43.8 %) and 41 NR (56.2 %) were identified improved CI_reserve (3.1 ± 1.1 vs 2.2 ± 1.5 $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, $p = 0.004$), SVi_reserve (10.4 ± 5.0 vs 6.3 ± 6.4 $\text{mL}\cdot\text{m}^{-2}$, $p = 0.004$), and HR_max (129.7 ± 26.7 vs 112.9 ± 25.2 bpm, $p = 0.007$).

CTi_reserve rose in 94 % of R (+ 64.3 ± 78.2 AU) and fell in 93 % of NR (− 13.2 ± 52.7 AU; $p < 0.001$). These results suggest that central contractile recruitment, rather than peripheral efficiency, drives functional improvement in HFrEF rehabilitation.

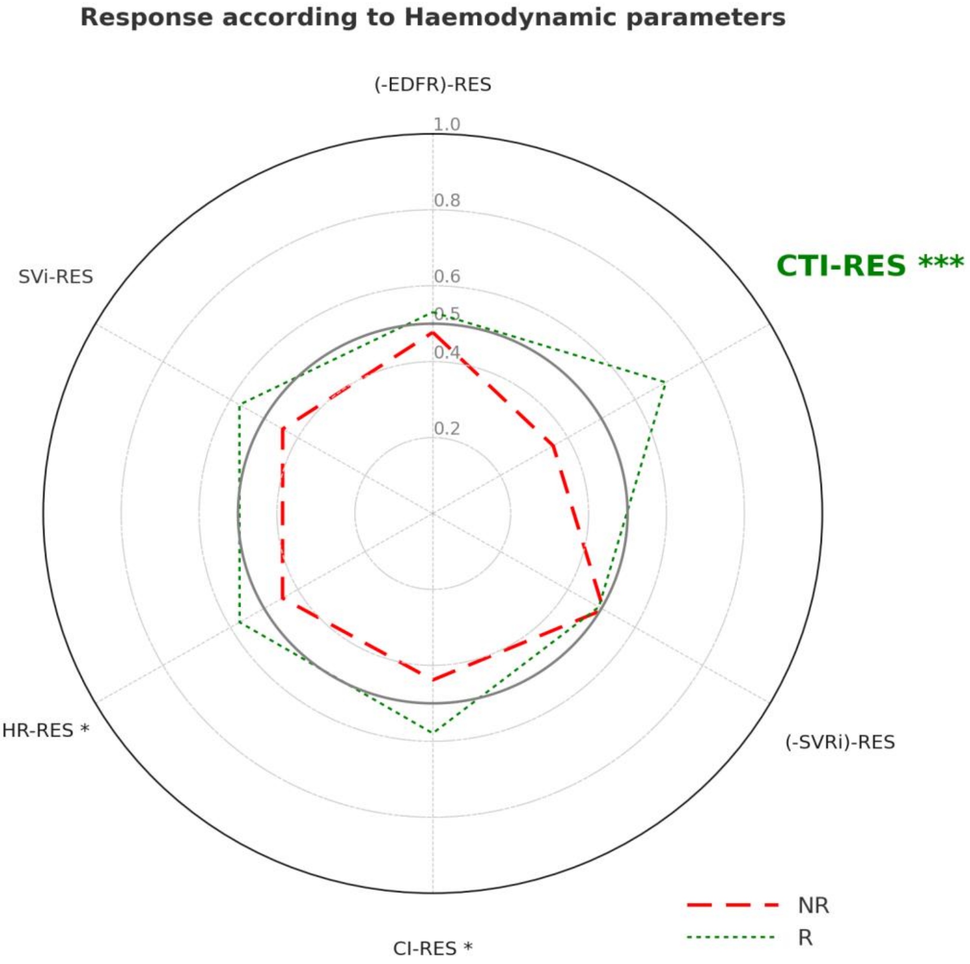


Illustration 29: Radar plot for Haemodynamic Parameters

RES = Reserve **SVi** = Stroke Volume index Index **CI** = Cardiac Index

SVRi = Systemic Vascular Resistance index **EDFR** = LV Preload index

Note: all axes are normalized around the mean value +/- 2SD

Table 9: Summary of the Four Thesis Studies

Study	Population	Response Criterion	CTi-related Findings	Interpretation
1	CVD (n = 72)	$\Delta\dot{V}O_2$peak ≥ 5 %; 85.7 % R vs 44 % NR; OR 8.7 ($p = 0.009$)	Baseline CTi predictive of response	Normal CTi = higher adaptive potential
2	CHF (LVEF 29 %) (n = 65)	$\Delta\dot{V}O_2$peak ≥ 5 %; 78 % R vs 64 % NR; OR 3.3	Normal CTi predicts $\Delta\dot{V}O_2$peak (+ 28 ± 30 % vs 14 ± 19 %)	CTi remains predictive despite disease severity
3	Cardiac (n = 58)	$\Delta\dot{V}O_2$peak ≥ 5 %; + 70.22 ± 55.38 % R vs − 12.03 ± 24.92 % NR ($p = 0.007$)	CTi_reserve improves in R only	Myocardial contractile plasticity
4	HFrEF (n = 73)	$\Delta\dot{V}O_2$peak ≥ 3.5 mL·min^{-1}·kg^{-1} and/or ≥ 24 W (1 MET)	94 % R ↑ CTi_reserve vs 93 % NR ↓ ($p < 0.001$)	Central hemodynamic adaptation drives outcome

The differences in predictive strength observed between the general CVD and CHF populations—particularly regarding the discriminative value of baseline CTi profiles—are analyzed in the following chapter.

2.3. CHAPTER 6: ANALYSIS OF THE THESIS STUDIES

2.3.1.Discussion

Drawing on the results presented in Chapter 5, this chapter integrates and interprets the findings, focusing on the mechanisms underlying CTi-based prediction and its clinical implications in cardiac rehabilitation. Across all populations, SM-ICG-derived CTi and CTi_reserve emerged as powerful, non-invasive indicators of both training responsiveness and physiological adaptation.

An important observation across the studies concerns the difference in predictive power of CTi profiles between cohorts. In the CVD population, baseline CTi profile was a strong discriminator (OR 8.7), whereas in CHF it remained significant but weaker (OR 3.3). This divergence can be explained by both physiological and methodological factors. The CVD cohort was more heterogeneous, encompassing patients with a broad range of baseline contractile function—from near-normal to moderately reduced—allowing CTi to effectively differentiate those with preserved cardiac reserve. In contrast, the CHF cohort was more homogeneous, composed largely of individuals with advanced systolic dysfunction and chronotropic limitation, where contractile variability is compressed. Furthermore, pharmacologic modulation (particularly β-blockers and ACE inhibitors) and autonomic dysfunction limit the amplitude of CTi and $\dot{V}O_2$ responses, even when adaptation occurs. Exercise prescriptions for CHF are often constrained to lower intensities, resulting in smaller measurable $\dot{V}O_2$ gains despite genuine central improvement. Together, these elements explain the lower odds ratio observed in the CHF group and highlight that CTi remains valuable precisely because it captures subtle hemodynamic changes that $\dot{V}O_2$peak alone may underestimate.

Mechanistic Interpretation:

CTi, reflecting the maximal slope of systolic impedance change, parallels dV/dt_max and thus quantifies inotropic state non-invasively. Across studies, improvements in CTi_reserve mirrored increases in $\dot{Q}c$ and SVi_reserve, confirming that enhanced contractile efficiency underlies CCR response.

The Fick-based analyses from Study 4 showed that while $\dot{V}O_2$peak and $\dot{Q}c$ _max increased, $(a\text{-}\bar{v})O_2$diff remained stable, indicating a central—not peripheral—mechanism of adaptation.

Even patients with initially abnormal CTi achieved substantial improvement (+ 70.22 ± 55.38 %), demonstrating true myocardial trainability. This evidence supports the concept of 'contractile plasticity'—a physiological substrate of functional recovery—and positions CTi_reserve as a direct biomarker of exercise-induced myocardial remodeling.

Clinical Implications

Clinically, CTi profiling can support three key functions: (1) stratification—predicting R before CR; (2) monitoring—tracking functional progress via CTi_reserve; and (3) optimization—adjusting workloads based on hemodynamic response. Because SM-ICG is quick, non-invasive, and compatible with CPET, it is easily deployable in rehabilitation centers.

Patients with preserved CTi_reserve can follow standard aerobic and resistance training protocols, while those with blunted responses may benefit from gradual, low-intensity regimens or medical optimization prior to full CR. The hybrid 1 MET criterion adopted in Study 4 also provides a clinically meaningful outcome threshold associated with an estimated 12 % mortality reduction per MET gain (Myers et al., 2002), and even more in HFrEF.

2.3.2.Limitations of the Studies

The studies presented herein—spanning two observational full-paper research and two complementary abstracts on a general CVD cohort and another one focused on HFrEF—carry several limitations that must be acknowledged to contextualize their findings and interpret the implications appropriately.

First, the relatively small sample sizes, though sufficient to yield statistically significant results, constrain the generalizability of the findings. In the primary studies involving the general CVD population, the number of patients eligible for analysis was limited despite a low exclusion rate. In contrast, the CHF studies reported a higher exclusion rate due to poor-quality SM-ICG signal acquisition, with 11% of recordings being discarded. This discrepancy might raise concerns regarding procedural adherence to signal acquisition protocols and emphasizes the need for standardization and operator training. Signal quality variability could represent a notable limitation for broader implementation of CTi monitoring.

Second, a significant gender imbalance was observed in both studies. In the general CVD cohort, only two women were included, while eleven were present in the CHF cohort. This reflects a systemic underrepresentation of women in CCR programs and limits the ability to assess potential sex-specific differences in hemodynamic adaptation and response prediction. It underscores the necessity of more inclusive recruitment strategies in future research to enable gender-sensitive interpretation of CTi responses.

Third, the monocentric, retrospective, and non-randomized design of all four studies restricts external validity but simultaneously confers strengths in methodological consistency. Uniformity in exercise testing, SM-ICG data acquisition, and interpretation protocols reduces inter-center variability and enhances internal validity.

Fourth, heterogeneity in patient characteristics—particularly pharmacological treatment—may have influenced hemodynamic responses. However, only one drug class, beta-blockers (specifically bisoprolol), possesses known negative inotropic effects. This drug was prescribed to fewer than one-third of patients in the CHF study and did not appear to confound the relationship between CTi_reserve and training response. Nonetheless, broader studies adjusting for drug treatment covariates are warranted.

Fifth, patient populations were focused on HFrEF and a broader CVD group that included CAD, with minimal representation of patients with preserved EF (HFpEF). Given prior evidence of abnormal hemodynamic responses in HFpEF patients using SM-ICG technology, future studies should explore whether CTi and its derived indices retain similar predictive and mechanistic value in this growing population.

Sixth, while CTi provides a promising surrogate of myocardial contractile performance, it is not a direct measure of contractility and may be influenced—albeit to a lesser extent—by changes in preload and afterload. CTi is derived from the normalized maximum first derivative of the impedance signal (dZ/dt_max), a parameter validated in several studies for its correlation with invasive indices of contractility. However, comparisons with echocardiographic markers like LVEF or GLS are limited due to differing measurement principles and the latter's known limitations during exercise.

Seventh, parameters used to estimate preload and afterload carry intrinsic limitations. Early Diastolic Filling Ratio (EDFR), while reflective of preload trends, does not equate to a volumetric measure such as end-diastolic volume. Similarly, SVR, used to approximate afterload, is susceptible to inaccuracies from estimated central venous pressure (CVP), non-invasive blood pressure readings during exercise, and the inherent assumptions of vascular compliance. Notably, SVR fails to capture pulsatile afterload components such as aortic impedance.

Eighth, the graphical classification of CTi slope reserve (CTi_reserve) relied on expert visual interpretation using the PhysioFlow® software's averaging tools. While analysis reproducibility was tested and found acceptable—only 5 of 58 cases showed interpretation discrepancies in the CTi profile, most of which were deemed abnormal profiles anyway by all operators—the potential for operator bias remains. The development of automated pattern recognition algorithms for CTi profile categorization could enhance standardization and reproducibility, especially in multicenter trials and clinical applications.

Ninth, a further limitation of this work is the primary reliance on $\dot{V}O_2$peak as the main functional outcome to characterize response to CCR. Although $\dot{V}O_2$peak is widely regarded as the reference index of global cardiorespiratory fitness and carries strong prognostic value, it may not represent the most clinically relevant or sensitive marker of adaptation in the context of conventional cardiac rehabilitation programs. Standard CR is predominantly based on moderate-intensity continuous exercise, which typically induces greater improvements in submaximal exercise tolerance than in maximal aerobic capacity. Consequently, functional adaptations are often more clearly expressed as increases in VT_1 than as changes in $\dot{V}O_2$peak. From a clinical perspective, VT_1 reflects the intensity domain associated with daily living activities, sustained functional autonomy, and perceived quality of life, and is therefore highly relevant for patient-centered evaluation and exercise prescription. Moreover, many patients undergoing cardiac rehabilitation—particularly older individuals, those with heart failure, frailty, or β-blocker therapy—do not consistently reach true maximal effort during cardiopulmonary exercise testing. In such cases, $\dot{V}O_2$peak may underestimate the true physiological and functional benefits of training. This raises the possibility that some individuals classified as "non-responders" based solely on $\dot{V}O_2$peak criteria may nevertheless experience clinically meaningful improvements in submaximal performance, which were not fully captured in the present analyses.

Although VT_1 was available and discussed as a complementary parameter, it was not used as a primary outcome in the definition of rehabilitation response. Future studies should therefore consider prioritizing VT_1, or combining maximal and submaximal indices (e.g., VT_1, OUES), to provide a more comprehensive and clinically grounded assessment of functional adaptation to cardiac rehabilitation, particularly in real-world patient populations.

Finally, a further limitation of the present studies relates to the determination VT_1. In all analyses, VT_1 was identified exclusively using the V-slope method, as originally described by Beaver et al. (1986). While the V-slope approach is widely accepted and recommended for VT_1 determination during cardiopulmonary exercise testing, it relies on visual or semi-automated identification of a breakpoint in the $\dot{V}CO_2$–$\dot{V}O_2$ relationship and is therefore subject to inter-observer variability and methodological uncertainty.

VT_1 was not systematically corroborated using complementary approaches such as ventilatory equivalents ($\dot{V}E/\dot{V}O_2$), $PETO_2$, or blood lactate measurements. The absence of cross-validation using multiple physiological criteria introduces a potential risk of misclassification of VT_1, particularly in patients with altered ventilatory control, abnormal breathing patterns, or low exercise tolerance, as commonly encountered in cardiac rehabilitation populations.

Given that VT_1 served as a reference for exercise prescription, training progression, and physiological stratification in the present work, inaccuracies in its determination may have influenced both training intensity allocation and subsequent interpretation of submaximal adaptations. Future studies should therefore consider a multimodal approach to VT_1 determination, combining metabolic, ventilatory, and, when feasible, biochemical indices, in order to enhance the robustness and reproducibility of threshold-based analyses in cardiac rehabilitation research.

Taken together, these limitations underscore both the promise and the current methodological challenges inherent in CTi monitoring via SM-ICG in CCR. Addressing these limitations through protocol optimization, expanded cohorts, automation tools, and prospective validation in broader populations will be essential for the robust integration of this technology into routine rehabilitation pathways

2.3.3. Perspective of the Thesis

Practical implementation of the results in cardiac rehabilitation

The studies conducted within this doctoral work highlight the practical clinical value of SM-ICG and its derived CTi in optimizing cardiac rehabilitation (CR). They show that measuring cardiac contractile reserve through CTi helps predict and guide individual responses to training—both in general CVD and CHF populations.

To make these results directly applicable, two perspectives should be considered: what the cardiologist should retain, and what the cardiac patient should retain.

What the Cardiologist Should Retain

- CTi identifies R: A higher or increasing CTi during exercise (CTi_reserve) predicts better improvements in $\dot{V}O_2$peak and SV with training.
- A practical, non-invasive marker: SM-ICG offers real-time evaluation of contractile reserve without echo or invasive testing, suitable for repeated use in CR.
- Individualized prescription: CTi profiling supports tailoring of exercise intensity — preserved CTi_reserve → standard aerobic + resistance training; blunted CTi_reserve → start with low-intensity, cardiovascular-focused sessions.
- Predictive for follow-up: Tracking CTi over time helps evaluate progress and adjust rehabilitation plans dynamically.
- Early identification of NR: Enables timely adjustment of therapy or pharmacologic optimization before or during CR.
- Efficient and scalable: Applicable in daily practice, even in centers without advanced imaging.

What the Cardiac Patient Should Retain

- Your heart can adapt—and we can measure it. The CTi tells us how strongly your heart contracts during effort and how it improves with training.
- Your program can be personalized. The measurements help your team choose the right training pace and safely increase it as your heart gets stronger.

- Progress can be tracked objectively. You and your care team can see if your cardiac reserve improves over time, not just your symptoms.
- Better results, fewer risks. Knowing your heart's contractile reserve means we can optimize your training safely, avoid overexertion, and target what really helps your recovery.
- Less need for complex tests. This method is non-invasive, fast, and can be repeated without discomfort.

In summary, the integration of SM-ICG and CTi into CCR represents a practical step toward personalized, physiology-based care. It allows clinicians to move beyond a 'one-size-fits-all' model, improving safety, precision, and long-term outcomes for patients recovering from CVD or HF.

The following flowchart summarizes a decision-making model that integrates CTi profiling into CCR planning:

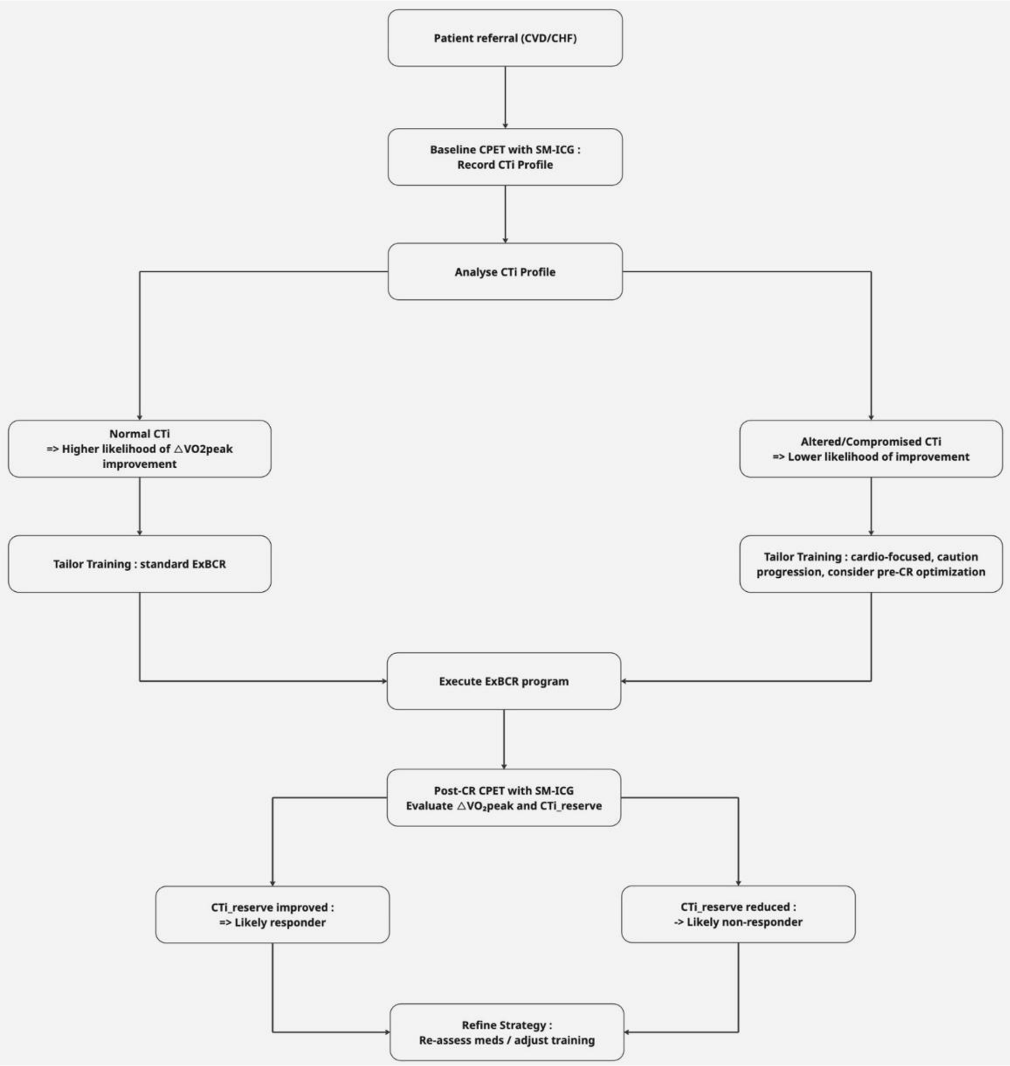


Illustration 30: Flow Chart CTi decision tree in CCR

However, significant barriers to implementation remain:

Illustration 31: The "systemic Stress Test"

1) Funding and reimbursement

Economic and policy barriers remain a primary obstacle to the widespread adoption of advanced physiological monitoring in CCR. While SM-ICG holds regulatory approval and technical maturity, it still lacks consistent reimbursement across health systems. In the United States, Current Procedural Terminology (CPT) codes exist but offer minimal remuneration (≈ 27 USD per ICG test, similar to the one applied in PR China), whereas no dedicated reimbursement pathway currently exists in Europe. Without financial recognition of its diagnostic or prognostic value, the method's clinical penetration is likely to remain limited to research or specialized centers (Ades et al., 2017; Balady et al., 2007).
However, the reimbursement landscape in the United States is slowly evolving. A growing number of healthcare institutions have recognized that unplanned 30-day rehospitalizations for CHF are no longer reimbursed under Medicare's Hospital Readmissions Reduction Program, resulting in substantial financial penalties and increased operating costs for hospitals (Centers for Medicare & Medicaid Services, 2024). Consequently, there is a mounting incentive to implement cost-effective strategies capable of predicting and preventing early readmissions. In this context, CCR—particularly when optimized with individualized physiological monitoring—has gained renewed strategic importance (Anderson & Taylor,

2014). Technologies such as SM-ICG provide real-time hemodynamic data that can identify high-risk patients, guide exercise intensity, and detect early signs of decompensation. Their integration into post-discharge rehabilitation workflows may therefore contribute to improved patient stability and a reduction in avoidable readmissions, aligning both clinical and economic objectives (Piepoli et al., 2010). As value-based care models expand and outcome-based reimbursement systems gain prominence, financial recognition for such predictive and preventive interventions is expected to progressively improve in the coming years.

