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POLYTECHNIQUE MONTREAL

affiliée à l'Université de Montréal

**Development, optimization, and validation of a cardiac magnetic resonance imaging
protocol under exercise stress conditions**

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Institut de génie biomédical

Thèse présentée en vue de l'obtention du diplôme de *Philosophiæ Doctor*

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protocol under exercise stress conditions**

présentée par **Egidie UWASE**

en vue de l'obtention du diplôme de *Philosophiæ Doctor*

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DEDICATION

This thesis is dedicated to my parents for their support and prayers.

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RÉSUMÉ

Le remodelage cardiaque est un processus qui survient en réponse à une maladie cardiaque et qui engendre une cascade de changements dans la masse, la géométrie et la fonction du cœur. Toutefois, ce processus peut mener à des conditions cardiaques graves telles que l'insuffisance cardiaque, qui est une cause importante de morbidité et de décès. Malgré des progrès significatifs, la détection de changements anormaux après le remodelage cardiaque, reste un défi en raison du manque de techniques de caractérisation fiables et précises. L'un des principaux problèmes est que les techniques existantes telles que l'échocardiographie et l'imagerie par résonance magnétique (IRM) effectuées au repos, ne permettent pas la détection d'anomalies subtiles des maladies cardiaques. En conséquence, l'IRM à l'effort émerge comme un outil permettant une meilleure caractérisation. En effet, l'IRM à l'effort démontre un fort potentiel de caractériser précisément le cœur et de révéler des anomalies non apparentes au repos chez les patients cardiaques. L'IRM à l'effort a également démontré sa capacité à différencier le remodelage physiologique due à l'effort au remodelage pathologique avec une meilleure précision. Pour améliorer l'efficacité de l'IRM à l'effort, les chercheurs ont combiné cette technique avec des modèles computationnels, permettant la quantification d'autres paramètres cardiaques difficiles à mesurer pendant l'imagerie, telles que les pressions cardiaques et les propriétés mécaniques cardiaques. Malgré l'utilité des protocoles de l'IRM à l'effort, leurs applications cliniques demeurent limitées en raison des risques de compromettre la sécurité des patients et la qualité des images. En conséquence, le besoin de développer un nouveau protocole de l'IRM à l'effort plus efficace demeure. Cette technique pourrait permettre une caractérisation cardiaque plus précise et pourrait améliorer ainsi la détection précoce de maladies cardiaques.

Pour développer un nouveau protocole d'IRM à l'effort, nous avons d'abord mené une étude pour mieux comprendre la relation entre les paramètres de l'IRM cardiaque et les propriétés mécaniques cardiaques des survivants du cancer de la leucémie lymphoblastique aiguë (LLA). Pour étudier la relation entre les propriétés mécaniques cardiaques et les temps de relaxation T1 et T2, ainsi que le coefficient de partition, nous avons analysé les résultats de 50 enfants survivants de la LLA ayant subi un examen d'IRM cardiaque sur un IRM Tesla 3T.

Chaque enfant était classé dans un groupe selon son niveau de risque, à la suite de son diagnostic (risque faible, risque élevé, et risque élevé avec prise d'agent cardioprotecteur (dexrazoxane). Après l'obtention des paramètres cardiaques à partir des images-Ciné, nous avons utilisé le modèle CircAdapt pour simuler les performances mécaniques cardiaques des participants (i.e. la rigidité du ventricule gauche (RVG), la contractilité (CVG), la pression minimale et maximale ($P_{\min}$ et $P_{\max}$), l'efficacité du travail cardiaque (ETC) et le couplage ventriculo-artériel (CVA). Les résultats ont montré que les propriétés cardiaques peuvent être prédites à partir de la combinaison des paramètres d'IRM cardiaque et vice versa. Par exemple, dans le groupe à risque faible, la RVG a été prédite à partir de la combinaison de paramètres de l'IRM cardiaque avec ($R^2 = 94,8 \%$, $r = 0,97$) et la CVG a été prédite avec ($R^2 = 93,7 \%$, $r = 0,96$). Le coefficient de partition a été prédit à partir de la combinaison des propriétés mécaniques cardiaques par ($R^2 = 72,6 \%$, $r = 0,85$) dans ce même groupe. Après analyse, nous constatons que les corrélations entre les propriétés mécaniques cardiaques et les paramètres d'IRM dans le groupe ayant un risque élevé, étaient marginales à cause de la dose plus élevée de doxorubicine reçue.

Dans la même cohorte, nous avons évalué l'impact de l'exercice sur la fonction cardiaque et sur la performance cardiaque à différents niveaux d'effort à partir des résultats de 63 enfants survivants de la LLA ayant à la fois passé des examens d'IRM cardiaque et ayant réalisé un test d'effort cardiopulmonaire sur ergocycle. Le modèle CircAdapt a été utilisé également, pour étudier les performances mécaniques cardiaques. En utilisant ce modèle, nous avons constaté que l'ETC était altérée ($< 85 \%$) et que le CVA était réduit de 24% dans cette population. Cependant, la performance cardiaque de ces enfants s'est améliorée suite à l'effort. Par exemple, en comparant le CVA au repos avec celui au niveau d'effort sous-maximal, nous constatons que le CVA s'est amélioré de 33% dans le groupe faible risque, de 26% dans le groupe risque élevé+dexarozane, et de 16% dans le groupe risque élevé. De plus, l'ETC s'est améliorée de $5,2 \%$ dans le groupe risque faible, de 8% dans le groupe risque élevé+dexarozane et de $1,4 \%$ dans le groupe risque élevé. Dans l'ensemble, l'étude a montré des différences significatives entre les différents niveaux d'exercice à la fois pour le CVA ($P < 0,0001$) et pour l'ETC ($P = 0,001$).

Sachant que les tests d'effort cardiaque ont un impact positif à la fois sur la fonction cardiaque et sur la performance cardiaque, nous avons réalisé une revue exploratoire pour donner un aperçu des

études existantes utilisant les tests d'IRM à l'effort et se concentrant sur le remodelage cardiaque chez les patients cardiaques. À travers cette étude, nous avons démontré la capacité de chaque protocole d'IRM à l'effort d'induire les déformations cardiaques et nous avons également mis en évidence les avantages et les limites de chaque protocole. Nos résultats révèlent que l'ergomètre et le handgrip sont les protocoles d'IRM à l'effort les plus utilisés pour évaluer le remodelage cardiaque et que les deux induisent suffisamment de contraintes à la suite de maladies cardiaques. Cependant, nous avons constaté que le handgrip a un avantage supérieur à l'ergomètre grâce à la haute qualité d'image qu'il procure. Ces résultats ont confirmé la nécessité de développer un nouveau protocole d'IRM à l'effort efficace qui pourrait améliorer la détection précoce des anomalies à la suite de maladies cardiaques.

La dernière partie de notre projet consiste à développer ce nouveau protocole d'IRM à l'effort. Pour ce faire, nous avons élaboré un protocole d'IRM à l'effort qui combine le handgrip et la manœuvre de Valsalva (Handgrip-Valsalva). Après avoir mis au point ce protocole, nous avons évalué sa faisabilité puis nous l'avons comparé à un protocole utilisant seulement un ergomètre. Des tests cardiaques ont été réalisés sur une cohorte de cinq participants en bonne santé. Après analyse des données, nous avons constaté que le protocole Handgrip-Valsalva et l'ergomètre provoquent les déformations cardiaques qui sont similaires. L'étude a également démontré que le protocole Handgrip-Valsalva est faisable (coefficient de corrélation intra classe, CCI = 0.83 - 0.93) et qu'il a le potentiel de surmonter les limitations associées à l'utilisation d'un ergomètre, telles que la qualité des images réduite liée aux artefacts respiratoires et la fatigue musculaire induite par la contraction d'un large groupe musculaire.

En conclusion, ce projet contribue à faire progresser les connaissances des maladies cardiaques et du remodelage cardiaque dû à l'exercice, ou à la suite de maladies cardiaques. De plus, les techniques présentées dans ce projet amélioreront la détection précoce des maladies cardiaques, aideront à anticiper la progression des pathologies et contribueront à améliorer le suivi des patients cardiaques. Nous sommes d'avis que les résultats de ce projet amélioreront l'utilisation clinique des protocoles d'IRM à l'effort, et permettront à plus de patients, dont ceux ayant une capacité d'exercice limitée, de bénéficier du protocole développé, car il est plus sécuritaire et ne nécessite pas plus d'effort.

ABSTRACT

Cardiac remodeling is a process that occurs in response to a cardiac disease and involves a cascade of changes in the heart's mass, geometry, and function. Unfortunately, this process can lead to serious cardiac conditions such as heart failure, which is a significant cause of death and morbidity. Despite significant advances, detecting abnormal changes after cardiac remodeling is still a challenge due to the lack of precise and accurate techniques. Currently, one of the main problems is that existing techniques such as echocardiography and magnetic resonance imaging (MRI) when performed at rest, do not allow for the detection of subtle abnormalities in cardiac diseases. As a result, exercise cardiovascular magnetic resonance (Ex-CMR) has emerged as a valuable tool that allows for an accurate characterization. Indeed, Ex-CMR revealed a strong potential to characterize accurately the heart and to unmask abnormalities not seen at rest in cardiac patients. Ex-CMR has also demonstrated the ability to differentiate between normal cardiac remodeling and pathological cardiac remodeling with considerable accuracy. To improve the effectiveness of Ex-CMR, researchers have combined this technique with computational models, allowing the quantification of other cardiac parameters that are not easily measured during imaging, such as cardiac pressures, and cardiac mechanical properties. Despite the usefulness of Ex-CMR protocols, their clinical applications are still limited, due to certain limitations that may compromise the safety of participants or the quality of the images. Therefore, researchers have demonstrated that the need to develop a new effective Ex-CMR protocol, still exists. This technique may allow for a more accurate heart characterization and may improve the early detection of cardiac diseases.

To develop a new Ex-CMR protocol, we first conducted a study to investigate the relationship between CMR parameters and cardiac mechanical properties in the survivors of acute lymphoblastic leukemia (ALL) cancer. To investigate the relationship between cardiac mechanical properties, T1 and T2 relaxation times, and the partition coefficient, we analyzed 50 childhood ALL survivors who underwent CMR exams on a 3T MRI system. These participants were initially classified into three risk groups: Standard Risk group (SR), High-Risk group (HR) and High Risk that took dexrazoxane as a cardioprotective agent (HR+DEX) group. After obtaining the cardiac parameters from Cine-images, we used the CircAdapt model to simulate participants' cardiac mechanical performance (i.e. left ventricle stiffness (LVS), contractility (LVC) and pressure ($P_{\min}$).

and $P_{\max}$), cardiac work efficiency (CWE) and ventricular arterial coupling (VAC). The results showed that cardiac properties can be predicted from the combination of CMR parameters and vice versa. For example, in the SR group, LVS was predicted from the combination of CMR parameters with ($R^2 = 94.8\%$, $r = 0.97$) and LVC was predicted with ($R^2 = 93.7\%$, $r = 0.96$). Partition coefficient was also predicted from the combination of cardiac mechanical properties by ($R^2 = 72.6\%$, $r = 0.85$) in the SR group. After analyses, we found that the high cumulative dose administered in the HR group limits the correlation between cardiac mechanical properties and CMR parameters in that group.

In the same cohort, we assessed the impact of exercise on the cardiac function and on the cardiac performance at different levels of effort among 63 childhood ALL survivors, who performed CMR exams while exercising on an ergometer. The CircAdapt model was also used to study cardiac mechanical performances. Using this model, we found that CWE was impaired ($< 85\%$) and VAC was significantly reduced by 24 % in this population. However, those children's cardiac performance was improved after exercising. For instance, when comparing at-rest to the submaximal level of effort, we found that the VAC parameter improved by 33% in the SR group, 26% in the HR+DEX group, and 16% in the HR group. Moreover, CWE improved by 5.2% in the SR group, 8% in the HR+DEX group and by 1.4 % in the HR group. Overall, the study showed significant differences between the different levels of exercise for both VAC ($P < 0.0001$) and CWE ($P = 0.001$) parameters.

Knowing that cardiac exercise testing has a positive impact on both cardiac function and cardiac performance in patients at high risk of developing heart disease, we conducted a scoping review to provide an overview of existing Ex-CMR studies, focusing on cardiac remodeling in cardiac patients. Through this study, we demonstrated the effectiveness of each Ex-CMR protocol used in cardiac diseases to induce cardiovascular responses and we also highlighted the advantages and limitations of each Ex-CMR protocol. Our findings revealed that cycle ergometer and isometric handgrip exercises are the most common Ex-CMR protocols, and both can induce enough stress following cardiac diseases. However, we found that the isometric handgrip has a superior advantage over the cycle ergometer as it provides a higher quality of the images. These findings

demonstrated the need to develop a new effective Ex-CMR protocol that may improve the early detection of abnormal cardiovascular responses after cardiac diseases.

The last part of our project consists in developing this new Ex-CMR protocol. To do so, we developed an Ex-CMR protocol that couples an isometric handgrip with a Valsalva maneuver to create a Handgrip-Valsalva protocol. After developing this protocol, we studied its reliability, and we compared it with a protocol using a cycle ergometer alone. Cardiac tests were performed on a cohort of five healthy participants. After data analysis, we found that the Handgrip-Valsalva protocol and the cycle ergometer protocol produce similar cardiac deformations. The study demonstrates also that the Handgrip-Valsalva protocol is a reliable protocol (intraclass correlation, ICC = 0.83 - 0.93) and that it has the potential to overcome the limitations associated with a cycle ergometer, such as poor image quality and muscle fatigue.

In conclusion, this project contributes to advance the knowledge of cardiac diseases, and the cardiac remodeling during exercise, or after a cardiac injury. In addition, the techniques presented in this project will improve the early detection of cardiac diseases, help anticipate the progression of the pathology, and contribute to improving the prognostic follow-up of cardiac patients. We believe that the findings of this project will increase the clinical applicability of the Ex-CMR protocols, and will allow more patients, especially those with limited exercise capability, to benefit from the developed protocol, which is safe and does not require more effort to perform.

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LISTE OF SYMBOLS AND ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
CAD	Coronary artery diseases
CARIM	Cardiovascular Research Institute of Maastricht
CCS	Canadian Cancer Society
CER	Research Ethics Committee
CH	Chamber view
CIHR	Canadian Institutes of Health Research.
CIM	Cardiac Image Modeller
CMR	Cardiovascular Magnetic Resonance Imaging
CO	Cardiac output
CP	Coefficient of partition
CPET	Cardiopulmonary exercise testing
CRS	Cancer Research Society
CVI42	Circle cardiovascular imaging
CWE	Cardiac work efficiency
CWE	Cardiac work efficiency
DBP	Diastolic blood pressure
DFCI	Dana Farber Cancer Institute
DFCI	Dana Farber Cancer Institute; O ₂ peak, maximum oxygen consumption.
DFCI-ALL	Dana Farber cancer institute acute lymphoblastic leukemia

Ea	Arterial Elastance
EDPVR	End diastolic pressure-volume relationship.
EDV	End diastolic volume.
Ees	Ventricular end-systolic elastance.
EF	Ejection fraction
ESPVR	End systolic pressure volume relationship.
ESV	End Systolic volume.
FA	Fractional anisotropy
FEA	Finite element analysis
FEM	Finite element model
FRQNT	Fonds de recherche du Québec - Nature et technologies
FTP	Functional Threshold Power.
HR	High risk without cardioprotective agent dexrazoxane
HR	High risk without dexrazoxane
HR	Heart rate
HR+DEX	High risk with dexrazoxane
HRDEX	High risk with cardioprotective agent dexrazoxane
ICC	Interclass correlation coefficient.
IRC	Institute of Cancer Research
JBI	The Joanna Briggs Institute
LVC	left ventricle contractility (LVC),
LVEDP	Left ventricle end diastolic pressure
LVS	left ventricle stiffness (LVS),

NSERC	Natural Sciences and Engineering Research Council of Canada
OICR	Ontario Institute for Cancer Research
OS-CMR	Oxygenation-sensitive CMR (OS-CMR)
Pdrop	pressure drop
PE	Potential Energy
Ped	end-diastolic pressure
Piso	isovolumic pressure
Pmax	maximum pressure
Pmax	Left ventricular maximum pressure.
Pmin	minimum Pressure
Pmin	Left ventricular minimum pressure.
POGO	Pediatric Oncology Group of Ontario
PSIR	Phase sensitive inversion recovery
PV	Pressure Volume loop
RMES	Root mean square
RPE	Rated perceived exertion
RV	Right ventricle
RV	Right ventricle
SAX	Short axis
SBP	Systolic blood pressure
SD	Standard deviation
SR	Standard risk

SR	Standard risk
SSc-PAH	Systemic sclerosis-associated pulmonary arterial hypertension.
STE	Speckle-Tracking Echocardiography
SV	Stroke volume
SW	Stroke Work
TOF	Tetralogy of Fallot
VAC	Ventricular arterial coupling
VAC	ventricular-arterial coupling
VAC	Ventricular-arterial coupling.
Ved	End diastolic volume.
Ves	End systolic volume.
Vo	Intercept volume
Vo2	peak oxygen uptake

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CHAPTER 1 INTRODUCTION

Heart failure is the leading cause of morbidity and mortality in Canada and worldwide [1]. It is also the main economic burden in terms of healthcare costs, accounting for approximately 457 billion US dollars in the United States, 169 billion euros in Europe and 12 billion CA dollars in Canada [1, 2]. Heart failure is often preceded by pathological cardiac remodeling, a process that is regulated by mechanical, neurohormonal and genetic factors that cause the changes in ventricular size, shape, and function [3]. The pathological remodeling occurs after the myocardial infarction or cardiac diseases such as cardiomyopathy, hypertrophy or valvular diseases in which pressure overload is important [4, 5].

1.1 Heart failure diagnosis

There are various diagnostic ways to detect cardiac remodeling, including the detection of morphological, hemodynamic and functional changes or the detection of cell markers such as changes in the expression of myosin chains, natriuretic peptides, or angiotensin-converting enzymes [6]. However, the latter diagnostic method is not commonly used in clinical practice. The two most frequently used methods to detect cardiac remodeling-associated changes are echocardiography and cardiac magnetic resonance imaging (cardiac MRI), but the latter provides more accurate, more reproducible and more reliable measurements than echocardiography [7]. In fact, compared with echocardiography, cardiac MRI, provides unique information regarding heart tissues, heart scars, viability, function and masses with considerable accuracy [8] in one exam.

Studies assessing cardiac remodeling using cardiac MRI reveal its potential to accurately differentiate between physiological and pathological ventricle remodeling [9]. The main cardiac MRI-associated cardiac remodeling predictors include relative percentage changes of LV end-diastolic ($\% \Delta EDV$), end-systolic ($\% \Delta ESV$) volumes, ejection fraction ($\% \Delta EF$), mass ($\% \Delta Mass$) and pressures in the cardiac chamber ($\% \Delta P$), which is the main determinant of ventricular wall stress. To characterize more accurately pathological changes occurring during cardiac diseases, researchers combined cardiac MRI to heart computational models that can provide quantitative

parameters that cannot be measured experimentally [10]. Indeed, cardiac parameters such as left ventricle pressures, left ventricle contractility or heart wall stress cannot be measured with imaging techniques and existing analytic models such as Laplace's laws have been reported to be inaccurate in predicting cardiac parameters [11]. The computational model provides novel pathological insights that would otherwise have remained concealed [10, 12].

1.2 Cardiac exercise stress testing

Despite the current diagnostic role of cardiac MRI imaging, there is still a lack of accuracy in resting parameters, with which pathological changes are not evident [13]. To overcome challenges occurring during resting heart assessments, Exercise stress Cardiovascular Magnetic Resonance Imaging (Ex-CMR) was developed and has allowed a more accurate characterization of cardiac deformations in both healthy and diseased participants, by underlying cardiovascular abnormalities which are not apparent at rest [14].

In fact, Ex-CMR has the potential to provide quantitative cardiac information to clinicians, that helps with the diagnostic and risk assessment of various cardiac diseases. Current CMR-compatible exercises include treadmill, supine cycle ergometer, upright cycle ergometer, supine stepper-stress and isometric handgrip exercises [14-16]. However, the most commonly performed exercises in Ex-CMR protocols in the clinical context are the treadmill positioned adjacent to the MRI table and the cycle ergometer. Even though these dynamic exercises allow to achieve peak stress and to induce sufficient deformations on heart muscles during exercise, they are associated with various limitations that can compromise the quality of the images and the safety of participants. Indeed studies that used dynamic CMR compatible exercises reported several issues such as increased physical and respiratory motion creating artifacts, ECG gating issues, no 12-lead ECG monitoring, possible disappearance of induced deformations, risk of falling after treadmill exercise, restricted leg movement and muscle fatigue during ergometer cycling [9, 14, 17]. An alternative to dynamic exercise is to use static exercise stress such as handgrips. Contrary to cycling, handgrip exercise appears to be an interesting alternative that minimizes motion artifacts, respiratory artifacts, and ECG gating artifacts [18]. Moreover, the handgrip is known as a diagnostic tool revealing hypertensive behavior in patients who are at risk of developing heart failure [19]. Though this exercise test allows overcoming some dynamic exercises' limitations during imaging, it requires specialized equipment and may not allow participants to achieve peak stress during exercising [20,

21]. To improve the effectiveness of isometric handgrip during cardiac MRI acquisition and to maintain longer exercise-induced deformations, handgrip can be coupled to breathing maneuvers which exhibit similar vascular effects as pharmacological vasodilators [22, 23] or those obtained with physiological stress[24]. One of the popular breathing maneuvers that has played a great role in revealing abnormal cardiac autonomic and which is defined as a biomarker of heart failure is Valsalva Maneuver (VM) [25, 26]. Indeed, normal arterial blood pressure response during VM is characterized by a distinct overshoot of the arterial blood pressure in the last phase of VM. For patients with heart failure, however, the overshoot in arterial blood pressure is absent and a square wave instead of a sinusoidal wave is presented [26, 27]. Studies have reported that for the VM to be optimal, the expiratory effort with intraoral equal to 40 mmHg should be applied and maintained for 15 seconds [28]. In fact, lower pressure may not be sufficient and higher pressures are associated with poor reproducibility [28]. Combining the Isometric Handgrip with the Valsalva Maneuver during MRI acquisition may improve the effectiveness of this isometric handgrip exercise.

1.3 Research questions and general objective.

Though Ex-CMR techniques play an important role for the diagnostic and prognostic of various cardiac diseases, their clinical utilization is still limited [29]. The main limitations to their clinical applicability include the lack of MR-compatible exercise equipment, the ECG gating issues and the high cost of the existing modalities. Developing a safe Ex-CMR protocol that can generate sufficient stress and allow an effective characterization of pathological changes occurring during cardiac remodeling can provide valuable insights to clinicians for the early detection of cardiac diseases. In this doctoral study, we are responding to two questions:

Can the mechanical behavior of the heart be characterized by MRI parameters?

Can the combination of handgrip and Valsalva maneuvers enable an effective heart characterization and allow to overcome the current Ex-CMR imaging protocol limitations?

To answer these two questions, we aimed to develop an Ex-CMR protocol that can be safely performed in an MRI scanner. We hypothesized that MRI parameters can reflect the mechanical behavior of cardiac tissue and that the new Ex-CMR protocol, which consists of a combination of handgrip and Valsalva maneuver, would induce sufficient heart deformations, and provide a

solution to different limitations associated with current Ex-CMR protocols. The development, optimization, and validation of an MRI protocol under exercise stress conditions will help to better highlight the effects of different cardiac diseases on cardiac muscles and characterize the changes in the hemodynamic and mechanical properties that can be biomarkers of cardiac diseases. It will also help to improve our knowledge of stress cardiology and to provide cardiologists with important information that can facilitate the early detection of cardiac diseases and help anticipate their progression.

1.4 Thesis plan

This thesis is presented by articles. The document is organized into nine chapters, which are presented as follows:

Chapter One: This chapter includes the introduction, context, research questions, and the main objective of the study.

Chapter Two: This chapter contains a literature review of the heart anatomy, different cardiovascular diseases, different imaging techniques used to detect cardiovascular diseases and different types of stress protocols used to detect cardiovascular diseases such as medication stress and different Ex-CMR protocols alongside their advantages and limitations. This chapter also presents the different effects of heart failure-associated diseases on the heart muscle and circulation. Through this chapter, we also describe cardiac remodeling during stress conditions and report different exercise-cardiac responses among cardiac patients.

Chapter Three: This chapter includes the first article [16] that has been conducted to highlight the existing Ex-CMR protocols used to assess cardiovascular responses in cardiac diseases. This article also provides a detailed description of Ex-CMR's advantages and limitations. The scoping review protocol that allowed us to extract the relevant studies included in this scoping review is available in Annexe 1. This protocol has been published in JBI Evidence Synthesis journal [16]

Chapter Four: This chapter explains in detail the different hypotheses and the specific objectives of this thesis. It also includes a literature review summary and introduces the next chapters and articles.

Chapter Five: This chapter includes the second article [30] which aims to investigate the relationship between Cardiac Mechanical Properties and Cardiac Magnetic Resonance Imaging at rest in Childhood Acute Lymphoblastic Leukemia Survivors. This study demonstrated how mechanical properties and CMR parameters can predict each other. It also showed how mechanical parameters can reveal doxorubicin-induced cardiotoxicity effects on cardiac muscle. The results of the study reveal that early characterization of mechanical properties in this population could allow the detection of doxorubicin-induced cardiotoxicity and prevent the progression of late cardiac effects.

Chapter Six: includes the third article [31] which aims to assess cardiac mechanical performance at different levels of exercise in Childhood Acute Lymphoblastic Leukemia Survivors. In order to achieve our objective, we utilized the CircAdapt model to simulate the cardiovascular system and assess the mechanical properties based on hemodynamic and cardiac function parameters obtained from CPET (Cardiopulmonary Exercise Testing) and CMR (Cardiovascular Magnetic Resonance) tests. The study results revealed a decrease in cardiac performance in these populations and also showed that exercise was effective in improving cardiac function and performance in this group.

Chapter Seven: Includes the fourth article which aims to study the feasibility and reliability of an Ex-CMR protocol that consists of a combination of isometric handgrip and Valsalva maneuver. This article has been submitted to the International Journal of Cardiovascular Imaging. This study emphasizes the reliability of a newly developed protocol and compares it to the Ex-CMR protocol that uses an ergometer alone. The results of the study show that the newly developed Ex-CMR protocol is both reliable and feasible and offers an advantage in characterizing cardiac deformations with fewer limitations than the ergometer protocol.

Chapter Eight: present a general discussion and relevant points that were not addressed during the articles. It also includes the impact of the project and the limitations of the project.

Chapter Nine: This chapter explains if the objectives were achieved or not. It also includes the conclusion and recommendations.

CHAPTER 2 LITTERATURE REVIEW

2.1 Heart Anatomy and Physiology

The heart is a muscular organ whose primary function is to pump blood throughout the body. The human heart consists of four chambers, namely two atriums and two ventricles. It is also made up of three layers of heart walls: epicardium, myocardium and endocardium. The heart has also four valves, which are the two atrioventricular valves (the tricuspid and mitral valves) and the semilunar valves (the aortic and pulmonary valves). During each cardiac cycle, the four heart valves respond to pressure changes in the ventricles to ensure one-directional blood flow between the pulmonary artery and circulatory system. The pumping sequence of the heart starts with an electrical stimulus that originates in the sinoatrial (SA) node, also known as the heart's "natural pacemaker"[32]. This spindle-shaped structure is located at the top of the right atrium. When the cardiac muscle is excited and contracted, the oxygenated blood is delivered to the body through arteries and capillaries and the deoxygenated blood is pumped into the lungs to remove carbon dioxyde. Figure 2.1 indicates the inner parts of the human heart.

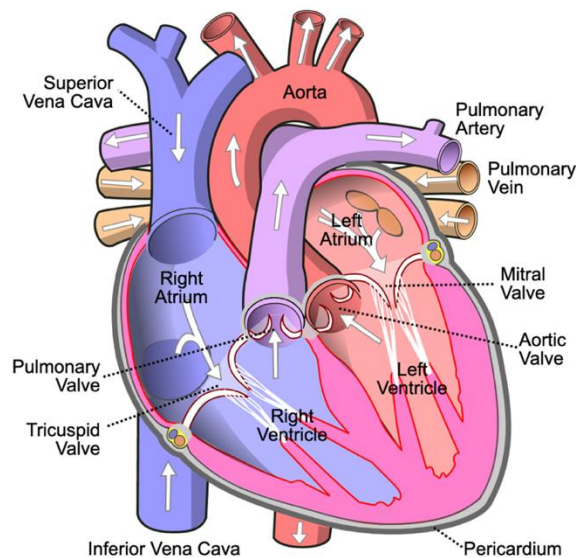


Figure 2.1 Human heart diagram [33].

To understand ventricular function and performance, one needs to analyze the various physiological and mechanical events happening during a cardiac cycle. The cardiac cycle is composed of two main phases which are the systole phase also known as ventricular contraction and the diastole phase also known as ventricular relaxation. The systole phase includes the isovolumic contraction and the ejection, whereas the diastole phase includes: isovolumic relaxation, rapid ventricular filling, slow ventricular filling also known as diastasis and the atrial contraction. Figure 2.2 indicates the pressure and volume changes occurring during one cardiac cycle.

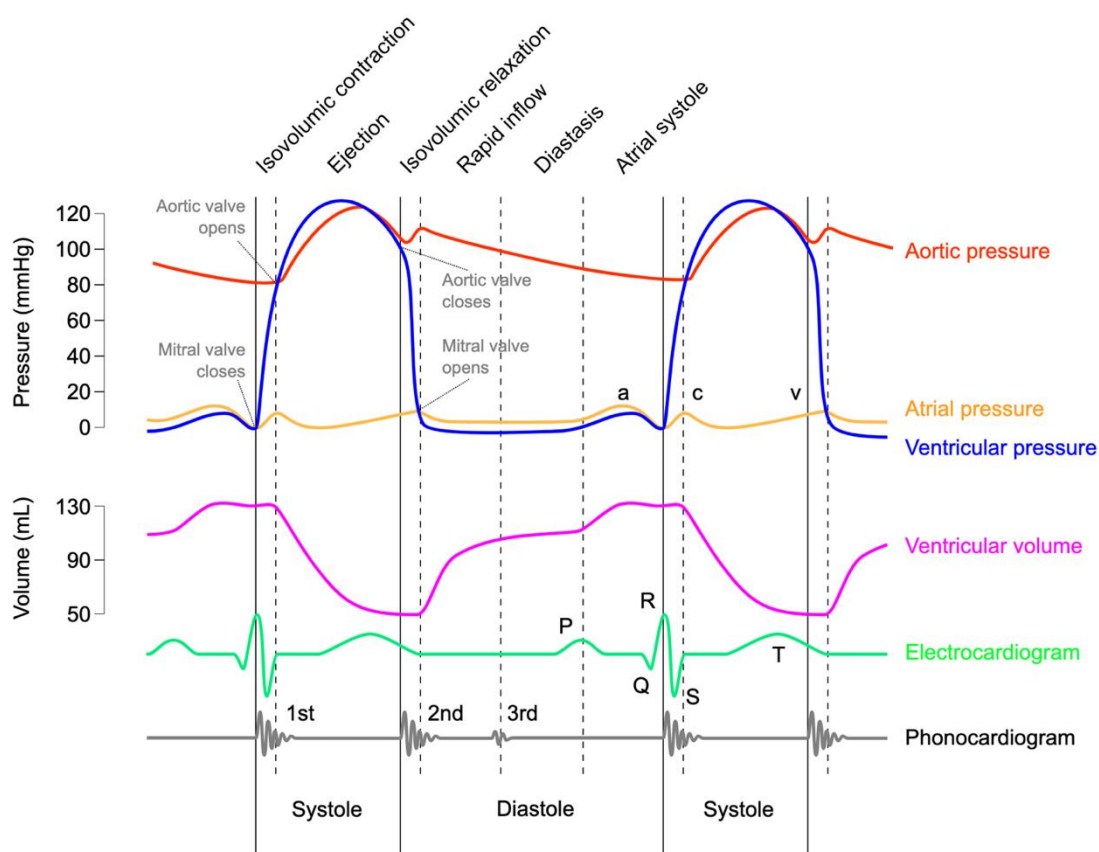


Figure 2.2 Pressure and volume changes occur during a cardiac cycle [34].