2) Professional territoriality

Professional territoriality continues to hinder the diffusion of diagnostic innovation in CCR and cardiology in many cases, particularly concerning the delegation of basic cardiac function assessments. While invasive diagnostics and advanced ultrasound rightly remain within the cardiologist's domain, non-invasive modalities such as point-of-care ultrasound and ICG are often withheld from rehabilitation physicians and pulmonologists. This reluctance is largely cultural, linked to the historical dominance of cardiologists in echocardiographic practice. As noted by Narula et al. (2020) in the American Journal of Cardiology, cardiologists have shown hesitation to adopt or delegate such techniques to non-cardiology disciplines, often due to perceived threats to diagnostic control and professional identity. Similar protective behaviors have been documented in radiology (Leslie, 2018). In CCR, this dynamic contributes to the underutilization of simple yet informative diagnostic techniques that could improve early risk detection and training personalization. In the experience of the author of this thesis, institutional resistance to decentralizing ICG remains common, despite its simplicity, safety and efficacy.

In practice, such territorial boundaries can delay or limit the integration of simple, safe, and informative techniques that would enhance early cardiovascular risk detection and optimize exercise prescription. **In** the experience of the author of this thesis, these professional silos are frequently visible in hospitals, where departments operate in isolation. Cardiologists are often unaware that pulmonologists already perform exercise hemodynamics with SM-ICG, or that pediatric cardiology services routinely use PhysioFlow for congenital or functional evaluations. Even within the same institution, the heart-failure unit may be unaware that another department applies the same technology successfully in its own patient group. This compartmentalization reflects an institutional inertia that continues to impede the broader adoption of scalable, non-invasive hemodynamic monitoring tools that could benefit both clinical and preventive cardiology

3) Shortage of staff and declining motivation

The implementation of individualized CCR strategies also faces workforce challenges. Across Europe and North America, many rehabilitation centers report shortages of qualified physiotherapists, exercise physiologists, and specialized nurses. Increased administrative workload, time pressure, and limited recognition of rehabilitation outcomes contribute to declining motivation and professional fatigue. The introduction of novel measurement tools such as SM-ICG may be perceived as additional complexity rather than as clinical enhancement, unless accompanied by targeted training and streamlined workflows. This situation has been exacerbated by the post-pandemic shift of healthcare resources toward acute care, often at the expense of chronic prevention and rehabilitation programs (Ambrosetti et al., 2021).

4) Technical and logistical integration challenges

Successful adoption of SM-ICG also requires integration within existing data ecosystems. In many centers, exercise testing, ECG telemetry, and CPET results are managed on separate software platforms, with limited interoperability or automated reporting. This fragmentation hampers longitudinal analysis of hemodynamic trends. Standardized acquisition protocols, unified data formats, and automated signal-quality validation would enhance reproducibility and facilitate implementation across centers. Collaboration with device manufacturers to integrate SM-ICG outputs into stress ECG systems, or CPET, and into electronic health records could further streamline usage and facilitate clinical decision-support tools.

5) Regulatory bureaucratic and educational inertia

Despite its clinical potential, SM-ICG remains underrepresented in national guidelines and professional training curricula. Lack of formal recognition in the European Association of Preventive Cardiology educational framework and limited regulatory clarity regarding its application in exercise testing slow its diffusion. Integrating impedance-based indices into official CR curricula and establishing certification pathways for allied professionals would promote safe, standardized utilization. Updating reimbursement and guideline structures to acknowledge hemodynamic parameters like CTi_reserve as legitimate markers of cardiac performance could substantially accelerate adoption.

In summary, the present studies contribute to bridging the gap between physiological understanding and clinical practice in CCR. By demonstrating that CTi dynamics reflect adaptive cardiac responses to exercise and can predict rehabilitation outcomes, this work supports the emergence of a physiology-guided, individualized rehabilitation model. Overcoming financial, organizational, and cultural barriers will be essential to translate these findings into routine care. If implemented within a multidisciplinary framework that values both precision and accessibility, CTi-based profiling may become a cornerstone of next-generation cardiac rehabilitation—one that combines mechanistic insight with pragmatic feasibility.

2.3.4. Future Perspectives and Research Directions for SM-ICG and CTi in Cardiac Rehabilitation and Beyond

The integration of SM-ICG into CCR practice represents a pragmatic step toward individualized cardiovascular care. Among SM-ICG's beat-to-beat hemodynamic parameters, the CTi provides actionable information on myocardial inotropy during exercise and recovery, complementing volumetric indices and ventilatory markers. Current evidence in this thesis and in the literature indicates that SM-ICG delivers physiologically sensitive, reproducible trends—well suited to serial testing in rehabilitation and ambulatory contexts—while its portability and affordability align with the scaling needs of diverse health systems. Recent findings in the present work underscore CTi's clinical value. In mixed CVD and CHF cohorts, SM-ICG-derived metrics (CTi, SV, CI) helped phenotype R versus NR and anticipated gains in $\dot{V}O_2$peak, while clarifying whether central (convective) or peripheral (diffusive) mechanisms dominate the training response. These observations support a tiered pathway in which SM-ICG serves as a first-line, scalable screen—paired with stress ECG—to triage who should be escalated to metabolic CPET or stress echocardiography.

1) Standardization of CTi-Based Phenotypes

Despite promising early findings, there is still no consensus on how to categorize patients based on CTi profiles. Establishing normative values across age, sex, and pathology (HFrEF/HFpEF, CAD, multimorbidity) is imperative. In this context, standardized CTi trajectories during exercise (from rest → ventilatory threshold(s) → peak → recovery) could help define clinically meaningful phenotypes—such as CTi R and NR, or blunted/paradoxical CTi reserve. This may allow clinicians to anticipate patient response to training, tailor interventions more precisely, and monitor them with greater reproducibility across centers.

2) Longitudinal Studies and Outcome Prediction

Large-scale prospective cohorts and registries are needed to validate CTi/CTi_reserve as predictive markers of benefit. Embedding serial SM-ICG within multicenter rehabilitation networks would provide insight into how early CTi dynamics relate to medium- and long-term improvements in $\dot{V}O_2$peak, rehospitalization, and all-cause mortality. In particular, CTi trends over time could serve as early indicators of insufficient training stimulus or impending clinical decompensation, thereby informing timely adjustments to therapy.

3) Comparative-Effectiveness Trials

While CTi is associated with physiological and prognostic markers, randomized controlled trials comparing CTi-guided versus standard (HR/VT_1-based) rehabilitation strategies remain scarce. Such studies should assess whether titrating intensity to optimize CTi (or avoid CTi drop-off) yields superior functional gains or fewer adverse outcomes within safe HR/BP limits. Preliminary findings presented by Pr. Leprêtre and colleagues (ESC 2018) suggest that stroke-volume–based prescriptions (e.g., training at peak SV power) may enhance $\dot{V}O_2$peak compared with heart-rate-based methods, providing a compelling rationale for CTi-guided exercise prescription as a scalable, non-imaging extension of the ventilatory threshold paradigm.

4) Mechanistic Studies Linking CTi to Myocardial Adaptation

To support CTi as a marker of cardiac contractile performance, mechanistic studies are warranted that validate its physiological correlates. Pairing SM-ICG with strain/strain-rate echocardiography, pressure–strain loops, or cardiac MRI tagging during stress—and, where appropriate, invasive pressure–volume indices—can test how closely CTi reflects inotropic reserve and myocardial work, and clarify preload/afterload effects in vivo.

5) Integration into Clinical Decision-Support Systems

For CTi to influence care broadly, it should be incorporated into user-friendly, interoperable decision-support. Algorithms that include CTi/CTi_reserve for individualized training prescriptions, medication optimization, and follow-up planning—integrated within electronic health records with automated alerts for blunted CTi_reserve—could accelerate adoption while reducing operator dependence.

6) Applications in Underserved or High-Risk Populations

Given its non-invasive, operator-light, and repeat-measure nature, SM-ICG is well suited to frail older adults, HFpEF, patients with multiple comorbidities, and low-resource settings where access to advanced imaging is limited. This aligns with international guidance (e.g., WHO PIR) prioritizing scalable, progressive exercise services with safety monitoring.

7) Pediatric and Congenital Heart Disease

The motion-tolerant and repeatable acquisition characteristics of SM-ICG make it attractive in pediatric and congenital cohorts, where acoustic windows may be challenging and repeated imaging burdensome. Formal validation of pediatric CTi reference trajectories across growth and training is a logical next step.

8) Potential Role in Prehabilitation of Surgical Patients

In addition to its applications in cardiac rehabilitation, SM-ICG may also have a role in the prehabilitation of surgical patients. Prehabilitation, aimed at improving physiological reserve before surgery, has been associated with better postoperative outcomes, particularly in major cardiothoracic or abdominal procedures. CPET—and specifically measures such as $\dot{V}O_2$peak—is widely used to assess baseline fitness and monitor response to prehabilitation. Integrating SM-ICG with CPET could add continuous, non-invasive assessment of myocardial contractility through CTi and provide additional circulatory insights (SV, $\dot{Q}c$). This may refine preoperative risk stratification by identifying individuals with limited inotropic or circulatory reserve who may benefit from more tailored conditioning. Moreover, tracking CTi trends over time might support individualized adjustments to prehabilitation programs. While the clinical use of SM-ICG in this context remains exploratory, randomized evidence shows that multimodal prehabilitation can improve $\dot{V}O_2$peak and reduce complications (e.g., Minnella et al., 2017). Incorporating SM-ICG into similar protocols is a logical next step to test whether added hemodynamic data enhance program effectiveness and risk prediction.

9) CVD Management: From Late Intervention to Early Detection

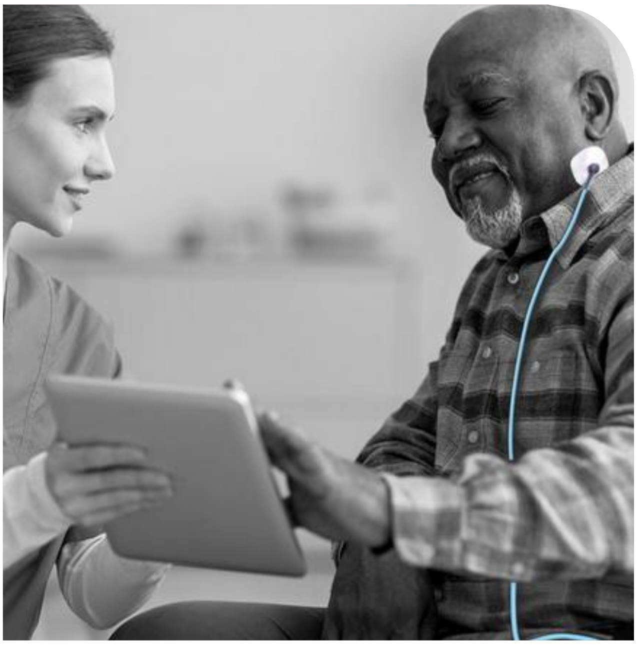


Illustration 32: SM-ICG, measuring and educating

The pandemic of cardiovascular risk factors—notably hypertension, diabetes, obesity, and physical inactivity—continues to expand across both industrialized and developing nations. Large proportions of at-risk individuals remain undiagnosed or undertreated, and the downstream burden of CVD exerts enormous economic pressure on health systems. If current trajectories persist, this burden risks becoming structurally and financially unsustainable within the coming decades—particularly in the United States, where the prevalence of multimorbidity, combined with escalating treatment costs and workforce shortages, threatens the long-term viability of existing care models. The background materials summarized earlier (e.g., CDC Diabetes/Hypertension statistics; American Diabetes Association economic analyses; WHO Non-communicable Disease and PIR reports) consistently show that lifestyle-only prevention measures have yielded limited population-level impact (except for smoking cessation), underscoring the urgent need for systematic case-finding and early functional assessment.

However, the prevailing therapeutic model in cardiology remains dominated by late-stage interventions—implantable devices, surgical procedures, and high-cost pharmaceuticals—that aim to mitigate established pathology rather than prevent its progression. A population-based study of 22 million adults in the United Kingdom demonstrated that, despite two decades of major healthcare investment, cardiovascular incidence and survival gains have largely plateaued (Conrad et al., BMJ 2024; 385: e078523). Such findings highlight the limited scalability and sustainability of approaches focused on end-stage management.

The recent collapse of the French company CARMAT, developer of the Aeson® total artificial heart, exemplifies this challenge: despite remarkable technological innovation, the high complexity, production cost, and limited indications of this device rendered the model economically unsustainable (Medscape, 2025). Similarly, Cardiac Resynchronization Therapy (CRT), while transformative for selected patients with systolic desynchrony, delivers suboptimal real-world performance, with up to half of recipients failing to achieve a meaningful hemodynamic or clinical response (Boriani, 2011; Odigwe et al., 2021). These limitations mirror broader trends observed with Left Ventricular Assist Devices (LVADs), whose destination-therapy cost-effectiveness ratios range between 79 000 and 130 000 USD per quality-adjusted life-year—well above many health systems' willingness-to-pay thresholds (Schaffer et al., 2025; Neyt et al., 2014). Pharmaceutical innovation has also slowed: while Guideline-Directed Medical Therapy (GDMT) continues to improve outcomes, recent drug classes offer only modest incremental benefits, particularly in HFpEF (Sapna, 2023; Yang et al., 2023).

Taken together, these examples illustrate that intensifying high-cost, technologically complex therapies is unlikely to reverse the global CVD trajectory. Instead, progress will require detecting cardiovascular abnormalities earlier—at a stage when they are more amenable to lifestyle, exercise, or pharmacological intervention, and before structural damage becomes irreversible.

Yet the standard diagnostic technologies are poorly suited to such early, large-scale detection. Invasive hemodynamic measurements (e.g., catheter-based thermodilution) are inappropriate for screening due to their procedural risk and cost. Echocardiography and stress echocardiography, although highly informative, are operator-dependent, time-consuming, and not readily scalable. Positron Emission Tomography (PET), while precise, remains expensive and confined to tertiary centers. Even $\dot{V}O_2$ testing—a gold standard for assessing integrated cardiopulmonary performance—relies on surrogate metabolic indicators rather than direct cardiac measures, limiting its specificity and feasibility for population-level screening. Finally, resting or stress electrocardiography (ECG), the most common first-line test, has well-documented sensitivity limitations: pooled data indicate only ≈ 67 % sensitivity for detecting myocardial ischemia or infarction in the general population (Mendoza, 2017), and up to one-third of ischemic events may present with a normal or non-diagnostic ECG (Akbar et al., 2024). In certain conditions such as Left Bundle Branch Block (LBBB), ST-segment analysis becomes unreliable for detecting ischemia, with sensitivities as low as 33–44 % (Ceballos-Naranjo, 2019; Scherbak et al., 2024). These limitations confirm that traditional technologies, although essential for diagnosis, are not optimized for scalable, preventive detection.

By contrast, SM-ICG represents a truly scalable, non-invasive, and operator-independent alternative. It continuously measures central hemodynamic parameters such as stroke volume, cardiac output, contractility index, and systemic vascular resistance at rest and during exercise, providing a direct physiological window into cardiovascular function. SM-ICG can reveal subclinical abnormalities in cardiac performance before structural disease manifests, offering clinicians a practical means of early risk identification. Compact, affordable, and easily deployable in both clinical and community settings, it can be used alongside stress ECG to triage patients who warrant escalation to echocardiography, CPET, or invasive evaluation. In this tiered model, SM-ICG ensures that specialist resources are focused where they add the greatest value, while enabling wide, equitable, and cost-effective access to preventive cardiovascular assessment.

Conclusion

Reconsidering the Paradigm: Toward a Multidimensional Assessment of Cardiac Rehabilitation Outcomes

For several decades, $\dot{V}O_2$peak has been widely regarded as the cornerstone parameter for evaluating the effectiveness of comprehensive cardiac rehabilitation (CCR) interventions. Its well-established association with long-term cardiovascular outcomes, including mortality and rehospitalization, has justified its use as both a primary endpoint in clinical trials and a reference indicator of patient improvement. Yet, this traditional emphasis on $\dot{V}O_2$peak—and especially on its change with training—has increasingly come under scrutiny for its conceptual and methodological limitations.

While $\dot{V}O_2$peak offers a global reflection of aerobic capacity, it primarily reflects integrative pulmonary gas exchange rather than direct cardiac performance. Parameters derived from cardiopulmonary exercise testing, such as the $\frac{\dot{V}E}{\dot{V}CO2}$ slope, have indeed emerged as powerful prognostic markers in chronic heart failure. However, they remain surrogate indicators, influenced by central, peripheral, and ventilatory factors. The $\frac{\dot{V}E}{\dot{V}CO2}$ slope, for example, may reflect abnormalities in ventilation–perfusion matching or chemoreceptor sensitivity, but provides only an indirect appraisal of left-ventricular function.

Conversely, an exclusive reliance on indices of central function—such as stroke volume, cardiac output, or myocardial contractility—offers valuable mechanistic insight but does not capture the full heterogeneity of training responses. A substantial proportion of patients with coronary artery disease or HFpEF may experience clinically meaningful gains through peripheral adaptations, including enhanced $(a–\bar{v})O_2$ difference, microvascular remodeling, and muscular efficiency. These improvements may occur independently of central hemodynamic augmentation and therefore remain invisible when outcomes are evaluated through a single physiological lens.

This dichotomy between ventilatory-centric and hemodynamic-centric perspectives underscores the need for a paradigm shift. Rather than privileging one variable as a universal proxy for clinical improvement, cardiac rehabilitation should embrace a multidimensional functional assessment framework that reflects the coordinated interplay of cardiac, pulmonary, vascular, and muscular systems. Importantly, this perspective is now explicitly endorsed by contemporary clinical guidelines. Both the European Society of Cardiology (ESC, 2021) and the American Heart Association / American College of Cardiology (AHA/ACC, 2019) recommend comprehensive, multidimensional functional evaluation to guide exercise prescription, risk stratification, and long-term management in cardiac rehabilitation.

Within this framework, the integration of multimodal and sensor-based technologies—such as CPET combined with signal-morphology impedance cardiography (SM-ICG)—provides an orthogonal and physiologically complete view of the rehabilitation response. The present work demonstrates that the Contractility Index (CTi) derived from SM-ICG, and particularly its reserve, tends to improve with training in responders but not in non-responders. Moreover, the shape and dynamics of the CTi profile recorded during the entry exercise test exhibit predictive value for subsequent classification as responder or non-responder.

These findings suggest that the contractile response to effort at baseline reflects intrinsic myocardial adaptability, conditioning the patient's potential for improvement under CCR. Unlike conventional static measures such as resting left-ventricular ejection fraction, CTi trajectories capture the functional responsiveness of the heart to exercise, offering a non-invasive means to anticipate rehabilitation outcomes and support individualized program design.

Each physiological domain—whether cardiac output, stroke volume, contractility, oxygen pulse, or ventilatory efficiency—should therefore be interpreted as an independent axis of adaptation rather than as a substitute for another. The assumption that $\dot{V}O_2$ alone encapsulates cardiac recovery, or that contractility alone dictates outcome, risks oversimplifying a multidimensional and patient-specific process. Recognizing these complementary dimensions is critical for accurately distinguishing responders from non-responders, tailoring exercise prescriptions to individual pathophysiological profiles, and identifying latent dysfunctions that remain obscured by univariate models.

From a clinical perspective, moving toward a multidimensional assessment paradigm may enable earlier recognition of maladaptive responses, optimization of training loads, and a more personalized continuum of care. It reframes cardiac rehabilitation not merely as an aerobic reconditioning program, but as a systems-level intervention integrating hemodynamic, ventilatory, and peripheral dimensions of recovery, in line with current international guideline recommendations.

In conclusion, cardiac rehabilitation is entering a new era in which physiological complexity becomes a strength rather than a limitation. By combining complementary parameters through sensor-fusion approaches such as SM-ICG and CPET, clinicians and researchers can better capture the true dynamics of recovery and resilience. The challenge ahead is not to identify a single "best" metric, but to integrate multiple complementary indicators—including predictive hemodynamic signatures such as CTi trajectories—into a coherent, scalable framework that reflects real-world patient trajectories and supports long-term, guideline-aligned management.

Bibliography and Appendices

Bibliography

Peer-reviewed Publications (Reproduced in Full)

Study 1

Signal-morphology impedance cardiography is a non-invasive tool for predicting responses to exercise-based cardiac rehabilitation

Frank Bour, Evan Milstein, Antoine Poty, Yves Garaud, Damien Vitiello, Pierre Marie Leprêtre

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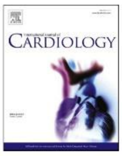

Signal-morphology impedance cardiography is a non-invasive tool for predicting responses to exercise-based cardiac rehabilitation

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ABSTRACT

Exercise Based Cardiac Rehabilitation (EBCR) is highly beneficial to improve the outcome and quality of life of patients suffering from cardiac diseases. Most of the time, it increases cardiorespiratory and muscle capacity. However, not all patients elicit these benefits because of the high variability in their response to EBCR. In this context, the present study aimed to determine the potential of a specific parameter, the Contractility index (CTi), to predict the response of cardiac patients to EBCR. This parameter is acquired during the baseline Cardiopulmonary Exercise Test (CPET), using Signal-Morphology based Impedance Cardiography (SM-ICG^{TM}). Methods: 58 cardiac patients (59.7 ± 10.2 years old) were retrospectively enrolled in this study and admitted to EBCR, and 57 could be analyzed. Results: The patients were divided into 2 groups based on their CTi response during CPET (normal versus altered or compromised). After the EBCR program, there was an overall increase in peak oxygen uptake (VO_2peak) (+13.6 ± 22.9 %). EBCR induced a higher VO_2peak improvement in patients with normal CTi response compared to their counterparts with altered or compromised CTi profiles (+24.1 ± 21.4 % vs. + 3.36 ± 19.5 %, $p < 0.01$) Patients with a normal CTi response during the baseline CPET were more likely to have a greater than 5% improvement in VO_2peak (odds ratio 8.7, $p = 0.012$) and benefit from EBCR, as compared to the patients in the altered or compromised CTi group. Conclusion: This study demonstrated the predictive potential of the CTi profile observed during the baseline CPET to anticipate the response to EBCR in cardiac patients.

1. Introduction

The benefits of exercise based cardiac rehabilitation (EBCR) are now well established, both in terms of reducing mortality and rehospitalization rates associated with coronary artery disease [1] or heart failure [2,3,11]. However, there is a high inter-individual variability in the degree of response to EBCR. Some patients remain non-responders and sometimes even see their peak oxygen uptake ($\dot{V}O_2$peak) decrease significantly, resulting in a less favorable prognosis [10,12]. A clinically accepted criterion for determining the response to EBCR is the change in $\dot{V}O_2$peak between cardiopulmonary exercise testing (CPET) performed before and after EBCR ($\Delta\dot{V}O_2$peak). The threshold above which a patient is considered a responder according to the $\Delta\dot{V}O_2$peak criteria varies according to the authors [4,8,9]. The possible mechanisms explaining the response or lack of response to EBCR have recently been described, mainly in terms of oxygen diffusion [4], peripheral and ventilatory responses [5], but also in terms of cardiopulmonary changes assessed by stress echo in combination with $\dot{V}O_2$ [6], or even hemodynamic changes measured by signal-morphology impedance cardiography (SM-ICG™) [7]. In this context, it remains difficult to identify parameters that could be used as a predictive tool to anticipate the response to exercise training in patients with cardiac disease. This is unfortunate, as they would help to better target patient populations suitable for EBCR, adapt the exercise training programme (modalities, duration and/or intensities),improve short-term outcomes and possibly also long-term patient adherence to lifestyle changes, which isessential to an overall improvement in

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outcomes [13]. Prediction of training response has been the subject of numerous studies focusing on central or peripheral physiological parameters, training modalities, and genetic or medical treatment-related factors. Despite some interesting results, no study seems to have definitively settled the issue. In particular, it seems that patients with impaired cardiac function, as evidenced by low maximal values of cardiac output ($\dot{Q}c$) or stroke volume (SV), have a higher probability of a negative response to training, whether on $\dot{V}O_2$peak or its determinants [4,14]. Belardinelli et al. identified changes in early left ventricular filling rate, as measured by radionuclide ventriculography, as a predictor of changes in $\dot{V}O_2$peak [15]; one study identified resting systolic arterial blood pressure as a factor [4], others identified patients' peak heart rate (HR) [6]. Chronotropic incompetence may also be a factor, but has not been confirmed in a more recent study [4,18].

Other studies focused on muscle deconditioning to explain the non-response [16,17]. The type of training proposed has also been analyzed [9]. An interesting study mentions left ventricular contractile reserve measured by stress echo as having some potential predictive value [6]. The genetic or epigenetic (circulating microRNAs) makeup of patients may also play an important role [19,20]. These methods, although sometimes promising in terms of predictive value, often appear difficult to implement in routine clinical practice because they require special skills and/or complex equipment and procedures [6,20]. Conversely, hemodynamic responses to exercise can now be assessed routinely and quite easily in a non-invasive and validated manner using a technology called Signal-Morphology based Impedance Cardiography (SM-ICG™). This technology has been used to improve the diagnosis during exercise testing in coronary artery disease [21,22], pulmonary hypertension [23] or ventricular dysfunction [24]. A SM-ICG™ specific parameter is the contractility index (CTi), of which the calculation is based on the velocity of the blood volume variation during the systole; reflected by the variations in heart impedance ($\frac{dZ}{dt}$). The aim of this study was to determine the predictive potential of the CTi profile, assessed during baseline CPET, on the response to cardiac rehabilitation in patients with cardiac disease.

2. Materials and methods

2.1. Study population

Fifty-eight patients were retrospectively included in this study. They were referred to the Leopold Bellan Prevention and Rehabilitation Center (Tracy le Mont, France) for in or out-patient EBCR between March 2019 and March 2020. All patients provided written informed consent for data analysis in this retrospective study. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The exclusion criteria were not specific to this study and were set in accordance with the French recommendations for EBCR [31,32]. All of these patients underwent at least one complete CPET with SM-ICG™ exercise hemodynamics on admission. They also all underwent a CPET after their EBCR was completed. All patients completed a full rehabilitation programme in accordance with the guidelines of the French Society of Cardiology for cardiac rehabilitation in adults[31,32]. Their treatments were not modified and no patient underwent a revascularization procedure during the rehabilitation programme (Table 1). Exercise training was performed once or twice a day, 5 times a week for 4 weeks, for a total of 20 aerobic and 12 resistance sessions. Briefly, the aerobic exercise sessions consisted of 20–50 min of a continuous cycling at the first ventilatory threshold (VT1) using a cycloergometer. The exercise intensity was regularly increased to reach the target heart rate [33]. Resistance training consisted of 2 sets of 10–15 repetitions of lower limb exercises (leg press, quadriceps leg extension, and standing calf raise) and 2 sets of 10–15 repetitions of upper limb exercises (lateral raise, triceps pushdown, and dumbbell curl), at 30–50 % of 1 repetition maximum [33]. Patients were considered responders (Resp) to EBCR if they displayed an increase in $\dot{V}O_2$peak value equal to or greater than 5 %, or non-responders (N-Resp) if not [18]. This is consistent with the rest-retest coefficient of variability of $\dot{V}O_2$peak, which is usually reported to be less than 4 % [34].

Table 1
Study population characteristics.

	Entire group (%)	Normal CTi profile	Altered + Compromised CTi profiles
Number (%)	57 (100)	28 (49.1)	29 (50.9)
Sex (Female/Male (%))	2/55 (3.5/ 96.5)	1/27 (3.6/ 96.4)	1/28 (3.4/96.6)
Age (years)	59.5 ± 10.3	58.4 ± 12.2	61.1 ± 8.0
Weight (Kg)	87.4 ± 15.2	88.7 ± 14.3	85.9 ± 16.7
Height (cm)	175.1 ± 7.9	174.6 ± 7.7	175.4 ± 8.3
BMI ($kg.m^{-2}$)	28.6 ± 4.3	29.1 ± 4.2	27.9 ± 4.3
Pathological context			
CAD (n (%))	32 (56.1)	17 (60.7)	15 (51.7)
CHF (n (%))	5 (8.8)	1 (3.6)	4 (13.8)
Valvular disease (n (%))	7 (12.7)	3 (10.7)	4 (13.8)
Risk factors (n (%))	11 (20.0)	6 (21.4)	5 (17.2)
Peripheral Arterial disease (n (%))	1 (1.8)	1 (3.6)	
Marfan disease (n (%))	1 (1.8)		1 (3.5)
Physiological parameters			
Baseline $\dot{V}O2$peak ($mL.min^{-1}.kg^{-1}$)	20.3 ± 5.7	19.8 ± 5.4	22.3 ± 6.0
Baseline Resting Left Ventricular Ejection Fraction (Echo) (%)	54.56 ± 10.92 $n = 54$	55.83 ± 13.01 n = 29	53.08 ± 8.77 n = 25
Duration of EBCR (weeks)	4.0	4.0	4.0

Legend: CTi: contractility index, BMI: body mass index, CAD: coronary artery disease, CHF chronic heart failure, $\dot{V}O_2$peak: peak of oxygen uptake, EBCR: exercise based cardiac rehabilitation. * Significant difference between Normal and Altered+Compromised CTi profile groups ($p<0.05$)

2.2. Cardiopulmonary Exercise Test (CPET)

All subjects performed a cardiopulmonary exercise test (CPET) in the upright position on an electronically braked cycloergometer (ERGOLINE 900, Schiller Medical SAS, Bussy St. Georges, France) in an air-conditioned room before and after the EBCR program. After 3 min of rest and 3 min of warm-up at 20 watts, each subject performed a 1-min incremental exercise test to voluntary exhaustion with a 10-watt work increment, as previously described [4,33]. Seat and handlebar height were adjusted for each subject according to personal preference. The cadence was fixed at 60 rpm and kept constant at all times. Respiratory Frequency (RF), Tidal Volume (TV), minute ventilation ($\dot{V}_E$), $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) were measured at rest and during exercise using a fixed gas analyzer (Quark-CPET, Cosmed, Rome, Italy). The software of the device was set to automatically eliminate ectopic values and to average the data every 5 s. The values of $\dot{V}O_2$peak and Maximal Tolerated Power (MTP) were defined as previously proposed in the literature [35]. The First Ventilatory Threshold VT1 was determined as the breakpoint in the curve of the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot (V-slope method) [33,36].

2.3. Cardiac hemodynamics during CPET

$\dot{Q}$c, SV, and CTi values were determined during CPET by morphological analysis of the beat-to-beat cardiac impedance signal using an advanced transthoracic impedance cardiograph, a technology called SM-ICG™ (PhysioFlow®, PF-05 Lab1, Manatec Biomedical, Macheren, France). The PhysioFlow® software used was version 2.8.0 and the electrodes were those marketed by the manufacturer (PhysioFlow® PF50). The patients' skin was shaved if necessary and prepared with some Nuprep® abrasive gel (Weaver and Company, Aurora, CO, USA). The manufacturer's instructions for use were strictly followed. After signal processing, which included a sophisticated built-in noise reduction filter called HD-Z™, the heart signals were analyzed beat by beat and the results were averaged over 5 s. This method of measuring exercise hemodynamics has been described previously [37] and has been validated for accuracy, reproducibility and sensitivity, including at maximal exercise [23,37–39]. It has been widely used in research on exercise hemodynamics [40].

2.4. Contractility Index (CTi) Profiles during CPET

The maximal rate of change of the impedance waveform ($\frac{dZ}{dt}$max), computed as the peak of the first mathematical derivative over time of the impedance waveform during systole (also called $\frac{d(HD-Z)}{dt}$ max by the manufacturer of PhysioFlow®), is a representation of the maximum ejection flow velocity during systole ($\frac{dV}{dt}$). It is a well-known parameter in impedance cardiography [41]. The $\frac{dZ}{dt}$max values are recorded during each cardiac cycle and graphically represented by the software in the form of trend curves averaged over 5 s under the name CTi (Fig. 1). A normal contractility profile during exercise is characterized by a rapid increase in CTi followed by a slower increase or plateau. This pattern has been described previously using other methods to assess myocardial contractility in healthy subjects [42]. The PhysioFlow® software allows manual scrolling of portions of these trend curves to evaluate a slope and average over the selected portion. This function is useful for determining slope changes and, in particular, the possible CTi slope inversion that can occur for at least one minute prior to the recovery phase of the exercise test (negative slope after the positive slope observed at the start of exercise). This change in slope (altered CTi profile) appears to be a sign of an abnormal response to exercise of the ejection flow provided by left ventricular function. Sometimes the CTi does not increaseduring exercise (slope is zero or close to zero) or even collapses at the beginning of exercise (negative slope), which seems to be a sign of deteriorated left ventricular function (compromised CTi profile) (Fig. 1). The normal CTi profile defined a first subgroup of patients, whereas the altered and compromised CTi profiles defined a second subgroup of patients (abnormal CTi profile). In order to minimize operator bias, the CTi profiles' analysis was conducted by two independent operators. In case of disagreement, a third operator would intervene. Both analyses were conducted in a blinded manner.

2.5. Statistical analysis

Statistical analyses were performed with JASP (version 0.17.1 for Apple Silicon, JASP Team, VU Amsterdam, Amsterdam, The Netherlands). All data are expressed as mean and standard deviation (±SD). According to the normality of the data evaluated by Shapiro-Wilk and equality of variance (Levene's test), independent samples Student *t*-test or Mann-Whitney test was performed to evaluate $\Delta\dot{V}O_2$peak and baseline LVEF values between both groups. Associations between CTi and CPET responses were evaluated using logistic regression, adjusting for several potential confounders, including duration of EBCR, age, chronic disease, baseline $\dot{V}O_2$peak and LVEF values [40]. The dependent variable was CTi responses to CPET. Adjusted models (covariates with $P < 0.10$) were fitted to estimate the effect of CTi on $\dot{V}O_2$peak in all subjects. The odds ratio (OR) was calculated for the associations [43]. The significance level was set at *p*-value <0.05 for 95 % confidence interval.

3. Results

A majority of these patients had a form of coronary artery disease (CAD) or displayed risk factors for CAD (Table 1). Sometimes the pathology was severe with multiple stenosis and these patients underwent

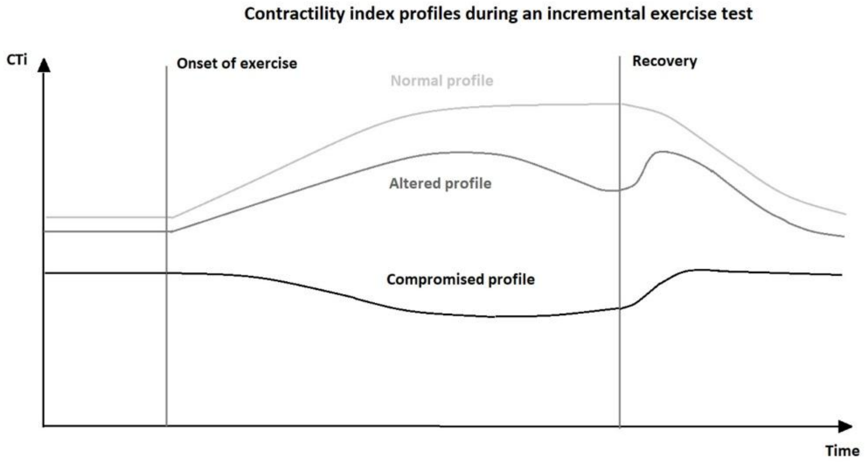

Fig. 1. Different CTi profiles obtained during exercise using the SM-ICG™ technique.
CTi: contractility index. Examples of CTi response of cardiac patients using SM-ICG™ during a CPET. These curves present the kinetics of CTi during exercise. Patients were classified into 3 categories according to their CTi response to CPET: 1) Normal profile is characterized by a rapid increase in CTi at the start of exercise followed by a plateau or pseudo-plateau, 2) Altered profile corresponds to an increase then a fall in CTi before the end of exercise, and 3) Compromised profile is characterized by no response or a decrease in CTi during exercise.

prior revascularization interventions (surgical or stents). The rest of the group is diverse (CHF, valvular surgery, etc.). 54 of the 58 patients had their LVEF recently measured by Echo, with an average value close to 54 % for the whole group. Only 7 out of these 54 patients presented with a mildly reduced ejection fraction (41 to 49 %) and 5 displayed a reduced ejection fraction (equal to or under 40 %). A post EBCR evaluation of LFEF could be performed on 30 of the 54 patients that had a baseline LVEF measured. All SM-ICG™ recordings were considered acceptable in terms of signal quality, except one (the signal was lost after some time, making the hemodynamic trends near maximal exercise uninterpretable). This left 57 patients for analysis in this study. On average, the entire group of 57 patients increased their $\dot{V}O_2$peak (+13.6 ± 22.9 %) and also their MTP (+23.9 ± 14.3 %). The two subgroups, divided according to their CTi profiles, appear homogeneous in terms of size, demographics, disease, physiological parameters and duration of the EBCR program (Table 1). The EBCR program induced a higher $\dot{V}O_2$peak improvement in patients with normal CTi response compared to their counterparts with altered or compromised CTi profiles (+24.1 ± 21.4 % vs. +3.36 ± 19.5 %, $p < 0.001$). Incidentally, this result correlates with a higher mean MTP increase in patients with normal compared to altered or compromised CTi profile groups (+29.7 ± 11.7 % vs. +18.1 ± 14.3 %, $p < 0.001$). Logistic regression analysis showed that patients with a normal exercise CTi profile were 8.7 times more likely to have a greater than 5 % improvement in $\dot{V}O_2$peak (odds ratio 8.7, $p = 0.012$) compared to patients with an altered or compromised exercise CTi profile (Fig. 2). Neither baseline $\dot{V}O_2$peak values, age nor number of EBCR days explained the changes in $\dot{V}O_2$peak with exercise training (Fig. 2). Clinically, the 28 patients with normal CTi rarely did not respond to EBCR (less than 5 % increase in $\dot{V}O_2$peak, $n = 3$), but mostly responded positively to CR (more than 5 % increase in $\dot{V}O_2$peak, $n = 25$) (Fig. 3). In patients with altered or compromised CTi profiles, responses to EBCR were mixed. It should be noted that the patients who lowered their exercise CTi from the onset of exercise (compromised CTI profile) all experienced a decrease in $\dot{V}O_2$peak after EBCR (Fig. 3). It is to be noted that there is no statistical relationship between baseline $\dot{V}O_2$peak and $\Delta\dot{V}O_2$peak (Pearson's $r = -0.381$, $p = 0.005$), and none between baseline resting LVEF and baseline $\dot{V}O_2$peak (Pearson's $r = 0.406$, $p = 0.002$), $\Delta\dot{V}O_2$peak (Pearson's $r = -0.085$, $p = 0.540$), or even exercise CTi profiles (Table 1). Interestingly, there is also no statistical relationship between the changes in resting LVEF (before and after ECBR) and $\Delta\dot{V}O_2$peak (Pearson's $r = 0.224$, $p = 0.233$).

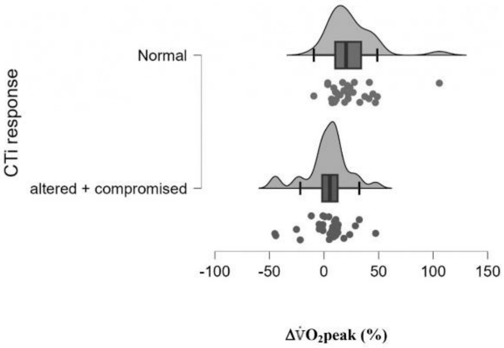

Fig. 2. Changes in peak value of oxygen uptake with exercise based cardiac rehabilitation.

CTi: contractility index, $\Delta\dot{V}O_2$ peak (%): changes in peak of oxygen uptake expressed in % of baseline value of peak of oxygen uptake. The graph on top represents the response in $\Delta\dot{V}O_2$ peak (%) for the normal CTi response group ($n = 28$). The graph below represents response in $\Delta\dot{V}O_2$ peak (%) for the altrered+compromised CTi response group ($n = 29$).

4. Discussion

The originality of the present study is to determine the predictive potential of the CTi profile assessed during baseline CPET for the response to cardiac rehabilitation in patients with cardiac disease. In this initial evaluation study, the focus was not on a specific pathology or type of patient, although a clear majority of CAD patients were included.

The decision to consider a rate of increase in $\dot{V}O_2$peak greater than 5 % as a qualifying response to training can be controversial. Some studies have chosen higher rates, in the order of +10 %, which may be very clinically significant and also closer to a statistical median [2,4]. However, using this criterion, only half of the study population would have been "responders", compared to 70 % using the +5 % criterion. Other studies have defined a + 0 % threshold for a positive EBCR response [8] (78 % of patients had a positive response to EBCR in this particular study). We believe that a 5 % criterion remains a good compromise: it is a "real" improvement (beyond technical and physiological variability) and is also clinically relevant for these patient groups and not based on a purely statistical approach. It should be noted that in our group of patients, the average response in terms of $\Delta\dot{V}O_2$peak (+13.6 ± 22.9 %) is consistent with the expected range of improvement observed in comparable studies (from +8.5 % to +16.0 %) [29,45.]. According to our results, a normal CTi profile, reflecting a healthy contractile function of the heart during exercise, seems to be a favorable predictor for improvements in patients' performance with training. Some patients with an altered or compromised CTi profile during exercise were responders and others were not. It is to be noted that the confidence intervals remain relatively large, highlighting a significant variability in the response to EBCR in both groups. This observation may be related to the nature of the myocardial injury, its severity, and its timing before the patient entered the CR program, which hypothesis would require further investigations. It is also to be noted that resting LVEF was not significantly correlated to these CTi profiles, suggesting again that the hemodynamic response to exercise matters more from a clinical standpoint, rather than resting evaluations.