For heart performance to be optimal, the cardiac cycle must be strictly coordinated so that both atria and ventricles contract and relax at the same time. In the presence of disease, this synchrony is absent and cardiac performance is impaired [35].

2.2 Cardiac remodeling during Heart failure.

Heart failure (HF) is the leading cause of morbidity and mortality in Canada and worldwide [1]. During HF, the left ventricle (LV) undergoes various modifications which include changes in size, shape, structure, and function. These changes are often known as characteristics of cardiac remodeling [36]. Cardiac remodeling is initiated by the index events that occur abruptly, such as cardiac load or myocardial injury, or those that develop over time, such as genetic cardiomyopathy injury [7, 36]. The cascade of changes that occur during cardiac remodeling can lead to further complications in the heart's structure and function, making it difficult for the heart to pump blood efficiently. Changes occurring following cardiac remodeling can either be hemodynamic, biological or mechanical changes [4]. Most frequent hemodynamic changes include excessive increases in heart rate, stroke volume, pressure, and volumes [5]. Biological changes include decreased expression of α -myosin heavy chain (MHC) gene, increased expression of β -myosin heavy chain gene (MHC), and the progressive loss of myofilaments in cardiac myocytes [4], whereas mechanical changes include: reduced contractile force, reduced pumping performance, LV dilation, increased wall stress (afterloads), myocardial desynchronization, sustained hemodynamic overloading and worsen activation of compensatory mechanisms. All of these cardiac remodeling alteration events significantly contribute to the progression of heart failure [4]. Figure 2.3 describes cardiac events occurring during cardiac remodeling.

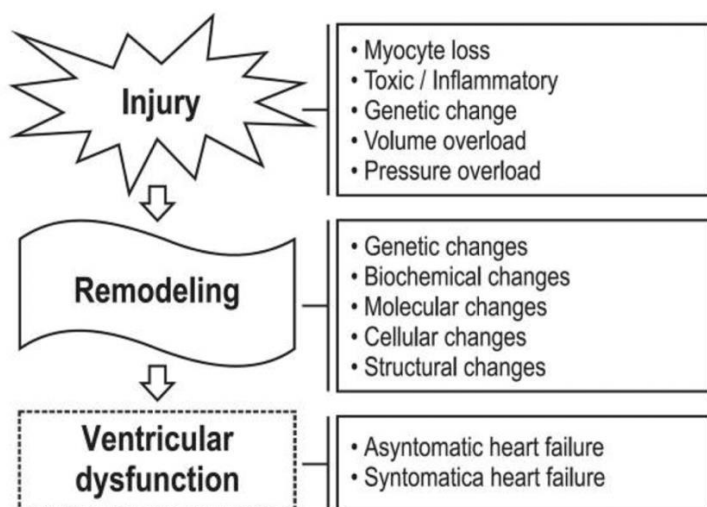


Figure 2.3 A sequence of events from cardiac injury to cardiac dysfunction [1].

Recent developments have demonstrated that in addition to biological biomarkers, heart failure can also be characterized by other markers such as high filling pressures, reduced stroke volume, reduced cardiac output, low or reduced ejection fraction [37], or mechanical markers such as elevated stiffness and impaired ventricular arterial coupling [38, 39].

2.3 Heart failure diagnosis and imaging techniques

2.3.1 Limitations of current imaging techniques during at-rest cardiac assessment.

To assess heart failure markers, more exams including imaging techniques, are prescribed. Imaging modalities have played an important role in the diagnostic, prognostic, and management of various diseases [40]. Most used imaging techniques include echocardiography and Cardiovascular Magnetic Resonance (CMR) [41, 42]. Though echocardiography is used as a first-line imaging technique in cardiac disease assessment due to its low cost, portability, and widespread availability [43], it has some limitations such as poor image quality. Contrary to echocardiography, CMR offers good image quality and allows one to precisely characterize the pathology, to stratify the risk and to select the appropriate therapy [41]. CMR has many advantages over other imaging modalities, but the most interesting is related to its properties: high image spatial resolution, the absence of ionizing radiation, its ability to adapt the acquisition sequences to limit artifacts due to biological movements such as breathing or heartbeat [44] and its high efficiency in quantifying volumes and assessing cardiac function [41]. Despite the diagnostic role of CMR, resting-based cardiac assessments are ineffective in detecting subtle pathological deformations during at-rest assessments [14]. As a solution, researchers and cardiologists have adopted the use of different cardiac stress imaging techniques and found that they provide important insights that can improve the diagnostic and risk assessment of various cardiac diseases [14].

2.4 Cardiac stress testing

2.4.1 Pharmacological cardiac stress testing

The functioning of a heart at rest may appear normal, even in the presence of heart disease. To characterize effectively pathological changes occurring during heart diseases, CMR has been combined with pharmacological stress agents [45, 46] or physiological exercise testing [14, 47]. Most pharmacological stress testing uses intravenous agents such as dobutamine or vasodilator perfusion agents such as adenosine or dipyridamole [45]. These agents cause heterogeneity in

coronary flow, where perfusion defects can be observed due to an oxygen supply/demand mismatch [48]. Pharmacological cardiac stress agents are mostly used to characterize different patterns of Coronary Arterial Disease (CAD), especially in patients who are unable to achieve a diagnostic endpoint during exercise testing [49]. Though pharmacological stress tests are essential tools in the diagnosis and prognosis of heart diseases, they are associated with the risk of serious adverse events such as bradycardia, severe hypertension, unstable angina, or acute pulmonary edema [45, 50]. To ensure an effective and safe heart characterization, Exercise Cardiovascular Magnetic Resonance (Ex-CMR), which consists of a combination of CMR imaging and physiological exercise stress, has been developed [14] and allows to overcome the limitations of resting assessments and pharmacological stress testing.

2.4.2 Exercise Cardiovascular Stress Testing

CMR has several well-established benefits over alternative imaging modalities, allowing a non-invasive comprehensive multi-parametric assessment, with few limitations from body habitus, and no ionizing radiation [51]. Combining this technique with exercise stress protocol improves the diagnostic accuracy of various cardiac diseases. In fact, Ex-CMR can accurately characterize the heart and reveal abnormalities not evident at rest. This imaging technique has the ability to assess several aspects of the heart, such as cardiac function, regional wall motion abnormalities, perfusion defects, and tissue characteristics, all in a single exam. Presently, there are various Ex-CMRs protocols including those that can be performed outside the MR scanner such as the treadmill or upright ergometer or the ones performed inside the scanner such as the supine cycle ergometer, supine stepper device and isometric handgrip. However, in-scanners have been clinically mostly chosen, to avoid challenges associated with outside scanner techniques such as increased risk of falling for participants and inability to acquire cardiac images while patients are still near their peak heart rate [52]. In fact, the time delay between the peak stress and acquisition time, when exercise is performed outside the MR scanner, is often greater than the preferred target of 60 seconds as reported by The American Heart Association [52, 53]. In clinical routine, most performed Ex-CMR scanner protocols include the MR Compatible Treadmill which is adjacent to the MR scanner, the supine ergometer and the isometric handgrip. A detailed description of each of these techniques is reported below.

Treadmill Ex-CMR protocol

One of the Ex-CMR protocols that induces significant deformations on the heart muscle during exercise is the treadmill located adjacent to the MRI scanner [16]. The treadmill is often designated as the most clinical and preferred method [14, 54-56]; however, it is associated with different challenges including the inability to acquire cardiac images while patients are still near their peak heart rate [52]. Though numerous modifications have been made on treadmill modalities to reduce the time delay between the peak stress and the time of acquisition [57], the quality of the image after exercise is still compromised as the participant has to move in order to be in the scanner bore right after the exercise, motion and respiratory artifacts are present in the images. Moreover, exercise-induced cardiac deformations are reduced as the heart starts recovering. The setup for MR compatible treadmill is demonstrated in Figure 2.4.



Figure 2.4 MRI-compatible scanner adjacent to a treadmill [14].

Ergometer Ex-CMR protocol

During an MRI exam, an ergometer is attached to the table to allow the acquisition of cardiac images at a desired level of exercise. This kind of exercise helps in observing variations in different hemodynamic parameters such as heart rate, systolic ejection fraction, longitudinal relaxation, systolic and diastolic volumes, and many others, and allows to acquire images right after the peak stress. Though an ergometer has numerous advantages over a treadmill, it also presents some limitations such as leg muscle fatigue caused by insurmountable resistance levels and respiratory motion artifacts which compromise the quality of the images [58]. Moreover, some patients may have breathing difficulties [59]. The set up for the cycle ergometer is demonstrated in Figure 2.5.

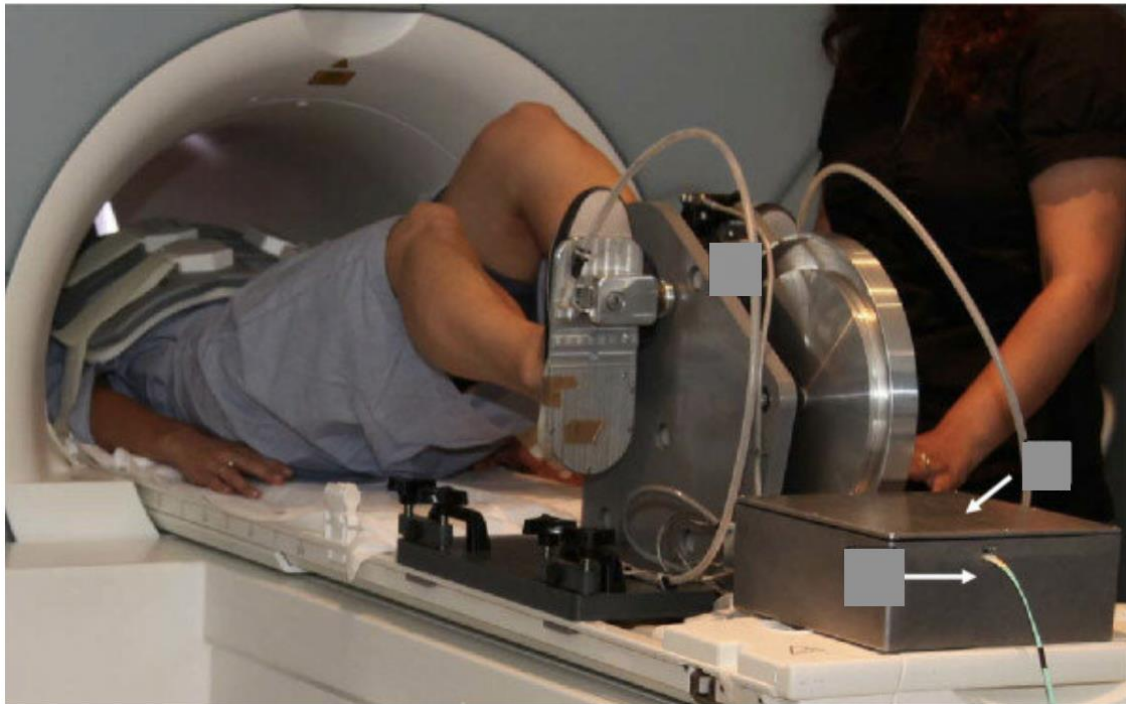


Figure 2.5 MRI-compatible Ergometer setting

Handgrip Ex-CMR protocol

In contrast to aerobic exercise, handgrip is a type of resistance exercise that increases LV afterload and myocardial oxygen demand in a reliable and reproducible manner, without causing any

respiratory or movement-related artifacts. This makes it a simple and highly effective tool compared to the ergometer [60]. The handgrip condition will allow to increase participant's blood pressure with a moderate increase in the participant's heart rate [61]. To perform effectively this maneuver, participants should sustain the device at 30% of their maximum grip strength [62] for a maximum of 6-8 minutes [18]. Contrary to other exercise stress conditions, handgrip could help maintain sufficiently high blood pressure without inducing fatigue for the participant [18]. While there is some information on the use of handgrip for clinical assessment, its clinical applicability is limited and less is known about its response in various cardiac conditions. Nevertheless, studies have shown that the use of handgrip can be beneficial in identifying prehypertensive behavior in patients who are at risk of developing hypertension [63]. In addition, isometric handgrip exercises have been suggested as an effective way to improve certain health-related factors, such as reducing blood pressure in hypertensive patients [63]. Some major limitations associated with isometric handgrip include the inability to achieve peak stress, thus inducing less cardiac deformations [14] and lack of MR-compatible equipment to perform this exercise. The setup of the isometric handgrip is shown in Figure 2.6 below.

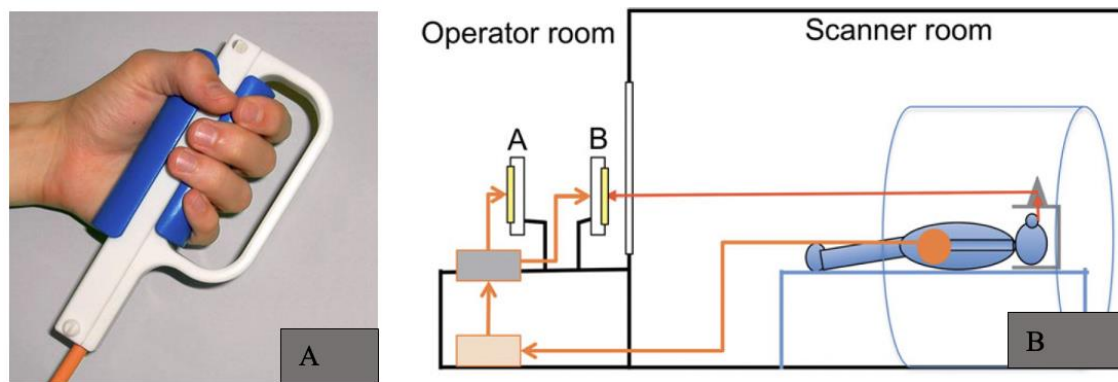


Figure 2.6 MRI-compatible Isometric Handgrip setup [18].

Breathing maneuvers

Breathing maneuvers can exhibit similar vascular effects as pharmacological vasodilators like adenosine [22] or those obtained with physiological stress [24]. The combination of breathing maneuvers to CMR techniques such as the oxygenation-sensitive CMR (OS-CMR) imaging technique, has improved the diagnosis of cardiac abnormalities [23]. Most known physiological breathing maneuvers include the breath-hold maneuver, hyperventilation [22] and Valsalva

maneuver [28]. Valsalva Maneuver (VM) is safe and non-invasive in addition to being one of the most used non-pharmacological resisting inotropic stresses [28, 64]. The maneuver is also used for the evaluation of autonomic dysfunction, the treatment of arrhythmias and as a marker of heart failure [65]. To perform a Valsalva maneuver, the participant applies a forcing expiration against a closed airway (closed mouth, pinched nose) in order to increase intrathoracic pressure [65]. Valsalva's cardiac response is demonstrated in four different phases (onset of the strain, continuous maintaining of the expiratory strain, release of the strain and recovery). In healthy populations, normal arterial blood pressure response to VM is characterized by a distinct overshoot of the arterial blood pressure in the last phase of VM, however for patients with heart failure, the overshoot in arterial blood pressure is absent and a square wave appears instead of a sinusoidal wave [26, 27]. VM is effective when the expiratory effort is applied with intraoral pressure equal to 40 mmHg and maintained for 15 seconds [28]. The diagram of the four phases of VM and different cardiac responses during the maneuver are shown in Figure 2.7.

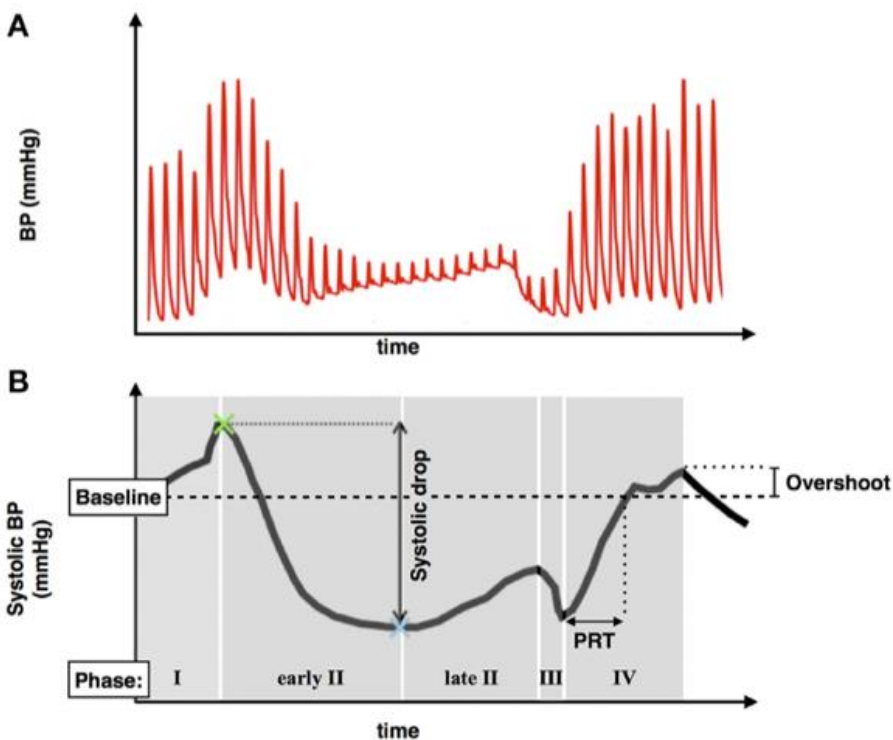


Figure 2.7 Typical pressure response to Valsalva maneuver. (B) Systolic blood pressure trace demonstrating Valsalva phases [66].

2.5 Mechanical behavior of the left ventricular myocardium.

Cardiac tissues are characterized as anisotropic and viscoelastic material, which means the heart behaves as an elastic and viscous material with different mechanical behaviors in different directions [67]. Both passive and active mechanical properties of the heart are determinants of cardiac function and performance. Most measured parameters to characterize cardiac mechanical behavior include ventricular stiffness, viscosity, compliance, wall stress, ventricular arterial coupling, or pressures in the ventricles. In most cardiac diseases, mechanical properties are altered, and cardiac function is compromised. For instance, when the myocardium is overloaded, mechanical factors such as preload (diastolic stretch) or afterload (systolic stress) trigger the release of growth-promoting factors such as angiotensin II, endothelin-1 and transforming growth factor- β , which leads to cardiac hypertrophy and heart failure [68, 69]. Moreover, impaired ventricular stiffness is associated with various cardiac diseases such as hypertension, hypertrophic cardiomyopathy, fibrosis and heart failure [70]. Cardiac mechanical properties can be measured by ex-vivo techniques. However, ex-vivo techniques are associated with some limitations including that they require tissue removal and are often limited by the contractile state of cardiomyocytes (passive only) [67]. In order to overcome these limitations various in vivo techniques including imaging techniques such as CMR and Speckle-Tracking Echocardiography (STE)[67] are used. One of the gold standard techniques to assess the ventricle performance is the pressure-volume loop measurement also known as PV loop [67]. Figure 2.8 demonstrates the Pressure Volume loop in a cardiac cycle.

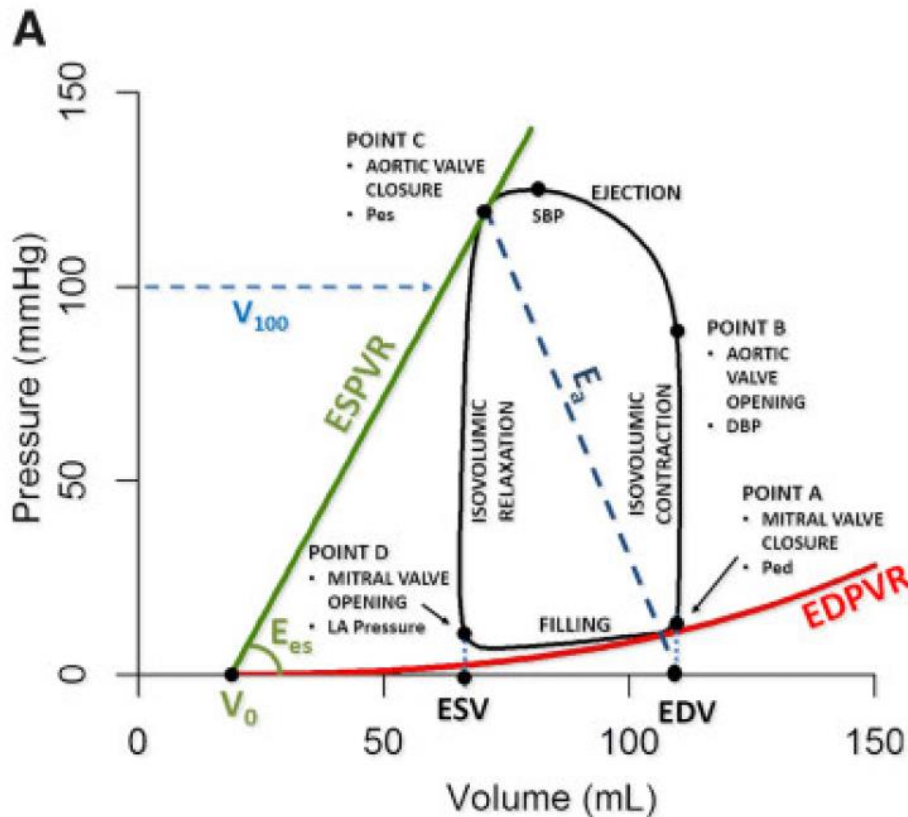


Figure 2.8 Essential principles of the left ventricular pressure-volume relationship [71]

Various important cardiac properties that are determinants of cardiac performance can be derived from the PV loop [71]. These parameters include for example Ventricular Arterial Coupling (VAC) which is calculated by dividing Ventricular Elastance (E_{es}) by Arterial Elastance (E_a). Another parameter is Cardiac Work Efficiency (CWE), which is determined by dividing the energy transferred from the ventricle to the arterial system (known as Stroke Work or SW) by the total energy. To gain more insights into the cardiac electrophysiology, blood flow dynamics and cardiac mechanics that can't be obtained in the ex-vivo measurement tests, medical image-based computational models have been developed [72].

2.5.1 Heart computational models in cardiology

Computational models are used extensively to study cardiovascular system dynamics and to quantify properties that are difficult or impossible to measure experimentally[69]. Currently, the

Finite Element (FE) method is considered as a gold standard numerical model in cardiac simulation, as reported in recent reviews [73-75]. Most heart models employ an inverse FE modelling approach and solve differential equations in order to identify various cardiac and vascular parameters [76]. Using in vivo medical data obtained from advanced imaging techniques such as MRI, heart models demonstrate their clinical usefulness by helping understand the mechanisms underlying cardiac disease, optimize their treatment and predict the patient's response [72, 74]. The image-based heart model framework is displayed in Figure 2.9.

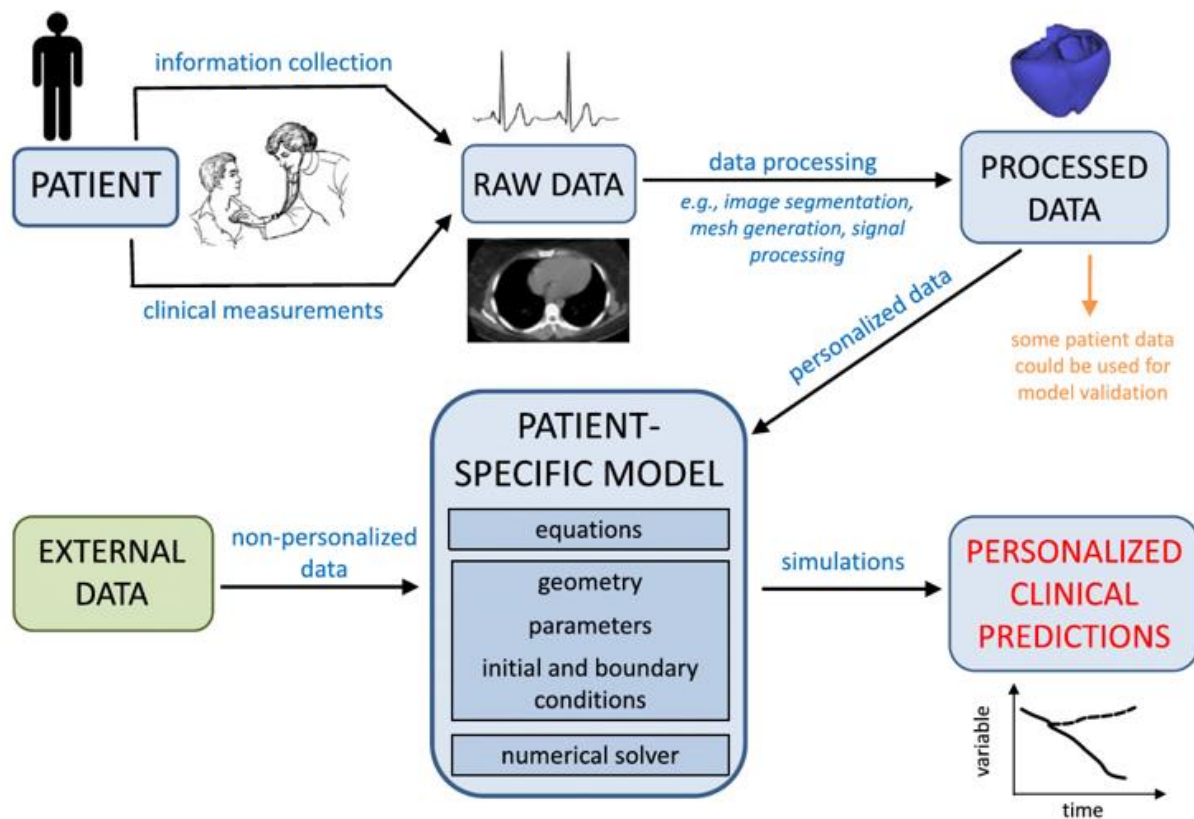


Figure 2.9 Patient-specific modeling framework: collecting data, processing and incorporating data into a mathematical model [77].

In the last decades, various heart models have been developed and allowed to understand various physiological and biomechanical processes of the cardiovascular system, including the cardiac

physiology, soft tissues, mechanics of the heart and fluid dynamics of blood flow [69]. Some of the popular 3D heart models include the model developed by Guccione and his team [76], the model developed by Serresant and his team in France [78], The CMISS model developed by Young et al. at the University of Auckland [10], the model developed by University of California San Francisco on human LV [79] and the model developed by Niederer and Smith that allowed to record LV mechanical properties using pressure–volume loops for heart failure patients [80].

Though Finite Element-based models seem to succeed in reproducing the complexity of the functioning of the cardiovascular system, they are associated with several limitations. Firstly, they require a large number of inputs which may not always be known [81]. Secondly, they are based on a number of assumptions [82] and personalizing the model to the patient is a time-consuming process [83]. Moreover, invasive methods are required to obtain the measurements of patients' intraventricular pressures [81]. To address these issues, a research group from Maastricht University developed a heart model, the CircAdapt model, that is capable of fast and realistic simulations of the cardiovascular system [84]. Moreover, this model allows the calculation of patients' intracardiac pressure non-invasively [2]. Other advantages of the Circadapt model over the FE models, include the use of a simplified ventricular geometry and a comprehensive simulation of the cardiovascular system with low computational effort, and a smooth hemodynamic incorporation of the heart within the entire circulation [2, 84]. The ability of CircAdapt, to allow real-time simulation of cardiac mechanics and hemodynamics widens the possibilities for patient-specific modeling, which is highly needed in clinical settings [85]. In the CircAdapt model, the cardiac muscle is represented by four chambers and three walls mechanically coupled to simulate the interaction between the LV and the right ventricles (RV) [84]. CircAdapt model uses different physiological adaptation rules to produce realistic simulations of flow, volumes, and pressures of the heart and large blood vessels [2, 86, 87]. Although this model has advantages, it has also limitations that may make simulation results less representative of reality. For instance, the model is constrained to the cardiovascular system and excludes other organs or systems that could affect the cardiovascular system such as nervous system [88].

In this study, Circadapt has been used to simulate various hemodynamic and mechanical parameters of the heart in patients at risk of developing heart failure and in normal healthy participants. The schematic diagram of Circadapt model is represented in Figure 2.10.

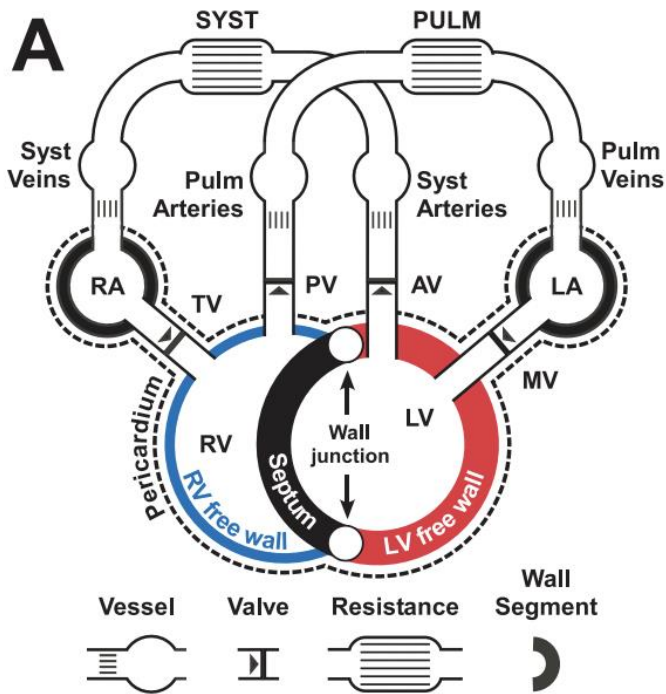


Figure 2.10 The CircAdapt model.

When the myocardium undergoes pathological changes, the tissue's mechanical properties are adversely affected, which leads to alterations in shape, size, and function of the LV ventricle [89, 90]. However, many questions remain unanswered about how cardiac cells respond to mechanical stimuli in cardiac diseases or how cardiac remodeling is linked to abnormal mechanical loads, which makes it a topic of continuous research [69]. The evaluation of the myocardial tissue properties offers the potential to investigate the mechanisms underlying cardiovascular pathologies [90, 91]. Using Advanced MRI-based computational heart models can effectively characterize the mechanical behavior of the heart and may provide valuable insights into the cardiac remodeling process and offers new biomarkers for the early detection of cardiac diseases.