Furthermore, it is possible that a very impaired CTi response (i.e., no increase at all during exercise) could be a negative predictive factor, but the small number of patients with this profile in this study ($n = 7$) precludes a definitive conclusion. It has previously been suggested that the absence of an increase in contractility during exercise is a sign of severely impaired cardiac function [30], and therefore a possible severe limitation to exercise capacity improvement with training. Conversely, a normal CTi response to exercise could imply that cardiac function is not a limiting factor for training-induced improvements in all physiological determinants of exercise capacity. These results and their potential clinical implications may be viewed by some clinicians as counterintuitive: it is often described that EBCR benefits sicker patients more than those in better health, but our data show that baseline resting LVEF or even baseline $\dot{V}O_2$peak is not predictive of $\Delta\dot{V}O_2$peak (which result is consistent with the literature). Other clinicians might even find them potentially counterproductive (if not ethically implemented): preselecting "healthier patients" based on CTi response might very significantly improve outcomes in the selected population, but then the therapeutic nature of EBCR might be questioned as a significant number of patients would be excluded. Further studies could be designed in order to determine if optimizing pre-EBCR therapeutic strategies would improve the patients' exercise CTi pattern and thus potentially qualify more patients for a successful rehabilitation. Even if in real life patients have increasingly complex cardiovascular profiles and a higher incidence of comorbidities, further studies could focus on more specific patient groups, such as heart failure or CAD patients. This could allow a

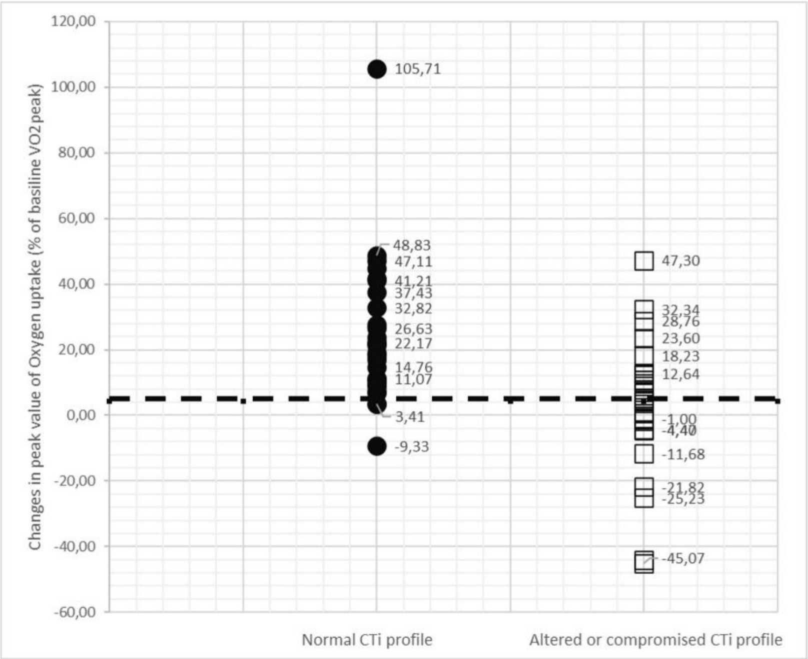

Fig. 3. Individual responses to cardiac rehabilitation.

CTi: contractility index, $\Delta\dot{V}O_2$ peak (%): changes in peak of oxygen uptake expressed in % of baseline value of peak of oxygen uptake. Each point and square represent a patient ($n = 57$). The dotted line represents the response threshold line ($\Delta\dot{V}O_2$ peak = 5 %). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

more detailed analysis of the predictive power of CTi profiles according to specific pathologies. The predictive power could also be improved by combining the CTi profile criteria with other metrics from the $\dot{V}O_2$ test or even cardiac ultrasound (e.g., LVEF). But it is to be noted again that baseline resting LVEF alone displayed no predictive value for the outcome of EBCR in this study.

4.1. Study limitations

The present study presented a certain number of limitations. Firstly, the relatively small sample size that could be analyzed, even if the differences are statistically significant and despite the small number of patients excluded from the study. Unfortunately, only two women were included in this study, which reflects the patient mix in this rehabilitation center at the time of data collection and also the general underrepresentation of women in EBCR [45]. Secondly, the relative heterogeneity of the population studied could be questioned. However, the diversity of pathologies, drug treatments and even the (limited) individualization of training protocols did not seem to be a limitation of this study, which reinforces its interest. Thirdly, the monocentric nature of this study could be discussed, but it ensures homogeneity in the protocols and in the interpretation of the exercise tests, and also in the supervision of the training protocol. The nature of the parameter used, CTi (or $\frac{dZ}{dt}$max) could also be discussed. It is undoubtedly related to cardiac contractility, but not a direct measure of this contractility. However, $\frac{dV}{dt}$max, which is closely related to $\frac{dZ}{dt}$max, has been successfully studied previously using different sensors, most of the time invasive [27,28]. CTi remains a parameter specific to the SM-ICG™ system that is difficult to correlate with other technologies, even if it is a strong contributor to the calculation of SV values and trends, which have been validated in comparative studies before, and also in application studies [29,30]. Interestingly, the strong predictive value of more conventional SM-ICG™ exercise hemodynamic parameters (i.e. Cardiac Index) has been established independently of other prognostic factors in several types of heart failure patients [25,26]. Finally, the determination of slope changes in CTi is purely graphical and relies on the averaging tool offered by the PhysioFlow® software, which is controlled by the physician in charge of interpretation (scrolling). An automated slope analysis could be welcome to limit potential analysis errors, especially by inexperienced users, and to guarantee reproducibility. However, the comparison between the expert analysis and the analysis by the team with no prior exposure to CTi profiles showed that only in 5 cases out of 58 recordings the interpretation could have been clearly different, leading to a potential reclassification of the CTi profile by the expert in 1 case out of 5 (a borderline case actually). However, these reclassifications were further analyzed and they did not alter the predictive power of the CTi profiles. These findings limit the potential for an operator bias.

5. Conclusion

This study highlights the value of adding noninvasive, continuous exercise hemodynamic measurements to $\dot{V}O_2$ testing in the routine evaluation of cardiac rehabilitation patients, at least in the initial assessment CPET. The exercise CTi profiles observed during this baseline CPET, as measured by SM-ICG™, appear to have a strong predictive value to anticipate the response to EBCR, confirming the original study hypothesis. It is also likely to be of interest as an independent criterion of rehabilitation outcome. Finally, the hemodynamic patterns and profiles observed during this baseline test could potentially be used as a tool to personalize exercise prescription.

Statement of authorship

All the author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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CRediT authorship contribution statement

Frank Bour: Writing – original draft, Methodology, Formal analysis. **Evan Milstein:** Methodology, Visualization. **Antoine Poty:** Data curation. **Yves Garaud:** Supervision, Investigation. **Damien Vitiello:** Writing – review & editing, Supervision. **Pierre Marie Leprêtre:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

Frank Bour is co-inventor of the SM-ICG^{TM} technology and co-founder and managing director of Manatec Biomedical, the company that develops and manufactures the PhysioFlow® device based on this technology.

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Study 2 (Abstract)

Signal-morphology impedance cardiography is a non-invasive tool to predict responses to exercise based cardiac rehabilitation in chronic heart failure patients

Frank Bour, Marie Christine Iliou, Damien Vitiello, Pierre-Marie Leprêtre

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Signal-morphology impedance cardiography is a non-invasive tool to predict responses to exercise based cardiac rehabilitation in chronic heart failure patients

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Funding Acknowledgements: None.

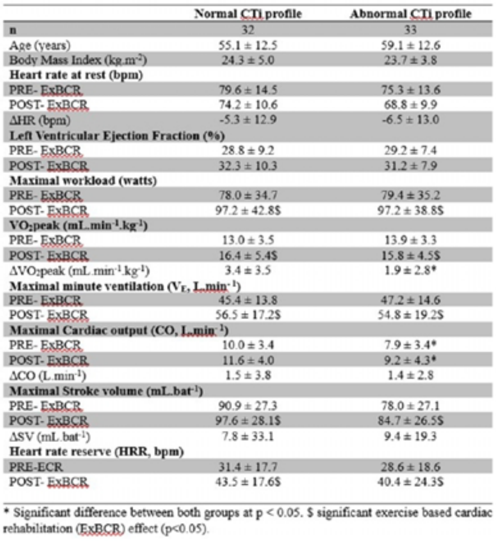
Background: All the studies and meta-analyses showed beneficial effects of the exercise based cardiac rehabilitation (ExBCR) on peak value of oxygen uptake (VO2peak) in patient with chronic heart failure (CHF). It is widely recognized that changes in VO2peak induced by training (ΔVO2peak) have a prognostic value. A 5.0% increase in ΔVO2peak has been associated with a significant clinical improvement1. However, 20 to 30 % of CHF are non-responders to ExBCR. The Signal-Morphology Impedance Cardiography (SM-ICGTM) technology has allowed previous researchers to show the role of cardiac output (CO) on DVO2peak2. CO responses may be partly attributed to the peak ejection flow velocity that can explain the impaired response to ExBCR.

Purpose: The study aimed to establish whether SM-ICGTM is an appropriate technology to predict responses to ExBCR in CHF patients.

Methods: A retrospective study was conducted on 65 CHF patients (LVEF: 29.0±8.3%). All patients performed a cardiopulmonary exercise test (CPET) on bicycle to determine ventilation (VE) and VO2peak before and after 20 ExBCR sessions. In addition, stroke volume (SV), heart rate (HR), and CO were continuously monitored by SM-ICGTM (PhysioFlow® Lab1). The value of peak ejection flow velocity, so called CTi by the manufacturer, was calculated as the peak of the first mathematical derivative over the time of the impedance waveform during the systole and measured by PhysioFlow® throughout the test. For the analysis of training response patients were divided in two groups: the normal CTi profile which was characterized by an initial increase followed by a plateau until CPET exhaustion, and the abnormal CTi response if CTi decreased at the onset of CPET or increased then decreased before exhaustion. Statistical analyses were performed with JASP. The significant level was set at p value < 0.05 for 95% confidence interval.

Results: Our study population consisted in 32 patients who presented a normal CTi profile and 33 with an abnormal CTi profile. As shown in Table 1, no significant difference was found at baseline between both groups. ExBCR induced significant changes in VO2peak even if 29 % patients were non-responders. Patients with normal CTi profile presented a greater DVO2peak compared to patients with abnormal CTi profile (28 ± 30 vs. 14 ± 19 %, p<0.01). 78% of patients with normal CTi profile versus only 64% of patients with abnormal CTi profile were ExBCR responders. The logistic regression showed that patient with normal CTi profile were 3.3 time more likely to present a ΔVO2peak ≥ 5%.

Conclusion: Exercise CTi profiles determined by SM-ICGTM prove to be an interesting tool to help predicting ExBCR responses in CHF patients and maybe highlighting the hemodynamic determinants of VO2 responses to exercise training.



	Normal CTi profile	Abnormal CTi profile
n	32	33
Age (years)	55.1 ± 12.5	59.1 ± 12.6
Body Mass Index ($kg.m^{-2}$)	24.3 ± 5.0	23.7 ± 3.8
Heart rate at rest (bpm)		
PRE- ExBCR	79.6 ± 14.5	75.3 ± 13.6
POST- ExBCR	74.2 ± 10.6	68.8 ± 9.9
ΔHR (bpm)	-5.3 ± 12.9	-6.5 ± 13.0
Left Ventricular Ejection Fraction (%)		
PRE- ExBCR	28.8 ± 9.2	29.2 ± 7.4
POST- ExBCR	32.3 ± 10.3	31.2 ± 7.9
Maximal workload (watts)		
PRE- ExBCR	78.0 ± 34.7	79.4 ± 35.2
POST- ExBCR	97.2 ± 42.8$	97.2 ± 38.8$
VO_2peak ($mL.min^{-1}.kg^{-1}$)		
PRE- ExBCR	13.0 ± 3.5	13.9 ± 3.3
POST- ExBCR	16.4 ± 5.4$	15.8 ± 4.5$
ΔVO_2peak ($mL.min^{-1}.kg^{-1}$)	3.4 ± 3.5	1.9 ± 2.8*
Maximal minute ventilation (V_E, $L.min^{-1}$)		
PRE- ExBCR	45.4 ± 13.8	47.2 ± 14.6
POST- ExBCR	56.5 ± 17.2$	54.8 ± 19.2$
Maximal Cardiac output (CO, $L.min^{-1}$)		
PRE- ExBCR	10.0 ± 3.4	7.9 ± 3.4*
POST- ExBCR	11.6 ± 4.0	9.2 ± 4.3*
ΔCO ($L.min^{-1}$)	1.5 ± 3.8	1.4 ± 2.8
Maximal Stroke volume ($mL.bat^{-1}$)		
PRE- ExBCR	90.9 ± 27.3	78.0 ± 27.1
POST- ExBCR	97.6 ± 28.1$	84.7 ± 26.5$
ΔSV ($mL.bat^{-1}$)	7.8 ± 33.1	9.4 ± 19.3
Heart rate reserve (HRR, bpm)		
PRE-ECR	31.4 ± 17.7	28.6 ± 18.6
POST- ExBCR	43.5 ± 17.6$	40.4 ± 24.3$

* Significant difference between both groups at $p < 0.05$. $ significant exercise based cardiac rehabilitation (ExBCR) effect ($p<0.05$).

Study 3 (Abstract)

Signal morphology impedance cardiography is a tool to explain the response of cardiac patients to cardiac rehabilitation in the presence of altered myocardial contractility profiles

Frank Bour, Evan Milstein, Pierre-Marie Leprêtre

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Illustration 33: Presentation at the EAPC congress, Milan April 2025

Signal morphology impedance cardiography is a tool to explain the response of cardiac patients to cardiac rehabilitation in the presence of altered myocardial contractility profiles

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Background: Exercise based cardiac rehabilitation (EXBCR) is highly beneficial to improve the outcome and quality of life of patients with cardiac disease. In most cases, it increases cardiorespiratory and muscular capacity. However, not all patients show these benefits because of the high variability in their response to EXBCR.

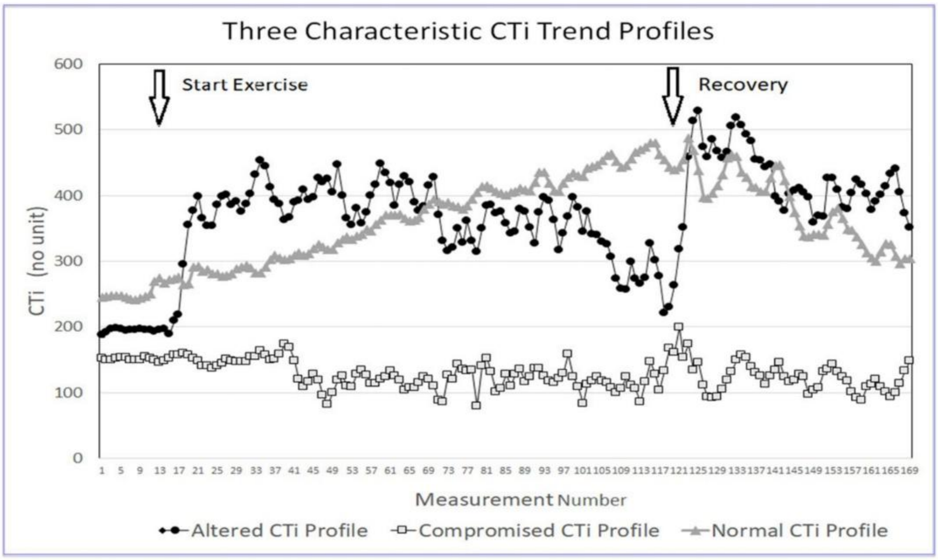
Purpose: In this context, the present study aimed to determine the potential of a specific parameter, the contractility index (CTi), to better understand the response of cardiac patients to EXBCR using a signal morphology impedance cardiography (SM-ICG) system.

Methods: 58 cardiac patients (50±10 years old, mostly affected by coronary artery disease and risk factors) were prospectively enrolled in this study and admitted to EXBCR, 42 underwent pre- and post-EXBCR cardiopulmonary exercise testing (CPET) combined with simultaneous SM-ICG. These 42 patients were divided into 2 groups based on their CTi response during the initial CPET+SM-ICG test: normal profile (increase throughout the exercise test or increase + plateau, 17/42) versus abnormal profile (relapse after an initial increase or no increase at all, 25/42).

Results: Even if, as demonstrated in a previous study performed in the same group of patients (1) and another one in a group of heart failure patients (2), the patients with a normal CTi profile have a very significantly higher chance of responding to EXBCR (positive response is defined as a >5% improvement in VO2peak), some of the patients with an abnormal CTi profile were still responders (16/25). Among the patients with abnormal CTi profiles, the responders were able to improve their RestCTi to PeakCTi difference (expressed as percentage increase of the CTi from the resting phase before exercise started, to its highest value during the test) much more compared to the non-responders (pre-post EXCBR variation of 70.22± 55.38% vs. -12.03±24.92%, $p=0.007$).

Conclusion: This study demonstrated that improving the contractility index response to exercise plays a significant role in improving overall fitness through cardiac rehabilitation in patients with impaired exercise contractility profiles. It may suggest that these specific patients could benefit from a personalised EXBCR programme with more emphasis on cardio training.

Contractiliy profiles during exercise



Screen shot pre-post EXBCR CTI change

CTI #1: 463.3

CTI #2: 632.2

Average: 370.7
Slope: 3.2217 /s

Average: 571
Slope: 1.3794 /s

Study 4

Exercise-Derived Contractility Index by Signal-Morphology Impedance Cardiography is a Determinant of Rehabilitation Response in Patient with HFrEF.

Frank Bour, Marie-Christine Iliou, Evan Milstein, Damien Vitiello,
Pierre Marie Leprêtre

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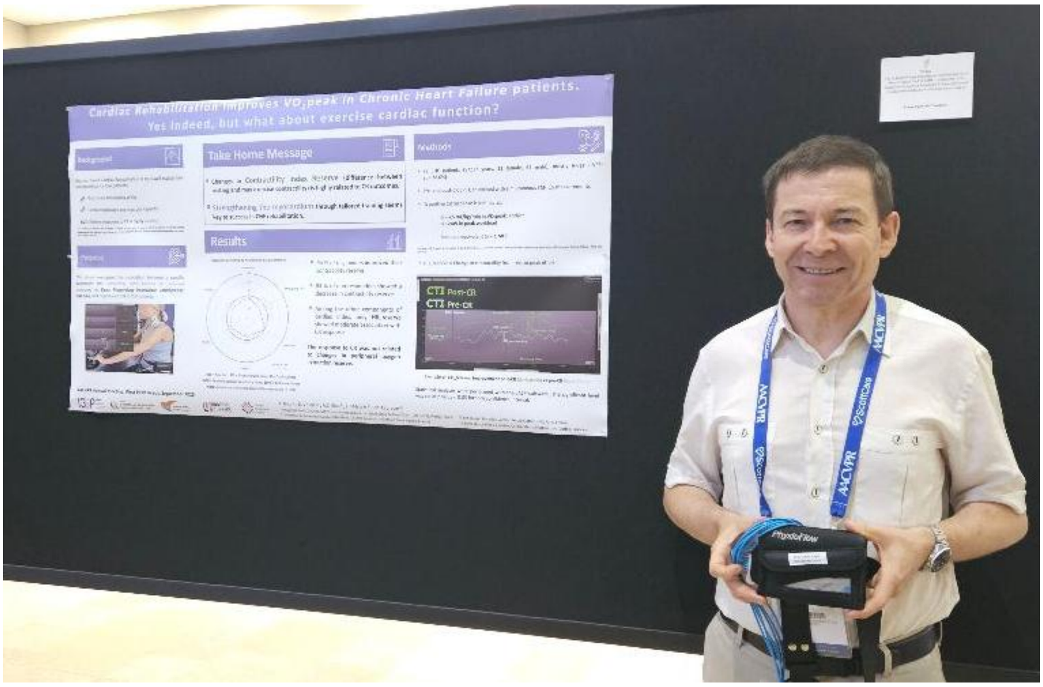

Illustration 34: Presentation at the AACVPR congress, West Palm Beach, September 2025

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European Journal of Preventive Cardiology

Exercise-Derived Contractility Index by Signal-Morphology Impedance Cardiography is a Determinant of Rehabilitation Response in Patient with HFrEF.