CHAPTER 3 ARTICLE 1: EXERCISE STRESS CARDIAC MAGNETIC RESONANCE IMAGING IN THE ASSESSEMENT OF INDUCED CARDIOVASCULAR RESPONSES IN CARDIAC PATIENTS: A SCOPING REVIEW

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3.1 Abstract

Exercise Cardiovascular Magnetic Resonance (Ex-CMR) enables the characterization of pathological deformations resulting from cardiac diseases. While these techniques offer crucial insights that enhance the detection and intervention of cardiac diseases, certain Ex-CMR methods pose challenges, limiting their clinical utility. To assess the effectiveness of each Ex-CMR technique, we conducted a scoping review of existing studies that focus on cardiac remodeling.

Within this review, we delineated the limitations and advantages associated with each Ex-CMR technique.

Methods: We conducted a systematic search across multiple databases to identify pertinent articles. The searched databases included PubMed, Ovid MEDLINE(R), Ovid All EBM Reviews, Ovid Embase, Clarivate Web of Science, OpenGrey, Grey Matters, and OAlster. The search adhered to the PRISMA-ScR checklist. The gathered findings were synthesized and presented in tables aligning with our research objectives.

Results: 24 studies evaluating cardiovascular responses in cardiac diseases using Ex-CMR techniques were considered. Cycle ergometer and isometric handgrip exercises were the most frequently performed Ex-CMR methods for studying cardiac remodeling. Stroke volume, cardiac output, heart rate and blood pressure responses to exercise were the most exercise-induced cardiovascular responses included in the studies.

Conclusions: This scoping review offers valuable insights into the role of Ex-CMR protocols in characterizing cardiac remodeling among patients with cardiac diseases. Both cycle ergometer and isometric handgrip protocols demonstrate effectiveness to induce sufficient stress to elicit cardiovascular responses in cardiac patients. Nevertheless, it underscores the necessity to develop an optimized Ex-CMR protocol for early detection of abnormal cardiovascular responses in individuals with cardiac diseases.

3.2 Keywords

Cardiac population; exercise-induced cardiac responses; heart function tests; MRI; scoping review; stress imaging.

3.3 Introduction

Exercise-induced cardiovascular responses in cardiac patients are essential to provide accurate diagnostic and prognostic information that is not observable at rest. Cardiovascular responses refer to the adaptations made by the cardiovascular system during exercise. Studies have shown that in response to exercise, cardiac patients could experience chronotropic incompetence, excessive increase or decrease of blood pressure, and impaired maximal oxygen consumption [9, 92, 93]. It has also been observed that several patients can suffer from abnormal cardiovascular responses due

to cardiac remodeling, defined as changes in the size, mass, geometry, and function of the heart [6, 94].

To improve the understanding of cardiac remodeling mechanisms in cardiac patients, exercise-induced cardiovascular responses have been combined with cardiac magnetic resonance imaging (Ex-CMR). CMR imaging is a non-invasive and effective imaging technique that accurately assesses cardiac morphology, ventricular function, myocardial perfusion, tissue characterization, and flow quantification. Studies focusing on cardiac remodeling during exercise have established the key role of Ex-CMR as a clinical tool to accurately quantify the functional capacities and structural modifications of the heart [13, 14]. In fact, Ex-CMR facilitates the characterization of the heart by differentiating between normal cardiac remodeling and pathological cardiac remodeling with considerable accuracy [9, 95].

Cardiac remodeling is the ultimate precursor of cardiac dysfunction and heart failure [6, 96]. Ex-CMR provides quantitative cardiac information to clinicians, in addition to offering a direct link between exercise, symptoms, and stress imaging [97]. It also provides important information with the diagnostic and the risk assessment of various cardiac diseases[20, 98]. Nevertheless, studies have reported various challenges when using Ex-CMR, limiting its clinical use [95]. Indeed, despite progress made to enable exercising in a magnetic resonance imaging (MRI) scanner, researchers have warned about the excessive motion that exercise conditions can produce and the lack of Ex-CMR studies that have taken the constraints imposed by the MRI scanner into consideration for the image acquisitions [97, 99].

Hence, there is a need for a scoping review to provide an overview of existing Ex-CMR studies focusing on cardiac remodeling in cardiac patients. This review will describe and synthesize previously reported data to map the current evidence as well as to identify gaps in knowledge and future research needs in this field. This review will be useful for clinicians, researchers, and health care providers to improve early detection of abnormal cardiovascular responses in response to exercise.

Before conducting this review, a preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted on April

13, 2022. No current or in-progress scoping reviews or systematic reviews on the topic were identified. The protocol of this scoping review has been published [100].

Review questions.

Our scoping review objectives translated to the following questions: What are the Ex-CMR testing protocols currently available to assess induced cardiovascular responses in cardiac patients aged 18 years or over? What are the reported advantages and limitations of Ex-CMR testing protocols currently available to assess induced cardiovascular responses in cardiac patients aged 18 years or over?

3.4 Methods

The proposed scoping review was conducted in accordance with the JBI methodology for scoping reviews [101] and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)[102].

Search strategy

The search strategy aims to identify published and unpublished original studies on the topic of interest. Prior to initiating the full search strategy, a librarian (PD) performed a limited search of MEDLINE to identify relevant published articles. The text words contained in the titles and abstracts of these articles, and the index terms used to describe these articles, were used to develop a full search strategy. The specific MeSH terms and keywords that are used in our scoping review can be found in our published protocol [100]. The initial search of PubMed, conducted from inception until August 4, 2022, identified 5,730 potential articles. This search suggested good feasibility and relevance of the search strategy.

The reference lists of all full-text articles included were screened for additional papers. Only articles written in English or French were included. Literature was searched from database inception until the present (October 2023). The following databases were searched: PubMed, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed

Citations, Daily and Versions(R), Ovid All EBM Reviews, Ovid Embase, Clarivate Web of Science, OpenGrey, Grey Matters, and OAlster.

Study selection

Following the search, all identified records were collated and uploaded into Covidence (Veritas Health Innovation, Melbourne, Australia). Duplicate articles were removed by the bibliographic software and were manually scanned. Titles and abstracts were screened by 2 independent reviewers (EU and MC) for assessment against the inclusion criteria. Potentially relevant reports were retrieved in full. The full texts of selected citations were assessed in detail against the inclusion criteria by 2 independent reviewers (EU and MC). Of note, reviews identified at the “title and abstract” screening level were retrieved in full to review references that may not have been retrieved by searching for primary research evidence. Reasons for exclusion of full-text studies that do not meet the inclusion criteria were recorded and reported in the scoping review (**Figure 1**). Any disagreements that arise between the 2 independent reviewers at each stage of the selection process were resolved through discussion or with a third reviewer (AL). The results of the search are presented in a PRISMA flow diagram in Figure 3.1.

This review included cardiac populations whose age at the time of the study was ≥ 18 years. Cardiovascular diseases, characterized as diseases of the heart, refer to a number of conditions, such as coronary artery and vascular disease, heart rhythm disorders, structural heart disease, and heart failure [13].

This review included studies that use Ex-CMR testing protocols to assess induced cardiovascular responses that reveal cardiac remodeling, defined as changes in the size, mass, geometry, and function of the heart. The parameters of interest are changes in cardiac volume, blood pressure, systemic vascular resistance, cardiac output, ejection fraction, and heart rate.

This scoping review considered quantitative study designs as well as mixed methods study designs if the latter include a quantitative component. Observational studies randomized controlled trials, nonrandomized controlled trials, and uncontrolled interventions (i.e., pre- and post-tests

without controls) were considered. Unpublished studies and gray literature were included in this review. Conference abstracts, case reports, short communications, systematic reviews, meta-analyses, theses, letters to the editor, and protocol papers were excluded.

Data extraction

The extracted data included specific information on (1) authors and year of publication; (2) participant characteristics (number of participants, sex, age at time of study, disease); (3) main objectives; (4) Ex-CMR testing protocols; (5) Ex-CMR testing advantages in relation to delivery, cost, feasibility, effectiveness, and patients' safety from both the authors' and health professionals' viewpoint; (6) Ex-CMR testing limitations in relation to delivery, cost, feasibility, effectiveness, and patients' safety from both the authors' and health professionals' viewpoint; (7) cardiovascular responses to exercise, including heart rate, blood volume (end systolic volume, end diastolic volume, stroke volume), blood pressure (systolic pressure, diastolic pressure, pulmonary capillary wedge pressure, pulmonary arterial wedge pressure, mean arterial blood pressure), ventricular mass, cardiac output, systemic vascular resistance, ejection fraction, rate pressure product, ventricular wall compliance; and (8) any other key findings relevant to the review questions.

Risk of bias assessment

In accordance with the methodological recommendations for scoping reviews [103], no risk of bias assessment was performed.

3.5 Results

The flow diagram is presented in **Figure 3.1** and includes the reasons for exclusion, in accordance with the PRISMA-ScR guidelines. The search strategy yielded a total of 10,604 records after duplicates were removed. After the first screening by title and abstract, 10,177 records were excluded, and 324 were sought for full-text review. A total of 24 studies met eligibility criteria and were included in this scoping review.

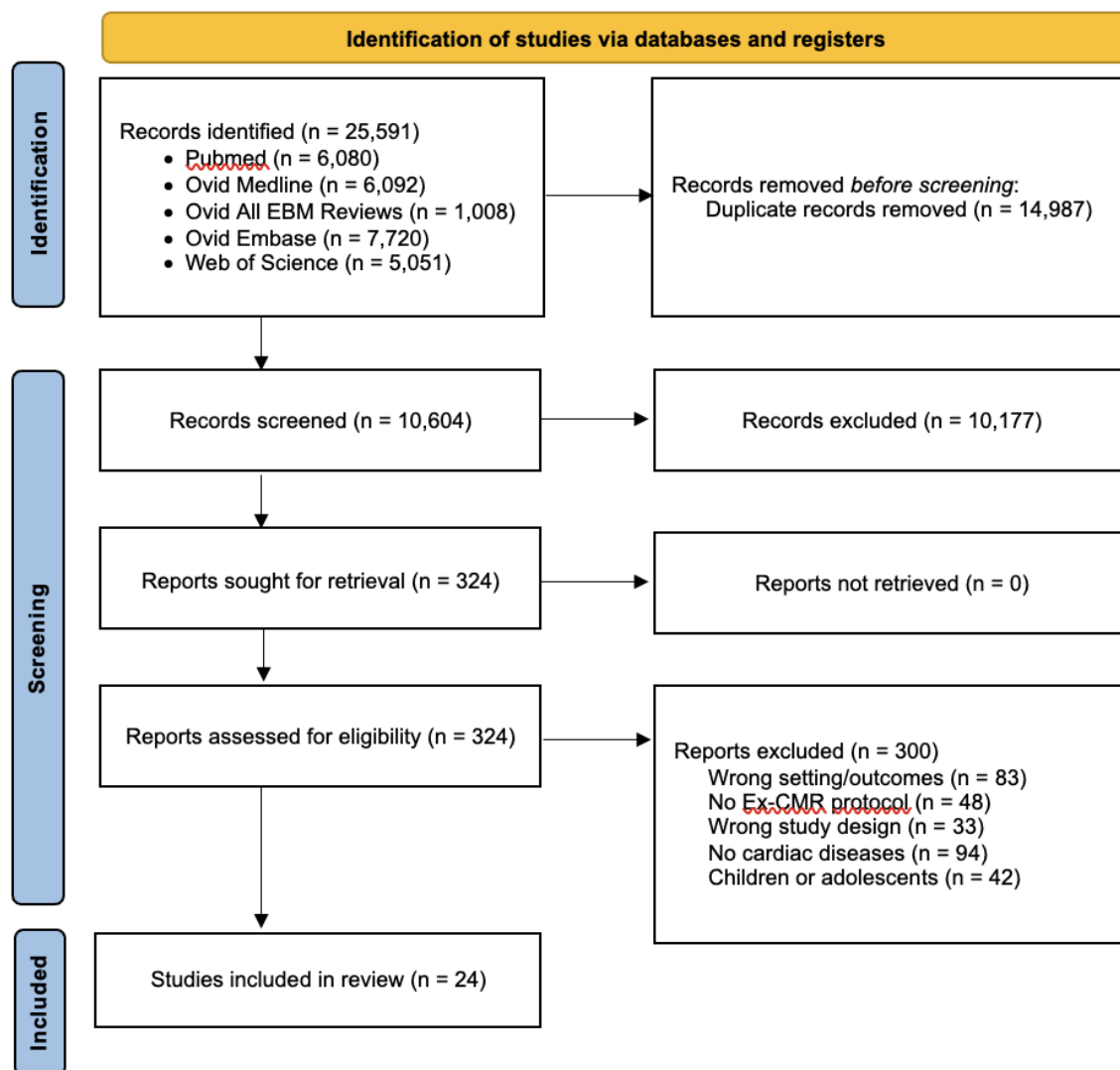


Figure 3.1 PRISMA-ScR flowchart of the literature search and study selection.

Participants' characteristics

Population characteristics of the 24 included articles are summarized in **Table 1** (available as supplement material). A total of 538 patients (265 males and 200 females) underwent an Ex-CMR procedure. Patients' sex was not documented in 3 studies. Most of the diagnosed cardiac diseases included: heart failure (HF) [104-108], pulmonary arterial hypertension (PAH) [9, 109-112],

coronary artery disease (CAD) [62, 93, 113], Tetralogy of Fallot (TOF) [114, 115] and ventricular arrhythmias [105, 116].

Ex-CMR testing protocols' characteristics.

Ex-CMR testing protocols include cycle ergometer, isometric handgrip exercise and stepper ergometer (**Table 1**). The majority of the included studies (20 out of 24) were conducted using a cycle ergometer [9, 13, 21, 93, 104-110, 112, 114-121]. Isometric handgrip exercise was used in 3 studies [21, 62, 113] and the stepper ergometer was used in only one study [111]. Out of the 20 studies that used a cycle ergometer, 13 studies were conducted at either maximal exercise intensity (i.e., 100% of maximal power) or submaximal exercise intensity [9, 104-107, 110, 112, 115, 116, 118, 119, 121, 122]. Interestingly, the included studies conducted their exercise protocol until participants reached their submaximal exercise level with either a targeted heart rate of HR >100 bpm [104, 107] or until a targeted percentage of maximal power was achieved (from 66% to 100%) [9, 105, 106, 116, 119, 121]. When using a stepper ergometer, researchers used a metronome beat [111], while they used a targeted hand grip strength (e.g., 30% of maximal grip strength) when using an isometric handgrip exercise [21, 62, 113]. Isometric handgrip exercise protocols were not standardized between studies. Some protocols were performed during 4.5 minutes of continuous exercise at 30% of maximal grip strength [62], while others were performed during 4 minutes of continuous exercise at 30% of maximal grip strength [113] or performed during 6 minutes of continuous exercise at 30% of maximal grip strength [21].

Exercise-induced cardiovascular responses.

Several exercise-induced cardiovascular responses, evaluated in both the left and right ventricles, have been identified and are summarized in **Table 1**. It has been noted that some cardiac responses are more commonly reported than others. The HR values have been reported in 22 out of the 24 included studies [9, 13, 21, 62, 93, 105-112, 114-122], the LVEF values have been reported in 13 studies [9, 62, 93, 105, 106, 109, 110, 112, 114, 116, 117, 119, 121] while the CI and LVEDV values have been reported in 9 [93, 104, 106, 107, 110, 112, 117, 119, 120] and 8 studies [105, 106, 108-110, 112, 116, 121], respectively.

As presented in **Table 1**, the CI values displayed a similar response to exercise, which can be interpreted as a slight increase after exercise in diseases such as heart failure, CAD, and PAH [93, 104, 110, 112]. However, one study that performed comparisons with a healthy control group [117] showed impaired CI response following exercise in patients with systemic sclerosis (SSc) and in systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) [117]. It was also noted that SV values were slightly increasing post-exercise in heart failure, ventricular arrhythmias and PAH [105, 111, 116]. However, SV values were unchanged in patients diagnosed with systemic sclerosis or systemic sclerosis-associated pulmonary arterial hypertension [109, 117]. The LVEDV was also of interest in >30% of the included and one study showed a slight increase in LVEDV values in mild dilated cardiomyopathy (DCM) [9], while studies in patients diagnosed with PAH [109], RTOF [114], transposition of the great arteries (TGA) mustard/Senning [119] and those who had an arterial switch operation (ASO) [121] demonstrated an impaired LVEDV response.

Other important cardiovascular responses were studied. The SBP post-exercise increased by 17 mmHg to 47 mmHg in all included studies [21, 106, 114, 119, 120]. The EF increased by 2.7 % to 11.98 % during exercise in the following studies [9, 93, 105, 106, 114, 116, 117, 119-121] and was reduced or remained unchanged in the following studies [13, 110, 112]. The ESV decreased during exercise in the following studies [105, 109, 110, 112, 114, 116, 119, 121]. The DBP slightly increased in the following studies [21, 93, 114]. The mean arterial pressure increased slightly in the following studies [9, 114]. The cardiac output increased slightly in the following studies [105, 111, 114]. The HR response to exercise was different between the included studies since some studies reported a slight increase ranging from 9 to 25 bpm [21, 62, 122] while other studies reported a modest increase ranging from 35 to 67 bpm [9, 13, 93, 106, 110-112, 115] or an exaggerated HR response ranging from 70 to 91 bpm [105, 107, 109, 116, 118, 119, 121]. The exaggerated increase in HR values was reported mostly in patients diagnosed with ventricular arrhythmia or pulmonary arterial hypertension [105, 109, 116, 118].

Reported Ex-CMR testing advantages and limitations.

Considered studies reported that cycle ergometer can induce significant cardiac changes but is subjected to motion artifacts. Conversely, isometric handgrip advantages include the ability to be

performed by patients with limited exercise capacity and to preserve image quality but cause lower cardiovascular responses. A detailed comparison of the advantages and limitations of these two Ex-CMR protocols is presented in the **Table 2** (available as supplement material).

3.6 Discussion

This scoping review has identified Ex-CMR protocols to provide an overview of the existing literature focusing on cardiovascular responses in cardiac patients. We found that cycle ergometer protocols and isometric handgrip exercises were the most common Ex-CMR protocols used to study cardiac remodeling. The included studies report the advantages and limitations associated with these Ex-CMR protocols. This review brings insightful information for clinicians, researchers, and health care providers to improve early detection of abnormal cardiovascular responses during exercise.

Exercise stress testing is a non-invasive procedure and is recognized as the gold standard in exercise physiology. It is an excellent diagnostic tool and allows to stratify patients at risk of coronary artery disease [14, 123]. The use of exercise stress testing has been extended to evaluate other cardiac conditions, including hypertensive heart disease, cardiomyopathy, and heart failure [124-126]. In our scoping review, the use of Ex-CMR protocols was extended to other uncommon cardiovascular conditions, such as Tetralogy of Fallot, left ventricular relaxation due to concentric remodeling, and transposition of the great arteries [106, 114, 119, 127]. Interestingly, only two different types of exercise were considered in the development of Ex-CMR protocols, despite a wide range of cardiac diseases. The use of a cycle ergometer was common (83%) among the included studies, while the use of isometric handgrip exercises and a stepper ergometer were less common. In fact, the use of a supine cycle ergometer protocol has been the subject of numerous publications since it enables participants to exercise at their maximum intensity in a favorable position to obtain high-quality images. Moreover, cycle ergometer protocols allow to control participants' workload, which increases protocol replicability and standardization.

Each Ex-CMR protocol included in this review has been developed to favor enough stress to induce cardiovascular responses in cardiac patients. During exercise, the muscles and other tissues experience an elevated demand for oxygen and nutrients [128]. In response to this metabolic

demand, the cardiovascular system adjusts by increasing the heart rate, stroke volume, cardiac output, and systolic blood pressure [129]. In healthy individuals, exercise improves the function of the heart and is associated with a 10% increase in LV EDV, a 10% decrease in LV ESV, a 15% to 20% increase in SV, and a 3.5- to 4-fold increase in CO, without any significant change in LV end-diastolic pressure [130, 131]. In cardiac patients, however, the cardiac response to exercise is often impaired and reflects the severity of the disease [131]. For example, heart rate and SBP increase during exercise is relatively small in heart failure patients [131]. One of the articles included, also reported a small increase of SBP in response to exercise in patients with Fontan disease [120]. However, in other studies focusing on hypertensive patients and patients with transposition of the great arteries, we observed an exaggerated increase in blood pressure and heart rate [119, 132]. Additionally, in a study conducted on patients with coronary artery diseases, we observed an incapacity to decrease ESV in response to exercise [133] while this parameter is expected to decrease by up to 10% in healthy individuals [131]. The authors mentioned that this response was associated with an increased mortality rate in patients with coronary artery diseases [133]. Therefore, our review highlight that cardiovascular responses during exercise differ from one cardiac condition to another and will be impacted by the type of exercise performed by cardiac patients, the position (e.g., supine versus upright), its intensity and its duration [14, 130, 134, 135].

Our review also revealed different cardiovascular responses to exercise, including stroke volume, cardiac output, and heart rate. The inability to increase stroke volume during exercise is commonly reported in cardiac patients, when the cardiac function is compromised [136, 137]. Notably, in response to exercise, stroke volume slightly increased in patients diagnosed with heart failure, ventricular arrhythmias, and systemic sclerosis-associated pulmonary arterial hypertension [105, 116, 117]. However, articles have also showed that cardiovascular responses to exercise were mostly impaired in patients with systemic sclerosis-associated pulmonary arterial hypertension, compared to PAH and ventricular arrhythmias patients [105, 116, 117]. Similarly, the cardiac output and heart rate increase in response to exercise in patients diagnosed with symptomatic ventricular arrhythmias, heart failure and pulmonary arterial hypertension [105, 111, 116]. However, these parameters do not seem to increase as they normally do in healthy individuals [130, 131]. For instance, our review showed that cardiac output only increases by 1 to 2-fold in cardiac patients [105, 114], whereas it increases by 3.5 to 4-fold in healthy individuals [131, 138] using

either isometric handgrip exercises or cycle ergometer protocols. Additionally, a small heart rate response was frequently observed in patients who performed isometric handgrip exercises [21, 62], while a significant increase in heart rate was observed in patients who performed a cycle ergometer protocol [105, 118, 119]. Similar results were observed for the blood pressures [21, 93, 114]. These findings are expected, since isometric handgrip exercises induce lower cardiovascular responses, compared to cycle ergometer protocols [139].

Finally, this review has documented the advantages and limitations associated with Ex-CMR protocols. It showed that while the Ex-CMR protocols using a cycle ergometer allow for more significant cardiac deformations and therefore, detail information about the patient's heart, it induces motion artifacts due to respiratory movements affecting the quality of the images. This explains, in part, why isometric handgrip exercises have started to be used in Ex-CMR protocols. Studies have reported an increase in cardiac parameters with important advantages that may improve the effectiveness of Ex-CMR protocols [140, 141]. These advantages include the ability to perform isometric handgrip exercises in patients with limited exercise capacity and to preserve the quality of the images which are compromised with cycle ergometer protocols. Studies have also reported that isometric handgrip exercises are safer in cardiac patients such as coronary artery disease [142] and in hypertensive patients [63]. Nevertheless, this review should be interpreted in the context of limitations where 20 studies used a cycle ergometer protocol and only 3 used an isometric handgrip protocol, limiting the scope of our findings. Among the included studies, no Ex-CMR protocols have used a treadmill protocol to assess cardiovascular responses in cardiac patients, limiting the scope of our discussion.

3.7 Conclusion

This scoping review allowed us to identify the existing Ex-CMR protocols that assessed cardiovascular responses among cardiac patients with their advantages and limitations. Based on the article included in our review, both cycle ergometer and isometric handgrip protocols seem effective to induce enough stress to induce cardiovascular responses in cardiac patients. However, to increase the clinical usability of isometric handgrip exercises, we recommend that future studies should compare this modality to others, such as cycle ergometers or treadmill. Therefore, developing an effective Ex-CMR protocol is necessary and may improve early detection of abnormal cardiovascular responses in cardiac patients.

CHAPTER 4 OBJECTIVES AND HYPOTHESES

4.1 Synthesis of literature review

Heart failure is a severe medical condition that affects a large number of the population. Although there have been significant technological advancements in the diagnosis of cardiac diseases, there is still a need for the development of new treatments and improved imaging techniques that can facilitate early diagnosis. Cardiac disease can lead to changes in the size and shape of the heart, which are considered as pathological changes or cardiac remodeling. Unfortunately, the mechanism behind cardiac remodeling is still unclear and lacks proper imaging. Currently, Magnetic Resonance Imaging (MRI) is considered an imaging technique that can characterize the heart with considerable accuracy. However, when performed at rest, it does not allow to characterize subtle cardiac deformations. Through the literature review, we found that CMR stress testing can reveal subtle changes not apparent at rest. These tests can be performed using either exercise stress testing (i.e. dynamic or static exercise) or using pharmacological products (i.e.: dobutamine, adenosine). Although the administration of pharmacological agents is often used, these products are nevertheless associated with various patient discomforts and can be harmful to patients.

Contrary to pharmacological agents, Exercise-CMR (Ex-CMR) is preferred because it can provide more accurate physiological responses. Various Ex-CMR protocols are used, which include MRI scanner-adjacent treadmills or in-scanner exercises using a supine cycle ergometer or isometric hand grip exercises. However, dynamic exercises such as treadmills or cycle ergometers can cause issues like ECG gating artifacts, delayed imaging, and leg muscle fatigue. Although dynamic exercises induce enough deformations on cardiac muscles, they can compromise the quality of the images. On the other hand, static exercise such as isometric handgrip was found to be beneficial in overcoming the limitations associated with dynamic exercises and in improving the image quality. However, it does not induce sufficient cardiac deformations when used alone. Based on the review that we have conducted, we found that there is still a lack of a robust and effective stress protocol that can improve and allow effective heart characterization while overcoming the limitations

associated with the current exercise imaging techniques. Such protocol could revolutionize stress CMR imaging and improve clinical diagnostic protocols.

4.2 Main objective

The main objective of this project is to develop, optimize and validate a cardiac magnetic resonance imaging protocol under exercise stress conditions. The development, optimization, and validation of an MRI protocol under exercise stress conditions will help to better highlight the effects of different cardiac diseases on cardiac muscles and characterize the changes in the hemodynamic and mechanical properties that can be biomarkers of cardiac diseases. It will also help to improve our knowledge of stress cardiology and provide cardiologists with important information that can facilitate the early detection of cardiac diseases and help anticipate their progression.

4.3 Specific objectives and hypotheses

In this context, we proposed specific objectives and hypotheses underlying this doctoral project.

The project's specific objectives and hypothesis are listed below.

1. To study the in vivo relationship between MRI parameters and mechanical properties during at-rest conditions. The assumption underlying this part of the project is that cardiac MRI parameters (i.e., T1 and T2 relaxation times and partition coefficient) reflect the mechanical behavior of cardiac tissue (i.e., left ventricle stiffness (LVS), contractility (LVC) and pressure (Pmin and Pmax), cardiac work efficiency (CWE) and ventricular arterial coupling).
2. To assess cardiac mechanical performance, at different levels of effort, in patients at high risk of developing heart failure (childhood acute lymphoblastic leukemia survivors). The hypothesis for this part of the project is that cardiac mechanical behavior evolves with increasing effort and that the Cardiopulmonary Exercise Testing (CPET) combined with CMR acquisitions will unmask potential cardiac conditions not observable during at-rest conditions. We also hypothesized in this study that doxorubicin treatment will affect survivors' cardiac performance at different levels of effort.

3. To analyze the effects of different Ex-CMR protocols on the heart and describe their advantages and limitations.
4. To establish an optimal Ex-CMR protocol under different exercise stress conditions in a cardiac MRI scanner. This part of the project hypothesizes that the newly developed Ex-CMR protocol will induce significant cardiac changes and will allow effective cardiac assessments while avoiding the limitations associated with the Ex-CMR protocol using a cycle ergometer.

These objectives are addressed in the following chapters. An article is proposed for each objective. The long-term objective of this project is to develop a stress MRI protocol that allows the characterization of the mechanical behavior of the heart and the diagnosis of cardiac abnormalities at an early stage. We hypothesize that cardiac mechanical properties are excellent indicators for the early detection of abnormalities in the myocardial tissue and in particular, for the early detection of cardiac ischemia.

The overall approach of this research work is based on investigating first the relationship between cardiac parameters and MRI. Secondary, is to assess how exercise affects the cardiovascular system function and performance in the participants at high risk of developing heart failure. The third step is to assess the impacts of exercises on cardiac tissues through a literature review and to study the effectiveness of the existing Ex-CMR in cardiac disease characterization. Based on the outcomes of this literature review, we developed an Ex-CMR protocol that can be easily executed during MRI scans. This protocol must induce sufficient deformations and allow to effectively characterize the heart.

Chapter 5 addresses the article: “Relationship between Cardiac Mechanical Properties and Cardiac Magnetic Resonance Imaging at Rest in Childhood Acute Lymphoblastic Leukemia Survivors”[30]. Chapter 6 addresses the article: “Cardiac Mechanical Performance Assessment at Different Levels of Exercise in Childhood Acute Lymphoblastic Leukemia Survivors”[31] and Chapter 7 addresses the article: “Assessing the Feasibility and Reliability of a New Exercise Cardiovascular Magnetic Resonance Protocol for the Characterization of Cardiac Function and Mechanics”. This article has been submitted to the International Journal of Cardiovascular Imaging.

The first contribution which is the scoping review was conducted to describe the existing Ex-CMR protocols, their limitations, and their gaps. The findings of this study have helped us to understand the effectiveness of existing techniques to unveil abnormal responses to exercise among cardiac diseases. From this study, we understood that there is a need to develop a new Exercise CMR protocol that can minimize the limitations associated with existing exercise protocols. Moreover, we understood that there is a need to explore other cardiac remodeling biomarkers that can improve the early detection of this pathological mechanism. From these insights, we conducted our second contribution to explore mechanical biomarkers in acute lymphoblastic leukemia survivors which is the population at high risk of developing heart failure. This study aimed to assess the relationship between cardiac mechanical properties and CMR parameters. The findings of this study helped us understand the importance of using CMR to predict the mechanical behaviour of the heart. The finding of this study provided insights into how CMR can be used to reveal various abnormalities in cardiac pathologies if combined with computation models. The third contribution aimed to assess cardiovascular performance at different levels of exercise in ALL survivors. This study highlighted the importance of exercise to unveil subtle pathological changes that happen in cardiac conditions. All the findings from these previous studies motivated us to develop a new protocol that can characterize the heart effectively but also that can be performed with various populations even for those with limited exercise capacity.

CHAPTER 5 ARTICLE 2: RELATIONSHIP BETWEEN CARDIAC MECHANICAL PROPERTIES AND CARDIAC MAGNETIC RESONANCE IMAGING AT REST IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA SURVIVORS

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5.1 Abstract

The characterization of cardiac mechanical properties may contribute to better understanding of doxorubicin-induced cardiotoxicity. Our study aims to investigate the relationship between cardiac mechanical properties T1 and T2 relaxation times and partition coefficient. Fifty childhood acute lymphoblastic leukemia survivors underwent a cardiac magnetic resonance (CMR) at rest on a 3T MRI system and included a standard ECG-gated 3(3)3(3)5 MOLLI sequence for T1 mapping and an ECG-gated T2-prepared TrueFISP sequence for T2 mapping. Partition coefficient, ejection fraction, end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated. CircAdapt model was used to study cardiac mechanical performance (left ventricle stiffness (LVS)), contractility (LVC) and pressure (Pmin and Pmax), cardiac work efficiency (CWE) and ventricular arterial coupling). In the whole cohort, our results showed that LVC ($R^2=69.2\%$, $r=0.83$), Pmin ($R^2=62.9\%$, $r=0.79$) and Pmax can be predicted by significant CMR parameters, while T1

($R^2=23.2\%$, $r=0.48$) and partition coefficient ($R^2=13.8\%$, $r=0.37$) can be predicted by significant cardiac mechanical properties. In SR group LVS ($R^2=94.8\%$, $r=0.97$), LVC ($R^2=93.7\%$, $r=0.96$) and Pmin ($R^2=90.6\%$, $r=0.95$) can be predicted by significant cardiac mechanical properties, while in HR+DEX group CWE ($R^2=49.8\%$, $r=0.70$) can be predicted by significant cardiac mechanical properties. Partition coefficient ($R^2=72.6\%$, $r=0.85$) can be predicted by significant CMR parameters in the SR group. Early characterization of cardiac mechanical properties from CMR parameters has the potential to early detect doxorubicin-induced cardiotoxicity.

5.2 Keywords

Doxorubicin-related cardiotoxicity; Survivorship; Late adverse effects; CMR Parameters; CircAdapt model; Cancer research.

5.3 Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer [143] and despite the successful advancements in cancer treatments, they are at high risk of developing doxorubicin-related cardiotoxicity [144]. It can appear early or late after the treatments ended and may vary from subclinical myocardial dysfunction to irreversible heart failure [145-147]. In childhood cancer survivors, cardiotoxicity is a common cause of morbidity and mortality [144]. In fact, they are seven times more likely to die from cardiovascular complications than their healthy peers [148]. To counter these long-term effects, dexrazoxane treatments are prescribed as cardioprotective agents when the cumulative dose of doxorubicin is high [149].

The growing number of survivors leads us to take an interest in doxorubicin-induced pathophysiological mechanisms because these mechanisms are not completely understood in childhood ALL survivors although some studies have been published in animal models[150]. To characterize these pathophysiological mechanisms, advanced imaging techniques, including echocardiography and cardiovascular magnetic resonance (CMR) imaging, have been extensively used [151]. Nevertheless, the use of echocardiography is limited to identify doxorubicin-related cardiotoxicity due to its lack of sensitivity for early doxorubicin damages [152]. Contrary, CMR imaging has been reported as an ideal early non-invasive biomarker to assess survivors' cardiac function and structure, and to detect multiple tissue damages [153, 154]. The use of T1 and T2

sequences with contrast-enhanced T1 imaging was proposed to early detect doxorubicin-related cardiotoxicity in cardio-oncology [155, 156].

Clinical studies showed that cardiac mechanical changes are often linked to various diseases such as hypertension, ischemic heart failure, cardiac hypertrophy, and many other cardiac abnormalities [157]. As a response to cardiac injury or damage, structural or functional changes can stiffen the myocardium and leads to diastolic dysfunction [158]. The characterization of cardiac mechanical properties encountered during cardiac remodeling may contribute to early characterization and better understanding of survivors' cardiotoxicity. Therefore, our study aims to investigate the relationship between cardiac mechanical properties and CMR parameters, and to explore whether doxorubicin and dexrazoxane treatments influence the relationship between cardiac mechanical properties and CMR parameters.

5.4 Methods

5.4.1 Participants

This study included 66 childhood ALL survivors who were diagnosed between 1987 and 2010, and treated according to the Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia (DFCI-ALL) 87-01 to 05-01 protocols [159] at Sainte-Justine University Health Center (SJUHC), Montreal (Quebec), Canada. Participants were restricted to survivors diagnosed before 19 years of age. The participants were initially recruited in the PETALE study [160], a multidisciplinary research project that aimed at identifying and comprehensively characterizing associated predictive biomarkers of long-term treatment-related complications in childhood ALL survivors. Survivors were classified into three groups: standard risk (SR) and high risk with and without cardio-protective agent dexrazoxane (HR and HR+DEX)[159]. The cumulative doxorubicin dosages were 60mg/m² for the standard risk group, 300mg/m² for the high risk with dexrazoxane group, and either 360mg/m² (DFCI-ALL protocols 87-01 and 91-01) or 300mg/m² (DFCI-ALL protocols 95-01 and 00-05) for the high risk without dexrazoxane group. These survivors had no history of refractory or recurrent diseases and did not receive a hematopoietic stem cell transplant. They were mostly (>95%) French-Canadian descent [160]. Participants who had suffered from congenital bone disease, or who had received osteotoxic drugs for non-ALL diseases, were excluded. Written informed consent was obtained from every patient or parent/legal guardian. The PETALE study

approved by the Ethics Review Committee of SJUHC.

5.4.2 Cardiac Magnetic Resonance Acquisitions

The CMR acquisitions were performed on a 3T MRI system (Skyra™, Siemens Healthcare, Erlangen, Germany) using an 18-channel phased array body matrix coil. The CMR protocol included a standard ECG-gated 3(3)3(3)5 MOLLI sequence for T1 mapping [161] and an ECG-gated T2-prepared TrueFISP sequence for T2 mapping [162]. Post-gadolinium T1 was acquired using Gadovist (0.1ml/kg) as a contrast agent at 14 ± 3 minutes post-injection. A standard ECG-gated cine TruFISP sequence was chosen because of its reliable image quality. Images were acquired at the end of the diastolic phase, during multiple breath-holds, at apical, mid-ventricular, and basal levels with a pixel resolution of 1.4mmx1.4mmx8.0mm, TR/TE/TI of 405/1.12/129 for T1, and TR/TE of 289/1.18 for T2. In short- and long-axis view, 14 slices and 4 slices, respectively, were acquired using the following acquisition parameters: slice thickness 8mm, repetition time 34.6ms, effective echo time 1.2ms, flip angle 38°, iPAT factor 3, matrix 208x210 and spatial resolution 1.25mmx1.25mm. A total of 25 phases of the cardiac cycle were acquired during multiple breath-holds. The overall acquisition time, including the 3-plane localizer scan, and the relaxation time sequence was approximately 30 minutes.

5.4.3 Cardiac Magnetic Resonance Analysis

To calculate CMR structural and functional parameters, the segmentation and the tracking of left ventricle (LV) wall boundaries were quantified using a semi-automatic segmentation (CIM v8.1, University of Auckland) [163]. An example of the semi-automatic segmentation using the CIM is presented in **Figure 5. 1**. This technique allows an accurate characterization of the LV shape and motion, and a rapid extraction of the LV boundaries from CMR data. Once the segmentation of the endocardial borders of the short axis cine images at the end of the diastole and systole was completed, both end diastolic volume (EDV) and end systolic volume (ESV) were calculated based on the Simpson disk summation method [151, 164].

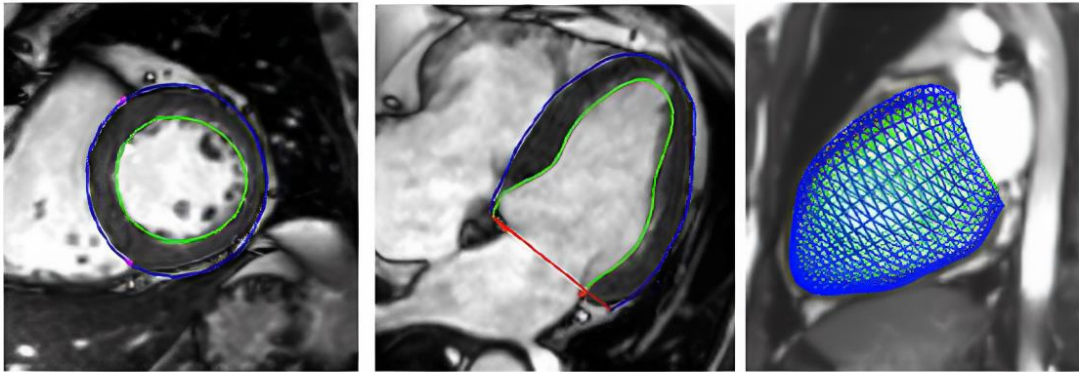


Figure 5.1 Semi-automatic segmentation using the CIM (v8.1, University of Auckland)

Then, stroke volume (SV) and ejection fraction (EF) were calculated from these volumes, as follows: $SV = (EDV - ESV)$, $EF = SV / EDV * 100\%$; according to the cardiac functional analysis recommendations [165, 166].

Native and post-gadolinium T1 along with T2 relaxation times means were evaluated at each segment using respective myocardial contours. T1 maps were generated using phase-sensitive inversion recovery (PSIR) fitting using a three-parameter signal model with motion correction [161]. Pixel-wise myocardial T2-maps were generated using unsupervised curve-fitting based on a two-parameter equation with motion correction [162]. The partition coefficient (λ) of gadolinium was also evaluated from measures of native T1 and post-gadolinium T1 in both myocardium and blood pools, as follows:

$$\lambda = \left(\frac{1}{T1_{Post\ M}} - \frac{1}{T1_{Nat\ M}} \right) / \left(\frac{1}{T1_{Post\ B}} - \frac{1}{T1_{Nat\ B}} \right)$$

where the term ‘Post’ is for post-contrast, ‘Nat’ is for native contrast, ‘M’ is for myocardium and ‘B’ is for blood.

5.4.4 CircAdapt workflow and Simulations

We used the CircAdapt model to study childhood ALL survivors’ cardiac mechanical properties. The CircAdapt model comes with the MATLAB source code which can be modified by the users depending on their needs. The workflow starts by the users running the main MATLAB files and entering the input parameters (**Figure 5.2**). The CircAdapt model uses different physiological

adaptation rules to produce realistic simulations of flow, volumes, and pressures of the heart and large blood vessels [2].

In other words, the CircAdapt model allows adaptation of cardiovascular system at rest conditions. It has the ability to adapt its own geometry so that mechanical loads in the tissues become very similar to physiological loads to propose a live simulation of the 4-chamber heart and the circulation at rest [167]. The most used inputs were considered: heart rate (HR), cardiac output (CO), systolic pressure [168] and diastolic pressure [40], as measured with a cardiac hemodynamic monitoring device (PhysioFlow, Manatec Biomedical, Macheren, France).

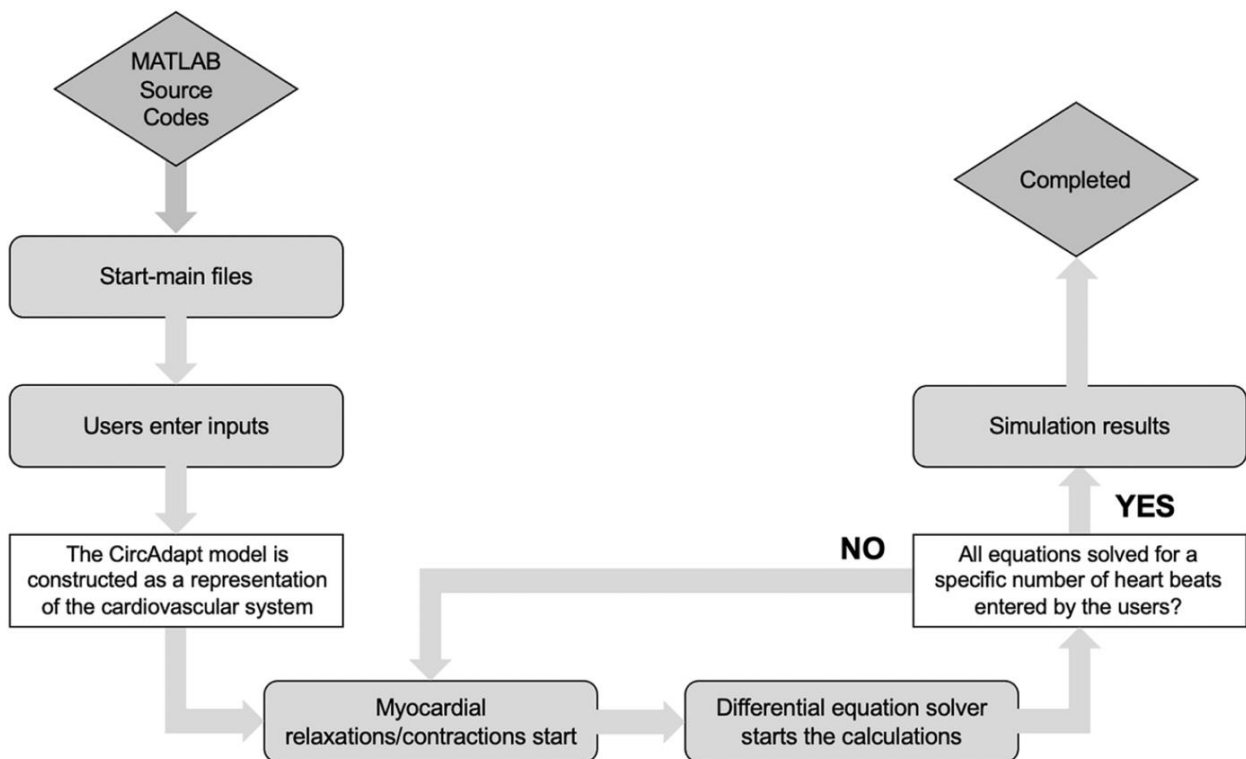


Figure 5.2 : CircAdapt model workflow

The CircAdapt model simulates changes in geometry due to adaptation rules [2]. Using differential equations various outputs of the model can be calculated. Those include the cavity volumes and cavity pressures. The model calculates outputs according to its MATLAB source code [2]. *For instance*, cavity pressures are calculated based on the concept of transmural pressure (p_W) as follows:

$$\begin{cases} p_{LV} &= p_p - p_{W,LW} \\ p_{RV} &= p_p + p_{W,RW} \end{cases} [88]$$

Where P_{LV} means pressure in the left ventricle; P_p , the pressure within the pericardium; P_w, LW , left ventricular free wall transmural pressure; P_{RV} , pressure in the right ventricle and p_W, RW means right ventricular free wall transmural pressure. The equation for the transmural pressure p_W derived for the spherical atrium is calculated as follows in the model: $p_W = 2TmCm$, where Tm means tension in each free wall and Cm means mid-wall curvature calculated from the geometry of the chamber [84]. The cavity volumes (V_{LV} and V_{RV}) are calculated in the model as follows:

$$\begin{cases} V_{LV} &= A_{LV} \cdot z \\ V_{RV} &= A_{RV} \cdot z \end{cases}$$

Where A_{LV} means the cross-section area of the left ventricle; A_{RV} means the cross-section area of the right ventricle and z means the height of the cylindrical three-wall segment [88].

In our study, we simulated the behavior of the LV. The following optimized mechanical properties of LV volumes were estimated at rest: stiffness (LVS), contractility (LVC), and pressure drop (Pdrop). The considerate outputs were the LV volumes and the left intra-ventricular pressure. Once LVS, LVC and Pdrop were obtained, the left ventricular minimum pressure (P_{min}) and left ventricular maximum pressure (P_{max}) were computed for each participant.

5.4.5 Analysis of pressure volumes cycles from the CircAdapt model

For each childhood ALL survivor at rest, we were able to compute the LV volumes and pressures non-invasively and individualize the LV pressure-volume cycles. To obtain the necessary information about survivors' cardiac function, cardiac work, and mechanical efficiency needed for the ventricle to contract, we used the LV pressure-volume cycles, coupled with the end-systolic and end-diastolic pressure-volume relation curves (ESPVR and EDPVR). To obtain the ESPVR, a logarithmic ESPVR curve type was considered and computed along three points, as follows: the estimated peak isovolumic pressure (Piso), the end systolic point (Ves, end systolic volume and Pes, end systolic pressure) located on the upper left corner of the pressure-volume cycle, and the intercept Vo (Vo,0). To obtain the EDPVR, the curve fitting was computed along two points, as follows: the end diastolic point (Ved, end diastolic volume and Ped, end diastolic pressure) located on the lower right corner of the pressure-volume cycle, and the intercept Vo (Vo,0).

5.4.6 Calculation of the cardiac work efficiency and ventricular-arterial coupling

Cardiac mechanical properties can be quantified non-invasively by the LV pressure-volume loops [169, 170]. In our study, the ventricular end systolic elastance [40] was calculated from two slopes: one tangential slope obtained from the ESPVR curve at the end systolic point (Ves, Pes), and another one slope passing through (Vo,0) and (Ved, Piso) points. This Ees parameter is defined as a characteristic of cardiac function, contractility and morphology and is independent of preload and afterload [171]. The effective arterial elastance (Ea) considered as an index of arterial vascular load was calculated directly as the ratio of the end systolic pressure and stroke volume. To obtain the CWE parameter, we first calculated the stroke work (SW), which is calculated as the pressure-volume cycle area. Then, we calculated the potential energy (PE), which is the area bounded by the ESPVR curve, the EDPVR curve and the left part of the pressure-volume cycle. Therefore, CWE parameter was obtained, as follows: $CWE = SW / (SW + PE)$. To obtain the VAC parameter, which is the coupling between the cardiac and the arterial system, the ratio between Ea and Ees was calculated, as follows: $VAC = Ea / Ees$.

5.4.7 Statistical analyses

Statistical analyses were performed using SigmaStat, version 4.0 (Systat Software Inc., San Jose, CA, USA). Normal distribution of data was verified by Shapiro-Wilk test. Data on demography

and clinical characteristics of the participants were presented with descriptive statistics. Participants' characteristics were also described according to their prognostic risk group (i.e., SR, HR+DEX and HR). To assess the relationship between cardiac mechanical properties and CMR parameters, multiple linear regressions were performed. Pearson correlation coefficient tests were performed to identify a possible relationship between the parameters of interest and were classified, as follows: as poor ($ICC < 0.40$), moderate (0.40 to 0.59), good (0.60 to 0.74) and excellent (0.75 to 1.00). First, we considered the following parameters: LVS, LVC, Pmin, Pmax, CWE and VAC, as dependent variables to predict cardiac mechanical properties based on CMR parameters. Second, we considered the following parameters: T1 and T2 relaxation times, partition coefficient, EF, EDV and ESV, as dependent variables to predict CMR parameters based on cardiac mechanical properties. To explore whether survivors' prognostic risk group might impact the relationship results between cardiac mechanical properties and CMR parameters, the same analyses were repeated with the different prognostic risk groups. For all statistical analysis, the differences were considered significant when the p-value was <0.05 with an alpha risk of 5%.

5.5 Results

5.5.1 Clinical characteristics

Among the 66 childhood ALL survivors included in this study, 16 were excluded from the analyses for the following reasons: the CircAdapt model was unable to stabilize and to converge towards realistic pressures and volumes ($n=13$) and CMR data were lacking for analysis ($n=3$). A total of 50 survivors were included in our analyses (**Table 5.1**). Participants' characteristics according to their prognostic risk groups are presented in **Table 5. 2**.

Table 5.1 Clinical characteristics of childhood ALL survivors

Characteristics	Total (N=50)
Gender, N (%)	
Male	16 (32.0)
Female	34 (68.0)
Age at interview, years	
Mean (SD)	22.6 (7.0)
Median (range)	22.0 (12.0-38.0)
Age at cancer diagnosis, years	
Mean (SD)	7.6 (4.9)
Median (range)	6.0 (0.9-17.0)
Time from diagnosis, years	
Mean (SD)	15.5 (5.6)
Median (range)	15.3 (5.5-28.1)
Risk groups, N (%)	
Standard risk	11 (22.0)
High risk with dexrazoxane	21 (42.0)
High risk without dexrazoxane	18 (36.0)
Treatment protocol, N (%)	
DFCI 87-01	3 (6.0)
DFCI 91-01	14 (28.0)
DFCI 95-01	12 (24.0)
DFCI 2000-01	13 (26.0)
DFCI 2005-01	8 (16.0)
Doxorubicin, mg/m²	
Mean (SD)	249.2 (96.8)
Median (range)	293.2 (45.6-400.0)
Dexrazoxane, N (%)	
Yes	21 (42.0)
No	29 (58.0)

Table 5.2 Clinical characteristics of childhood survivors according to their prognostic risk groups

Characteristics	SR (N=11)	HR+DEX (N=21)	HR (N=18)	p-value
Gender, N (%)				
Male	3 (27.3)	3 (14.3)	10 (55.6)	-
Female	8 (72.7)	18 (85.7)	8 (44.4)	
Age at interview, years				
Mean (SD)	20.0 (5.5)	23.5 (7.4)	23.2 (7.2)	0.377
Median (range)	18.0 (12.0-29.0)	23.0 (14.0-38.0)	22.5 (12.0-35.0)	
Age at cancer diagnosis, years				
Mean (SD)	4.5 (2.3)	9.6 (4.7)	7.3 (5.4)	0.016
Median (range)	4.0 (2.0-9.0)	10.0 (2.0-17.0)	6.0 (0.9-16.0)	
Time from diagnosis, years				
Mean (SD)	18.9 (6.4)	11.0 (3.7)	18.3 (3.0)	<0.0001
Median (range)	20.8 (8.8-28.1)	11.8 (5.5-17.1)	18.9 (10.6-22.9)	
Doxorubicin, mg/m²				
Mean (SD)	89.9 (89.1)	279.7 (45.7)	295.8 (50.6)	<0.0001
Median (range)	60.0 (45.6-325.6)	297.6 (142.8-324.1)	300.0 (209.8-400.0)	
Dexrazoxane, mg/m²				
Mean (SD)	-	2855.3 (362.7)	-	-
Median (range)	-	2977.6 (1872.8-3240.7)	-	

5.5.2 Prediction of cardiac mechanical properties from CMR parameters

Analyses revealed that the following cardiac mechanical properties: LVS, LVC, Pmin, Pmax and CWE can be predicted from CMR parameters.

In the whole cohort, results showed that LVC can be predicted ($R^2=69.2\%$, $r=0.83$) by the following significant predictors: EF ($p=0.011$), EDV ($p=0.003$) and ESV ($p=0.026$). Results also showed that Pmin can be predicted ($R^2=62.9\%$, $r=0.79$) by the significant predictor T1 ($p=0.037$), while Pmax can be predicted ($R^2=28.5\%$, $r=0.53$) by the significant predictor T1 ($P=0.011$). When analyses were performed according to survivors' prognostic risk group, we found that LVS can be predicted ($R^2=94.8\%$, $r=0.97$) by the significant predictors T1 ($p=0.008$) and partition coefficient ($p=0.034$),

while LVC can be predicted ($R^2=93.7\%$, $r=0.96$) by the significant predictor EF ($p=0.043$) in the SR group.

We also observed that Pmin can be predicted ($R^2=90.6\%$, $r=0.95$) by the following significant predictors: EDV ($p=0.011$), ESV ($p=0.013$) and EF ($p=0.013$) in the SR group. In the HR+DEX group, CWE can be predicted ($R^2=49.8\%$, $r=0.70$) by the significant predictor EDV ($p=0.049$), while no CMR parameters could predict cardiac mechanical properties in the HR group. Coefficients of determination (R^2) and significant predictor results for the prediction of cardiac mechanical properties from CMR parameters are presented in **Table 5. 3**. The equations to predict the relationship between cardiac mechanical properties and CMR parameters are available in **supplementary material, S1**.

Table 5.3 Coefficients of determination and significant predictors results for the prediction of cardiac mechanical properties from CMR parameters.

Cardiac mechanical properties	R^2 and significant predictors			
	Total (N=50)	SR (N=11)	HR+DEX (N=21)	HR (N=18)
Left ventricle stiffness	23.2%	94.8% T1 ($p=0.008$) Partition coefficient ($p=0.034$)	50.1%	47.9%
Left ventricle contractility	69.2% EF ($p=0.011$) EDV ($p=0.003$) ESV ($p=0.026$)	93.7% EF ($p=0.043$)	71.3%	69.0%
Left ventricular minimum pressure	62.9% T1($p=0.037$)	90.6% EDV ($p=0.011$) ESV ($p=0.013$) EF ($p=0.013$)	57.7%	76.9%
Left ventricular maximum pressure	28.5% T1 ($p=0.011$)	39.4%	29.4%	39.9%
Cardiac work efficiency	30.6%	28.8%	49.8% EDV ($p=0.049$)	56.0%
Ventricular-arterial coupling	27.4%	28.0%	56.0%	43.7%

5.5.3 Prediction of CMR parameters from cardiac mechanical properties

Analyses revealed that the following CMR parameters: T1 relaxation time and partition coefficient can be predicted from cardiac mechanical properties. In the whole cohort, results showed that T1 relaxation time can be predicted ($R^2=23.2\%$, $r=0.48$) by the following significant predictors: Pmin ($p=0.012$), and Pmax ($p=0.030$). Results also showed that partition coefficient can be predicted ($R^2=13.8\%$, $r=0.37$) by the significant predictor CWE ($p=0.040$). When analyses were performed according to survivors' prognostic risk group, we found that partition coefficient can be predicted ($R^2=72.6\%$, $r=0.85$) by the significant predictor LVS ($p=0.049$). No cardiac mechanical properties could predict CMR parameters in HR+DEX and HR groups. Coefficients of determination (R^2) and significant predictor results for the prediction of CMR parameters from cardiac mechanical properties are presented in **Table 5.4**. The equations to predict CMR parameters from a combination of cardiac mechanical properties are available in **supplementary material, S2**.

Table 5.4 Coefficients of determination (R^2) and significant predictors results for the prediction CMR parameters from cardiac mechanical properties.

CMR parameters	R^2 and significant predictors			
	Total (N=50)	SR (N=11)	HR+DEX (N=21)	HR (N=18)
T1	23.2% Pmax ($p=0.030$) Pmin ($p=0.012$)	71.5%	28.0%	59.5%
T2	8.3%	40.0%	19.4%	43.1%
Partition coefficient	13.8% CWE ($p=0.040$)	72.6% LVS ($p=0.049$)	57.4%	47.1%

5.6 Discussion

The present study found that cardiac mechanical properties can be predicted from a combination of CMR parameters, and conversely. We noted that some CMR parameters (i.e., T1 relaxation time, EF, EDV and ESV) contributed more to the prediction of cardiac mechanical properties than the others. When exploring survivors' prognostic risk group, we found that the following CMR parameters: T1 relaxation time, partition coefficient, EF and EDV were important significant predictors to predict cardiac mechanical properties in SR and HR+DEX groups.

No cardiac mechanical properties could predict CMR parameters in HR+DEX and HR groups, and only LVS was a significant predictor to predict CMR parameters in SR group. To our knowledge this is the first study to highlight the relationship between cardiac mechanical properties and CMR parameters in childhood ALL survivors.

Our findings showed that CMR parameters were sensitive enough to predict cardiac mechanical properties. However, we found that its sensitivity was altered by high cumulative dose of doxorubicin received during cancer treatments. Indeed, when our analyses were performed according to survivors' prognostic risk group, we found that CMR parameters may predict cardiac mechanical properties in SR group and HR+DEX groups. Clinical studies reported that the cumulative dose of doxorubicin that exceeds 450 mg/m² are related to serious cardiac adverse effects that increase the risk of cardiovascular diseases in survivors of diffuse large B-cell lymphoma [172]. In childhood ALL survivors, high cumulative dose of doxorubicin can cause significant changes in survivors' cardiac mechanical properties and reduce CMR sensitivity to detect cardiac mechanical changes. For LVS, its coefficient of determination in the SR group ($R^2=94.8\%$, $r=0.97$) was almost twice the ones in the HR+DEX and HR groups ($R^2=47.9\%$, $r=0.69$ and $R^2=50.1\%$, $r=0.70$ respectively), which support the negative impact of high cumulative dose of doxorubicin. The level of correlation coefficient of LVS in the SR group was a very strong correlation (r value in the range of 0.90 to 1.00), the level of correlation of LVS in the HR+DEX was a moderate correlation (r in the range of 0.4 to 0.69) and the level of correlation of LVS in the HR group, was a strong correlation. Survivors in HR+DEX and HR groups are those who received a high cumulative dose of doxorubicin and it has been documented that they are at higher risk of myocardial damage and cardiac dysfunction than survivors in the SR group. In fact, no CMR parameters could predict cardiac mechanical properties in the HR group. Survivors who received dexrazoxane treatments benefits from cardiac protection, which is not the case for survivors in HR group. Our findings reinforced that the cardioprotective agent plays an important role in the prevention of long-term cardiac damage.

In cardio-oncology, the early diagnosis of cancer therapeutics-related cardiac dysfunction in those receiving doxorubicin treatments remains an important challenge. Thus, it has been found that childhood ALL survivors are in the first stage of heart failure and at an increased risk for premature cardiovascular diseases such as congestive heart failure [147, 173]. In line with these findings,

several studies have reported that cardiac fibrosis induces myocardial stiffening and changes in the partition coefficient that can reveal the severity of various cardiac pathologies including fibrosis, hypertrophic cardiomyopathy, and aortic stenosis [174, 175]. Our findings found that T1 relaxation time, partition coefficient, EF, EDV, ESV (CMR parameters) were important significant predictors to predict cardiac mechanical properties (LVS, LVC, Pmin and CWE) in SR and HR+DEX groups. T1 relaxation time and partition coefficient are sensitive biomarkers of early doxorubicin damage. Another promising finding from our analyses is that T1 relaxation time and partition coefficient are important contributors of LVS ($R^2=94.8\%$, $r= 0.97$) in the SR group. Analyses also revealed that the following CMR parameters: T1 relaxation time and partition coefficient can be predicted from cardiac mechanical properties. We found that Pmin and Pmax were significant contributors of T1 relaxation time, while CWE was a significant contributor of partition coefficient in the whole cohort. In the SR group, LVS was a significant contributor of partition coefficient. Previous study has reported that untreated high left ventricle blood pressure can lead to LV remodeling such as LV hypertrophy which increases the incidence of heart failure [176]. Our findings have the potential to early detect doxorubicin-induced cardiotoxicity and prevent the progression of late cardiac effects by the early characterization of cardiac mechanical properties from CMR parameters. However, it is important to note that T2 relaxation time was not a significant contributor to predict cardiac mechanical properties.

The absence of results in T2 relaxation time may be due to its sensitivity to survivors' cardiac mechanical changes. It has been observed that T2 mapping is more sensitive to collagen damage or changes than cardiac muscle composition in heart failure patients [177]. However, T2 remains an important parameter to detect myocardial changes in childhood ALL survivors [178] and in early doxorubicin-related cardiotoxicity assessments, T2 may have a strong relationship with cardiac mechanical properties. Future studies exploring this relationship should be considered.

5.7 Limitations of the study

Although our study documents the relationship between cardiac mechanical properties and CMR parameters in childhood ALL survivors, we encountered some limitations that could be addressed in future research. Thus, we recognize that our sample size can limit the power of our analyses and

explain the absence of other significant predictors to predict CMR parameters or cardiac mechanical properties in the different prognostic risk groups. Large sample size should be considered in future studies to better understand whether doxorubicin and dexrazoxane treatments influence the relationship between cardiac mechanical properties and CMR parameters. Future studies should also investigate the sensitivity of T2 relaxation time to cardiac mechanical changes to better understand the impact of doxorubicin and dexrazoxane treatments on this relationship. It could also be interesting to investigate the relationship between other CMR parameters such as T2* or spin-lock relaxation time and cardiac mechanical properties. Diffusion parameters (e.g., apparent diffusion coefficient ADC and fractional anisotropy FA) could also be added in future analyses, however, *in vivo* acquisitions remain challenging in childhood ALL survivors[179].