--Manuscript Draft--

Manuscript Number:	
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Article Type:	Full Research Paper
Section/Category:	Cardiac Rehabilitation
Keywords:	Congestive Heart Failure, Exercise Training, Outcome Data, Thoracic Electrical Bioimpedance, Non-Invasive Hemodynamic Monitoring, V O2peak, Cardiac Function Tests, Cardiac Output, Indexed Stroke Volume, Myocardial Contractility.
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Abstract:	Background: Comprehensive cardiac rehabilitation (CCR) improves outcomes in most patients with chronic heart failure with reduced ejection fraction (HFrEF). Changes in cardiac index (CI) and its hemodynamic determinants—heart rate (HR) and stroke volume index (SVi)—may explain variability in response to CCR. Objective: The study aimed to compare exercise-derived CI and its components between CCR responder (R) and non-responder (NR) patients with HFrEF. Methods: Seventy-three patients (57.0 ± 12.0 years, BMI: 23.9 ± 4.2 kg.m-^{2}, LVEF: 28.8 ± 8.0%) performed cardiopulmonary exercise testing before and after standardized CCR. Signal-morphology impedance cardiography (SM-ICG) continuously measured CI, HR, SVi, and contractility index (CTi), during these tests. For each parameter, the reserve was calculated as the difference between maximal and resting values. R patients were defined as patients achieving ≥3.5 mL.min-1.kg-1 increase in peak oxygen uptake or ≥24 W increase in peak workload. Results: Overall, 43.8% of patients (n = 32) were in the R group. Post-CCR reserve CI was higher in R than NR (3.1 ± 1.1 vs. 2.2 ± 1.5 L.min-1.m-^{2}, p = 0.004), with greater changes in reserve CI with training (1.0 ± 0.9 vs. 0.5 ± 1.0 L.min-1.m-^{2}, p = 0.016). Reserve SVi values (10.4 ± 5.0 vs. 6.3 ± 6.4 mL.min-1.m-^{2}, p = 0.004) and maximal HR (129.7 ± 26.7 vs. 112.9 ± 25.2 bpm, p = 0.007) were also higher in R than NR patients. CCR induced significant increases in reserve CTi in 94% of R (64.3 ± 78.2 AU), whereas reserve CTi decreased in 93% of NR (−13.2 ± 52.7 AU). Conclusion: SM-ICG-derived CTi during exercise may serve as a sensitive,

Exercise-Derived Contractility Index by Signal-Morphology Impedance Cardiography is a Determinant of Rehabilitation Response in Patient with HFrEF.

Running head: Cardiac Contractility and Rehabilitation Outcomes

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Author contribution: FB, MCI, EM, DV, PML.

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Frank Bour is the co-inventor of SM-ICG technology and the co-founder and co-managing director of Manatec Biomedical. Manatec Biomedical develops and manufactures the PhysioFlow® device based on SM-ICG technology.

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Abstract

Background: Comprehensive cardiac rehabilitation (CCR) improves outcomes in most patients with chronic heart failure with reduced ejection fraction (HFrEF). Changes in cardiac index (CI) and its hemodynamic determinants—heart rate (HR) and stroke volume index (SVi)—may explain variability in response to CCR.

Objective: The study aimed to compare exercise-derived CI and its components between CCR responder (R) and non-responder (NR) patients with HFrEF.

Methods: Seventy-three patients (57.0 ± 12.0 years, BMI: 23.9 ± 4.2 kg.m^{-2}, LVEF: 28.8 ± 8.0%) performed cardiopulmonary exercise testing before and after standardized CCR. Signal-morphology impedance cardiography (SM-ICG) continuously measured CI, HR, SVi, and contractility index (CTi), during these tests. For each parameter, the reserve was calculated as the difference between maximal and resting values. R patients were defined as patients achieving ≥3.5 mL.min^{-1}.kg^{-1} increase in peak oxygen uptake or ≥24 W increase in peak workload.

Results: Overall, 43.8% of patients (n = 32) were in the R group. Post-CCR reserve CI was higher in R than NR (3.1 ± 1.1 vs. 2.2 ± 1.5 L.min^{-1}.m^{-2}, p = 0.004), with greater changes in reserve CI with training (1.0 ± 0.9 vs. 0.5 ± 1.0 L.min^{-1}.m^{-2}, p = 0.016). Reserve SVi values (10.4 ± 5.0 vs. 6.3 ± 6.4 mL.min^{-1}.m^{-2}, p = 0.004) and maximal HR (129.7 ± 26.7 vs. 112.9 ± 25.2 bpm, p = 0.007) were also higher in R than NR patients. CCR induced significant increases in reserve CTi in 94% of R (64.3 ± 78.2 AU), whereas reserve CTi decreased in 93% of NR (−13.2 ± 52.7 AU).

Conclusion: SM-ICG-derived CTi during exercise may serve as a sensitive, noninvasive marker of response to CCR in patients with HFrEF.

Abstract word count: 276

Keywords: Congestive Heart Failure, Exercise Training, Outcome Data, Thoracic Electrical Bioimpedance, Non-Invasive Hemodynamic Monitoring, $\dot{V}O_2$peak, Cardiac Function Tests, Cardiac Output, Indexed Stroke Volume, Myocardial Contractility.

Introduction

The benefits of Comprehensive Cardiac Rehabilitation (CCR) in reducing morbidity and mortality, including rehospitalization rates associated with Coronary Artery Disease (CAD) and Chronic Heart Failure (CHF), are well-established (1). However, evidence regarding its impact on long-term prognosis is inconsistent. Some patients do not respond to CCR and sometimes even experience a decrease in peak oxygen uptake ($\dot{V}O_2$peak), resulting in a less favorable prognosis (2). In this context, some of the mechanisms that may explain responses to or lack of responses to CCR have recently been described. Physiological adaptations induced by training, including cardiac, ventilatory, and neuromuscular responses, have received considerable attention. While optimizing drug therapy has not been shown to consistently influence these patients' physiological responses to CCR, factors such as muscle deconditioning and training modalities could partly account for nonresponse (2–4). Patients with muscle deconditioning or microvascular limitations may exhibit reduced Oxygen Diffusion (DO_2), which is associated with an elevated $\dot{V}_E/\dot{V}CO_2$ slope and reduced $\dot{V}O_2$peak (5). The $\dot{V}_E/\dot{V}CO_2$ slope reflects ventilatory efficiency and has been shown to improve with training in subgroups of patients without lung function impairment (6). It is also mechanistically related to cardiac output ($\dot{Q}$c), which is also a major component of Oxygen Convection ($\dot{Q}O_2$). DO_2 and $\dot{Q}O_2$ have shown promising value in phenotyping $\dot{V}O_2$peak responses to CCR (5). A recent study focusing on CHF patients and their responses to various therapeutic interventions (including CCR) emphasized the importance of explaining these responses in terms of not only $\dot{V}O_2$ peak but also $\dot{Q}$c and the arteriovenous oxygen content difference ($(a\text{-}\bar{v})O_2$diff), with blood flow distribution possibly playing a pivotal role (7). Another recent study highlighted the high discriminating power of $\dot{Q}$c between responders (R) and nonresponders (NR) in a heart failure patient population, demonstrating the central role of $\dot{Q}$c in the response to CCR (8).

However, while the role of $\dot{Q}$c in oxygen transport is easily understood (Fick's law), $\dot{Q}$c itself is a complex parameter. It is the product of Heart Rate (HR) and Stroke Volume (SV). The latter is determined by three components: Left Ventricular (LV) preload, LV contractility, and LV afterload. These components interact in a complex fashion, as described by Frank-Starling's law, for example. These components can be estimated using transthoracic echocardiography; however, this approach is complex, costly, and dependent on the operator and the patient, especially during exercise (9). Now, detailed hemodynamic responses to exercise can be assessed easily and routinely in a noninvasive and validated manner using a technology called Signal-Morphology Impedance Cardiography (SM-ICG) that has been previously described and validated (10). SM-ICG has been used to improve diagnoses of CAD, pulmonary hypertension, and ventricular dysfunction during exercise testing. Recent research has shed light on the potential of this method to improve our understanding of the hemodynamics of cardiac rehabilitation (8,11). Studies involving the SM-ICG method helped establish joint recommendations from the American Heart Association and the European Association of Cardiopulmonary Rehabilitation for the noninvasive determination of $\dot{Q}$c in a specific patient population, primarily those with CHF (12). Besides computing $\dot{Q}$c as the product of HR, Stroke Volume index (SVi), and Body Surface Area (BSA), the SM-ICG technology features surrogate parameters for the three components of SVi. The first parameter is the Early Diastolic Filling Ratio (EDFR). EDFR is a noninvasive hemodynamic parameter that reflects the early ventricular filling mechanism (essential for LV preload) by determining the ratio of the velocity of the early diastolic heart impedance wave (O wave) to the velocity of the peak ejection (S wave) (Figure 1). The second parameter is the Systemic Vascular Resistance index (SVRi). The SVRi value is the most widely accepted surrogate for LV afterload in impedance cardiography and uses Mean Arterial Pressure (MAP), Cardiac Index (CI), and an estimation of Central Venous Pressure (CVP). SVRi has been studied at rest and in exercising heart failure patients (13). The last parameter is the LV Contractility Index (CTi), which is based on the velocity of the peak ejection. A study involving over 1,200 CHF patients established that the CTi value has strong predictive value for risk (14). Two recent studies have provided evidence that CTi is a useful predictor of responses to cardiac rehabilitation, particularly in patients with CAD (15) and in patients with CHF (11). One of these studies found that the response to CCR in cardiac patients (mostly with CAD) with abnormal entry contractility profiles was associated with improvements in cardiac contractility, i.e., CTi, during exercise (15).

The present study aimed to analyze variations in CI components between baseline and final CCR Cardiopulmonary Exercise Test (CPET) relative to the response to training in patients with heart failure with reduced left ejection ventricular function (HFrEF). In our study, CPET tests combine conventional $\dot{V}O_2$ parameters with exercise hemodynamics using SM-ICG. Additionally, this study attempts to explain the possible physiological mechanisms behind these changes.

Materials and Methods

Study Population and Training Protocol

Ninety-nine CHF patients were retrospectively included in this study. They were referred to the Corentin Celton Hospital Rehabilitation Center (part of the Assistance Publique des Hôpitaux de Paris organization, Issy-les-Moulineaux, France) for out or in-patient CCR between June 2017 and December 2019. All patients provided written informed consent for data analysis in this retrospective study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Corentin Celton Hospital ethics committee. Patients were eligible if they were clinically stable and aged 18 to 85 years and had a New York Heart Association (NYHA) functional class of II to IIIb. Seventy-two patients had their Left Ventricular Ejection Fraction (LVEF) measured by echocardiography at the beginning of the program, with an average value of 28.8% ± 8.0%. 98.0% of the population are patients diagnosed with HFrEF (n = 97) and 2.0% of the patients presented a heart failure with moderate reduced LVEF (HFmrEF).

Patients were excluded if they had valvular heart disease requiring surgery; acute or decompensated HF for less than 15 days; myocardial infarction, coronary intervention, and/or cardiac surgery within four weeks; severe pulmonary disease; if they were were unable to perform an exercise test; had a contraindication to cardiac rehabilitation according to French guidelines (16); patients presented a resting Systolic Blood Pressure (SBP) of less than 80 or greater than 180 mmHg; and/or had a hemoglobin concentration of less than 9 g/dL. All patients underwent a physical examination and laboratory testing, including Brain Natriuretic Peptide (BNP), creatinine, and glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula. They also underwent a CPET, combined with an assessment of cardiac hemodynamic parameters using SM-ICG before and after their CCR program. The CCR program included exercise training, patient education, dietary education, smoking cessation counseling, and psychosocial counseling.

Cardiopulmonary Exercise Test (CPET)

The CPET was performed on a cycle ergometer (Cardiosoft ^{TM}, GE Health Care, General Electric Company, Cincinnati, USA)) in a seated position. A ramp protocol of 10 W/min was used until the patient met one of the following criteria: respiratory exchange ratio >1.05; inability to maintain cycling; exhaustion due to fatigue; or clinical symptoms (e.g., dyspnea); Electrocardiography (ECG); or blood pressure abnormalities. During exercise testing, HR, SBP, and Diastolic Blood Pressure (DBP) were recorded at the beginning of each minute and at maximal exercise intensity. Gas exchange parameters were measured breath by breath during testing and averaged every 15 seconds for minute ventilation ($\dot{V}_E$, L.min^{-1}), oxygen uptake ($\dot{V}O_2$, L.min^{-1}) and carbon dioxide production ($\dot{V}CO_2$, L.min^{-1}) using an automated gas analyzer system (CPX Vyntus, Vyvaire Medical GmbH, Höchberg, Germany). The value of $\dot{V}O_2$peak, expressed in L.min^{-1} and mL.min^{-1}.kg^{-1}, net$\dot{V}O_2$peak (i.e the difference between peak and rest $\dot{V}O_2$ values) and other conventional ventilatory and gas exchange parameters were also determined (17).

Cardiac hemodynamics assessed during CPET.

Hemodynamic values were determined by morphological analysis of the beat-to-beat cardiac impedance signal using an advanced transthoracic impedance cardiograph (SM-ICG technology; PhysioFlow® PF-05 Lab1, Manatec Biomedical, Poissy, France) (10). The PhysioFlow® software version 2.8.0 was used. The electrodes were those marketed by the manufacturer (PhysioFlow® PF50) and used before their expiration date. The patients' skin was prepared with Nuprep® abrasive gel (Weaver and Company, Aurora, Colorado, USA), and shaved, if necessary, in accordance with the manufacturer's instructions. After signal processing, which included a built-in, advanced noise reduction filter called HD-Z^{TM}, the heart signals were analyzed beat by beat, and the results were averaged over five seconds. Physiological parameters were measured at rest, prior to the initiation of the exercise test (X_rest), and at peak exercise immediately before the onset of recovery (X_max). Reserve (X_reserve) was defined as the difference between maximal and resting values (X_max - X_rest). The timing of the maximal exercise for the hemodynamic parameters is like the timing of $\dot{V}O_2$peak in this patient population.

Contractility assessment with SM-ICG (CTi)

The method for assessing exercise contractility using SM-ICG was described before (11,15,18). Briefly, the dZ/dt maximum rate of change of the impedance waveform (dZ/dt_max), also called the peak of the first mathematical derivative of the impedance waveform during systole by the PhysioFlow® manufacturer, is a representation of the maximum ejection flow velocity during systole (similar to dV/dt). It is a well-known parameter in impedance cardiography (19). The dZ/dt_max values were recorded during each cardiac cycle and graphically represented by the software as trend curves averaged over five seconds under the name CTi. The PhysioFlow® software features a function that allows for manual scrolling of these trend curves to evaluate slopes and averages over selected sections of the trend. Attention was paid to applying it to stable, non-artefactual portions of the trendlines, especially at max exercise, and readings were confirmed by a second operator, not expert in SM-ICG, but who was trained to use the software.

Early Diastolic Filling Ratio (EDFR) assessment with SM-ICG

The EDFR is a noninvasive hemodynamic parameter that reflects early ventricular filling and measured by SM-ICG. The EDFR is the ratio of the early diastolic filling peak velocity (O-wave, see Figure 1) to the systolic peak velocity (S-wave), expressed as a percentage:

$$\mathrm{EDFR} = \frac{\mathrm{O}}{\mathrm{S}} \times 100$$

According to the manufacturer, a high resting EDFR (>67%) is usually associated with excessive LV preload, following the Frank-Starling law.

Estimation of left ventricular after load based on resting and maximal values of indexed Systemic Vascular Resistance (SVRi)

Resting value of SVRi was derived from the following equation:

$$\mathrm{SVRi} = \frac{(\mathrm{MAP} - \mathrm{CVP}) \times 80}{\mathrm{CI}}$$

Where SVRi is expressed in $\mathrm{dyn{\cdot}s{\cdot}cm^{-5}.m^2}$, CVP represents the Central Venous Pressure, which is approximately 6.4 mmHg at rest (20), and MAP is the Mean Arterial Pressure (in mmHg). MAP was calculated as:

$$\mathrm{MAP} = \frac{1}{3}\mathrm{SBP} + \frac{2}{3}\mathrm{DBP}$$

Where SBP and DBP are the resting values of systolic and diastolic arterial blood pressures, respectively, and expressed in mmHg.

During exercise, the maximal SVR value is estimated using a formula described elsewhere (21):

$$\mathrm{SVRimax} = \frac{\left(\mathrm{SBPmax} + 0.01e^{\left(4.14 - \frac{40.74}{\mathrm{HRmax}}\right)}\right) \times (\mathrm{SBPmax} - \mathrm{DBPmax}) - \mathrm{CVPmax}}{\mathrm{CImax}}$$

Where SBPmax and DBPmax are the maximal values of the Systolic arterial Blood Pressure and the Diastolic arterial Blood Pressure, respectively, and CVPmax, expressed in mmHg, represents the central venous pressure at the peak of exercise and estimated at 17.4 mmHg (20).

CCR exercise training intervention

The exercise training intervention implemented in this study has been detailed previously (8) and comprised a multidisciplinary regimen incorporating endurance, resistance, and balance/stretching exercises. All sessions were supervised by physiotherapists under the clinical oversight of a cardiologist. Endurance training was conducted using a cycle ergometer, scheduled five times per week for a duration of 30 minutes per session, over a period of three to four weeks. Each session commenced with a five-minute warm-up and concluded with a five-minute cool-down. The weekly program alternated between continuous and interval training modalities. Continuous sessions were initially prescribed at an intensity corresponding to the first Ventilatory Threshold (VT1). Interval training included one-minute bouts of exercise at 85–90% of $\dot{V}O_2$peak, interspersed with three- to four-minute recovery periods conducted at an intensity below VT1. Exercise intensity was progressively adjusted every two to three sessions by increasing the workload by 5–10 watts, with reference to Borg’s perceived exertion scale (target range: 12–14). Resistance training was scheduled three times per week, also lasting 30 minutes per session, and focused on bodyweight strengthening exercises targeting both upper and lower limb muscle groups. In addition, participants engaged in 30-minute balance and flexibility training sessions five times per week.

CCR response criterion and statistical analysis

Patients were considered R to CCR if they had an increase in $\dot{V}O_2$peak value of at least 3.5 $mL.min^{-1}.kg^{-1}$ (equivalent to one Metabolic Equivalent of Task [MET]) or an increase in peak Workload (Wpeak) of at least 24 watts (22). They were deemed NR if they did not meet either criterion.

Statistical analyses were performed using JASP (version 0.17.1 for Apple Silicon, JASP Team, VU Amsterdam, Amsterdam, the Netherlands). All data are expressed as the mean and standard deviation (± SD). According to the normality of the data, as evaluated by the Shapiro-Wilk test, and the equality of variance, as evaluated by the Levene's test, an independent samples Student's t-test, Welsh test or a Mann-Whitney test was performed to evaluate the difference in $\dot{V}O_2$peak and other parameters between the two groups. Paired tests were applied to isolate the training effect on the parameters. To control the inflation of Type I error due to multiple hypothesis testing, the Bonferroni correction was employed. The conventional significance level ($p = 0.05$) was adjusted by dividing it by the number of independent comparisons (two), thereby establishing a more stringent criterion for statistical significance ($p = 0.025$).

Results

Patient characteristics are summarized in Table 1. Of the initial 99 patients, six did not complete their final CPET, nine had incomplete SM-ICG recordings, and 11 had unstable SM-ICG recordings. This resulted in a final cohort of 73 patients with analyzable data: 11 females and 62 males with an average age of 57.0 ± 12.0 years, BMI of 23.9 ± 4.2 $kg.m^{-2}$, and LVEF of 28.8% ± 8.0%. Applying the CCR response criteria yielded 32 R and 41 NR, aligning with the severity of the patients' pathologies and reduced physical condition. Pre-CCR resting transthoracic echocardiography revealed higher sPAP values in NR patients than in R patients (40.4 ± 10.9 vs. 32.1 ± 9.0 mmHg, $p < 0.025$) and different resting LVEF changes with training between the two groups (R vs. NR: 5.0% ± 8.5% vs. 1.0% ± 5.7%, $p = 0.021$).

Effects of CCR on cardiorespiratory responses

As shown in Table 2, for all patients, exercise training resulted in an increase of 2.5 ± 2.4 mL.min^{-1}.kg^{-1} in $\dot{V}O_2$peak (+15.7 ± 26.5%) and an increase of 19.7 ± 19.0 watts in Wpeak (+24.8 ± 23.9%). Our results showed a greater increase in $\dot{V}O_2$peak in R patients than in NR patients with CCR (4.6 ± 3.3 vs. 0.4 ± 2.5 mL.min^{-1}·kg^{-1}, $p < 0.001$). The same response pattern is observed with Wpeak (+32.2 ± 15.6 vs. +8.0 ± 14.0 w, $p<0.001$). Only the R group achieved a Minimal Clinically Important Difference (MCID) with training for these two parameters. Training improved peak and net peak (reserve) values for $\dot{V}O_2$ and $\dot{V}_E$ for both the R and NR groups. However, $\dot{Q}c$ (max and reserve) only improved for the R group. $(a\text{-}\bar{v})O_2$diff was not modified by training.