5.8 Conclusion

This study showed that cardiac mechanical properties (LVS, LVC, Pmin, Pmax and CWE) can be predicted from CMR parameters, and that CMR parameters (T1 relaxation time and partition coefficient) can be predicted from cardiac mechanical properties. This is the first study to show the relationship between cardiac mechanical properties and CMR parameters in childhood ALL survivors. Early characterization of cardiac mechanical properties from CMR parameters has the potential to early detect doxorubicin-induced cardiotoxicity and prevent the progression of late cardiac effects. Our study contributes to improve survivors' prognostic follow up. Moreover, we believe that the use of numerical computation models such as CircAdapt model, will help in assessing short and long terms effects of chemotherapy treatments, allowing to prevent cardiac sequelae's following the treatments. It will also make it possible to provide more accurate diagnostic information's than those currently available in this population using the conventional imaging techniques, which will help in clinical decision-making.

5.9 Acknowledgements

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CHAPTER 6 ARTICLE 3: CARDIAC MECHANICAL PERFORMANCE ASSESSMENT AT DIFFERENT LEVELS OF EXERCISE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA SURVIVORS

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6.1 Abstract

Background

There is a shortage of relevant studies interested in cardiac mechanical performance. Thus, it is clinically relevant to study the impact of cancer treatments on survivors' cardiac mechanical performance to improve our knowledge.

Methods: The first objective of this study is to assess survivors' cardiac mechanical performance during a cardiopulmonary exercise test (CPET) using both ventricular-arterial coupling (VAC) and cardiac work efficiency (CWE) from cardiac magnetic resonance (CMR) acquisitions. The second objective is to assess the impact of doxorubicin and dexrazoxane (DEX) treatments. A total of 63 childhood acute lymphoblastic leukemia survivors underwent a CMR at rest on a 3T magnetic

resonance imaging system, followed by a CPET on ergocycle. The CircAdapt model was used to study cardiac mechanical performance. At different levels of exercise, arterial elastance, end-systolic elastance, VAC, and CWE were estimated.

Results: We observed significant differences between the different levels of exercise for both VAC ($P < 0.0001$) and CWE parameters ($P = 0.001$). No significant differences were reported between prognostic risk groups at rest and during the CPET. Nevertheless, we observed that survivors in the SR group had a VAC value slightly lower than HR+DEX and HR groups throughout the CPET. Moreover, survivors in the SR group had a CWE parameter slightly higher than HR+DEX and HR groups throughout the CPET.

Conclusion: This study reveals that the combination of CPET, CMR acquisitions and CircAdapt model was sensitive enough to observe slight changes in the assessment of VAC and CWE parameters. Our study contributes to improving survivors' follow-up and detection of cardiac problems induced by doxorubicin related cardiotoxicity.

6.2 Keywords

Cardiac performance, cardiac work efficiency, ventricular- arterial coupling, late adverse effects, doxorubicin-related cardiotoxicity, cancer research.

6.3 Introduction

Childhood acute lymphoblastic leukemia (ALL) is the most diagnosed pediatric cancer worldwide [143, 180]. Due to advances in chemotherapy regimens, survival rates have increased remarkably to reach 90% [181, 182]. However, chemotherapy treatments (e.g., doxorubicin) have been associated with increased risks of adverse outcomes such as late mortality, secondary malignancies, social/psychological disorders and cardiovascular diseases [181]. It has been reported that doxorubicin treatments are associated with childhood ALL survivors' cardiotoxicity [183, 184].

Doxorubicin-related cardiotoxicity can appear early or late after treatments and may vary from subclinical myocardial dysfunction to irreversible heart failure [145-147]. The incidence of doxorubicin-related cardiotoxicity in childhood ALL survivors is mainly related to the cumulative dose of doxorubicin [185]. In fact, when the cumulative dose of doxorubicin is high ($>300 \text{ mg/m}^2$), dexrazoxane treatments are prescribed as cardioprotective agents to reduce patients' cardiotoxicity [149].

To counteract survivors' late adverse effects and to increase their quality of life, regular practice of physical activity and good cardiorespiratory fitness are promoted in childhood cancer survivors [186-188]. Indeed, it has been reported that the cardiac function and cardiac performance are related to the level of cardiopulmonary fitness, also known as the peak of oxygen uptake (VO_2 peak)[189]. In exercise physiology, cardiopulmonary exercise testing (CPET) is used to measure the VO_2 peak, enhance the follow up of childhood ALL survivors and to unmask potential cardiac risks not observable at submaximal level [190]. However, although various studies assessed cardiorespiratory fitness and exercise efficacy in childhood ALL survivors [187, 191], there is still a shortage of relevant studies interested in cardiac mechanical performance. In this sense, it is clinically relevant to study the impact of doxorubicin and dexrazoxane treatments on survivors' cardiac mechanical performance at a different level of exercise to improve our knowledge. In the general population without heart disease, cardiac mechanical performance is the result of optimal coupling between the heart and the vascular system [192, 193]. In heart failure patients, however, it has been reported that the left ventricle and arterial system are not optimally coupled together to maximize patients' cardiac work efficiency (CWE), compared to healthy people [194]. Similar observations are reported in childhood ALL survivors [2]. Indeed, the ventricular-arterial coupling (VAC) was reported to be impaired in survivors due to the late adverse effects of chemotherapy treatments (e.g., large artery stiffening) [193-195]. To diagnose cardiac conditions and assess cardiac mechanical performance, cardiologists can use both VAC and CWE parameters assessed from cardiac imaging technics such as cardiac magnetic resonance (CMR)[196].

In light of the literature, exercise can play an important role in cardio-oncology. As stated above, decoupling often occurs in pathological states, but it can be restored to improve cardiac mechanical performance during exercise [197]. Evidence-based medicine supports that the VAC coupling can be significantly attenuated during exercise in patients exposed to anthracycline treatments who

suffer from impaired cardiac mechanical performance [198]. Thus, the first objective of this study is to assess childhood ALL survivors' cardiac mechanical performance using both VAC and CWE parameters from CMR acquisitions at different level of exercise. We hypothesized that the CPET combined to CMR acquisitions will unmask potential cardiac conditions not observable in resting condition. The second objective of this study is to assess the impact of doxorubicin and dexrazoxane treatments on survivors' cardiac performance at different level of exercise. We hypothesized that doxorubicin treatment will affect survivors' cardiac performance at different level of exercise, while dexrazoxane treatments will have the potential to limit survivors' cardiac mechanical performance deterioration.

6.4 Methods

6.4.1 Participants

This study included childhood ALL survivors who were diagnosed between 1987 and 2010, and treated according to the Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia (DFCI-ALL) 87-01 to 05-01 protocols [159] at Sainte-Justine University Health Center (SJUHC), Montreal (Quebec), Canada. Participants were restricted to survivors diagnosed before 19 years of age. The participants were initially recruited in the PETALE study [160], a multidisciplinary research project that aimed at identifying and comprehensively characterizing associated predictive biomarkers of long-term treatment-related complications in childhood ALL survivors. Survivors were classified into three groups depending on prognostic risk group (i.e. standard risk (SR) and high risk with and without cardio-protective agent dexrazoxane (HR and HR+DEX))[159]. The cumulative doxorubicin dosages were 60 mg/m^2 for the standard risk group, 300 mg/m^2 for the high risk with dexrazoxane group, and either 360 mg/m^2 (DFCI-ALL protocols 87-01 and 91-01) or 300 mg/m^2 (DFCI-ALL protocols 95-01 and 00-05) for the high risk without dexrazoxane group. These survivors had no history of refractory or recurrent diseases and did not receive a hematopoietic stem cell transplant. They were mostly (>95%) of French-Canadian descent[160]. Participants who had suffered from congenital bone disease, or who had received osteotoxic drugs for non-ALL diseases, were excluded. Written informed consent was obtained from every patient or parent/legal guardian. The PETALE study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Review Committee of Sainte-Justine University Health Center.

6.4.2 CMR Acquisitions

The CMR acquisitions were performed at rest, before the CPET, on a 3T MRI system (Skyra™, Siemens Healthcare, Erlangen, Germany) using an 18-channel phased array body matrix coil. A standard ECG-gated cine TruFISP sequence was chosen because of its reliable image quality. In short- and long-axis view, 14 slices and 4 slices, respectively, were acquired using the following acquisition parameters: slice thickness 8mm, repetition time 34.6ms, effective echo time 1.2ms, flip angle 38°, iPAT factor 3, matrix 208x210 and spatial resolution 1.25mmx1.25mm. A total of 25 phases of the cardiac cycle were acquired during multiple breath-holds. The endocardial volume of the left ventricle was quantified from a semi-automatic segmentation (CIM v8.1, University of Auckland).

6.4.3 CPET

The McMaster incremental cycle protocol [199] was performed on an electromagnetic cycle ergometer (Ergoline, ER900, Bitz, Germany). It is one of the most commonly used incremental cycle protocols in clinical population to measure accurately the participant's oxygen consumption [199, 200]. The McMaster incremental cycle protocol allows to assign participants into a specific exercise protocol of 2-minute increment at predetermined work rates based on the height and sex of the participant [199] which would allow an optimal duration of the CPET between 8 and 12min [201]. In this sense, this test consisted of a standard incremental procedure at a pedaling cadence of 50–70rpm starting at 25W, increasing the load by 25W or 50W (depending on the height and sex of the participant) every 2min. At the end of the test, an active rest period at 25W for 3min was followed by a passive rest period of 3min. The O₂peak was measured with a breath-by-breath system (Oxycon Pro, Viasys Healthcare, Germany) calibrated prior to each test. Breath-by-breath data were averaged in 20 sec intervals to measure the O₂ peak value. All subjects were monitored continuously during the test with 12-leads electrocardiograms (CASE Exercise Testing, GE Marquette, Milwaukee, WI, USA). Throughout the duration of the tests, participants were monitored continuously with a PhysioFlow device (Manatec Biomedical, Macheren, France) [202–204]. The PhysioFlow is a reliable and accurate non-invasive cardiac hemodynamic monitoring device allowing to assess cardiac output (CO) and hemodynamic parameters (heart rate (HR) and

vascular resistance). Blood pressure was measured every 2min (Tango M2, SunTech Medical, Morrisville, NC, USA). The survivor's perception of effort was measured with a rated perceived exertion (RPE) scale (0-10 scale). Both the cardiologist and the exercise physiologist ensured that the cardiopulmonary exercise test was not limited by symptoms. They determined whether the survivors reached two out of three of the following criteria to validate their O_2 peak: peak respiratory exchange ratio [40] value ≥ 1.15 , RPE score >7 , and $HR_{max} \geq 85\%$ of the predicted value [205].

Table 6.1 Clinical characteristics of childhood ALL survivors

Characteristics	Total (N=63)
Gender, N (%)	
Male	28 (44.4)
Female	35 (55.6)
Age at interview, years	
Mean (SD)	22.9 (6.9)
Median (range)	22.0 (12.0-38.0)
Age at cancer diagnosis, years	
Mean (SD)	7.7 (5.2)
Median (range)	6.0 (0.9-18.0)
Time from diagnosis, years	
Mean (SD)	13.4 (5.6)
Median (range)	13.1 (3.4-26.2)
Risk groups, N (%)	
Standard risk	15 (23.8)
High risk with dexrazoxane	26 (41.3)
High risk without dexrazoxane	22 (34.9)
Treatment protocol, N (%)	
DFCI 87-01	7 (11.1)
DFCI 91-01	16 (25.4)
DFCI 95-01	15 (23.8)
DFCI 2000-01	17 (27.0)
DFCI 2005-01	8 (12.7)
Doxorubicin, mg/m²	
Mean (SD)	236.2 (103.1)
Median (range)	276.9 (45.6-400.0)
Dexrazoxane, N (%)	
Yes	26 (41.3)
No	37 (58.7)
Ejection fraction with biplane Simpson method (%)	
Mean (SD)	55.4 (5.3)
Median (range)	55.9 (39.0-66.0)
Heart rate at rest, bpm	
Mean (SD)	90.1 (13.8)
Median (range)	88.0 (63.0-126.0)
Maximum heart rate during exercise test, bpm	
Mean (SD)	186.5 (13.9)
Median (range)	188.5 (136.0-206.0)
$\dot{V}O_2$ peak during exercise test, mL·kg⁻¹·min⁻¹	
Mean (SD)	30.2 (7.6)
Median (range)	29.8 (14.1-47.3)

6.4.4 CircAdapt Simulations

We used the CircAdapt model to study childhood ALL survivors' cardiac mechanical performance. The CircAdapt model uses different physiological adaptation rules to produce realistic simulations of flow, volumes, and pressures of the heart and large blood vessels [2]. Moreover, the CircAdapt model allows adaptation of cardiovascular system at rest conditions in addition to simulating the different level of exercise condition during the CPET [206]. In other words, the CircAdapt model has the ability to adapt its own geometry so that mechanical loads in the tissues become very similar to physiological loads to propose a live simulation of the 4-chamber heart and the circulation at rest and during an exercise stress test [167]. In our study, we simulated the behavior of the left ventricle at different workloads during the CPET. The following inputs were considered: HR, CO, systolic pressure [168] and diastolic pressure [40], as measured with the PhysioFlow device at different level of exercise conditions. The following optimized mechanical properties of LV were also estimated at rest: stiffness, contractility, and pressure drop. The considerate outputs were the LV volumes and the left intraventricular pressure.

6.4.5 Analysis of Pressure Volumes Cycles from the CircAdapt model

For each childhood ALL survivor at different level of exercise condition, we were able to compute the LV volumes and pressures non-invasively and individualize the LV pressure-volume cycles. To obtain the necessary information about survivors' cardiac function, cardiac work, and mechanical efficiency needed for the ventricle to contract during the CPET, we used the LV pressure-volume cycles, coupled with the end-systolic and end-diastolic pressure-volume relation curves (ESPVR and EDPVR). To obtain the ESPVR, a logarithmic ESPVR curve type was considered and computed along three points, as follows: the estimated peak isovolumic pressure (Piso), the end systolic point (Ves, end systolic volume and Pes, end systolic pressure) located on the upper left corner of the pressure-volume cycle, and the intercept V_0 ($V_0, 0$).

Table 6.2 Clinical characteristics of childhood ALL survivors according to their prognostic risk groups.

Characteristics	SR (N=15)	HR+DEX (N=26)	HR (N=22)	p-value
Gender, N (%)				
Male	7 (46.7)	8 (30.8)	13 (59.1)	-
Female	8 (53.3)	18 (69.2)	9 (40.9)	
Age at interview, years				
Mean (SD)	20.4 (6.3)	23.9 (6.8)	23.4 (7.2)	0.266
Median (range)	18.0 (12.0-36.0)	23.0 (14.0-38.0)	23.0 (12.0-35.0)	
Age at cancer diagnosis, years				
Mean (SD)	3.8 (2.1) ^a	10.1 (5.2) ^a	7.6 (5.4)	0.001
Median (range)	2.1 (2-9.0)	10.0 (2.0-18.0)	6.0 (0.9-17.0)	
Time since the end of the treatment, years				
Mean (SD)	15.1 (6.1) ^b	9.3 (3.7) ^{b,c}	17.3 (3.5) ^c	<0.0001
Median (range)	13.2 (6.5-26.2)	9.7 (3.4-16.5)	17.4 (9.3-24.1)	
Doxorubicin, mg/m²				
Mean (SD)	81.3 (70.3) ^d	281.8 (42.2) ^{d,e}	287.8 (59.0) ^c	<0.0001
Median (range)	60.0 (45.6-325.6)	297.3 (142.8-324.1)	282.3 (170.7-400.0)	
Dexrazoxane, mg/m²				
Mean (SD)	-	2864.6 (337.8)	-	-
Median (range)	-	2973.4 (1872.8-3240.7)	-	
Ejection fraction with biplane Simpson method (%)				
Mean (SD)	55.7 (4.8)	55.7 (5.6)	54.9 (5.4)	0.860
Median (range)	57.0 (43.0-62.0)	55.6 (45.0-65.0)	55.3 (39.0-66.0)	
Heart rate at rest, bpm				
Mean (SD)	89.0 (13.6)	93.0 (13.8)	87.5 (13.9)	0.372
Median (range)	88.0 (66.0-113.0)	91.5 (63.0-126.0)	83.0 (65.0-120.0)	
Maximum heart rate during exercise test, bpm				
Mean (SD)	187.7 (10.0)	190.5 (11.0)	181.1 (17.5)	0.059
Median (range)	188.5 (171.0-203.0)	190.0 (169.0-206.0)	187.0 (136.0-206.0)	
$\dot{V}O_2$ peak during exercise test, mL·kg⁻¹·min⁻¹				
Mean (SD)	33.2 (6.7)	30.3 (7.8)	28.0 (7.7)	0.124
Median (range)	33.8 (20.2-42.2)	27.5 (15.9-47.3)	29.0 (14.1-44.9)	

^ap-value = <0.0001 between SR and HR+DEX groups

^{b,c}p-value = <0.0001 between SR and HR+DEX groups and <0.0001 between HR+DEX and HR groups

^{d,e}p-value = <0.0001 between SR and HR+DEX groups and <0.0001 between SR and HR groups

To obtain the EDPVR, the curve fitting was computed along two points, as follows: the end diastolic point (V_{ed} , end diastolic volume and P_{ed} , end diastolic pressure) located on the lower right corner of the pressure-volume cycle, and the intercept V_0 ($V_0, 0$).

6.4.6 Calculation of the cardiovascular parameters

Cardiac mechanical performance can be quantified non-invasively by the LV pressure-volume cycle [169, 170]. In our study, the ventricular end systolic elastance [40] was calculated from two slopes: one tangential slope obtains from the ESPVR curve at the end systolic point (V_{es} , P_{es}), and another one slope passing through ($V_0, 0$) and (V_{ed} , P_{iso}) points. The effective arterial elastance (E_a) considered as an index of arterial vascular load was calculated directly as the ratio of the end systolic pressure and stroke volume. To obtain the CWE parameter, we first calculated the stroke work (SW), which is calculated as the pressure-volume cycle area. Then, we calculated the potential energy (PE), which is the area bounded by the ESPVR curve, the EDPVR curve and the left part of the pressure-volume cycle. Therefore, CWE parameter was obtained, as follows: $CWE = SW / (SW + PE)$. To obtain the VAC parameter, which is the coupling between the cardiac and the arterial system, the ratio between E_a and E_{es} was calculated, as follows: $VAC = E_a / E_{es}$.

6.4.7 Statistical analysis

Statistical analyses were performed using IBM SPSS statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Normal distribution of data was verified by Shapiro-Wilk test. Data on demography and clinical characteristics of the participants were presented with descriptive statistics. Participants' characteristics were also described according to their prognostic risk group (i.e., SR, HR+DEX and HR). To address the first aim of our study, we first described CWE, E_{es} , E_a , and VAC data at the different level of exercise. The different levels of exercise condition were determined from the McMaster incremental cycle protocol, depending on the height and sex of the participants [199] and were expressed, as follows: rest (0W), workload 1 (25-50W), workload 2 (50-75W), workload 3 (75-100W), workload 4 (100-125W), workload 5 (125-150W), workload 6 (150-175W), and workload 7 (175-200W). Then, we conducted a one-way ANOVA to determine whether there are significant differences in the whole cohort between the different levels of exercise for each variable of interest (CWE, E_{es} , E_a , and VAC data). Finally, we performed a one-way

ANOVA to determine whether there are significant differences between male and female survivors. To address the second aim of our study, we performed a one-way ANOVA to determine whether there are significant differences between survivors' prognostic risk groups (i.e., SR, HR+DEX and HR) at different level of exercise for each variable of interest (CWE, Ees, Ea, and VAC data). When a significant effect was observed, a post-hoc analysis using the Bonferroni correction for multiple comparisons was performed. For all statistical analysis, the differences were considered significant when the p-value was <0.05 with an alpha risk of 5%.

6.5 Results

6.5.1 Clinical Characteristics

A total of 63 childhood ALL survivors were included in this study. Participants' characteristics are presented in **Table 6.1**. The survivors' mean age was of 22.9 ± 6.9 years with a mean age at cancer diagnosis of 7.7 ± 5.2 years and a mean time from cancer diagnosis of 13.4 ± 5.6 years. Based on the CPET, survivors' mean VO_2 peak was of $30.2 \pm 7.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($83.5 \pm 17.3\%$ of VO_2 peak predicted) with a mean heart rate and power at the peak of the CPET of $186.5 \pm 13.9 \text{ bpm}$ and $166.5 \pm 60.0 \text{ W}$, respectively. The mean heart rate at rest was of $90.1 \pm 13.8 \text{ bpm}$. In the whole cohort, the survivors' mean left ventricle ejection fraction at rest was of $55.4 \pm 5.3 \%$. Participants' characteristics according to their prognostic risk groups are presented in **Table 6.2**. We observed significant differences between prognostic risk groups for the age at cancer diagnosis ($p=0.001$), the time from diagnosis ($p<0.0001$) and the cumulative dose of doxorubicin ($p<0.0001$). Post-hoc analyses results are reported in **Table 6.2**. The left ventricle ejection fraction at rest was not different between prognostic risk groups but was slightly reduced in the HR group ($54.9 \pm 5.4\%$) than in SR and HR+DEX groups (55.7 ± 4.8 and $55.7 \pm 5.6 \%$, respectively). Similar observations were reported for the mean VO_2 peak between prognostic risk groups since VO_2 peak was reduced in the HR group ($28.0 \pm 7.7 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) than in SR and HR+DEX groups (33.2 ± 6.7 and $30.3 \pm 7.8 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively). Maximal heart rate appeared to be lower in the HR group ($181.1 \pm 17.5 \text{ bpm}$) than in SR and HR+DEX groups (187.7 ± 10.0 and $190.5 \pm 11.0 \text{ bpm}$, respectively).

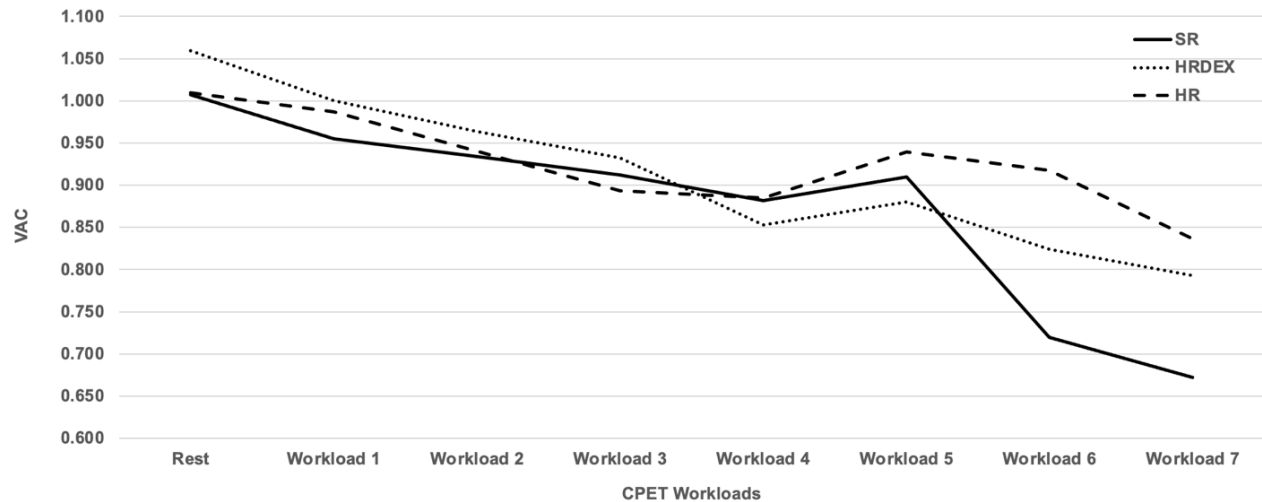


Figure 6.1 Childhood ALL survivors' VAC assessed during the CPET at different levels of exercise according to their prognostic risk groups.

6.5.2 Cardiac Mechanical performance

Ventricular Arterial Coupling

The measures of childhood ALL survivors' VAC assessed during the CPET at different levels of exercise are presented in **Table 6.3**. We observed significant differences between the different levels of exercise ($p < 0.0001$). Post-hoc analysis for VAC parameter at different levels of exercise revealed significant differences between rest and workload 2 ($p = 0.003$), rest and workload 3 ($p < 0.0001$), rest and workload 4 ($p < 0.0001$), rest and workload 5 ($p = 0.003$), rest and workload 6 ($p < 0.0001$), rest and workload 7 ($p < 0.0001$), workload 1 and 3 ($p = 0.036$), workload 1 and 4 ($p < 0.0001$), workload 1 and 6 ($p = 0.001$), workload 1 and 7 ($p < 0.0001$), workload 2 and workload 4 ($p = 0.030$), workload 2 and workload 6 ($p = 0.041$), and workload 2 and workload 7 ($p = 0.005$). No significant differences were reported between prognostic risk groups whether at rest and during the CPET, as presented in **Table 6.3**. We observed in **Figure 6.1**, that survivors in the SR group had a VAC value slightly lower than HR+DEX and HR groups throughout the CPET. When comparing rest to workload 7, VAC parameter decreased by 33% in the SR group, by 26% in the HR+DEX group, and by 16% in the HR group. Results of childhood ALL survivors' Ees and Ea assessed

during the CPET at different levels of exercise are available as supplementary material (**Table S1** and **Table S2**).

Table 6.3 Childhood ALL survivors' VAC assessed during the CPET at different levels of exercise according to their prognostic risk groups.

	Prognostic risk groups	N	Mean	(SD)	95% Confidence Interval		p-value
					Lower Bound	Upper Bound	
Rest	SR	13	1.007	(0.095)	0.950	1.064	0.101
	HR+DEX	24	1.060	(0.098)	1.019	1.101	
	HR	21	1.009	(0.071)	0.977	1.042	
	Total	58	1.030	(0.090)	1.006	1.053	
Workload 1	SR	14	0.955	(0.098)	0.899	1.011	0.349
	HR+DEX	24	1.000	(0.097)	0.959	1.041	
	HR	19	0.987	(0.080)	0.949	1.026	
	Total	57	0.985	(0.092)	0.960	1.009	
Workload 2	SR	13	0.934	(0.133)	0.853	1.015	0.666
	HR+DEX	25	0.964	(0.100)	0.922	1.005	
	HR	19	0.940	(0.104)	0.890	0.990	
	Total	57	0.949	(0.108)	0.920	0.978	
Workload 3	SR	10	0.912	(0.158)	0.799	1.026	0.620
	HR+DEX	22	0.933	(0.107)	0.885	0.980	
	HR	17	0.893	(0.124)	0.830	0.957	
	Total	49	0.915	(0.123)	0.880	0.950	
Workload 4	SR	5	0.882	(0.118)	0.735	1.028	0.826
	HR+DEX	16	0.853	(0.130)	0.784	0.922	
	HR	11	0.885	(0.165)	0.774	0.995	
	Total	32	0.868	(0.138)	0.819	0.918	
Workload 5	SR	4	0.910	(0.188)	0.611	1.209	0.779
	HR+DEX	7	0.880	(0.099)	0.788	0.972	
	HR	3	0.939	(0.040)	0.839	1.039	
	Total	14	0.901	(0.116)	0.834	0.968	
Workload 6	SR	2	0.720	(0.137)	-0.515	1.955	0.330
	HR+DEX	5	0.824	(0.122)	0.673	0.976	
	HR	2	0.917	(0.095)	0.065	1.770	
	Total	9	0.822	(0.126)	0.725	0.918	
Workload 7	SR	2	0.672	(0.183)	-0.969	2.313	0.786
	HR+DEX	2	0.793	(0.228)	-1.256	2.842	
	HR	1	0.836				
	Total	5	0.753	(0.165)	0.549	0.958	

Cardiac Work Efficiency

The measures of childhood ALL survivors' CWE parameter assessed during the CPET at different levels of exercise are presented in **Table 6.4**. We observed significant differences between the different levels of exercise ($p=0.001$). Post-hoc analysis for CWE parameter at different levels of exercise revealed significant differences between rest and workload 6 ($p=0.033$), rest and workload 7 ($p=0.003$), workload 1 and workload 7 ($p=0.019$), and workload 4 and workload 7 ($p=0.024$). No significant differences were reported between prognostic risk groups whether at rest and during the CPET, as presented in **Table 6.4**. We observed in **Figure 6.2**, that survivors in the SR group had a CWE parameter slightly higher than HR+DEX and HR groups throughout the CPET. Indeed, when comparing rest to workload 7, CWE parameter increased in the SR and HR+DEX groups (5.2% and 8.0%, respectively), whereas in HR group, CWE parameter only increased by 1.4 %. At rest, CWE parameter was reduced by 84.2% in the SR group, 83% in the HR+DEX group, and 83.7% in the HR group.

Table 6.4 Childhood ALL survivors' CWE assessed during the CPET at different levels of exercise according to their prognostic risk groups

		Prognostic risk groups	N	Mean	(SD)	95% Confidence Interval		p-value
						Lower Bound	Upper Bound	
Rest	SR	13	0.840	(0.020)	0.828	0.852	0.084	
	HR+DEX	24	0.829	(0.010)	0.824	0.833		
	HR	21	0.835	(0.015)	0.828	0.842		
	Total	58	0.834	(0.015)	0.830	0.838		
Workload 1	SR	14	0.851	(0.027)	0.835	0.867	0.130	
	HR+DEX	24	0.835	(0.019)	0.828	0.843		
	HR	19	0.840	(0.024)	0.829	0.852		
	Total	57	0.841	(0.023)	0.835	0.847		
Workload 2	SR	13	0.854	(0.042)	0.829	0.880	0.453	
	HR+DEX	25	0.841	(0.023)	0.832	0.851		
	HR	19	0.848	(0.031)	0.833	0.863		
	Total	57	0.847	(0.031)	0.838	0.855		
Workload 3	SR	10	0.857	(0.044)	0.825	0.889	0.543	
	HR+DEX	22	0.843	(0.026)	0.832	0.855		
	HR	17	0.847	(0.033)	0.830	0.864		
	Total	49	0.847	(0.032)	0.838	0.857		
Workload 4	SR	5	0.849	(0.029)	0.814	0.885	0.941	
	HR+DEX	17	0.838	(0.082)	0.796	0.880		
	HR	11	0.840	(0.039)	0.814	0.867		
	Total	33	0.840	(0.063)	0.818	0.863		
Workload 5	SR	4	0.856	(0.032)	0.805	0.906	0.524	
	HR+DEX	7	0.850	(0.025)	0.827	0.873		
	HR	3	0.834	(0.002)	0.829	0.839		
	Total	14	0.848	(0.024)	0.834	0.862		
Workload 6	SR	2	0.895	(0.005)	0.850	0.941	0.484	
	HR+DEX	5	0.870	(0.039)	0.822	0.918		
	HR	2	0.855	(0.009)	0.771	0.940		
	Total	9	0.872	(0.031)	0.848	0.896		
Workload 7	SR	2	0.897	(0.031)	0.617	1.176	0.770	
	HR+DEX	2	0.911	(0.080)	0.194	1.627		
	HR	1	0.854					
	Total	5	0.894	(0.049)	0.833	0.954		

6.6 Discussion

To assess cardiac mechanical performance in childhood ALL survivors, the interactions between ventricle and systemic arterial system must be understood in both normal physiological and pathological cardiac conditions. To characterize these interactions noninvasively, we used imaging techniques such as CMR and instantaneous pressure-volume based models to quantify VAC and CWE parameters. To our knowledge this is the first study to highlight the evolution of cardiac mechanical performance using CPET combined to CMR acquisitions and the numerical CircAdapt model.

In support to the first hypothesis, our findings showed the importance of this combination method to assess noninvasively childhood ALL survivors' cardiac performance using both VAC and CWE parameters. Indeed, significant differences were observed at different levels of exercise in both VAC and CWE parameters, allowing us to document the evolution of these mechanical parameters during exercise. A study in cardiac patients reported that VAC parameter provides an additional mechanical performance insight on cardiac pathophysiology conditions such as heart failure [195]. Although the first objective was attained, we could not clearly show the impact of doxorubicin and dexrazoxane treatments on survivors' cardiac mechanical performance at different levels of exercise. Nevertheless, our analyses showed slightly better results in the SR group for both VAC and CWE parameters throughout the CPET compared to HR+DEX and HR groups.

Table 6.5 Childhood ALL survivors' CWE assessed during the CPET at different levels of exercise according to their prognostic risk groups.

	Prognostic risk groups	N	Mean	(SD)	95% Confidence Interval		p-value
					Lower Bound	Upper Bound	
Rest	SR	13	1.007	(0.095)	0.950	1.064	0.101
	HR+DEX	24	1.060	(0.098)	1.019	1.101	
	HR	21	1.009	(0.071)	0.977	1.042	
	Total	58	1.030	(0.090)	1.006	1.053	
Workload 1	SR	14	0.955	(0.098)	0.899	1.011	0.349
	HR+DEX	24	1.000	(0.097)	0.959	1.041	
	HR	19	0.987	(0.080)	0.949	1.026	
	Total	57	0.985	(0.092)	0.960	1.009	
Workload 2	SR	13	0.934	(0.133)	0.853	1.015	0.666
	HR+DEX	25	0.964	(0.100)	0.922	1.005	
	HR	19	0.940	(0.104)	0.890	0.990	
	Total	57	0.949	(0.108)	0.920	0.978	
Workload 3	SR	10	0.912	(0.158)	0.799	1.026	0.620
	HR+DEX	22	0.933	(0.107)	0.885	0.980	
	HR	17	0.893	(0.124)	0.830	0.957	
	Total	49	0.915	(0.123)	0.880	0.950	
Workload 4	SR	5	0.882	(0.118)	0.735	1.028	0.826
	HR+DEX	16	0.853	(0.130)	0.784	0.922	
	HR	11	0.885	(0.165)	0.774	0.995	
	Total	32	0.868	(0.138)	0.819	0.918	
Workload 5	SR	4	0.910	(0.188)	0.611	1.209	0.779
	HR+DEX	7	0.880	(0.099)	0.788	0.972	
	HR	3	0.939	(0.040)	0.839	1.039	
	Total	14	0.901	(0.116)	0.834	0.968	
Workload 6	SR	2	0.720	(0.137)	-0.515	1.955	0.330
	HR+DEX	5	0.824	(0.122)	0.673	0.976	
	HR	2	0.917	(0.095)	0.065	1.770	
	Total	9	0.822	(0.126)	0.725	0.918	
Workload 7	SR	2	0.672	(0.183)	-0.969	2.313	0.786
	HR+DEX	2	0.793	(0.228)	-1.256	2.842	
	HR	1	0.836				
	Total	5	0.753	(0.165)	0.549	0.958	

There was also a slight difference in survivors' cardiac function among subgroups during the CPET. Indeed, the left ventricle ejection fraction and the VO₂ peak values were lower in the HR group than in SR and HR+DEX groups. These results are consistent with the previous study that reported that high cumulative dose of doxorubicin reduces maximal oxygen consumption during the CPET [190] and impedes cardiac function[147, 207]. Despite their impaired cardiac function due to

doxorubicin treatments, all childhood ALL survivors were able to achieve a safe CPET, as previously reported [190].

Ventricular-arterial Coupling

The VAC parameter offers a valuable framework in the physiology of cardiac and aortic mechanics, as well as in the pathophysiology of cardiac disease [208]. In the healthy population, the optimal coupling between LV and arterial system at rest is maintained when the coupling ratio (E_a/E_{es}) is closer to 1, with $E_a \approx 2.2$ and $E_{es} \approx 2.3$ [193]. Conversely, when this coupling ratio is >1 , SW significantly decreases, and the LV becomes progressively less efficient [39]. While no significant differences were observed in VAC parameters between prognostic risk groups at rest, we found significant differences in VAC parameter at different levels of exercise ($p < 0.0001$). When comparing rest to workload (175W to 200W), the VAC parameter decreased by 33% in the SR group, by 28% in the HR+DEX group, and by 16% in the HR group. A previous study in breast cancer survivors exposed to anthracycline treatments showed a significant reduction of 28% in VAC parameter from rest to exercise which is consistent with our findings [198]. These findings highlight the crucial role of exercise to improve VAC parameter. Although, no significant differences were observed between prognostic risk groups whether at rest or during the CPET, we can assume that doxorubicin treatments prevent the normal reduction of VAC parameter during the CPET. Indeed, our findings showed that survivors in the SR group had a VAC value slightly lower than HR+DEX and HR groups throughout the CPET. Those who received dexrazoxane treatments had a VAC value slightly lower than the HR group. It has been reported that the VAC parameter is strongly predictive of cancer therapeutics-related cardiac dysfunction in those receiving doxorubicin treatments [209]. These observations are exacerbated at higher levels of exercise, as reported in our study. We also observed a steep decline in VAC at workload 6 and 7 in the SR group. It seems that under normal conditions in healthy subjects, VAC varies around 0.6 [71]. In our study, we observed that VAC decreases toward the optimal coupling as the workload increases. However, the decline in VAC becomes important at the submaximal level and can become crucial to peak exercise level, as reported in a previous study [193]. This same study reported that the decline in VAC during exercise is age-dependent and is blunter in older populations compared with younger populations. On the basis of these reported findings, the steep decline in VAC occurring at workload 6 and 7 in the SR group could be explained by the fact that this is a submaximal level

of effort and that our population is much younger, meaning that the declining response in VAC should be sharp instead of blunt. Using CPET combined with CMR acquisitions and CircAdapt model was sensitive enough to observe slight changes in the assessment of the VAC parameter, despite no significant differences between survivors' prognostic risk groups.

CWE

Similar to the discussion reported in the previous section, no significant differences were reported between prognostic risk groups whether at rest and during the CPET. At rest, however, it is known that the CWE parameter can decrease up to 96% in healthy people with no cardiovascular disease [210, 211]. In our study, at rest, CWE parameter was reduced to 84.2% in the SR group, 83% in the HR+DEX group, and 83.7% in the HR group. These findings are similar to the ones previously published in cardiac population where CWE parameter can decrease to 86% in patients with myocardial infarction and between 61% and 69% in patients with heart failure [210, 211].

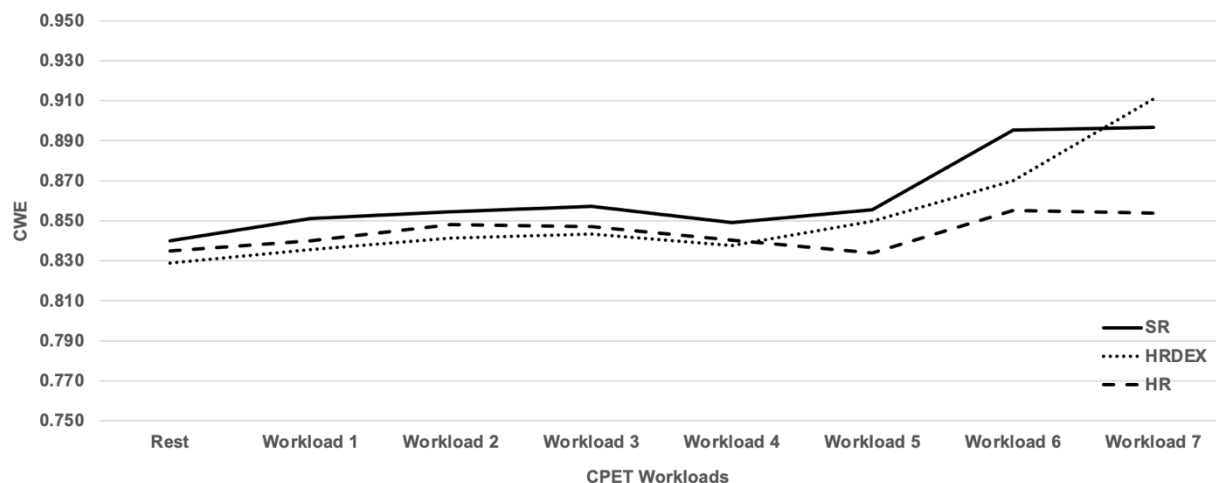


Figure 6.2 Childhood ALL survivors' CWE assessed during the CPET at different levels of exercise according to their prognostic risk groups.

In our study, data obtained at rest condition with the CWE parameter are very similar between prognostic risk groups and do not allow to observe and unmask potential cardiac conditions. However, throughout the CPET, we observed significant differences between the different levels of exercise ($p=0.001$). Although no significant differences were reported between prognostic risk

groups during the CPET, slight changes were reported between the groups. Indeed, from rest to workload (175W-200W), the CWE parameter increased in the SR and HR+DEX groups (5.2% and 8.0%, respectively), whereas in HR group, the CWE parameter only increased by 1.4 %. Previous studies reported that the CWE parameter is preserved during exercise in healthy individuals [212], while it decreases in cardiac patients[213]. Survivors in SR group are those who received a low cumulative dose of doxorubicin and it has been documented that they are at lower risk of myocardial damage, than survivors in the HR+DEX and HR groups. Moreover, survivors who received dexrazoxane treatments benefits from cardiac protection, which is not the case for survivors in HR group. Our findings showed that the cardioprotective agent play an important role in the prevention of long-term cardiac damage investigated by the CWE parameter at different levels of exercise. Unfortunately, survivors in HR group are the ones who suffer the most cardiac damage. At workload (175W-200W), the CWE parameter decreased in HR group, which is in accordance with a previous study observing that the CWE parameter decreases in patients with cardiac diseases [213]. Using CPET combined to CMR acquisitions and CircAdapt model was sensitive enough to observe slight changes in the assessment of the CWE parameter, despite no significant differences between survivors' prognostic risk groups. Our findings unmask potential cardiac conditions not observable in resting condition in childhood ALL survivors.

6.7 Limitations of the study

In the current study we encountered some limitations that could be addressed in future research. The first limitation is related to the sample size of our cohort that can limit the power of our analyses and explain the absence of significant differences between prognostic risk groups. Large sample size should be considered in future studies to better identify the impacts of doxorubicin and dexrazoxane treatments on survivors' cardiac mechanical performance during CPET. The second limitation is that our study did not have a control group, which could limit the bearing of our findings. The last limitation is related to the computation model CircAdapt that we used in our analyses. Initially, CircAdapt model has been designed for at-rest conditions with a cardiac output of 5.1 l/min and a heart rate of 70 bpm [214]. Subsequently, to simulate exercise state, cardiac output was tripled and heart rate was doubled during the adaptation process [2, 214]. Contrary to the at-rest state, not all simulations appeared realistic at high level of effort [2]. In our study,

CircAdapt model was used to simulate childhood ALL survivors' cardiac mechanical performance at different levels of exercise, ranging initially from rest (0 W) to the maximal level of exercise (325 W). For all risk groups, the model was unable to stabilize and to converge towards realistic pressures and volumes at maximal level of exercise. It is important to note that this convergence issue was more important for survivors in the HR group and for those with an heart rate ≥ 180 bpm. Despite this limitation, the model was able to simulate realistic and useful data for submaximal level of exercise (175W-200W). To ensure good data quality, we decided to analyze only the data at this workload.

6.8 Conclusion

Our study showed that using CPET combined to CMR acquisitions and CircAdapt model was sensitive enough to observe slight changes in the assessment of VAC and CWE parameters, despite no significant differences between survivors' prognostic risk groups. Thus, this is the first study to characterize the evolution of childhood ALL survivors' cardiac mechanical performance at different levels of exercise. Our findings unmask potential cardiac conditions not observable in resting condition in childhood ALL survivors. Our study contributes to improving survivors' follow up and clinical decision-making, in addition to addressing early detection of cardiac problems induced by doxorubicin-related cardiotoxicity treatments.

6.9 Acknowledgements

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CHAPTER 7 ARTICLE 4: ASSESSING THE FEASIBILITY AND RELIABILITY OF A NEW EXERCISE CARDIOVASCULAR MAGNETIC RESONANCE PROTOCOL FOR THE CHARACTERIZATION OF CARDIAC FUNCTION AND MECHANICS.

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7.1 Abstract

Background: Exercise Cardiovascular Magnetic Resonance (Ex-CMR) imaging protocols can detect subtle cardiac changes that are not visible during rest. However, some protocols affect image quality or do not provide sufficient cardiac muscle stress.

Purpose: To assess the feasibility and reliability of the Handgrip-Valsalva protocol and compare it with a cycle ergometer protocol.

Study Type: Prospective

Population: Six healthy participants (26 ± 4.56 years old), 50 % females and 50% males with no cardiovascular diseases or family history of cardiovascular diseases were recruited.

Field Strength/Sequence: 3T scanner, Balanced Steady State Free Precession (bSSFP) full coverage (10 slices in short axis view, 10 mm Slice Thickness, 2 mm Slice Gap, $2.0 \times 2.0 \times 10 \text{ mm}^3$)

Voxel Size, 25 Number of Phases, 1 Heartbeat per Slice, a single slice acquired for long axis 2-chambers, 3-chambers, and 4-chambers views).

Assessment: Participants underwent Handgrip-Valsalva and ergometer tests during image acquisitions. Cardiac volumes, cardiac output (CO) and ejection fraction (EF) were quantified from Cine-images using SEGMENT software. Left ventricular end-diastolic pressure (LVEDP) and left ventricle stiffness were quantified using the CircAdapt model and Finite Element Model (FEM). Reliability was tested by scan/rescan of three participants and three post-processing repetitions.

Statistical Tests: Intra-class correlation coefficients (ICCs), one-way ANOVA. A P value <0.05 was considered statistically significant.

Results: The Handgrip-Valsalva protocol demonstrated good to excellent reliability with ICC values of 0.83 to 0.93. No significant difference in cardiac function parameters between the rest and ergometer protocols was reported ($p = 0.98$). No significant difference was detected in LVEDP and stiffness measurements ($p = 0.65$) and ($p = 0.80$) respectively.

Data Conclusion: Handgrip-Valsalva can effectively characterize exercise-induced cardiac remodeling and demonstrate promise to overcome limitations associated with ergometer protocols.

7.2 Keywords

Exercise-CMR, Cardiac remodeling, Cardiac function, Left ventricle stiffness, Left ventricle end-diastolic pressure.

7.3 Introduction

Exercise cardiovascular MRI (Ex-CMR) protocols play a crucial role in enhancing the diagnostic value and risk assessment of cardiac diseases across various populations [215]. While pharmacological stress testing, involving agents like dobutamine and adenosine, is commonly employed in clinical practice to unveil perfusion defects, it is linked to significant adverse events such as bradycardia, severe hypertension or hypotension, and unstable angina or acute pulmonary edema [45]. In contrast, Ex-CMR testing is associated with fewer reported adverse events and

better patient tolerance [93]. As a result, Ex-CMR has emerged as a valuable tool for accurately evaluating patients' heart structure, viability, and function. Over the past 25 years, Ex-CMR has integrated the superior image qualities of CMR with exercise stress testing [14]. Moreover, Ex-CMR possesses the unique capability to identify pathological changes that may remain unnoticed at rest or with alternative imaging modalities lacking an exercise component. Examples include pathological dilated cardiomyopathy and physiological exercise-induced cardiac remodeling [13].

Ex-CMR protocols are typically conducted with patients in the scanner to optimize data acquisition during the exam. These protocols often involve MR-compatible dynamic tests, with treadmills and cycle ergometers being widely utilized [14]. However, treadmills have certain limitations, including delayed imaging and the inability to capture images at varying exercise intensities [56]. The cycle ergometer overcomes these limitations, but other clinical barriers have been described [216]. Ex-CMR protocols using cycle ergometers have reported limitations inherent to exercise such as respiratory artifacts, ECG artifacts, increased physical movement, and significant skeletal muscle fatigue that precludes adequate testing. These limitations are particularly noticeable in sedentary patients, who constitute a substantial portion of the patient population [216]. In response to these challenges, static exercises have been proposed as viable alternative modalities [18]. Isometric handgrip, as a static exercise, induces moderate sufficient hemodynamic changes with minimal movement, ensuring the quality of CMR images is not compromised [39]. Consequently, isometric handgrip has gained popularity in recent Ex-CMR protocols [14]. Nevertheless, patients may not reach their exercise peak stress to elicit adequate physiological responses using this approach [20].

Building on a scoping review that evaluated Ex-CMR protocols in evoking cardiovascular response [16], this study aims at assessing the feasibility and reliability of a new Ex-CMR protocol that combines isometric handgrip with the Valsalva maneuver (Handgrip-Valsalva). We compared the cardiac changes induced by the Handgrip-Valsalva protocol against those elicited using a cycle ergometer as a reference.

7.4 Methods

7.4.1 Participants

Six healthy participants, three females and three males (26 ± 4.56 years old), with no cardiovascular diseases or family history of cardiovascular diseases were recruited from the Mechanical Lab at Polytechnique Montreal. The exclusion criteria included: contraindications to MRI (i.e., cardiac pacemakers or metallic fragments) or inability to exercise. All participants completed a questionnaire to obtain information about their health with specific questions related to pregnancy, cardiac conditions (pacemaker or implant) and past surgical operations, prior to performing the exercise tests. All participants provided written informed consent. The ethical approval was obtained from the Research Ethics Boards of Polytechnique Montréal (CER-2122-21-P) and Sainte-Justine University Hospital Centre in Montreal (CER- 2022-3912).

7.4.2 CMR protocols

Ex-CMR protocol using an isometric handgrip coupled with the Valsalva maneuver.

The Handgrip-Valsalva protocol involved sequences of repetitions of handgrip maneuvers and Valsalva maneuvers performed in a supine position during the MRI scan. This Ex-CMR protocol was developed to favor an increase in participants' systolic blood pressure ($>150\text{mmHg}$) without significantly increasing participants' heart rate ($<120\text{bpm}$) [217] to obtain acceptable image quality during MRI acquisitions [218]. To confirm that the exercise method induced enough stress on the cardiac muscle, 150 to 160 mmHg was set as the target systolic blood pressure [219]. The Handgrip-Valsalva protocol (**Figure 7.1**) is summarized below:

- 1st phase (pre-MRI acquisition): Participants were asked to squeeze an exercise ball at 30 % to 60% of their maximum voluntary muscular contraction. The Valsalva maneuver involved blowing air into the intraoral pressure monitor until it reached 40 mmHg. The pre-MRI acquisition phase lasted, on average, for three minutes and ten seconds, with intercepts of fifteen seconds.

- 2nd phase (MRI acquisition): Participants were asked to squeeze an exercise ball at 30 % of their maximum voluntary contraction during acquisition. The MRI acquisition phase lasted, on average, for one minute and fifty seconds and included breath holding phases.

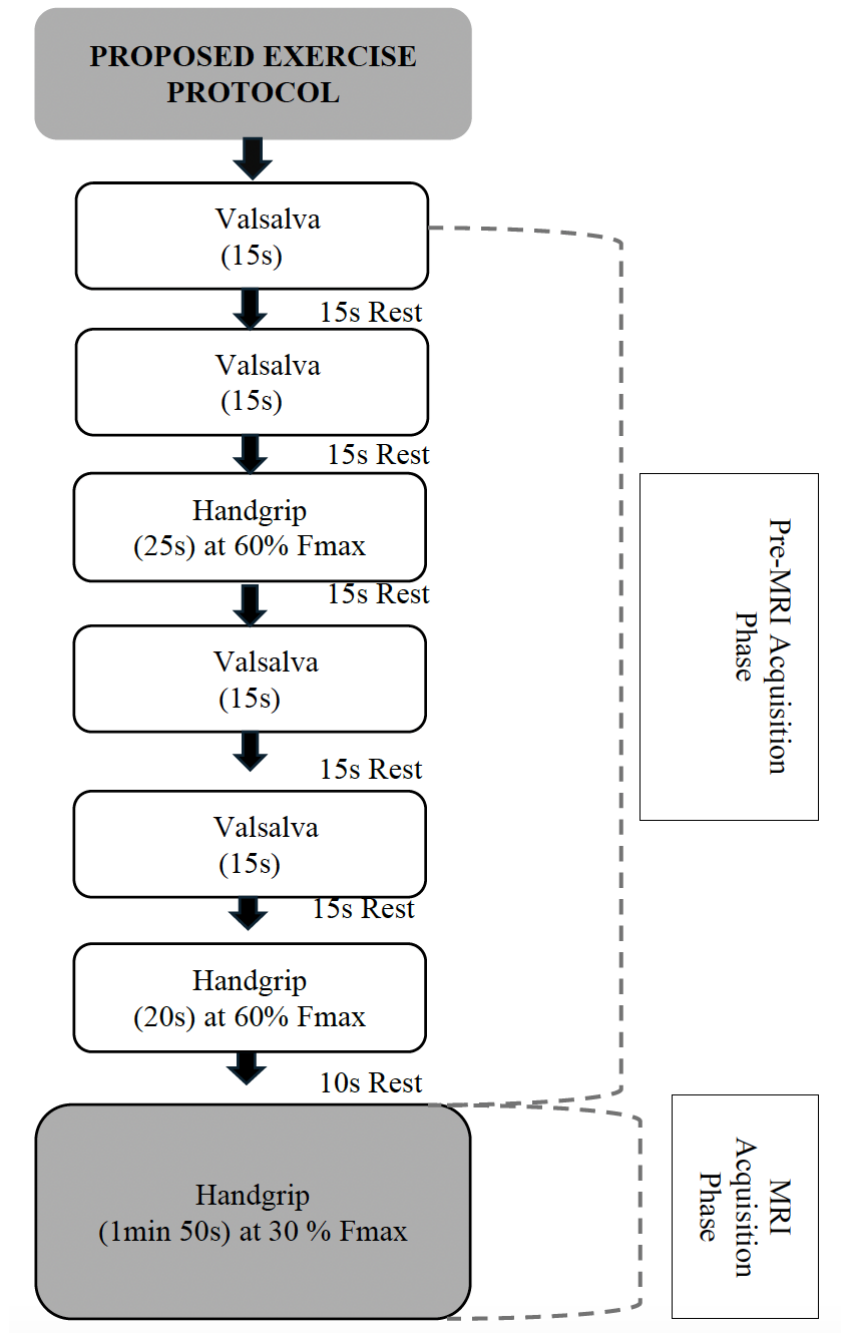


Figure 7.1 Sequences of Handgrip-Valsalva protocol

Ex-CMR protocol using only a cycle ergometer.

All participants performed exercise on a cycle ergometer (Ergoline 800S, Bitz, Germany) following a predetermined protocol described below. Prior to performing the protocol, participants' age, weight, and height were recorded to predict their Functional Threshold Power (FTP), which represents the highest power that an individual can maintain without fatigue for approximately one hour [220]. The protocol involved a warm-up phase at 20% of participants' FTP for 2 minutes, followed by a 2-minute cycling phase with an incremental workload consisting of 1 minute of cycling at 40% of the participants' FTP and 1 minute of cycling at 60% of participants' FTP. At the final stage, participants were asked to cycle at 70% of their FTP for 4 minutes.

7.4.3 MRI acquisitions

Participants underwent cine-MRI imaging under three distinct conditions: at rest, during the Handgrip-Valsalva, and during a cycle ergometer. Cine-MRI acquisitions were performed on a Siemens Skyra 3 Tesla system using an 18-channel body coil. bSSFP full coverage sequences included 10 slices acquired in short axis view (10 mm Slice Thickness, 2mm Slice Gap, $2.0 \times 2.0 \times 10 \text{ mm}^3$ Voxel Size, 25 Number of Phases, 1 Heartbeat per Slice) and a single slice acquired for long axis 2- chambers, 3-chambers, and 4-chambers views over several apnea phases. The following hemodynamic parameters of the heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded during the acquisitions.

7.4.4 Segmentation of cardiac images

Cine-MRI images were analyzed using the SEGMENT software (Medviso AB, Lund, Sweden) [221] to quantify functional cardiac parameters: end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), cardiac output (CO) and ejection fraction (EF). This cardiac image analysis software was initially developed for the research community for cardiovascular analysis purposes [221]. Using the automatic segmentation tool, endocardial and epicardial contours were automatically segmented and manual corrections were made where necessary. As the measured parameters are indicators of cardiac function [222, 223], they were analyzed to assess participants' behavior during rest and exercise. An example of the image segmented using automatic segmentation using SEGMENT software is presented in **Figure 7.2**. Red contours indicate

endocardium and green contours indicate epicardium. The yellow line on LAX views is the level of the first SAX slice.

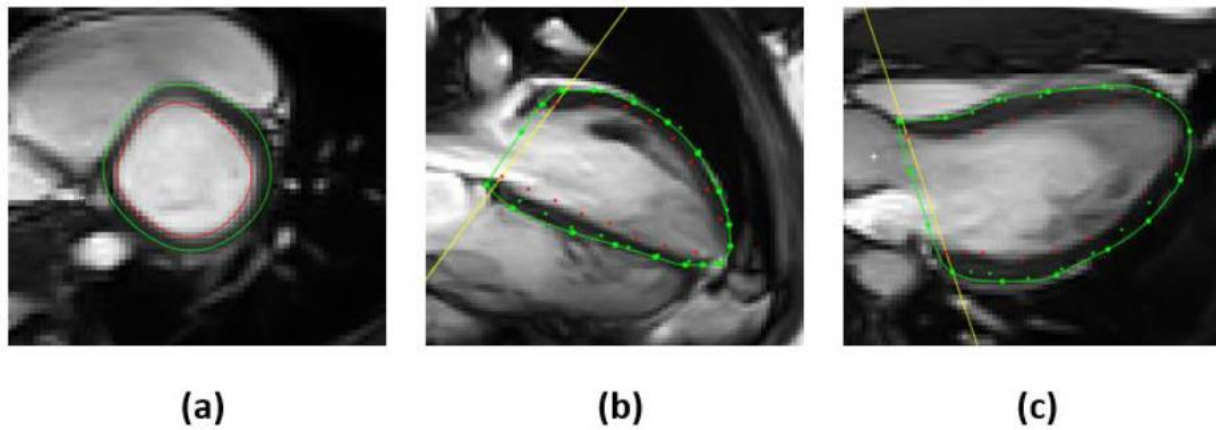


Figure 7.2 Segmented cardiac images in short axis view SAX(a), 3-chamber view 3 CH(b) and 4-chamber view 4 CH(c).

7.4.5 Calculation of left ventricle pressures and stiffness

Elevated left ventricular end-diastolic pressure (LVEDP) is often associated with a stiff ventricle which occurs when cardiac function and performance are impaired [224]. Participants' pressures were estimated using the CircAdapt heart model, which has been developed by the Cardiovascular Research Institute of Maastricht (CARIM) [2]. This model allows a simulation of the cardiovascular system and provides realistic simulations of the heart and large blood vessel flow, volumes, and pressures [167]. Prior to simulations, participants' hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR), were entered into the model. After the inputs have been entered, the simulation of the cardiovascular system starts [2] and the following LV mechanical properties: stiffness (LVS), contractility (LVC), and pressure drop (Pdrop) are optimized. LV volumes and the left intra-ventricular pressures are then calculated and displayed as outputs of the model [2]. A 25-point pressure curve covering the cardiac cycle was obtained and the LVEDP corresponding to the first point on the curve was extracted. These pressures were then applied as loading on the endocardial and epicardial surfaces using a Finite Element Model (FEM) to estimate the stiffness of the left ventricle. The finite element method (FEM) is a computational tool that analyzes any physical phenomena or any

complex geometry and provides numerical solutions. The ideal LV geometry mesh (a) and participant-customized geometry mesh (b) are represented in **Figure 7.3**.

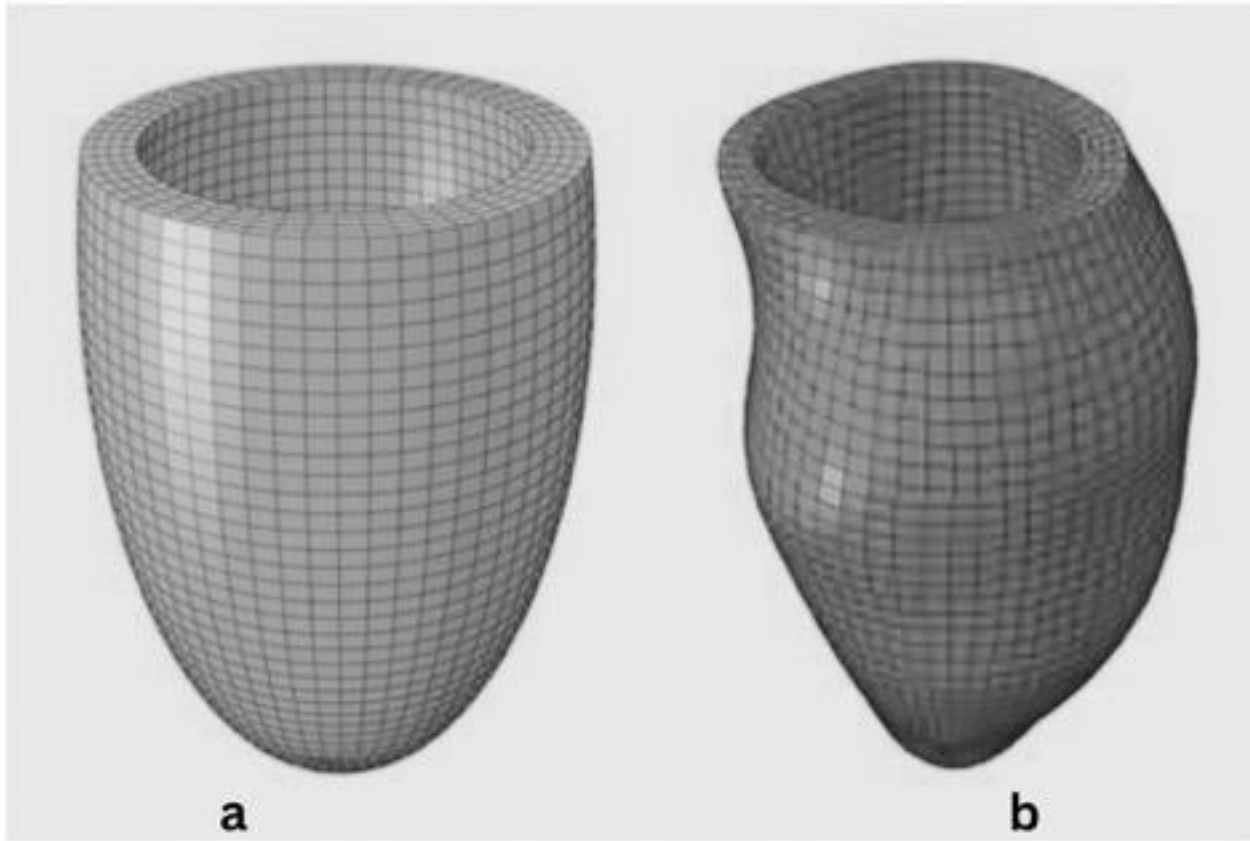


Figure 7.3 Ideal geometry mesh (a) and participant-customized LV geometry mesh (b).