There were no significant differences in resting or maximal values of $\dot{V}O_2$, $\dot{V}_E$, $\dot{Q}c$, or $(a\text{-}\bar{v})O_2$diff between the R and NR groups at baseline. CCR did not induce significant changes in resting cardiorespiratory values between groups. Our results showed a greater increase in $\dot{V}O_2$peak in R patients than in NR patients with CCR (0.8 ± 3.3 vs. 4.9 ± 3.3 mL.min^{-1}.kg^{-1}, $p < 0.001$), and also a higher $\dot{V}_E$_max (62.5 ± 22.3 vs. 51.1 ± 15.6 L.min^{-1}, $p = 0.017$) and $\dot{Q}c$_max (11.6 ± 3.9 vs. 8.9 ± 3.5 L.min^{-1}, $p = 0.003$). Consequently, the mean values of net$\dot{V}O_2$peak, $\dot{V}_E$_reserve, and $\dot{Q}c$_reserve differed significantly between the R and NR patients after CCR. However, no CCR group effect was found on maximal and reserve values of $(a\text{-}\bar{v})O_2$diff (Figure 2).

Effects of CCR on hemodynamic parameters

Table 2 shows improvements in all maximum and reserve hemodynamic parameters with training in the R group, except for SVRi and EDFR. Resting HR also improved. In the NR group, training only improved resting HR and CTi; meanwhile, CTi reserve deteriorated.

A group effect of CCR was observed for some parameters. At baseline, resting CI values were lower in R patients than in NR patients (2.8 ± 0.5 vs. 2.6 ± 0.5 L.min^{-1}.m^{-2}, $p = 0.018$). There were no significant differences in any other resting or maximal parameters between the R and NR groups, except for the maximal SVRi value, which was lower in responder patients (R: 846.0 ± 413.0 vs. NR: 1096.0 ± 501.0 dyn·s/cm^5.m^2, $p = 0.020$). There was no significant difference in resting values of CI, HR, EDFR, or CTi between R and NR after CCR except for EDFR, which was significantly lower in R (57.7 ± 10.9% vs. 69.2 ± 17.9%, $p < 0.001$). In contrast, a significant group effect was observed for the maximal post-CCR values of CI, HR, and EDFR. Consequently, the post-CCR reserve CI_reserve was higher in R than in NR (R vs. NR: 3.1 ± 1.1 vs. 2.2 ± 1.5 L.min^{-1}.m^{-2}, $p = 0.004$). Furthermore, the changes in CI_reserve (R vs. NR: 1.0 ± 0.9 vs. 0.5 ± 1.0 L.min^{-1}.m^{-2}, $p = 0.016$) and SVi_reserve values (R vs. NR: 10.4 ± 5.0 vs. 6.3 ± 6.4 mL.m^{-2}, $p = 0.004$) were greater in R than in NR (Figure 3). Finally, CCR induced significant increases in maximal and reserve CTi values in 94% of R patients (CTi_max: 64.3 ± 78.2 AU; CTi_reserve: 49.9 ± 54.3 AU; n = 30), whereas these values decreased in 93% of NR patients (CTi_max: −13.2 ± 52.7 AU; CTi_reserve: −35.2 ± 44.1 AU; n = 38, $p <0.001$).

Discussion

The novelty of this study lies in its demonstration that non-invasive measurement of the determinants of CI and SVi can be used to better understand the physiological mechanisms underlying the response to cardiac rehabilitation CCR in patients with CHF. According to our results, cardiac contractility expressed by the CTi parameter is the main determinant of the response. By analyzing both central and peripheral determinants through the Fick equation, this study highlights how differential adaptations to training distinguish R from NR.

Determinants of the Fick equation and hemodynamic adaptations

Among the determinants of the Fick equation, both $\dot{V}O_2$peak and net$\dot{V}O_2$peak improved after CCR, as expected. These improvements were observed predominantly in the R group, which is logical given that these parameters form part of the response criteria. $\dot{V}_E$_max exhibited a similar pattern to $\dot{V}O_2$peak. This is consistent with the tight coupling typically observed between ventilation and oxygen uptake during cardiopulmonary exercise testing (CPET), especially when assessed using a conventional breath-by-breath metabolic cart (23). Central hemodynamic parameters also followed this pattern. Both $\dot{Q}$c_max and $\dot{Q}$c_reserve improved significantly with training, but only in the R group. This reflects enhanced circulatory function following rehabilitation. Interestingly, the concomitant rise in $\dot{V}O_2$ and $\dot{Q}$c with training appeared to "neutralize" changes in peripheral oxygen extraction as calculated by the Fick equation. This contrasts with earlier study conducted on smaller CHF cohorts exercising at lower intensities but over similar durations, which emphasized peripheral rather than central adaptations (24). CI showed a similar trajectory to $\dot{Q}$c, with intergroup differences after CCR largely explained by the R group's higher HR_max following training, as well as the training response in HR_max and HR_reserve in this group. The markedly greater SVi_reserve post-CCR in the R group, and the training response in SVi_max and SVi_reserve are also contributors to this improved CI_max. A higher pre-CCR CI_rest in the R group appeared primarily related to higher resting heart rate, though this difference was not statistically significant. We hypothesize that patients who are still able to compensate for impaired cardiac function at rest at the onset of the CCR program are more likely to respond favorably to training. This interpretation is consistent with the lower resting sPAP observed pre-CCR in the R group; pulmonary hypertension is known to negatively impact exercise $\dot{Q}$c (and hence CI) (25).

LV preload, afterload, and their variability in response

LV preload indicators (EDFR_rest and EDFR_max) post-CCR suggest a more favorable fluid balance among responders (26, 27). However, the pre- to post-CCR trend was inconsistent, likely due to substantial interindividual variability—perhaps reflecting heterogeneous medication regimens. Following the Frank–Starling law and the way EDFR is calculated, these observations likely reflect improved LV contractility rather than a pure preload effect. According to the developers of the SM-ICG method, a high EDFR (>67%) is usually associated with excessive LV preload, following the Frank-Starling law. However, there have been no formal comparative studies with ultrasound or invasive catheterization (e.g., pulmonary capillary wedge pressure) because the approaches to LV preload differ greatly. For example, the E/A ratio in Doppler echocardiography is not the same as the EDFR, though both are related to diastolic function and LV preload (28). Nevertheless, this LV preload parameter has been successfully studied in patients with various cardiovascular disease and also spinal cord injury (27). Surprisingly, changes in LV afterload (SVRi) during exercise or with training were not associated with the response to CCR (29). Even though SVRi_max was lower at baseline and improved post-CCR in the R group, these changes were not predictive of training response. Again, considerable interpatient variability was observed. This aligns with previous evidence that peripheral vascular adaptations to training often require longer periods to manifest fully (30)

Contractile function and reverse remodeling

A central finding of this study concerns cardiac contractility, assessed non-invasively via the SM-ICG CTi parameter. Training-induced changes in cardiac function have been shown using various methods. Echocardiographic assessments of Global Longitudinal Strain (GLS) have documented significant improvements, though typically at rest. For instance, CCR has been associated with cardiac reverse remodeling (31), likely the principal mechanism for improved LV function with training. One study reported increased LVEFpeak among CCR responders after myocardial infarction but found no differences in CI, SV, wall motion score index, or systolic myocardial velocities before and after CCR using stress echocardiography (32). The significant increases in CTi_max and CTi_reserve post-CCR in the R group—contrasted with deterioration or lack of improvement in the NR group—highlight the critical role of LV contractile reserve during exercise in determining rehabilitation outcomes. These results are consistent with echocardiographic studies examining LV contractile reserve after CCR (8) and with recent pilot work from our group linking CCR response to improvements in CTi_reserve in mostly coronary artery disease patients (18).

Outliers and measurement considerations

A small number of outliers were identified. In the NR group, 7 % (n = 3) showed paradoxical increases in CTi_reserve amplitude. Two of these cases were within the 5 % coefficient of variation of SM-ICG technology, while the third likely reflected a patient with poor baseline physical condition (BMI > 29, no $\dot{V}O_2$ increase between ventilatory threshold and peak) whose heart may have started to respond to CCR and might have benefited from a longer program. Conversely, 6% patients (n = 2) exhibited a response to CCR that differed from that of the majority of patients in the R group. One patient improved peak $\dot{V}O_2$ by +27 % without significant changes in Wpeak, $\dot{V}O_2$ at ventilatory threshold, peak HR or BP. The other exhibited dramatic post-CCR decreases in CTi_rest and CTi_max despite otherwise good training response, likely due to post-CCR SM-ICG measurement error. CTi, a normalized value for dZ/dt_max, is a surrogate marker of contractility rather than a direct measurement. Although dV/dt_max, closely related to dZ/dt_max, has been validated invasively (33), CTi remains specific to the SM-ICG system and difficult to correlate directly with standard measures such as LVEF or GLS, particularly during exercise when echocardiographic accuracy can be limited (9). This underscores the exploratory nature of our work. Nevertheless, CTi is integral to the computation of SV and its trends, which have been validated in previous comparative and application studies (10).

Clinical Implications and Response Criteria

Unlike VO_2peak or O_2-pulse—which reflect overall fitness and combine central and peripheral determinants such as stroke volume and arteriovenous O_2 extraction—CTi from SM-ICG is more directly linked to systolic ejection flow/velocity and myocardial inotropic performance, though, like echocardiographic functional indices, it remains influenced by preload and afterload (34). That CTi can discriminate training responders in a physiologically complex CHF population underscores its potential clinical value. Importantly, SM-ICG provides continuous data during exercise and does not depend on operator skill or acoustic window quality, unlike stress echocardiography. Given the observed role of CTi in CCR outcomes, training strategies targeting myocardial function, such as interval training, merit further investigation. However, caution is warranted in this frail population, as overreaching in cardiac rehabilitation may be more common than generally recognized. A pilot study suggested that tailoring training to SV_peak rather than anaerobic threshold may offer additional benefits (35). Finally, the choice of response criterion warrants discussion. We used a hybrid criterion: an increase in $\dot{V}O_2$peak ≥ 3.5 $mL.min^{-1}.kg^{-1}$ and/or a ≥ 24 watt increase in Wpeak. While some studies rely solely on $\dot{V}O_2$peak with cutoffs of 0–10 %, others combine multiple physiological markers (36). Our 1 MET ($\dot{V}O_2$peak and/or Wpeak) threshold is associated with a 12 % improvement in survival (37). This yielded a balanced distribution of 41 NR and 32 R, consistent with the moderate and heterogeneous fitness improvements observed in this physiologically complex cohort. Peripheral adaptations, such as blood flow redistribution, may enhance exercise capacity without large $\dot{V}O_2$peak gains (7). Notably, eight patients would have been classified as NR based solely on $\dot{V}O_2$peak despite Wpeak gains of up to 43 W, mostly among older individuals—likely reflecting improved peripheral oxygen delivery or pedaling efficiency.

Summary

In summary, limited improvements in peak workload, resting cardiac function, and exercise ventilation were observed in NR, largely due to the absence of meaningful hemodynamic gains—particularly in LV contractile reserve. In contrast, enhanced cardiac contractility emerged as the primary mechanism driving improved hemodynamics and exercise capacity in R, rather than changes in preload or afterload. These findings emphasize the central role of myocardial adaptations in determining CCR outcomes in patients with CHF.

Conclusion

This study explored the value of incorporating noninvasive, continuous exercise hemodynamic monitoring into the routine evaluation of cardiac rehabilitation patients during CPET. Specifically, improvements in the CTi parameter with training, as measured by SM-ICG, may be a relevant mechanism that explains the response to CCR in CHF patients. CTi may also be of interest as an independent criterion of rehabilitation outcome that could complement conventional criteria. Additionally, hemodynamic patterns and profiles observed during the baseline test could be used to personalize exercise prescriptions. This study also paved the way for broader research demonstrating the safety and effectiveness of training protocols based on SM-ICG, such as SVi and CTi.

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Table 1. Baseline Characteristics of Patients According to Their Training Response Status

Variable	**All patients (n = 73)**	**NR (n = 41)**	**R (n = 32)**
Demographic characteristics			
Female-to-male ratio (%)	11/62 (15/85%)	8/33 (20/80%)	3/29 (9/91%)
Age (years)	57.0 ± 12.0	59.0 ± 12.0	55.0 ± 13.0
Height (cm)	173.2 ± 9.2	172.0 ± 8.3	174.7 ± 10.3
weight (kg)	72.0 ± 14.7	72.8 ± 12.8	71.0 ± 17.0
BMI (kg.m^{-2})	23.9 ± 4.2	24.6 ± 3.9	23.1 ± 4.5
BSA (m^{2})	1.9 ± 0.2	1.9 ± 0.20	1.9 ± 0.3
Blood analysis			
Hemoglobin (g.dL^{-1})	13.0 ± 2.2	12.5 ± 2.1	13.6 ± 2.2
Creatinine (µmol.L^{-1})	96.9 ± 37.0	106,0 ± 47.7	88.3 ± 20.9
Median of BNP values (pg.mL^{-1})	406	401	460
C-reactive protein (mg.L^{-1})	15.7 ± 19.7	14.3 ± 16.5	17.4 ± 23.3
Total cholesterol (mg.dL^{-1})	4.5 ± 1.4	4.4 ± 1.3	4.6 ± 1.5
Cardiovascular etiology and risk factors			
Dilated cardiomyopathy (%)	26 (36)	14 (34)	12 (37)
Coronaropathy (%)	24 (33)	15 (37)	9 (28)
Hypertension (%)	15 (20)	10 (24)	5 (16)
Atrial fibrillation (%)	5 (7)	4 (10)	1 (3)
Implantable cardioverter-defibrillator (%)	17 (23)	11 (27)	6 (19)
Type 2 diabetes (%)	7 (10)	5 (12)	2 (6)
Baseline medication			
Bisoprolol	31 (42)	16 (39)	15 (47)
Ramipril	27 (37)	13 (32)	14 (44)
Eplerenone	27 (37)	14 (34)	13 (41)
Sacubitril /Valsartan	6 (8)	3 (7)	3 (9)
Furosemide	29 (40)	17 (41)	12 (37)
Resting echographic parameters			
LVEDD (mm)	63.5 ± 8.0	64.8 ± 5.4	61.9 ± 10.3
LVEF (%)	28.4 ± 7.1	27.7 ± 7.0	29.3 ± 7.4
E/A ratio	2.0 ± 1.6	1.9 ± 1.2	2.1 ± 2.0
E/E' ratio	11.5 ± 5.0	12.1 ± 5.6	10.6 ± 5.1
LVMI (g.m^{-2})	1.2 ± 0.8	1.3 ± 0.9	1.1 ± 0.7
sPAP (mmHg)	36.7 ± 10.9	**40.4 ± 10.9**	**32.1 ± 9.0**

Legend: BMI: body mass index; BSA Body surface area; BNP: brain natriuretic peptide; LVEDD: Left Ventricular End-Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; LVMI: Left Ventricular Mass Index; sPAP: Systolic Pulmonary Artery Pressure. Responders (R): +3.5 mL/min/kg $\dot{V}O_2$ peak or +24 W power. Note: **Bold characters**: significant difference between N and NR ($p<0.025$).

Table 2: Main effects of Comprehensive cardiac rehabilitation on cardiorespiratory responses and hemodynamic parameters.

Variable		NR (n = 41)	R (n = 32)	P value
WPeak (Watts)	Pre	73.4 ± 28.7	85.7 ± 39.1	0.193
	Post	**81.4 ± 29.2** ***	**117.9 ± 45.6** ***	**<0.001**
	Change	**8.0 ± 14.0**	**32.2 ± 15.6**	**<0.001**
$\dot{V}O_2$_rest (mL.min^{-1}.kg^{-1})	Pre	5.0 ± 2.2	5.7 ± 1.7	0.083
	Post	4.7 ± 1.4	5.6 ± 1.7	0.063
	Change	-0.4 ± 2.7	-0.2 ± 2.0	0.881
$\dot{V}O_2$peak (mL.min^{-1}.kg^{-1})	Pre	12.9 ± 3.5	14.6 ± 3.5	0.095
	Post	**13.3 ± 2.8**	**19.2 ± 5.0** ***	**< 0.001**
	Change	**0.4 ± 2.5**	**4.6 ± 3.3**	**< 0.001**
Net $\dot{V}O_2$peak (mL.min^{-1}.kg^{-1})	Pre	7.9 ± 3.6	8.8 ± 3.4	0.241
	Post	**8.6 ± 2.9**	**13.7 ± 4.9** ***	**<0.001**
	Change	**0.8 ± 3.3**	**4.9 ± 3.3**	**<0.001**
$\dot{V}_E$ _rest (L.min^{-1})	Pre	15.0 ± 5.3	15.8 ± 4.2	0.181
	Post	14.3 ± 4.3	14.7 ± 4.2	0.688
	Change	-0.7 ± 6.1	-1.1 ± 4.9	0.726
$\dot{V}_E$ _max (L.min^{-1})	Pre	47.4 ± 13.1	47.5 ± 15.5	0.961
	Post	**51.1 ± 15.6** *	**62.5 ± 22.3** ***	**0.017**
	Change	**3.8 ± 10.3**	**15.0 ± 13.2**	**<0.001**
$\dot{V}_E$ _reserve (L.min^{-1})	Pre	32.4 ± 13.7	31.7 ± 15.2	0.701
	Post	**36.9 ± 14.7** **	**47.8 ± 20.7** ***	**0.009**
	Change	**4.4 ± 10.2**	**16.1 ± 11.8**	**<0.001**
$\dot{Q}c$_rest (L.min^{-1})	Pre	4.7 ± 1.2	5.1 ± 1.5	0.220
	Post	4.5 ± 1.0	5.0 ± 1.3	0.066
	Change	-0.2 ± 1.1	-0.1 ± 1.0	0.729
$\dot{Q}c$_max (L.min^{-1})	Pre	8.5 ± 3.3	9.0 ± 3.3	0.512
	Post	**8.9 ± 3.5**	**11.6 ± 3.9** ***	**0.003**
	Change	**0.4 ± 2.6**	**2.6 ± 3.5**	**0.003**
$\dot{Q}c$_reserve (L.min^{-1})	Pre	3.8 ± 2.8	3.9 ± 2.7	0.934
	Post	**4.4 ± 3.1**	**6.6 ± 3.0** ***	**0.002**
	Change	**0.6 ± 2.5**	**2.7 ± 3.1**	**0.003**
$(a-\bar{v})O_2$diff _rest (mLO$_2$.dL^{-1})	Pre	7.5 ± 2.8	8.0 ± 2.6	0.385
	Post	7.5 ± 2.4	8.2 ± 2.6	0.273
	Change	0.0 ± 3.8	0.2 ± 3.2	0.947
$(a-\bar{v})$ O_2diff _max (mLO$_2$.dL^{-1})	Pre	11.9 ± 3.2	11.9 ± 4.1	0.578
	Post	12.1 ± 3.6	13.1 ± 4.6	0.299
	Change	0.1 ± 3.4	1.2 ± 3.4	0.026

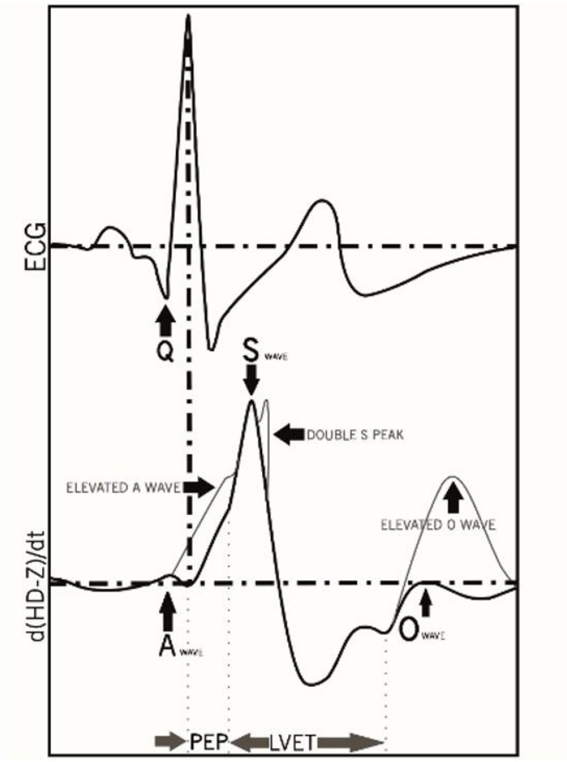
(a-v̄) O_2diff _reserve (mLO_2.dL^{-1})	Pre Post Change	4.4 ± 3.5 4.5 ± 3.7 0.1 ± 4.8	3.9 ± 4.1 4.9 ± 3.7 1.0 ± 3.8	0.331 0.683 0.464

Variable		**NR (n = 41)**	**R (n = 32)**	**P value NR vs R**
CI_rest (L.min^{-1}.m^{2})	**Pre**	**2.6 ± 0.5**	**2.8 ± 0.5**	**0.018**
	Post	2.5 ± 0.3	2.6 ± 0.4	0.037
	Change	-0.1 ± 0.5	-0.1 ± 0.4	0.613
CI_max (L.min^{-1}.m^{2})	Pre	4.3 ± 1.4	4.9 ± 1.2	0.031
	Post	**4.6 ± 1.5**	**5.8 ± 1.2** ***	**< 0.001**
	Change	**0.4 ± 0.9**	**0.9 ± 0.9**	**0.016**
CI_reserve (L.min^{-1}.m^{2})	Pre	1.7 ± 1.3	2.1 ± 1.1	0.147
	Post	**2.2 ± 1.5**	**3.1 ± 1.1** ***	**0.004**
	Change	**0.5 ± 1.0**	**1.0 ± 0.9**	**0.016**
HR _rest (bpm)	Pre	78.6 ± 17.1	83.6 ± 13.3	0.172
	Post	71.9 ± 12.0**	77.0 ± 11.9 **	0.080
	Change	-6.7 ± 14.8	-6.7 ± 13.7	0.701
HR _max (bpm)	Pre	108.0 ± 22.7	119.5 ± 22.4	0.034
	Post	**112.9 ± 25.2**	**129.7 ± 26.7** ***	**0.007**
	Change	4.9 ± 12.9	10.2 ± 16.5	0.129
HR _reserve (bpm)	Pre	29.4 ± 18.2	35.8 ± 17.8	0.133
	Post	41.0 ± 22.5	52.7 ± 23.4 ***	0.033
	Change	11.6 ± 14.8	16.9 ± 17.3	0.034
SVi_rest (mL.beat^{-1})	Pre	33.2 ± 5.2	33.6 ± 6.2	0.804
	Post	34.5 ± 6.0	34.5 ± 5.9	0.999
	Change	1.2 ± 4.2	0.9 ± 5.9	0.786
SVi_max (mL.beat^{-1})	Pre	39.6 ± 8.9	40.9 ± 7.9	0.520
	Post	40.8 ± 9.1	44.9 ± 7.4 **	0.040
	Change	-0.1 ± 6.5	3.1 ± 6.6	0.175
SVi_reserve (mL.beat^{-1})	Pre	6.3 ± 6.1	7.3 ± 7.0	0.541
	Post	**6.3 ± 6.4**	**10.4 ± 5.0** *	**0.004**
	Change	-0.1 ± 6.5	3.1 ± 6.6	0.175
EDFR _rest (%)	Pre	73.0 ± 29.4	68.8 ± 23.4	0.673
	Post	**69.2 ± 17.9**	**57.7 ± 10.9**	**< 0.001**
	Change	-3.8 ± 30.5	-11.2 ± 24.8	0.089
EDFR _max (%)	Pre	74.4 ± 19.3	72.9 ± 26.5	0.356
	Post	**80.2 ± 17.7**	**67.4 ± 20.2**	**0.005**
	Change	5.8 ± 21.4	-5.5 ± 22.6	0.033
EFDR _reserve (%)	Pre	1.4 ± 35.4	4.1 ± 24.4	0.726
	Post	10.9 ± 19.3	9.8 ± 21.9	0.807
	Change	9.6 ± 39.4	5.7 ± 26.3	0.616
SVRi_rest	Pre	2091.0 ± 501.0	2049.0 ± 516.0	0.631

(dyn·s·cm^{-5}·m^2)	Post	2265.0 ± 456.0	2197.0 ± 650.0	0.309
	Change	173.0 ± 475.0	148.0 ± 606.0	0.730
SVRi_max (dyn·s·cm^{-5}·m^2)	**Pre**	**1096.0 ± 501.0**	**846.0 ± 413.0**	**0.020**
	Post	1029.0 ± 460.0	856.0 ± 330.0 ***	0.063
	Change	71.0 ± 534.0	-7.0 ± 421.0	0.427
SVRi_reserve (dyn·s·cm^{-5}·m^2)	Pre	-995.0 ± 501.0	-1182.0 ± 382.0	0.111
	Post	-1215.0 ± 586.0	-1341.0 ± 622.0 *	0.537
	Change	-220.0 ± 678.0	-177.0 ± 699.0	0.657
CTi_rest (%)	Pre	138.0 ± 66.0	175.0 ± 80.0	0.033
	Post	160.0 ± 68.0 **	190.0 ± 76.0	0.085
	Change	22.0 ± 49.0	14.0 ± 56.0	0.567
CTi_max (%)	Pre	215.0 ± 98.0	268.0 ± 137.0	0.139
	Post	**201.0 ± 85.0**	**333.0 ± 127.0** ***	**< 0.001**
	Change	**-13.0 ± 53.0**	**65.0 ± 77.0**	**< 0.001**
CTi_reserve (%)	Pre	77.0 ± 69.0	92.0 ± 94.0	0.405
	Post	**41.0 ± 061.0** ***	**143.0 ± 94.0** ***	**< 0.001**
	Change	**-35.0 ± 44.0**	**51.0 ± 53.0**	**< 0.001**

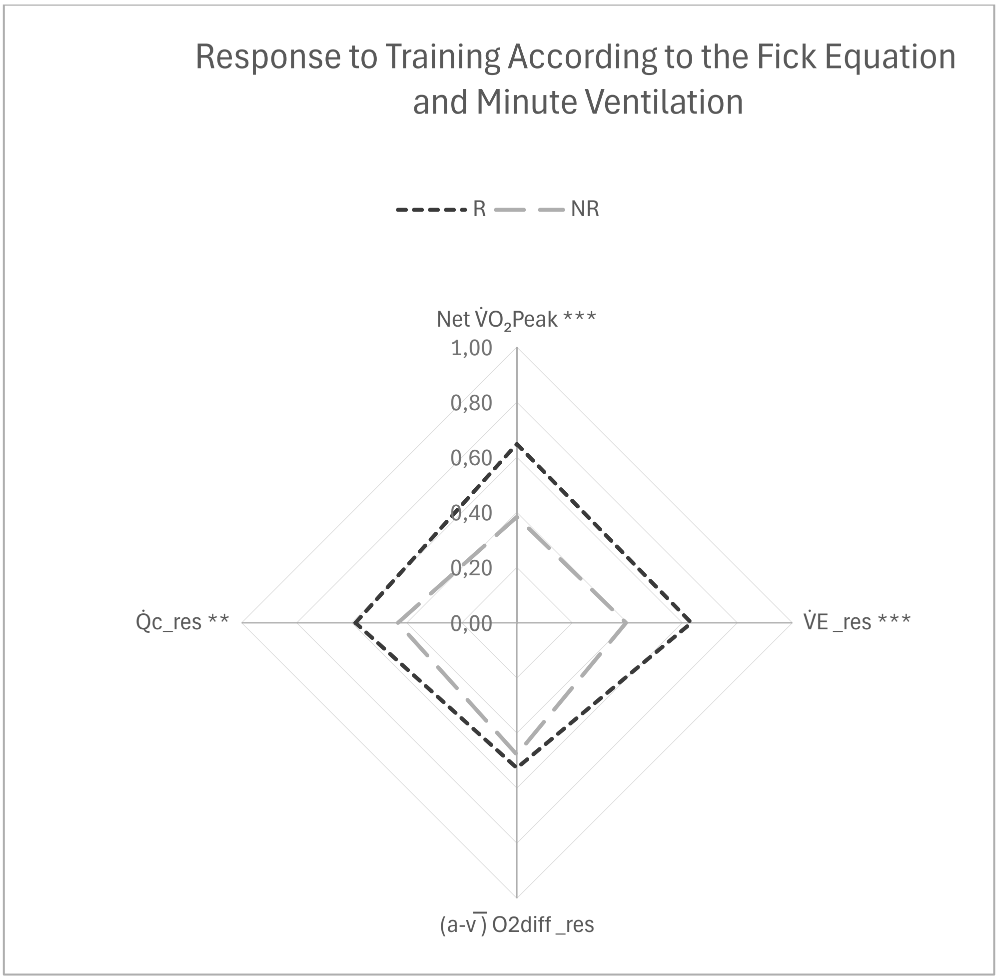
Legend: R represents responders to exercise-based cardiac rehabilitation, while NR represents non-responders. Responders (R): +3.5 mL/min/kg in $\dot{V}O_2$peak or +24 in Wpeak. Pre = before CCR starts; Post = After CCR is completed, Change = Post-Pre training effect. $\dot{V}O_2$ = oxygen consumption, $\dot{V}_E$ = minute ventilation, $\dot{Q}c$ = cardiac output, $(a-\bar{v})O_2$diff = arterio-venous oxygen content difference. CI = Cardiac Index, HR = Heart Rate, SVi = Stroke Volume index, EDFR = Early Diastolic Filling Ratio, CTi = Contractility Index, SVRi = Systemic Vascular Resistance index. Note: **Bold characters**: significant difference between groups ($p<0.025$). * = significative training effect ($p<0.025$), ** = ($p<0.01$), *** = ($p<0.001$)

Figure 1: Characterization of S and O Waves via Signal-Morphology Impedance Cardiography



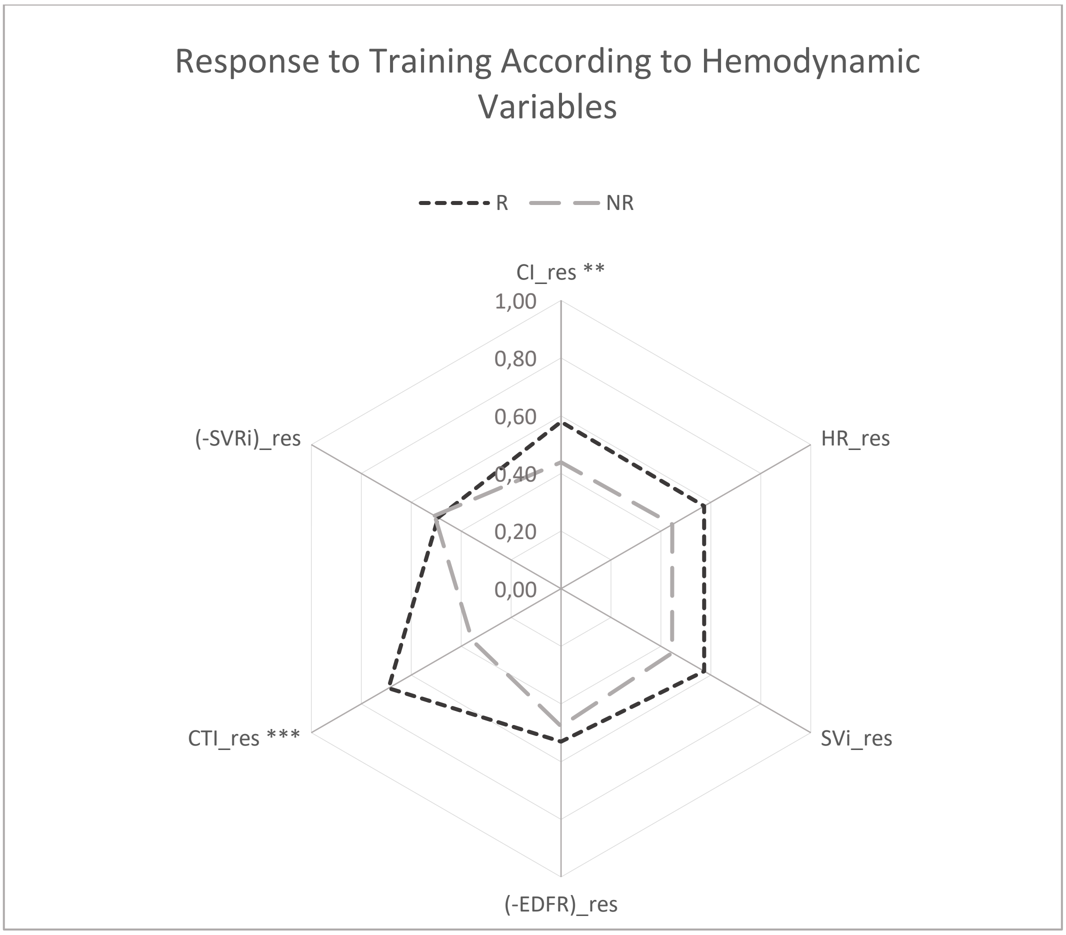
Legend: The black trace represents the normal physiological response, whereas the grey trace demonstrates deviations indicative of abnormalities that may be encountered in specific pathological conditions. Note that d(HD-Z)/dt corresponds to the dZ/dt signal processed through the proprietary HD-Z filtering algorithm.

Figure 2: Changes in Peak Values of Oxygen Uptake, Pulmonary Ventilation, Arteriovenous Oxygen Content Difference and Cardiac Output with Training.



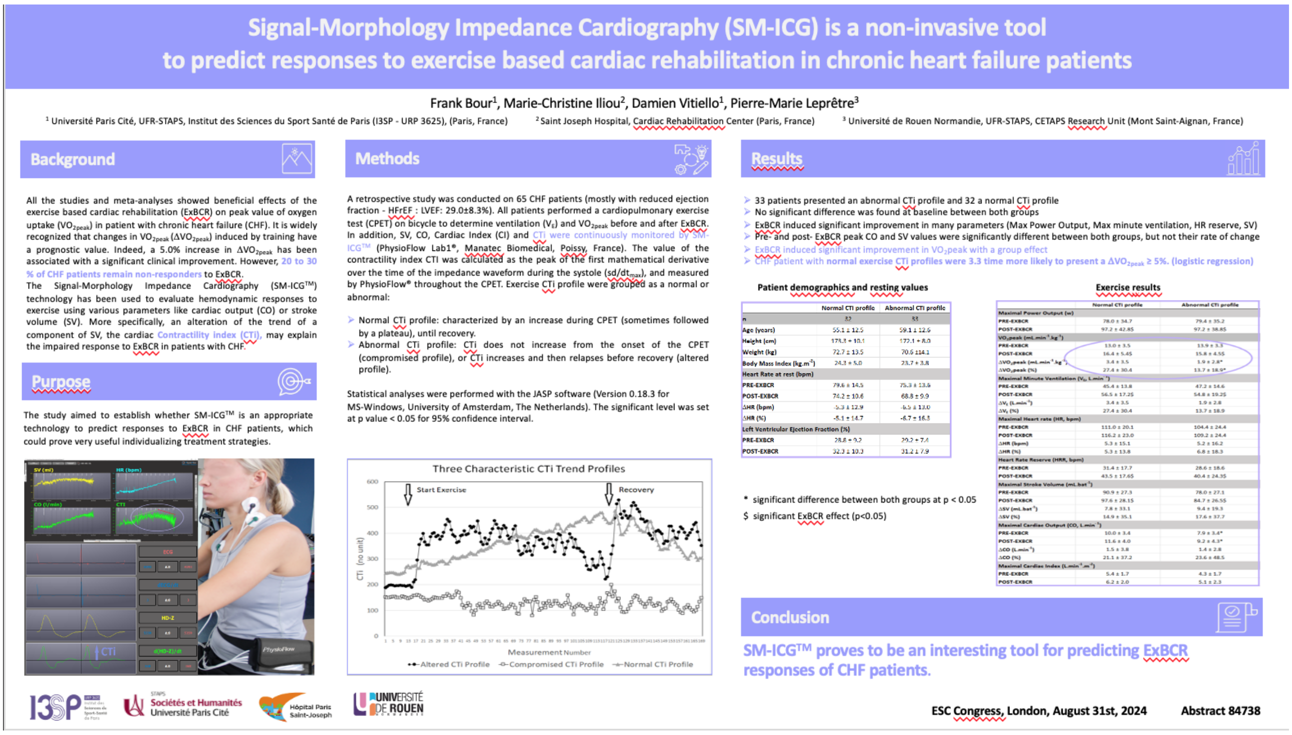
Legend: NetV̇O₂Peak = Oxygen uptake difference between peak and rest V̇E _res = Minute ventilation reserve, (a-v̄O2)diff_res = Peripheral oxygen extraction reserve, Q̇c _res= Cardiac output reserve. The dotted black line represents responders to exercise-based cardiac rehabilitation (R), while the dotted gray line represents non-responders (NR). Responders (R): +3.5 mL/min/kg in V̇O₂ peak or +24 watts in Wpeak. For legibility and ease of comparison purposes, all the axes are normalized as follows: 0 = Mean value-2 SD, and 1.0 ≡ mean value + 2 SD. * = significative difference with NR group (p<0.025); ** = (p<0.01); *** = (p<0.001).

Figure 3: **Changes in Hemodynamic Parameters with Training**



Legend: CI_res = Cardiac Index reserve, HR_res = Heart Rate reserve, SVi_res = Stroke Volume index reserve, EDFR_res = Early Diastolic Filling Ratio reserve, CTi_res = Contractility Index reserve, SVRi_res = Systemic Vascular Resistance index reserve. The dotted black line represents responders to exercise-based cardiac rehabilitation (R), while the dotted gray line represents non-responders (NR). Responders (R): +3.5 mL/min/kg in $\dot{V}O_2$peak or +24 watts in Wpeak. For legibility and ease of comparison purposes, all the axes are normalized as follows: 0 = Mean value-2 SD, and 1.0 ≡ mean value + 2 SD. For EDFR and SVRi, the negative value was chosen instead of the absolute value as for these two parameters, as a reduction mean clinical improvement. * = statistically significant difference with NR group (p<0.025); ** = (p<0.01); *** = (p<0.001).

Poster 1 : European Society of Cardiology Congress, London 2024



Signal-Morphology Impedance Cardiography (SM-ICG) is a non-invasive tool to predict responses to exercise based cardiac rehabilitation in chronic heart failure patients

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Background

All the studies and meta-analyses showed beneficial effects of the exercise based cardiac rehabilitation (ExBCR) on peak value of oxygen uptake (VO_{2peak}) in patient with chronic heart failure (CHF). It is widely recognized that changes in VO_{2peak} (ΔVO_{2peak}) induced by training have a prognostic value. Indeed, a 5.0% increase in ΔVO_{2peak} has been associated with a significant clinical improvement. However, 20 to 30 % of CHF patients remain non-responders to ExBCR.

The Signal-Morphology Impedance Cardiography (SM-ICG™) technology has been used to evaluate hemodynamic responses to exercise using various parameters like cardiac output (CO) or stroke volume (SV). More specifically, an alteration of the trend of a component of SV, the cardiac Contractility index (CTi), may explain the impaired response to ExBCR in patients with CHF.

Purpose

The study aimed to establish whether SM-ICG™ is an appropriate technology to predict responses to ExBCR in CHF patients, which could prove very useful individualizing treatment strategies.

Methods

A retrospective study was conducted on 65 CHF patients (mostly with reduced ejection fraction - HFrEF : LVEF: 29.0±8.3%). All patients performed a cardiopulmonary exercise test (CPET) on bicycle to determine ventilation (V_E) and VO_{2peak} before and after ExBCR. In addition, SV, CO, Cardiac Index (CI) and CTi were continuously monitored by SM-ICG™ (PhysioFlow Lab1®, Manatec Biomedical, Poissy, France). The value of the contractility index CTI was calculated as the peak of the first mathematical derivative over the time of the impedance waveform during the systole (sd/dt_{max}), and measured by PhysioFlow® throughout the CPET. Exercise CTi profile were grouped as a normal or abnormal:

- Normal CTi profile: characterized by an increase during CPET (sometimes followed by a plateau), until recovery.
- Abnormal CTi profile: CTi does not increase from the onset of the CPET (compromised profile), or CTi increases and then relapses before recovery (altered profile).

Statistical analyses were performed with the JASP software (Version 0.18.3 for MS-Windows, University of Amsterdam, The Netherlands). The significant level was set at p value < 0.05 for 95% confidence interval.