An optimization strategy based on LV displacements was performed using Abaqus software (Dassault Systems Simulia Corp, US) as the forward solver [225]. Abaqus is a finite element analysis (FEA) software tool used to solve mechanical and design engineering problems [222].

The objective was to minimize the root mean square error (RMSE) between the displacements obtained from the segmentations of images and those obtained from the simulation using a patient-specific finite element model (FEM) developed by the Mechanical Lab at Polytechnique Montreal, Montreal, QC, Canada [226]. Throughout the optimization process, LV stiffness was optimized for both the ideal LV model and the participant-specific model [226]. The flowchart for the LVEDP calculation process and stiffness optimization process is shown in **Figure 7.4**.

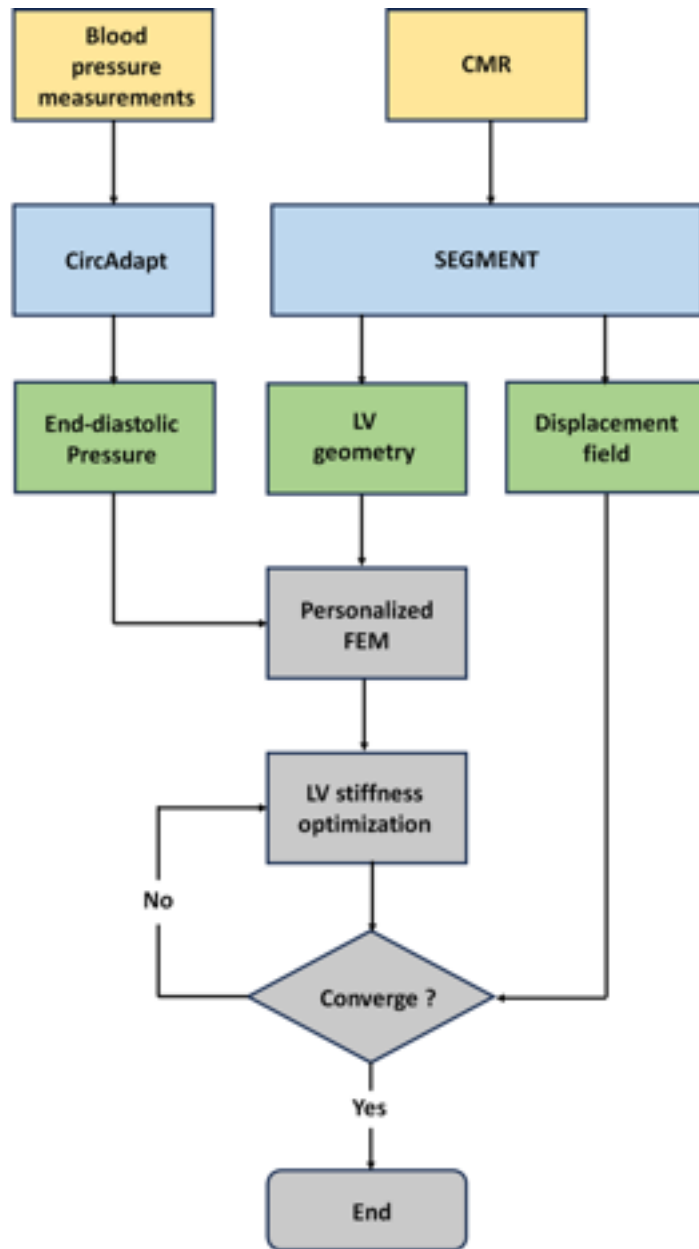


Figure 7.4 The flowchart for the LVEDP calculation process and stiffness optimization process.

7.4.6 Reliability Analysis

Reliability of the Ex-CMR protocol using an isometric handgrip coupled with the Valsalva maneuver.

To assess the reliability of the developed protocol, three participants were asked to perform the Handgrip-Valsalva protocol on three different days under identical conditions.

Reliability of the Segmentation Method.

To assess the reliability of the segmentation method, three independent reviewers, from the Mechanical Lab at Polytechnique Montreal, with expertise in SEGMENT software (v3.3 R10187 (Medviso AB, Lund, Sweden), have independently segmented participants' cardiac images.

7.4.7 Statistical analyses

Recorded cardiac parameters are continuous variables, therefore we assessed the agreement between measurements across individuals using the intra-class correlation coefficients (ICC) [227]. ICC values were defined as poor (ICC <0.50), moderate (ICC between 0.50 and 0.75), good (ICC between 0.75 and 0.90), and excellent (>0.90) [228]. ICC values for the reliability study were calculated from the mean square's variances obtained using Friedman's ANOVA with a 95% confidence interval and $p < 0.05$. To assess the impact of Ex-CMR protocols on cardiac function and mechanics, we compared participants' cardiac function parameters and cardiac mechanical parameters. The analysis was conducted using a one-way ANOVA and the alpha level was set at 0.05 (IBM SPSS Statistics for Macintosh, Version 29.0 Armonk, NY: IBM Corp).

7.5 Results

7.5.1 Participants

Participants' demographics are summarized in Table 7.1

Table 7.1 Participants Demographics

	Males N=3	Female N=3	Total N=6
Age, years	23.00 $\pm$ 0.00	29.00 $\pm$ 5.00	26.00 $\pm$ 4.56
Height, m	1.78 $\pm$ 0.06	1.63 $\pm$ 0.04	1.73 $\pm$ 0.09
Mass, kg	72.06 $\pm$ 5.97	63.43 $\pm$ 7.01	67 $\pm$ 7.50
Body mass index, kg/m ²	22.82 $\pm$ 1.29	23.84 $\pm$ 3.39	23.33 $\pm$ 2.36
Physical activity levels (FTP=Watts)	128.3 $\pm$ 18.00	83.3 $\pm$ 15.00	105.83 $\pm$ 5.5

7.5.2 Quality of cardiac images

The images obtained from the acquisitions in both short axis (SAX) views and 4 chambers (4CH) views are presented in Figure 4 and Figure 5. The quality of the images obtained using the Handgrip-Valsalva protocol (b) was better than the quality of the images obtained using the cycle ergometer protocol (c). The cycle ergometer protocol images demonstrated an artifact caused by cardiac and respiratory motion. The Orange arrow demonstrates artifacts caused by cardiac and respiratory motion and blue arrow demonstrates an artifact caused by cardiac and respiratory motion.

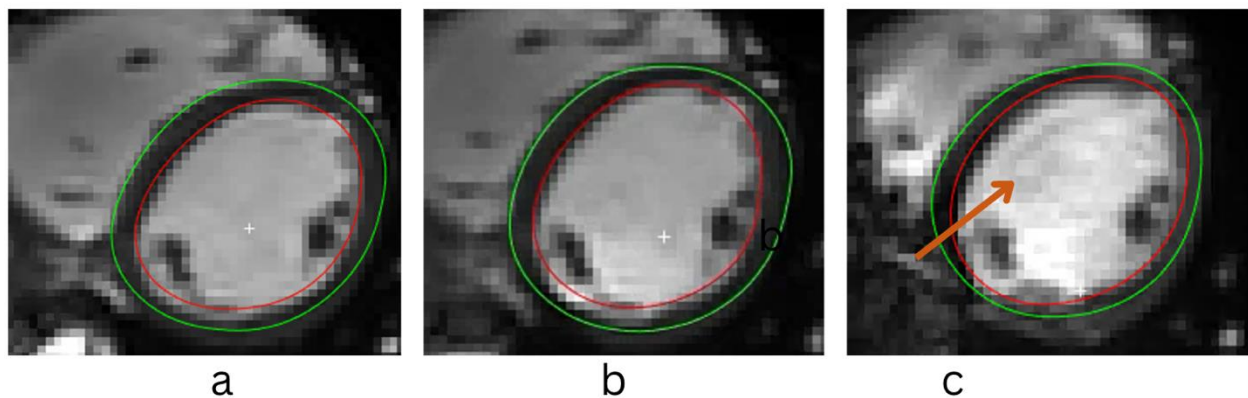


Figure 7.5 SAX views: images at rest(a), during Handgrip-Valsalva protocol(b), during ergometer (c).

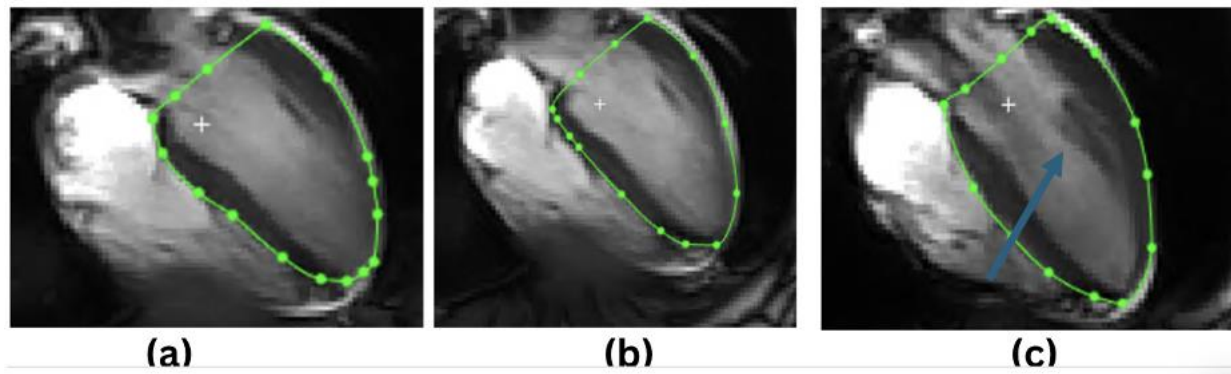


Figure 7.6 4-CH views: images at rest(a), during Handgrip-Valsalva protocol(b), during ergometer(c).

7.5.3 Reliability of the Handgrip-Valsalva protocol

The ICC values obtained from the parameters measured are presented in Table 7. 2. The Handgrip-Valsalva protocol demonstrated good to excellent reliability with ICC values of 0.83 to 0.93 for both scan-rescan data and repeated post-processing.

Table 7.2 Intraclass Correlation Coefficients (ICC) between measurements.

Measures	ICC	95% Confidence Interval		F Test with True Value			
		Lower Bound	Upper Bound	Value	df1	df2	P value
EDV (ml)	0.948	0.431	0.999	14.202	2	4	0.015
ESV (ml)	0.972	0.784	0.999	49.771	2	4	0.001
SV (ml)	0.861	-0.842	0.997	5.713	2	4	0.067
EF (%)	0.929	0.496	0.998	14.680	2	4	0.014
HR (bpm)	0.363	5.637	0.987	1.405	2	4	0.345

Intraclass Correlation Coefficients (ICC) values obtained from the parameters measured by the Handgrip- Valsalva protocol. EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; HR, heart rate.

7.5.4 Reliability of the Segmentation method

The ICC values obtained from the segmented images' parameters are presented in Table 7 3. The reliability of the used segmentation method is in the range of moderate to excellent (ICC ranging from 0.67 to 0.98).

Table 7.3 Intraclass Correlation Coefficients (ICC) between measurements

Measures	ICC	95% Confidence Interval		F Test with True Value			
		Lower Bound	Upper Bound	Value	df1	df2	P value
EDV (ml)	0.978	0.838	0.999	59.020	2	4	0.001
ESV (ml)	0.823	0.087	0.995	62.148	2	4	0.001
SV (ml)	0.674	-0.009	0.988	19.730	2	4	0.008
EF (%)	0.771	0.034	0.993	28.429	2	4	0.004
HR (bpm)	0.931	0.390	0.998	44.988	2	4	0.002

7.5.5 Comparison of the Handgrip-Valsalva and cycle ergometer protocols

Cardiac function parameters.

Cardiac function parameters measured during rest and during both Ex-CMR protocols are reported in Table 7.4.

Table 7.4 Cardiac Function parameters during rest and during exercise.

Cardiac parameters	Rest	Handgrip-Valsalva	Cycle ergometer
EDV (ml)	146.83 $\pm$ 20.03	145.67 $\pm$ 29.55	123.40 $\pm$ 4.62
ESV (ml)	60.33 $\pm$ 12.23	60.67 $\pm$ 17.56	44.40 $\pm$ 9.32
SV (ml)	86.67 $\pm$ 10.23	85.17 $\pm$ 15.50	74.40 $\pm$ 14.08
EF (%)	59.17 $\pm$ 3.87	58.83 $\pm$ 5.42	62.40 $\pm$ 8.02
CO (l/min)	5.58 $\pm$ 0.54	6.20 $\pm$ 0.82	7.66 $\pm$ 1.26
SBP (mmHg)	116.50 $\pm$ 15.24	127.83 $\pm$ 13.53	126.40 $\pm$ 13.79
DBP (mmHg)	65.17 $\pm$ 17.97	72.50 $\pm$ 13.81	65.20 $\pm$ 17.73
HR (bpm)	65.17 $\pm$ 7.25	74.17 $\pm$ 10.65	104.60 $\pm$ 18.69

Cardiac function parameters at rest, during Handgrip-Valsalva protocol and during the ergometer protocol. Data are mean $\pm$ SD.

We found significant differences in the following parameters: end-systolic volume (ESV) with a p-value of 0.01, cardiac output (CO) with a p-value of 0.02, and heart rate (HR) with a p-value of 0.006. No significant differences were found between rest and cycle ergometer for ESV, EDV, EF, DBP, and SBP (p=0.27). Both the Handgrip-Valsalva protocol and the cycle ergometer protocol resulted in similar increases in systolic blood pressure (SBP). Among all participants, the Handgrip-Valsalva protocol slightly increased EDV measurements (mean increase of +4.0 ml), while the cycle ergometer protocol resulted in a slight decrease (mean reduction of 25.4 ml).

7.5.6 Cardiac mechanical parameters.

Left ventricle end-diastolic pressures (LVEDP) measured during rest and during exercises are summarized in **Table 7.5**. No significant differences were observed between the Handgrip-Valsalva protocol and the cycle ergometer protocol for LVEDP ($p=0.65$), between rest and Handgrip-Valsalva protocol ($p=0.99$), and between rest and the cycle ergometer protocol ($p=0.65$). When comparing both Ex-CMR protocols to rest, we found that LVEDP slightly increased during the Handgrip-Valsalva protocol whereas it slightly decreased during the cycle ergometer protocol.

Table 7.5 Left ventricle end-diastolic pressures measured by CircAdapt.

Participants LVEDP measurements	Rest	Handgrip-Valsalva	Cycle ergometer
P01(kPa)	1.42	1.35	1.41
P02 (kPa)	1.3	2.1	-
P03 (kPa)	1.35	1.11	0.71
P04 (kPa)	1.2	1.16	3.35
P05 (kPa)	1.54	3.15	1.19
P06 (kPa)	3.41	2.13	0.80
Mean $\pm$ SD (ml)	1.70 $\pm$ 0.84	1.83 $\pm$ 0.79	1.26 $\pm$ 1.08

Stiffness values during rest and exercise are summarized in **Table 7.6**. There were no significant differences observed in stiffness between the Handgrip-Valsalva protocol and the cycle ergometer protocol ($p=0.80$). Similarly, there was no significant difference observed in stiffness between the rest and the Handgrip-Valsalva protocol ($p=0.88$). Additionally, no significant difference was found in stiffness values between rest and the cycle ergometer protocol ($p=0.67$).

Table 7.6 Optimized stiffness results.

Participants stiffness measurements	Rest	Handgrip-Valsalva	Cycle ergometer
P01 (kPa)	6.94	6.72	4.36
P02 (kPa)	7.66	4.20	-
P03 (kPa)	6.10	5.29	8.77
P04 (kPa)	5.16	1.95	13.17
P05 (kPa)	8.55	14.63	6.63
P06 (kPa)	19.16	14.61	6.45
Mean $\pm$ SD (ml)	8.93 $\pm$ 5.15	7.90 $\pm$ 5.43	7.88 $\pm$ 3.34

7.6 Discussion

The present study has shown that the Handgrip-Valsalva protocol is a reliable method of measuring exercise-induced cardiac function and mechanics. Furthermore, the study demonstrated that the Handgrip-Valsalva protocol has a significant advantage over the ergometer protocol as the responses it elicits closely correlated with the normal cardiac responses observed in healthy populations. Additionally, it helps to maintain the quality of the image, which is compromised during the ergometer protocol.

7.6.1 Cardiac function response to Ex-CMR protocols

Our findings support the reliability of the Handgrip-Valsalva protocol to quantify exercise-induced cardiac function and mechanics, in addition to guaranteeing participants' safety. Studies have reported that isometric handgrip exercise and Valsalva maneuvers are independent reliable tools for assessing patients' cardiovascular system dynamics [229, 230]. In both Ex-CMR protocols, we observed that hemodynamic parameters (i.e., end-systolic volume (ESV) and stroke volume (SV), diastolic blood pressure (DBP) and systolic blood pressure (SBP) increased slightly during exercise. This aligns with studies in healthy participants that observed that cardiac output, cardiac volumes, and diastolic blood increased slightly during exercise [97, 231]. In heart failure patients,

however, hemodynamic parameters are impaired in response to exercise (i.e., cardiac output and stroke volume) [232], and an exaggerated hypertensive response in systolic blood pressure (>200 mmHg) is reported [233], mainly during ergometer or treadmill exercises.

Our study shows that both the Handgrip-Valsalva protocol and the ergometer protocol produce similar cardiac function parameter changes. These results are encouraging since previous studies have shown that a cycle ergometer is the best strategy to induce enough cardiac muscle changes to allow accurate and effective cardiac assessments [231], while isometric handgrip exercises alone could only allow modest hemodynamic responses on cardiac muscle [14]. Therefore, the efficacy of the Handgrip-Valsalva was increased due to the coupling of the isometric handgrip to the Valsalva maneuver. Both these exercise maneuvers are known to cause favorable responses on cardiac function (i.e., increase in mean heart rate, systolic blood pressure and diastolic blood pressure) [26, 234], which our findings confirmed.

7.6.2 Cardiac mechanical parameters

Regarding the cardiac mechanical parameters studied, no significant differences were found between the developed Handgrip-Valsalva and the cycle ergometer for both LVEDP and stiffness. These findings provide strong evidence that the Handgrip-Valsalva protocol is at least equally effective as a cycle ergometer. This is an important finding since the cycle ergometer is the most widely used exercise strategy during Ex-CMR protocol to assess cardiac responses in healthy and cardiac-diseased populations due to its ability to induce important changes in cardiac parameters. [97] When comparing both Ex-CMR protocols to rest, we showed that LVEDP remains relatively unchanged during the Handgrip-Valsalva protocol, while during cycle ergometer, LVEDP tends to decrease. Nevertheless, no significant differences were observed. These findings are in accordance with the literature, as the isometric handgrip exercises are known to increase the left ventricular pressure [60] and the cycle ergometer is known to significantly increase the heart rate [235]. As a result, both Ex-CMR protocols induced minimal stress in the left ventricle. We observed that the mean LVEDP during the cycle ergometer was 1.49 kPa, while the mean LVEDP during the Handgrip-Valsalva protocol was 1.83 kPa. This is in line with other studies in healthy participants, reporting that the mean LVEDP remains stable or slightly increases to a $\text{LVEDP} \leq 2.2$ kPa during

cycle ergometer and isometric handgrip exercises [236, 237]. In heart failure patients, however, the mean LVEDP tends to increase during these types of exercises (≥ 3.50 kPa) [237, 238]. Therefore, our Ex-CMR protocols were adapted and showed consistency across the studies.

7.6.3 Quality of the images

We demonstrated that the Handgrip-Valsalva produced good-quality images, while the ergometer protocol resulted in lower-quality images. These results are consistent with published studies in this domain [18, 116]. To ensure good image quality, Handgrip-Valsalva was developed to favor an increase in participants' systolic blood pressure (>180 mmHg) without significantly increasing participants' heart rate (<120 bpm). Therefore, CMR protocol using exercise should favor participants' heart rate under 120 bpm. Moreover, they should favor exercises that avoid excessive movements during the MRI scan [218]. In our study, the mean heart rate only increased by 9.00 ± 7.87 bpm with the Handgrip-Valsalva protocol, and by 37.00 ± 19.74 bpm with the cycle ergometer. Our results can be explained by the fact that cycle ergometers caused motion-induced artifacts (cardiac and respiratory motion) due to excessive movements, resulting in poor image quality. Conversely, Handgrip-Valsalva did not cause motion-induced artifacts, making it a better Ex-CMR option to obtain good-quality cardiac imaging during exercise.

7.7 Limitations of the study

Our study has some limitations that need to be acknowledged. During the cycle ergometer protocol, participants experienced discomfort and muscle fatigue, which may have led to premature termination of exercise. During the Handgrip-Valsalva use, we noticed that participants experienced difficulties reaching the targeted intra-oral pressure of 40 mmHg, which was needed to optimize the Valsalva maneuver. Therefore, we designed a new mouthpiece, which allowed all participants to reach the targeted intra-oral pressure force. Moreover, while the participants were asked to squeeze an exercise ball at 30 % to 60 % of their maximum voluntary contraction, we did not have control over the grip force applied to the handgrip balls. This might have induced variability among participants. Nevertheless, this did not prevent us from achieving the targeted blood pressure and heart rate. Future studies should consider designing an MR-compatible device

that can allow the monitoring of the applied grip force during the isometric handgrip exercise. Finally, it is important to mention our sample size has limited the power of our analysis and, as a result, limited the scope of our findings.

7.8 Conclusion

Our study has shown that the Handgrip-Valsalva is feasible and reliable. The findings demonstrated that this protocol induces sufficient cardiac changes, enabling the characterization of functional and mechanical changes occurring during exercise-induced cardiac remodeling. The Handgrip-Valsalva protocol also has the potential to overcome the limitations associated with a cycle ergometer, such as poor image quality and muscle fatigue. Our study also found that the Handgrip-Valsalva protocol required less effort for participants than the cycle ergometer. In fact, participants could complete sequences with isometric handgrip, but only half could do it with a cycle ergometer during exercise. Therefore, Handgrip-Valsalva could be a better option for patients who are physically deconditioned, such as patients with heart failure. Moreover, the Handgrip Valsalva protocol is more practical and cost-efficient compared to the ergometer protocol. As a result, more patients can benefit from our protocol. The clinical feasibility of this protocol is promising and could be used in clinical settings to detect early pathological deformations following cardiac remodelling.

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CHAPTER 8 GENERAL DISCUSSION

In this chapter, we present a summary of our project's work. We also highlight the impact of our research work and the various strength and limitations we encountered.

8.1 Discussion of the results

Overall, this study achieved its objectives successfully. Firstly, we demonstrated that cardiac mechanical properties can be predicted from a combination of CMR parameters and vice versa [30]. Secondly, we demonstrated that survivors of childhood acute lymphoblastic leukemia, who are at long-term risk of cardiac diseases, have impaired cardiac mechanical performance and cardiac function due to doxorubicin-induced cardiotoxicity [31]. Moreover, the study highlighted the positive impact of exercise stress on this population as it improved their cardiac performance during exercise. Lastly, the study showed that the Handgrip-Valsalva protocol is a reliable tool that induces sufficient deformations on the cardiac muscle, enabling effective characterization of cardiac deformations without compromising the quality of the image (article submitted to the International Journal of Cardiovascular Imaging).

Despite advancements in imaging techniques and computational modeling, accurately estimating parameters for cardiac disease populations remains a significant hurdle. Issues such as inter-observer variability, image quality, and the complex nature of cardiac diseases contribute to the difficulty in reproducibility and validation of computational models. Previous studies by Aboelkassem et al. (2018) and Smith et al. (2020) have highlighted the need for improved standardization of imaging protocols and computational modeling techniques to enhance reproducibility and validation in cardiac disease populations. Additionally, the study by Johnson et al. (2019) emphasized the importance of multi-center collaborations and larger patient cohorts to ensure the robustness of computational models in this context. Despite these challenges, ongoing efforts in standardization and collaboration offer promising avenues for improving the accuracy and reliability of computational modeling-based parameter estimation in cardiac disease populations. These efforts have also been put into the CircAdapt model that was used in our studies to validate it according to The ASME V&V 40 standard [239]. For instance, Lumens and team [2] conducted comprehensive validation studies, verifying the code, calculation, computational model,

comparator, and assessment using the CircAdapt model. As the results, they demonstrated that there was consistency of trends between normal and pathological subjects across simulations and subject data which validates the CircAdapt model for relative comparisons. Moreover, the previous study that verified the sensitivity of the CircAdapt model among cancer survivors demonstrated that the model is used within its range of validation to detect subtle changes in the mechanical properties of the left ventricle [240].

8.1.1 Correlations between cardiac mechanical properties and CMR parameters

Through this study, we were able to demonstrate the relationships between cardiac mechanical properties and CMR parameters. Equations that allow to estimate the relationship between cardiac mechanical properties and CMR parameters were established and validated. The coefficients of correlations demonstrated that some CMR parameters including T1 relaxation time, coefficient of partition (CP), ejection fraction (EF) and cardiac volumes are significant predictors of the mechanical properties. For instance, the study revealed that in the Standard Risk group (SR), LVS strongly correlated with T1, ($R^2=94.8\%$; $p=0.008$), and LVC strongly correlated with the ejection fraction EF ($R^2=93.7\%$; $p=0.043$). Left ventricular minimum pressure (P_{min}) also strongly correlated with cardiac volumes ($R^2 = 90.6\%$; EDV ($p = 0.011$) and ESV ($p = 0.013$) in the SR group. Though these correlations were strong in this SR group, it was not the case for other prognostic groups such as the high-risk group (HR). For example, LVS was estimated from the combination of CMR parameters with only 50.1% in the HR + DEX and 47.9 % in the HR group as coefficients of determination. These results demonstrate not only the negative impact of a high cumulative dose of doxorubicin on cardiac function but also how it reduces the sensitivity of CMR to predict cardiac mechanical properties. No CMR parameters could predict cardiac mechanical properties in the HR group. Therefore, this study sheds light on the cardiotoxicity induced by chemotherapy treatments in childhood ALL survivors. It also demonstrates that the characterization of cardiac mechanical properties may help detect early cardiac damage and prevent the progression of late cardiac effects. This study also reveals that CMR parameters can also be predicted from cardiac mechanical properties. For example, T1 relaxation time ($R^2 = 71.5\%$, $r=0.84$) and the coefficient of partition ($R^2 = 72.6\%$, $r=0.85$) can be predicted by significant mechanical properties in the SR group. To our surprise, we did not find any correlation between

mechanical parameters and the T2 relaxation time in any of the subgroups. This finding was opposite to previously reported results where T2 was found to be more sensitive to cardiac changes in early doxorubicin-related cardiotoxicity assessments [177].

8.1.2 Cardiac mechanical performance of childhood acute lymphoblastic leukemia survivors at different levels of exercise.

This study allowed us to characterize successfully cardiac mechanical performance among Childhood Acute Lymphoblastic Leukemia (ALL) survivors at different levels of effort. We were also able to confirm our hypothesis stating that cardiac mechanical behavior evolves with increasing effort and that the Cardiopulmonary Exercise Testing (CPET) combined with CMR acquisitions can unmask potential cardiac conditions not observable during at-rest conditions. Indeed, we found that patients who are at high risk of developing heart failure (ALL survivors) exhibited impaired cardiac work efficiency and ventricular arterial coupling (CWE= 83.7 %, VAC=1.050) compared to healthy participants whose CWE = 96.0 %, and VAC ranges from 0.6 to 1. This finding confirmed the negative impact of cumulative doxorubicin dose on cardiac function and mechanical performance among this population. Through this study, we also found that the exercise capacity is limited in participants who have had a high cumulative dose of doxorubicin.

The study revealed also that the mechanical properties can be improved through exercise and improvement can be more significant if participants can exercise to the peak stress levels. Indeed, we found that at a submaximal level of exercise (175 to 200W), CWE can be improved by 5.2 % in the standard risk (SR) group, by 8.0 % among the high-risk group that received a cardioprotective agent dexrazoxane (HR+DEX) and by 1.4 % for the High-Risk group (HR). At the submaximal level, we also found that VAC improves toward the optimal value by 33% in the SR group, by 26% in the HR+ DEX group and by 16 % in the HR group. These results are encouraging especially for this population whose cardiac performance is impaired due to cardiotoxicity. Performing exercise at an early stage among these populations may lead to great improvements in cardiac performance and function. In general, this study provided insights into the effects of chemotherapy-induced

cardiotoxicity on cardiac function and performance among ALL survivors and highlighted the role of exercise stress testing in improving heart performance and function. It also suggests that mechanical properties can be good biomarkers of the cardiac damage induced by cardiotoxicity among ALL survivors. Combining CMR, CircAdapt model, and CPET can help detect early cardiac sequelae, which may improve the cardiac patient's follow-up and clinical decision-making.

8.1.3 Ex-CMR Protocol for the Characterization of Cardiac Function and Mechanics.

We were able to develop successfully an Ex-CMR protocol that combines isometric handgrip with the Valsalva maneuver (Handgrip-Valsalva). Through various preliminary tests, we confirmed our hypothesis that the Handgrip-Valsalva is a reliable Ex-CMR protocol that can induce significant cardiac changes and allow effective cardiac assessments. In fact, this study revealed that dynamic Ex-CMR protocols, such as ergometers and treadmills, induce sufficient deformations on cardiac muscles but are associated with serious issues compromising the quality of the images and the safety of participants. On the other hand, static Ex-CMRs, such as handgrip used alone, induce only modest stress in cardiac muscle.

The development of this new stress protocol was achieved through the following phases: the development of the protocol, the optimization, and the validation phase.

Phase 1: Development of the stress-CMR protocol

After exploring the limitations associated with the existing Ex-CMR protocols, we opted for the option of coupling the isometric handgrip and the Valsalva maneuver. This option was considered after discovering that the Valsalva maneuver can increase stress on cardiac muscle as other exercise or pathological agents can [26]. Combining Valsalva with handgrip, which is already known as a safe exercise stress that causes a modest increase in hemodynamic parameters, was a suitable option to achieve the intended results. Indeed, we wanted to develop a protocol that induces enough cardiac deformations (blood pressure between 150 mmHg to 160 mmHg) and limits the heart rate to ≤ 120 bpm to ensure high-quality images. After choosing the exercise types, we tested different exercise conditions to assess which one may be more efficient and will allow us to reach our goal. The following exercise stress conditions were tested:

Exercise stress condition n°1: The participant was asked to perform handgrip by squeezing a hand ball in each hand at 30% of his/her maximum voluntary contraction for 3 minutes.

Exercise stress condition n°2: The participants were asked to perform the Valsalva maneuver for 15 seconds interspersed with 15 seconds of recovery for 3 minutes.

Exercise stress condition n°3: Exercise stress condition n°1 was coupled with exercise stress condition n°2.

All of these conditions were tested at Sainte-Justine University Hospital Center (Montreal, Canada) on healthy participants and induced hemodynamic effects for each stress condition were recorded using a cardiac hemodynamic monitoring device (PhysioFlow, Manatec Biomedical, Macheren, France).

The first exercise condition was performed by demanding participants to perform the first handgrip maneuver in one hand, then two hands at 30%. The result of this preliminary test demonstrated that handgrip on the one hand does not have a significant impact on hemodynamic parameters. Therefore, we chose the two-hand option as this option demonstrated a positive impact on hemodynamic parameters.