Three Characteristic CTi Trend Profiles

Results

- 33 patients presented an abnormal CTi profile and 32 a normal CTi profile
- No significant difference was found at baseline between both groups
- ExBCR induced significant improvement in many parameters (Max Power Output, Max minute ventilation, HR reserve, SV)
- Pre- and post- ExBCR peak CO and SV values were significantly different between both groups, but not their rate of change
- ExBCR induced significant improvement in VO_2peak with a group effect
- CHF patient with **normal exercise CTi profiles were 3.3 time more likely to present a ΔVO_{2peak} ≥ 5%. (logistic regression)**

Patient demographics and resting values

	Normal CTI profile	Abnormal CTI profile
n	32	33
Age (years)	55.1 ± 12.5	59.1 ± 12.6
Height (cm)	173.3 ± 10.1	172.1 ± 8.0
Weight (kg)	72.7 ± 13.5	70.6 ±14.1
Body Mass Index ($kg.m^{-2}$)	24.3 ± 5.0	23.7 ± 3.8
Heart Rate at rest (bpm)		
PRE-EXBCR	79.6 ± 14.5	75.3 ± 13.6
POST-EXBCR	74.2 ± 10.6	68.8 ± 9.9
ΔHR (bpm)	-5.3 ± 12.9	-6.5 ± 13.0
ΔHR (%)	-5.1 ± 14.7	-6.7 ± 16.3
Left Ventricular Ejection Fraction (%)		
PRE-EXBCR	28.8 ± 9.2	29.2 ± 7.4
POST-EXBCR	32.3 ± 10.3	31.2 ± 7.9

* significant difference between both groups at p < 0.05

$ significant ExBCR effect (p<0.05)

Exercise results

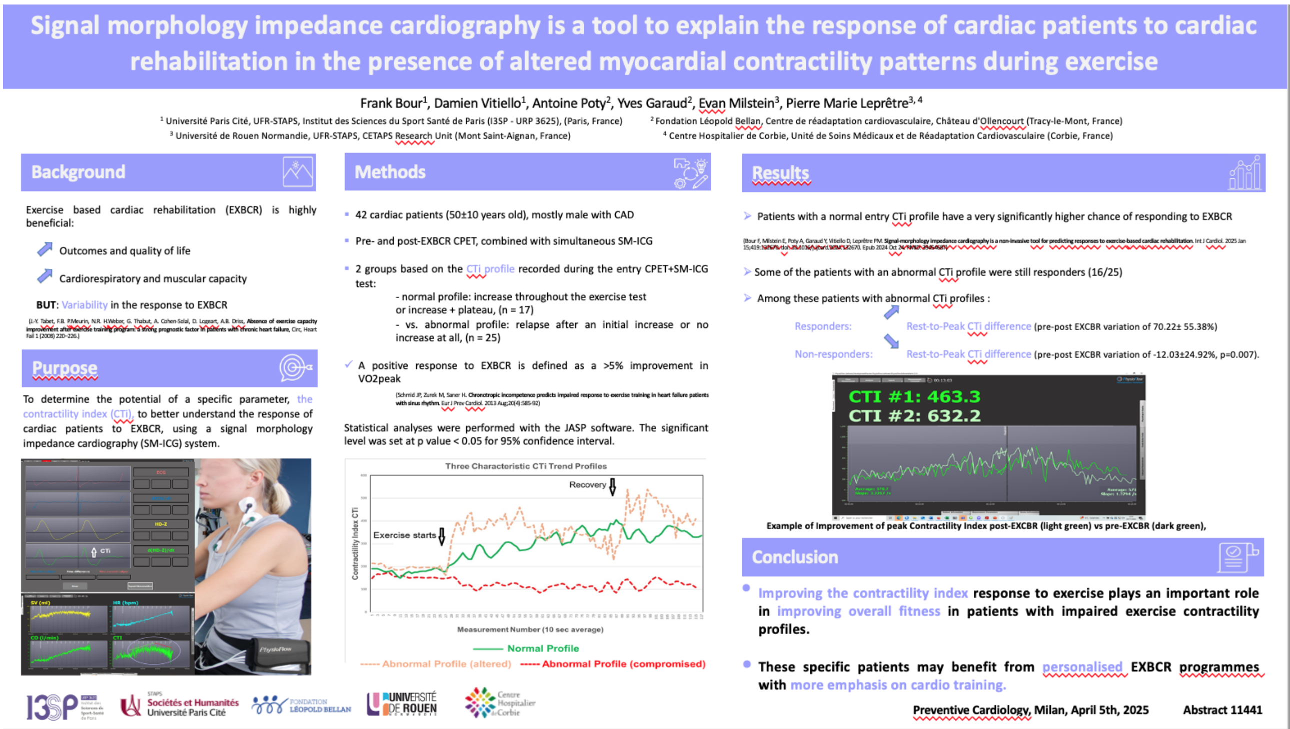
	Normal CTi profile	Abnormal CTi profile
Maximal Power Output (w)		
PRE-EXBCR	78.0 ± 34.7	79.4 ± 35.2
POST-EXBCR	97.2 ± 42.8$	97.2 ± 38.8$
VO_2peak ($mL.min^{-1}.kg^{-1}$)		
PRE-EXBCR	13.0 ± 3.5	13.9 ± 3.3
POST-EXBCR	16.4 ± 5.4$	15.8 ± 4.5$
ΔVO_2peak ($mL.min^{-1}.kg^{-1}$)	3.4 ± 3.5	1.9 ± 2.8*
ΔVO_2peak (%)	27.4 ± 30.4	13.7 ± 18.9*
Maximal Minute Ventilation (V_E, $L.min^{-1}$)		
PRE-EXBCR	45.4 ± 13.8	47.2 ± 14.6
POST-EXBCR	56.5 ± 17.2$	54.8 ± 19.2$
ΔV_E ($L.min^{-1}$)	3.4 ± 3.5	1.9 ± 2.8
ΔV_E (%)	27.4 ± 30.4	13.7 ± 18.9
Maximal Heart rate (HR, bpm)		
PRE-EXBCR	111.0 ± 20.1	104.4 ± 24.4
POST-EXBCR	116.2 ± 23.0	109.2 ± 24.4
ΔHR (bpm)	5.3 ± 15.1	5.2 ± 16.2
ΔHR (%)	5.3 ± 13.8	6.8 ± 18.3
Heart Rate Reserve (HRR, bpm)		
PRE-EXBCR	31.4 ± 17.7	28.6 ± 18.6
POST-EXBCR	43.5 ± 17.6$	40.4 ± 24.3$
Maximal Stroke Volume ($mL.bat^{-1}$)		
PRE-EXBCR	90.9 ± 27.3	78.0 ± 27.1
POST-EXBCR	97.6 ± 28.1$	84.7 ± 26.5$
ΔSV ($mL.bat^{-1}$)	7.8 ± 33.1	9.4 ± 19.3
ΔSV (%)	14.9 ± 35.1	17.6 ± 37.7
Maximal Cardiac Output (CO, $L.min^{-1}$)		
PRE-EXBCR	10.0 ± 3.4	7.9 ± 3.4*
POST-EXBCR	11.6 ± 4.0	9.2 ± 4.3*
ΔCO ($L.min^{-1}$)	1.5 ± 3.8	1.4 ± 2.8
ΔCO (%)	21.1 ± 37.2	23.6 ± 48.5
Maximal Cardiac Index ($L.min^{-1}.m^{-2}$)		
PRE-EXBCR	5.4 ± 1.7	4.3 ± 1.7
POST-EXBCR	6.2 ± 2.0	5.1 ± 2.3

Conclusion

SM-ICG™ proves to be an interesting tool for predicting ExBCR responses of CHF patients.

ESC Congress, London, August 31st, 2024 Abstract 84738

Poster 2 : European Preventive Cardiology Congress, Milan 2025



Signal morphology impedance cardiography is a tool to explain the response of cardiac patients to cardiac rehabilitation in the presence of altered myocardial contractility patterns during exercise

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Background

Exercise based cardiac rehabilitation (EXBCR) is highly beneficial:

- ↗ Outcomes and quality of life
- ↗ Cardiorespiratory and muscular capacity

BUT: Variability in the response to EXBCR

(J.-Y. Tabet, F.B. P.Meurin, N.R. H.Weber, G. Thabut, A. Cohen-Solal, D. Logeart, A.B. Driss, **Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure**, Circ, Heart Fail 1 (2008) 220–226.)

Purpose

To determine the potential of a specific parameter, the contractility index (CTi), to better understand the response of cardiac patients to EXBCR, using a signal morphology impedance cardiography (SM-ICG) system.

Methods

- 42 cardiac patients (50±10 years old), mostly male with CAD
- Pre- and post-EXBCR CPET, combined with simultaneous SM-ICG
- 2 groups based on the CTi profile recorded during the entry CPET+SM-ICG test:
  - normal profile: increase throughout the exercise test or increase + plateau, (n = 17)
  - vs. abnormal profile: relapse after an initial increase or no increase at all, (n = 25)

✓ A positive response to EXBCR is defined as a >5% improvement in VO2peak

(Schmid JP, Zurek M, Saner H. **Chronotropic incompetence predicts impaired response to exercise training in heart failure patients with sinus rhythm.** Eur J Prev Cardiol. 2013 Aug;20(4):585-92)

Statistical analyses were performed with the JASP software. The significant level was set at p value < 0.05 for 95% confidence interval.

Three Characteristic CTi Trend Profiles

Results

- Patients with a normal entry CTi profile have a very significantly higher chance of responding to EXBCR

(Bour F, Milstein E, Poty A, Garaud Y, Vitiello D, Leprêtre PM. **Signal-morphology impedance cardiography is a non-invasive tool for predicting responses to exercise-based cardiac rehabilitation.** Int J Cardiol. 2025 Jan 15;419:132670. doi: 10.1016/j.ijcard.2024.132670. Epub 2024 Oct 24. PMID: [illegible])

- Some of the patients with an abnormal CTi profile were still responders (16/25)
- Among these patients with abnormal CTi profiles :

Responders: ↗ Rest-to-Peak CTi difference (pre-post EXCBR variation of 70.22± 55.38%)

Non-responders: ↘ Rest-to-Peak CTi difference (pre-post EXCBR variation of -12.03±24.92%, p=0.007).

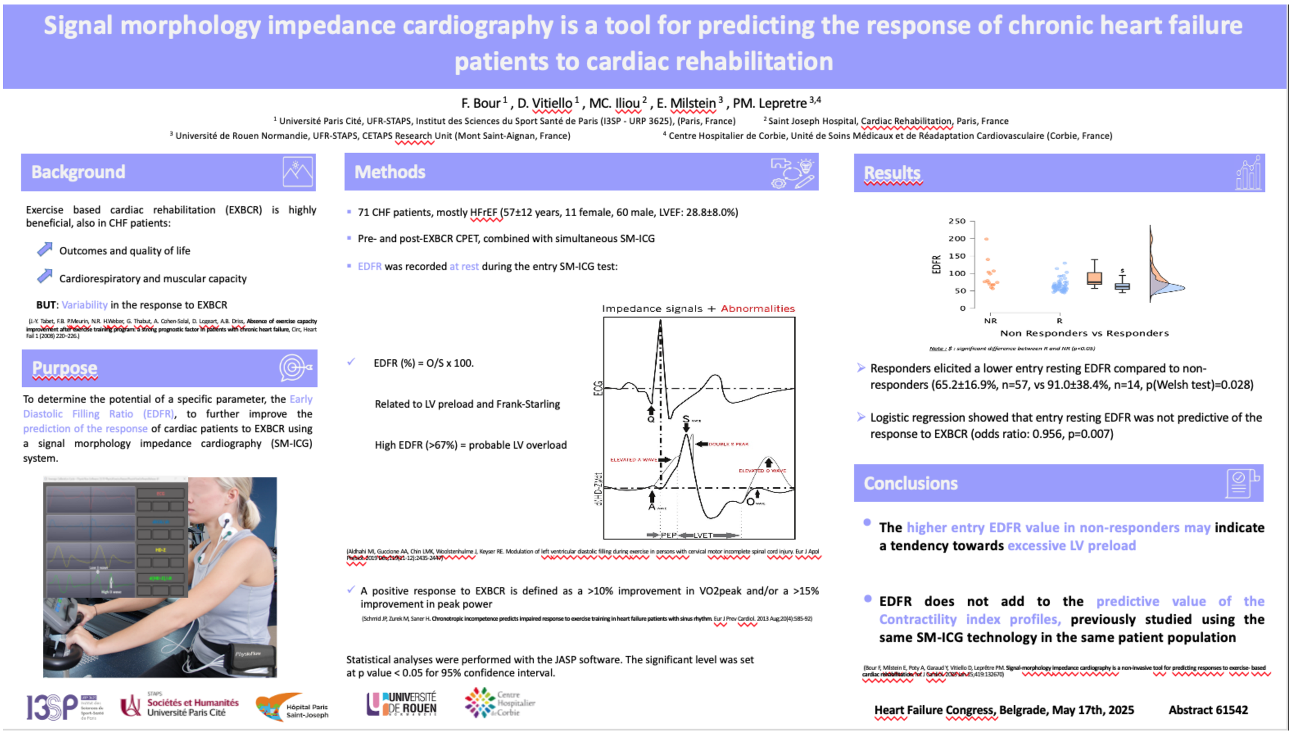
Example of Improvement of peak Contractility Index post-EXCBR (light green) vs pre-EXCBR (dark green),

Conclusion

- **Improving the contractility index response to exercise plays an important role in improving overall fitness in patients with impaired exercise contractility profiles.**
- **These specific patients may benefit from personalised EXBCR programmes with more emphasis on cardio training.**

Preventive Cardiology, Milan, April 5th, 2025 Abstract 11441

Poster 3 : European Heart Failure Congress, Belgrade 2025



Signal morphology impedance cardiography is a tool for predicting the response of chronic heart failure patients to cardiac rehabilitation

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Background

Exercise based cardiac rehabilitation (EXBCR) is highly beneficial, also in CHF patients:

- ↗ Outcomes and quality of life
- ↗ Cardiorespiratory and muscular capacity

BUT: Variability in the response to EXBCR

(J.-Y. Tabet, F.B. P.Meurin, N.R. H.Weber, G. Thabut, A. Cohen-Solal, D. Logeart, A.B. Driss, **Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure**, Circ, Heart Fail 1 (2008) 220–226.)

Purpose

To determine the potential of a specific parameter, the Early Diastolic Filling Ratio (EDFR), to further improve the prediction of the response of cardiac patients to EXBCR using a signal morphology impedance cardiography (SM-ICG) system.

Methods

- 71 CHF patients, mostly HFrEF (57±12 years, 11 female, 60 male, LVEF: 28.8±8.0%)
- Pre- and post-EXBCR CPET, combined with simultaneous SM-ICG
- EDFR was recorded at rest during the entry SM-ICG test:

✓ EDFR (%) = O/S x 100.

Related to LV preload and Frank-Starling

High EDFR (>67%) = probable LV overload

Impedance signals + Abnormalities

(Aldhahi MI, Guccione AA, Chin LMK, Woolstenhulme J, Keyser RE. Modulation of left ventricular diastolic filling during exercise in persons with cervical motor incomplete spinal cord injury. Eur J Appl Physiol. 2019 Dec;119(11-12):2435-2447)

✓ A positive response to EXBCR is defined as a >10% improvement in VO2peak and/or a >15% improvement in peak power

(Schmid JP, Zurek M, Saner H. **Chronotropic incompetence predicts impaired response to exercise training in heart failure patients with sinus rhythm.** Eur J Prev Cardiol. 2013 Aug;20(4):585-92)

Statistical analyses were performed with the JASP software. The significant level was set at p value < 0.05 for 95% confidence interval.

Results

Note : $: significant difference between R and NR (p<0.05)

- ➢ Responders elicited a lower entry resting EDFR compared to non-responders (65.2±16.9%, n=57, vs 91.0±38.4%, n=14, p(Welsh test)=0.028)
- ➢ Logistic regression showed that entry resting EDFR was not predictive of the response to EXBCR (odds ratio: 0.956, p=0.007)

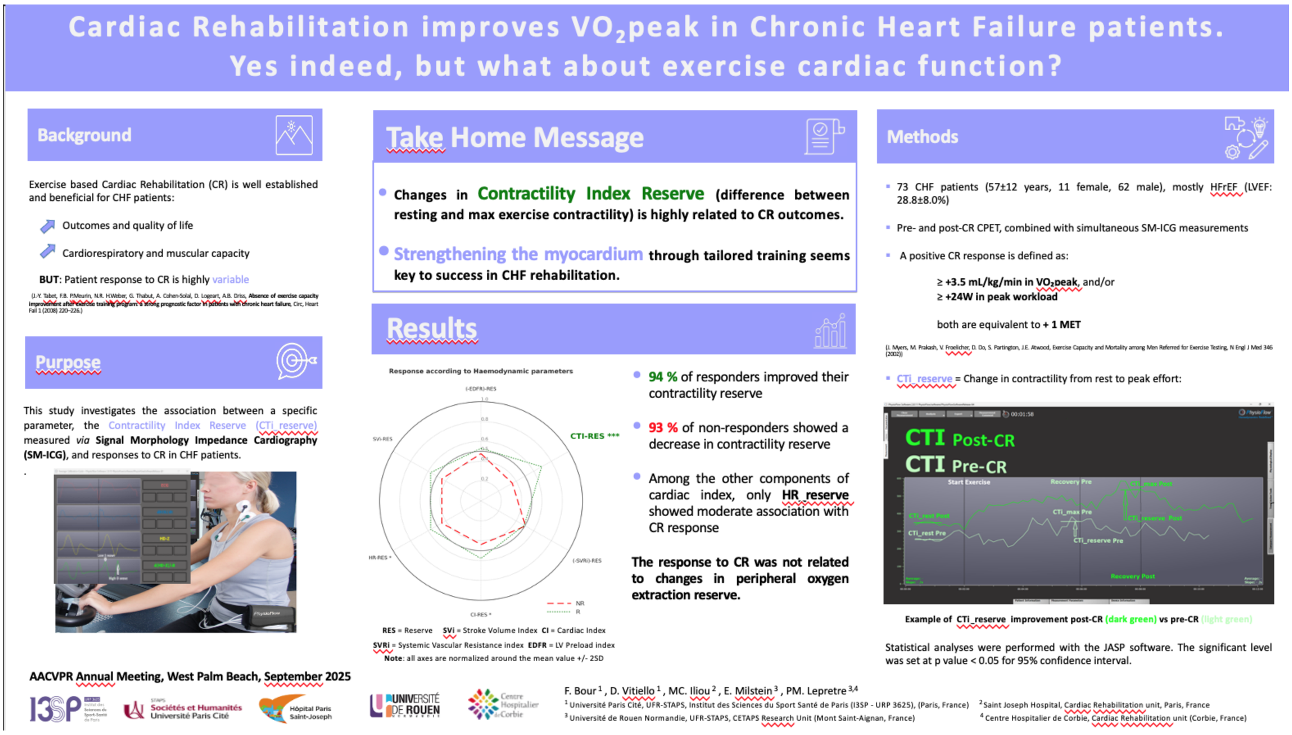
Conclusions

- **The higher entry EDFR value in non-responders may indicate a tendency towards excessive LV preload**
- **EDFR does not add to the predictive value of the Contractility index profiles, previously studied using the same SM-ICG technology in the same patient population**

(Bour F, Milstein E, Poty A, Garaud Y, Vitiello D, Leprêtre PM. **Signal-morphology impedance cardiography is a non-invasive tool for predicting responses to exercise- based cardiac rehabilitation.** Int J Cardiol. 2025 Jan 15;419:132670)

Heart Failure Congress, Belgrade, May 17th, 2025 **Abstract 61542**

Poster 4 : 40th Congress of American Association of Cardiovascular and Pulmonary Rehabilitation



Cardiac Rehabilitation improves VO_2peak in Chronic Heart Failure patients. Yes indeed, but what about exercise cardiac function?

Background

Exercise based Cardiac Rehabilitation (CR) is well established and beneficial for CHF patients:

- ↗ Outcomes and quality of life
- ↗ Cardiorespiratory and muscular capacity

BUT: Patient response to CR is highly variable

(J.-Y. Tabet, F.B. P.Meurin, N.R. H.Weber, G. Thabut, A. Cohen-Solal, D. Logeart, A.B. Driss, **Absence of exercise capacity improvement after exercise training program: a strong prognostic factor in patients with chronic heart failure**, Circ, Heart Fail 1 (2008) 220–226.)

Purpose

This study investigates the association between a specific parameter, the Contractility Index Reserve (CTi_reserve) measured *via* **Signal Morphology Impedance Cardiography (SM-ICG)**, and responses to CR in CHF patients.

AACVPR Annual Meeting, West Palm Beach, September 2025

Take Home Message

- **Changes in Contractility Index Reserve (difference between resting and max exercise contractility) is highly related to CR outcomes.**
- **Strengthening the myocardium through tailored training seems key to success in CHF rehabilitation.**

Results

Response according to Haemodynamic parameters

RES = Reserve **SVi** = Stroke Volume Index **CI** = Cardiac Index
SVRi = Systemic Vascular Resistance index **EDFR** = LV Preload index
Note: all axes are normalized around the mean value +/- 2SD

- 94 % of responders improved their contractility reserve
- 93 % of non-responders showed a decrease in contractility reserve
- Among the other components of cardiac index, only **HR reserve** showed moderate association with CR response

The response to CR was not related to changes in peripheral oxygen extraction reserve.

Methods

- 73 CHF patients (57±12 years, 11 female, 62 male), mostly HFrEF (LVEF: 28.8±8.0%)
- Pre- and post-CR CPET, combined with simultaneous SM-ICG measurements
- A positive CR response is defined as:

  ≥ +3.5 mL/kg/min in VO_2peak, and/or
  ≥ +24W in peak workload

  both are equivalent to **+ 1 MET**

(J. Myers, M. Prakash, V. Froelicher, D. Do, S. Partington, J.E. Atwood, Exercise Capacity and Mortality among Men Referred for Exercise Testing, N Engl J Med 346 (2002))

- CTi_reserve = Change in contractility from rest to peak effort:

Example of CTi_reserve improvement post-CR (dark green) vs pre-CR (light green)

Statistical analyses were performed with the JASP software. The significant level was set at p value < 0.05 for 95% confidence interval.

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1. Part I: Review of the Literature.. 20
1.1. CHAPTER 1: CARDIOPULMONARY PHYSIOLOGY IN REHABILITATION............... 21
1.1.1. *Objectives and Benefits of Cardiac Rehabilitation* 21

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1.2.2. The Originality of Signal-Morphology Impedance Cardiography 44

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1.3. Chapter 3: APPLICATION OF SM-ICG TECHNOLOGY TO CARDIAC REHABILITATION..53
1.3.1. State of the Art of Studies on ICG and SM-ICG in Rehabilitation.. 53

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2. Part II: Presentation of the Thesis Studies.. 74

2.1. CHAPTER 4: METHODOLOGY OF THE THESIS..62

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2.1.1. *Cardiopulmonary Exercise Test* 62
2.1.2. *Signal Morphology Impedance Cardiography* 63

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2.1.3. *Patient Populations and Training protocols* 71
2.1.4. *Response criteria and Statistical Methods* 76

***2.2. CHAPTER 5: RESULTS OF THE THESIS* 79**
2.2.1. *Study 1 – Predictive Value of Baseline CTi Profile in a CVD Population* 79
2.2.2. *Study 2 – Validation of CTi Predictive Role in CHF* 79
2.2.3. *Study 3 – Mechanistic Evidence of Contractile Plasticity* 79
2.2.4. *Study 4 – Hemodynamic Determinants of Response in HFrEF* 79

***2.3. CHAPTER 6: ANALYSIS OF THE THESIS STUDIES* 82**
2.3.1. *Discussion* 82
2.3.2. *Limitations of the Studies* 83
2.3.3. *Perspective of the thesis* 103

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Conclusion **.. *94***

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