Exercise condition 2 was performed using a manometer connected to the flexible tube with a mouthpiece mounted on it to allow participants apply intraoral pressure during the blowing effort. During this exercise condition participants achieved a mean intra-oral pressure of 33 mmHg instead of the targeted intra-oral pressure of 40 mmHg. Moreover, they reported jaw muscle fatigue due to the difficulties of holding the mouthpiece. Hemodynamic parameters were also recorded to assess the efficiency of the maneuver on the cardiac muscle.

Phase 2: Optimization of the stress-CMR protocol

At this phase, we performed the third exercise condition (i.e., a combination of isometric handgrip and Valsalva). After performing this condition, we found that it has a more significant impact on

the hemodynamic parameters than the first two exercise conditions. To optimize the protocol, we performed two tasks. Firstly, we designed a new mouthpiece that was comfortable and allowed participants to reach the targeted 40-mmHg intra-oral pressure without jaw muscle fatigue. With the new design, no jaw muscle fatigue was reported, and participants achieved a mean intra-oral pressure of 40.5 mmHg.

The second task performed was to redefine the sequence of the maneuvers that would allow effective recording of the hemodynamic parameters during exercises. We conducted several preliminary tests and found that there were more errors in blood pressure measurements when hemodynamic parameters were recorded while the participants were performing the handgrip exercise.

Therefore, we found that the new protocol which consisted of the following sequences: *15s (Valsalva)- 15s Rest -15s (Valsalva)- 15s Rest - 25s Handgrip (60% Fmax)- 15s Rest - 15s (Valsalva) - 15s Rest - 15s (Valsalva) - 15s Rest - 20s Handgrip (60% Fmax) - 10s Rest -1 min 50s Handgrip (30% Fmax)* significantly increases the stress and facilitates the recording of the hemodynamic parameters.

Phase 3: Validation of the stress-CMR protocol

The phase of validation was done by comparing functional and mechanical cardiac responses induced by the two Exercise-CMR protocols: the newly developed protocol and the ergometer protocol. This step was achieved in our fourth objective which aimed to assess the feasibility and reliability of the new Ex-CMR protocol imaging protocol and compare its ability to induce sufficient deformations on the cardiac muscle and to limit the challenges encountered during the ergometer protocol.

Our study shows that the new Ex-CMR protocol (Handgrip-Valsalva) is a safe, reliable and effective tool that can induce sufficient cardiac deformations during exercise stress testing. Moreover, we did not find any significant differences between the Handgrip-Valsalva-induced changes and the cardiac changes induced by the cycle ergometer. These results were encouraging

since previous studies have shown that a cycle ergometer is the best strategy to induce enough cardiac muscle changes to allow accurate and effective cardiac assessments [231]. Though there was no significant difference between the two Ex-CMR protocols, we found that some parameters such as end-diastolic volumes (EDV) and diastolic blood pressure (DBP) were more important during Handgrip-Valsalva than with the ergometer protocol. Additionally, the newly developed Ex-CMR protocol produced high-quality images, while the ergometer protocol caused respiratory and cardiac motion artifacts. Based on our study results, we recommended the use of the new Handgrip-Valsalva Ex-CMR protocol for clinical assessments of cardiac diseases as it induces significant cardiac deformations during exercise and has the potential to minimize the limitations associated with the Ex-CMR protocols that use a cycle ergometer. Overall, the new Handgrip-Valsalva Ex-CMR protocol offers a more effective approach for assessing cardiac diseases and reveals important cardiac remodeling predictors.

8.2 Clinical impact of the project

During this project, we have developed a deeper understanding of the difficulties involved in assessing cardiac diseases using existing imaging techniques. We have also observed that the absence of early diagnostic tools for cardiac diseases is a significant burden for cardiac patients. As part of the project, we have introduced several diagnostic tools that can help in characterizing various cardiac conditions and assist in following-up with patients with different cardiac conditions. These tools can also predict future cardiac events and prevent the manifestation of late adverse events among patients. The study has also highlighted the potential benefits of exercise stress in improving the cardiac performance of patients with serious cardiac conditions.

Throughout this project, we provided insights into physiological cardiac remodeling and identified additional cardiac parameters that could predict pathological remodeling. The systematic review conducted on existing Ex-CMR protocols allowed us to identify the existing Ex-CMR that are commonly used to assess cardiac-induced responses to exercise. We were also able to highlight the advantages and limitations associated with each Ex-CMR protocol. The information presented in this study is highly valuable as it can help clinicians, researchers, and healthcare providers in identifying abnormal cardiovascular responses during exercise at an early stage. Currently, cardiac

remodeling is a complex mechanism that needs to be understood. This review will help to better understand cardiac remodeling mechanisms, which will ultimately facilitate the early detection of cardiac diseases and save lives.

Another impact of this project is the new and reliable Ex-CMR protocol (Handgrip-Valsalva) that we developed, which can be used in clinical settings to detect early pathological deformations. We anticipate that the clinical use of the developed protocol will expand the clinical use of Ex-CMR protocols which is currently limited. Additionally, the developed protocol can benefit a large number of participants with limited exercise ability. Overall, the developed tools can provide new biomarkers of cardiac diseases, help anticipate the progression of pathology, and contribute to improving cardiac patients' prognostic follow-up. This project will also pave the way for further research advancements in this important field, aiming for an early characterization of cardiac diseases.

8.3 Limitations and strength of the project

In this project, we encountered several limitations that we need to be acknowledge. Firstly, the sample size that we used in this project was small, thus limiting the power of our analyses and could explain the absence of significant results between analyzed parameters. This sample size limitation occurred among the three out of five studies that composed this project.

Secondly, we experienced convergence issues for some patients during the simulation of cardiac mechanical performance using the CircAdapt model. These convergence issues predominantly occurred in patients who exercised at high levels of effort (200 to 325W) and those who achieved a heart rate of $HR \geq 180$ bpm while exercising. As Circadapt was designed initially with heart rates up to 140 bpm/min during exercise (<https://www.circadapt.org/documentation/>), we concluded that high hemodynamic load may affect cardiovascular adaptation during the simulation. However, this hypothesis needs further verification. As a result, those patients were excluded from the statistical analyses to ensure the good quality of data. Another limitation is associated with the Ex-CMR ergometer protocol where participants experienced discomfort and muscle fatigue, which

could have led to premature termination of exercise. Additionally, two participants who were above 180 cm in height had difficulties cycling into the MRI scanner as their leg movement was limited.

For the Handgrip-Valsalva exercise protocol, we encountered some limitations too. Although participants were asked to squeeze an exercise ball at 30% to 60% of their maximum voluntary contraction, we had no control over the grip force applied to the handgrip balls, which may have led to variability among participants. Another general limitation is that we couldn't test the Handgrip- Valsalva protocol on cardiac disease patients due to safety process steps that we didn't want to skip. Studies demonstrate that pathological cardiac remodeling changes are more obvious in cardiac disease patients than in healthy populations. Testing this new Ex-CMR protocol on cardiac-diseased patients or participants with limited exercise capacity would have allowed us to highlight more its reliability and effectiveness in cardiac disease assessment. Despite these limitations, we were able to achieve our targeted hemodynamic values (i.e., $HR \leq 120$ bpm and $SBP \leq 150$ mmHg) and ensure the development of a protocol that can produce high-quality images.

This thesis offers a comprehensive approach to investigate different aspects of cardiac health. It presents new biomarkers for cardiac conditions, new equations to predict cardiac muscle health, and new imaging tools to characterize cardiac diseases. The findings of this thesis have significant clinical implications, including the potential for early detection of cardiac damage, improvement of diagnostic tools, and enhancement of follow-up and prognostic assessment of cardiac patients. The thesis also provides future recommendations for research, such as refining protocols and conducting additional studies to test the efficacy of developed protocols on patients with known cardiac conditions.

Despite its reported limitations, the thesis makes significant contributions to the understanding of cardiac health assessment and introduces innovative approaches that have the potential to enhance clinical practice in the field of cardiology.

CHAPTER 9 CONCLUSION AND RECOMMENDATIONS

In conclusion, the objectives of this study were achieved. The diagnostic and prognostic tools developed in this study show great promises. These tools will contribute towards improving the quality of life for patients, as well as help understanding the mechanisms of cardiac remodeling and characterizing it at an early stage to prevent the progression of cardiac diseases. The developed tools can also be used to follow up on other types of cardiac disease treatments to prevent occurrence of late diverse effects. Additionally, they can be used for diagnosing other various diseases. Given that current diagnostic and prognostic tools for cardiac diseases are quite expensive, using the tools developed in this study will help reduce the costs associated with imaging techniques in cardiac assessments. Furthermore, patients with limited exercise capacity can benefit from these tools, which will allow assessment of a large population.

The first part of the project focused on evaluating the effects of doxorubicin-induced cardiotoxicity in childhood Acute Lymphoblastic Leukemia survivors and their impact on cardiac mechanical properties. We also assessed the relationship between the CMR parameters and mechanical properties. Through this study, we established various equations that can allow us to predict mechanical properties from a combination of CMR parameters. Moreover, CMR parameters can also be estimated from cardiac mechanical properties, through the developed equations. Though we noticed that some parameters such as left ventricle stiffness and contractility can be strongly predicted from a combination of CMR parameters, some other parameters didn't show a strong correlation. For future studies, to increase the power of the correlations, a large sample size should be considered. Secondly, to highlight the sensitivity of CMR parameters to detect changes in cardiac muscles, participants at an early stage of the disease should be considered. We noticed that the sensitivity of T2 to detect the changes in mechanical properties among the participants was limited, especially in participants who received a high cumulative dose of doxorubicin. Another improvement that can be done, would be to use the Circle cvi42 (Circle Cardiovascular Imaging (Circle), CANADA, 2007) software to segment the images and quantify the cardiovascular function parameters. From the reliability study conducted in this project, we found that the reliability of the SEGMENT software is classified as good (ICC=0.81), whereas the reliability of the Circle cvi42 software is reported in the literature as excellent tool (ICC=0.99) [241]. Using this

cvi42 software as a cardiac analysis tool may improve the accuracy of the measured cardiac parameters. Additionally, further studies can explore the correlations between cardiac mechanical properties with other CMR parameters such as T1 ρ or T2*.

The second study in this project aimed at assessing the evolution of cardiac mechanical performance at different levels of exercise performed during CMR testing. We also aimed to assess the impact of doxorubicin and dexrazoxane (DEX) treatments. Though we were able to demonstrate the differences in cardiac mechanical performance parameters between the different levels of exercise, we could not achieve our second objective, which consisted of demonstrating the impact of doxorubicin and dexrazoxane treatments on survivors' cardiac mechanical performance at different levels of exercise. Moreover, we couldn't demonstrate significant differences at rest and during CEPT among the prognostic groups. To improve the accuracy and reliability of the findings of this study we propose the following improvements. Firstly, it is important to include more participants. Increasing the sample size may allow to have enough data to be analyzed and may increase the ability to detect the difference among prognostic groups. This may also help in demonstrating more accurately the impact of doxorubicin and dexrazoxane on survivors' cardiac mechanical performance evolution during CPET among subgroups. Secondly, we recommend considering participants who did not suffer significant cardiac damage for in-depth analysis. This study considered ALL survivors and all of them have received a cumulative dose of doxorubicin, meaning that their cardiac function is somehow impeded. As a consequence, during exercise, most participants who received an important dose of doxorubicin attained a heart rate above 180 bpm at high workloads. While simulating these participants, we noticed that they do not provide realistic simulations or cause convergence issues during CircAdapt simulations. Selecting participants with less cardiac damage may allow the CircAdapt model to converge well to realistic values. Another alternative would be to conduct the exercise testing using an exercise stress protocol which induces enough cardiac deformations without significantly increasing the heart rate. This may help more participants to perform the exercises without major complications. Further studies using MRI-compatible exercise testing coupled with CircAdapt to assess mechanical cardiac performance, should be conducted. These studies may help us understand the functionality and limitations of the CircAdapt model in different pathologies especially during stress conditions.

Though the developed Ex-CMR protocol demonstrated a promising role in the characterization of exercise-induced physiological deformations and pathological deformations following cardiac diseases, several improvements can be made to the Handgrip-Valsalva protocol.

An important improvement in the handgrip maneuver experiment would be to develop an MRI-compatible device that can control the grip force applied by participants. In this project, participants were asked to squeeze the balls at 30 % to 60 % of their maximum force, but it's unclear whether they have achieved the targeted intensity values as it is the case for the Valsalva maneuver (i.e.: 40 mmHg).

During our preliminary tests, we used the digital handgrip manufactured by Handexer (California, USA; see link: <https://www.handexer.com/products/handexer-digital-hand-dynamometer-265lb-120kg-with-case>) to measure precisely the participants grip strength. This hand-dynamometer is made of plastic and non-ferromagnetic metal but has one iron spring inside that is ferromagnetic. Thus, we couldn't use it for our MRI acquisitions. To improve the handgrip maneuver, the iron spring can be replaced by a spring made of non-magnetic metal such as Austenitic Stainless-Steel material.

To enhance the handgrip maneuver, a digital monitor can be added to display the level of effort outside of the MRI scan. Copper wires can be connected to the digital monitor to enable the reading of the achieved level of effort.

For future studies, we recommend conducting additional studies to test the newly developed Handgrip-Valsalva Ex-CMR protocol on patients with known cardiac conditions. This is important because it has been shown that pathological deformations are significant in these patients. Therefore, by further refining this Handgrip-Valsalva protocol, its efficacy can be improved. The following hypothesis stating that Handgrip-Valsalva Ex-CMR protocol with precise grip force control and digital monitoring will enhance its efficacy in detecting pathological deformations in patients with known cardiac conditions can be verified.

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APPENDICES

APPENDIX A ARTICLE 5: EXERCISE STRESS CARDIAC MAGNETIC RESONANCE IMAGING IN THE ASSESSMENT OF INDUCED CARDIOVASCULAR RESPONSES IN CARDIAC PATIENTS: A SCOPING REVIEW PROTOCOL.

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Abstract

Objective: This scoping review will describe cardiac magnetic resonance imaging testing protocols used in combination with exercise (Ex-CMR) to assess cardiovascular responses. The review will document the advantages and limitations of these protocols in cardiac patients.

Introduction: Ex-CMR characterizes the heart, differentiating between normal and pathological cardiac remodeling with considerable accuracy. However, there is no review detailing existing Ex-CMR protocols. This is particularly important since not all Ex-CMR protocols seem to induce enough stress to effectively characterize cardiac remodeling, hence the need for a review to report on the current evidence.

Inclusion criteria: This review will consider studies that use Ex-CMR testing protocols to assess cardiovascular responses, revealing cardiac remodeling in patients whose age at the time of the study was ≥ 18 years.

Methods: The review will be conducted in accordance with the JBI methodology for scoping reviews and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews. The following databases will be searched: PubMed, Embase, ISI Web of Science, OpenGrey, Grey Matters, and OAlster. Articles in English and French will be included and there will be no limitation set for the date of publication. Data will be extracted from papers included in the scoping review by 2 independent reviewers and will be classified in summary tables.

Keywords: cardiac population; exercise-induced cardiac responses; heart function tests; MRI; scoping review; stress imaging.

Introduction

Exercise-induced cardiovascular responses are the cornerstone of providing diagnostic and prognostic information to cardiac patients. These responses refer to the adaptations made by the cardiovascular system during exercise. Often characterized by the increase in hemodynamic parameters, changes in the size or shape of the heart, they allow the system to meet the metabolic demands of the body and to maintain an adequate perfusion. Moreover, exercise-induced cardiovascular responses in cardiac patients play an important role to underline abnormal cardiovascular responses that are not observable at rest. Such responses include chronotropic incompetence, excessive increase or decrease of blood pressure and impaired maximal oxygen consumption [9, 92, 93]. Studies have also observed that in response to exercise, several cardiac patients have an abnormal cardiovascular response due to cardiac remodeling, defined as changes in the size, mass, geometry and function of the heart [6, 94].

Although there are many cardiac remodeling predictors [9, 242], the following predictors are systematically studied: heart rate, left ventricle ejection fraction, left ventricle end-diastolic volume, left ventricle end-systolic volume, stroke volume, left ventricle mass, left ventricle mean arterial pressure and cardiac output. These cardiac remodeling predictors reflect cardiac function, which is compromised during exercise in various cardiac pathologies (i.e., hypertrophic cardiomyopathy, fibrosis, pulmonary hypertension) [9]. To improve the understanding of cardiac

remodeling mechanisms and to enhance prognostic accuracy, exercise-induced cardiovascular responses have been combined with cardiac magnetic resonance imaging (Ex-CMR). CMR imaging is a non-invasive and effective imaging technique that allows an accurate assessment of cardiac morphology, ventricular function, myocardial perfusion, tissue characterization and flow quantification in various cardiac conditions and diseases. Studies interested in cardiac remodeling during exercise have demonstrated the key role of Ex-CMR as a clinical tool to accurately quantify the functional capacities and structural modifications of the heart [13, 14].

Indeed, Ex-CMR facilitates the characterization of the heart and allows differentiation between normal cardiac remodeling and pathological cardiac remodeling with considerable accuracy [9, 95]. In fact, for a normal exercising heart, both heart rate and stroke volume increase, which leads to an increase in the ejection fraction, cardiac output, diastolic volume and mean arterial blood pressure in response to exercise [9, 222]. Conversely, in cardiac patients, cardiac function is compromised and an abnormal hemodynamic adaptation to exercise is reported [222]. The most common abnormal responses in patients who have pathological cardiac remodeling are pressure and volume overload, increased vascular resistance and chronotropic incompetence [243, 244]. Cardiac remodeling is the ultimate precursor of cardiac dysfunction and heart failure [6, 96]. Thus, Ex-CMR has the potential of providing quantitative cardiac information to clinicians, in addition to offering a direct link between exercise, symptoms, and stress imaging [97]. Ex-CMR offers important information that contributes to the diagnostic and risk assessment of various cardiac diseases [20, 98].

Nevertheless, studies have reported various challenges when using Ex-CMR. One of the first challenges is the inability to acquire cardiac images while patients are still near their heart rate peak [52]. Indeed most Ex-CMR require exercises performed outside the magnetic resonance imaging (MRI) scanner and *authors have reported that the imaging acquisitions were of poor quality due to the time delay needed to transfer the patients from the exercise station to the MRI scanner* [245]. A study using a treadmill installed outside the MRI room revealed a time delay of 61 ± 24 seconds because the patients were asked to walk 20 feet from the treadmill station to the MRI scanner [245]. Another study using a treadmill adjacent to the MRI scanner revealed a time delay of 24 ± 4 seconds [52]. As reported in these studies, this delay resulted in the immediate disappearance of exercise-induced stress on the cardiac muscle [95, 97]. As a solution to these limitations, researchers have

recommended using exercises that were compatible with MRI scanners to characterize cardiac responses during exercise [14]. The most commonly reported exercise protocols allowing patients to stay in the MRI scanner to optimize acquisition safely, include: supine cycle ergometer or supine stepper-stress, upright cycle ergometer, isometric handgrip exercises and prone exercise using either knee flexion or extension with resistance from cables or nonferromagnetic weights [14, 15]. Nevertheless, the most clinically performed exercises in Ex-CMR protocol are the supine cycle ergometer and the isometric handgrip exercises[14]. Despite numerous reported advantages of these two types of Ex-CMR protocols, previous studies have reported some limitations including motion artifacts and leg muscle fatigue during supine cycle ergometer [58] and the inability to achieve peak stress when performing an isometric handgrip exercise [14]. In fact, studies using the supine ergometer test have reported that leg muscle fatigue led to premature test termination [215] and some patients' imaging acquisitions were excluded due to motion artifacts [246]. Another study using isometric handgrip demonstrated that the hemodynamic changes achieved during exercise did not reach the extent of bicycle or treadmill exercises performed to maximum exertion [18].

Despite progress made to enable exercising in an MRI scanner, researchers warn about the excessive motion that exercise conditions can produce and the lack of Ex-CMR studies that have taken the constraints imposed by the MRI scanner into consideration for the acquisition of images [97, 99]. These warnings have the consequence of limiting the clinical utilization of Ex-CMR protocols [95] whereas there is no review detailing the existing Ex-CMR protocols and their strengths. Moreover, not all Ex-CMR protocols seem to induce enough stress for an effective characterization of cardiac remodeling, justifying and strengthening the need for a review to report the current evidence.

Prior to writing this protocol, a preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted (date of consultation: April 13th, 2022) on and no current or in-progress scoping reviews or systematic reviews on the topic were identified. The proposed scoping review will provide an overview of existing Ex-CMR studies focusing on cardiac remodeling in cardiac patients. The review will describe and synthesize previously reported data to map the current evidence as well as to identify gaps in knowledge and future research needs in this field [103, 247].

Review questions

What are the Ex-CMR testing protocols currently available to assess induced cardiovascular responses in cardiac patients aged 18 years or over? What are the reported advantages and limitations of Ex-CMR testing protocols currently available to assess induced cardiovascular responses in cardiac patients aged 18 years or over?

Inclusion criteria**Participants**

This review will consider studies cardiac populations (i.e., coronary artery and vascular disease, heart rhythm disorders, structural heart disease and heart failure) whose age at the time of the study was ≥ 18 years.

Concept

The assessment of induced cardiovascular responses in cardiac patients during Ex-CMR is challenging and can limit the clinical use of Ex-CMR protocols. Therefore, this review will consider studies that use Ex-CMR testing protocols to assess induced cardiovascular responses that reveal cardiac remodeling, defined as changes in the size, mass, geometry, and function of the heart. The parameters of interest are the changes in cardiac volume, blood pressure, systemic vascular resistance, cardiac output, ejection fraction and heart rate. They are the most appropriate parameters described in the literature to assess induced cardiovascular responses in cardiac patients in response to various Ex-CMR protocols. This review will also identify Ex-CMR protocols that induce enough stress during exercise testing. Moreover, the review will document the reported advantages and limitations of Ex-CMR testing protocols in cardiac patients in relation to delivery, cost, feasibility, effectiveness, and patient safety, both from authors' and health professionals' viewpoint. The findings of this review will provide important information for clinicians, researchers, and health care providers.

Context

Ex-CMR testing protocols can be conducted in any geographic location depending on clinical settings. The inclusion of cardiac patients in our review will not be limited to specific cultural or subcultural factors, racial or gender-based interests. This will ensure that all Ex-CMR testing protocols are captured, providing a thorough review of the literature.

Types of sources

This scoping review will consider quantitative study designs as well as mixed methods study designs if the latter include a quantitative component. Observational studies randomized controlled trials, nonrandomized controlled trials, and uncontrolled interventions (ie, pre- and post-tests without controls) will also be considered. Unpublished studies and gray literature will be included in this scoping review. However, conference abstracts, case reports, short communications, systematic reviews, metaanalyses, theses, letters to the editor, and protocol *papers will be excluded*.

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [101] and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [102].

Search strategy

The search strategy will aim to identify published and unpublished original studies on the topic of interest. Prior to initiating the full search strategy, a librarian (PD) performed a limited search of MEDLINE to identify relevant published articles. The text words contained in the titles and abstracts of these articles, and the index terms used to describe these articles, were used to develop a full search strategy. The specific MeSH terms and keywords that will be used in our scoping review can be found in Appendix I. The initial search of PubMed, conducted from inception until August 4, 2022, identified 5730 potential articles. This search suggests good feasibility and relevance of the search strategy. The reference lists of all full-text articles included will be screened for additional papers. Only articles written in English or French will be included. Literature will be searched from database inception until the present. The following databases will be searched: PubMed, Embase (Ovid), ISI Web of Science, OpenGrey, Grey Matters, and OAlster.

Study/Source of evidence selection

Following the search, all identified records will be collated and uploaded into Covidence (Veritas Health Innovation, Melbourne, Australia). Duplicate articles will be removed by the bibliographic software and will be manually scanned. Titles and abstracts will then be screened by 2 independent reviewers (EU and MC) for assessment against the inclusion criteria. Potentially relevant reports will be retrieved in full, and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia) [248]. The full texts of selected citations will be assessed in detail against the inclusion criteria by 2 independent reviewers (EU and MC). Of note, reviews identified at the “title and abstract” screening level will be retrieved in full to review references that may not have been retrieved by searching for primary research evidence. Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with a third reviewer (AL). The results of the search will be reported in full in the final scoping review and presented in a PRISMA flow diagram [102, 249].

Data extraction

Data will be extracted from papers included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers (Appendix II). The data extracted will include specific information on: (1) authors and year of publication, (2) participants characteristics (number of participants, sex, age at time of study, disease), (3) the study design, (4) main objectives, (5) Ex-CMR testing protocols, (6) reported Ex-CMR testing advantages in relation to delivery, cost, feasibility, effectiveness and patients' safety from the authors' viewpoint and the health professional's viewpoint when reported, (7) reported Ex-CMR testing limitations in relation to delivery, cost, feasibility, effectiveness and patients' safety from the authors' viewpoint and the health professional's viewpoint when reported, (8) reported cardiovascular responses to exercise including: heart rate, blood volumes (end systolic volume, end diastolic volume, stroke volume), blood pressures (systolic pressure, diastolic pressure, pulmonary capillary wedge pressure,

pulmonary arterial wedge pressure, mean arterial blood pressure), ventricular mass, cardiac output, systemic vascular resistance, ejection fraction, rate pressure product, ventricular wall compliance, and (9) other key findings relevant to the review question. *Extracting the cardiovascular responses* to exercise in the included studies will provide an overview of possible cardiovascular responses during Ex-CMR testing in cardiac patients. Furthermore, this will help us to document the ability of each Ex-CMR protocol to induce enough stress during exercise testing. Additionally, the extracted data will provide more information on abnormal hemodynamic responses during Ex-CMR. This will be useful for clinicians, researchers, and health care providers to improve early detection of abnormal cardiovascular responses in response to exercise. Any modification to the data extraction tool will be detailed in the full published scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Corresponding authors of included papers will be contacted up to twice to request missing or additional data, where required.

Data analysis and presentation

To address the first research question, which is to identify and describe Ex-CMR testing protocols assessing induced cardiovascular responses in cardiac patients, we will use the data extracted from the full-text papers to create a table describing Ex-CMR testing protocols (see Appendix III). To address the second research question, which is to document and describe the reported advantages and limitations of the Ex-CMR testing protocols in cardiac patients, we will use the data extracted from the full-text papers to create a table describing reported advantages and limitations of the Ex-CMR testing protocols (see Appendix III).

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Author contributions

MC, EU, AL, DC, and DP conceived the study. PD performed the systematic searches. The first draft of the manuscript was written by EU and MC and all authors (AL, PD, DC and DP) commented on previous versions of the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy

Table A.1 Search strategy

Search	Query	Records retrieved
#1	Cardiovascular Diseases[mh] OR Stroke[mh] OR Aneurys*[TIAB] OR angina*[TIAB] OR Angiodysplasi*[TIAB] OR Angioedem*[TIAB] OR Angiomatos*[TIAB] OR Aorti*[TIAB] OR arhythmi*[TIAB] OR arrhythmi*[TIAB] OR arrythmi*[TIAB] OR arterial occlus*[TIAB] OR Arterioscleros*[TIAB] OR arythmi*[TIAB] OR atheroscleros*[TIAB] OR cardia*[TIAB] OR cardio*[TIAB] OR coronar*[TIAB] OR CVA[TIAB] OR heart*[TIAB] OR hypertensi*[TIAB] OR hypotensi*[TIAB] OR infarct*[TIAB] OR ischaem*[TIAB] OR ischem*[TIAB] OR myocard*[TIAB] OR sick sinus*[TIAB] OR stroke[TIAB] OR strokes[TIAB] OR tachycardi*[TIAB] OR thrombo*[TIAB] OR Vascular[TIAB] OR ventric*[TIAB]	
#2	Exercise Test[MH] OR Exercise test*[tiab] OR Exercise tolerance test*[tiab] OR exercise electrocardiogr*[tiab] OR exercise ECG[tiab] OR "Ex-ECG"[tiab] OR Exercise cardiovascular magnetic resonance[tiab] OR Exercise CMR[tiab] OR "Ex-CMR"[tiab] OR "Exercise magnetic resonance"[tiab] OR Exercise MRI*[tiab] OR exercise imaging[tiab] OR effort test*[tiab] OR ergometric test*[TIAB] OR ergometry test*[TIAB] OR ergometer*[tiab] OR ergometre*[tiab] OR stress cardiac[tiab] OR stress cardiovascular[tiab] OR stress test*[tiab] OR cardiac stress[tiab] OR myocardial stress[tiab] OR stress myocard*[tiab] OR stress CMR[tiab] OR stress perfusion[tiab] OR stress imaging[tiab] OR stress MR[tiab] OR stress MRI[tiab] OR isometric stress[TIAB] OR isometric hand*[TIAB] OR handgrip stress[tiab] OR hand grip stress[tiab] OR handgrip test*[tiab] OR hand grip test*[tiab] OR handgrip exercis*[tiab] OR hand grip exercis*[tiab] OR treadmill*[tiab] OR bicycle*[tiab] OR bike[tiab] OR cycling[tiab]	
#3	Magnetic Resonance Imaging[MH] OR Myocardial Perfusion Imaging[MH] OR Magnetic resonance[tiab] OR resonance imaging[tiab] OR MRI[tiab] OR MRIs[tiab] OR NMR Imag*[tiab] OR MR Tomograph*[tiab] OR NMR Tomograph*[tiab] OR Spin Echo Imag*[tiab] OR CMR[tiab] OR Myocardial Perfusion Imaging[tiab] OR Myocardial Scintigraph*[tiab] OR cardiac stress imaging[tiab]	
#4	#1 #1 AND #2 AND #3 AND (english[LA] OR French[LA])	5,730

Table A. 2: Data extraction tool

Authors & Year	Participants characteristics	Study design	Main objectives	Ex-CMR protocol	Cardiovascular responses to exercise	Other key findings
	Number of participants: Sex: Age at time of study: Disease:					

Table A.3: Exercise-Cardiovascular Magnetic Resonance Imaging testing protocols

Authors & Year	Ex-CMR testing protocols	Reported Ex-CMR testing advantages	Reported Ex-CMR testing limitations

APPENDIX B : Supplementary material, S1. Significant equations to predict the cardiac mechanical properties from a combination of cmr parameters.

- **Left ventricle contractility:** 69.2% of LVC can be predicted ($r=0.832$) from a linear combination of CMR parameters (T1 and T2 relaxation time, coefficient partition, EF, EDV and ESV), as follows:

$$\text{LVC} = -1,870 - (0,000853 * \text{T1}) + (0,00739 * \text{T2}) + (0,407 * \text{CP}) - (0,0284 * \text{EDV}) + (0,0475 * \text{ESV}) + (0,0757 * \text{EF})$$

- **Left ventricular minimum pressure:** 69.9% of Pmin can be predicted ($r=0.793$) from a linear combination of CMR parameters (T1 and T2 relaxation time, coefficient partition, EF, EDV and ESV), as follows:

$$\text{Pmin} = -4,666 - (0,0284 * \text{T1}) + (0,128 * \text{T2}) + (5,614 * \text{CP}) - (0,0837 * \text{EDV}) + (0,368 * \text{ESV}) + (0,476 * \text{EF})$$

- **Left ventricular maximum pressure:** 28.5 % of Pmax can be predicted ($r=0.534$) from a linear combination of CMR parameters (T1 and T2 relaxation time, coefficient partition, EF, EDV and ESV), as follows:

$$\text{Pmax} = 59,931 + (0,0322 * \text{T1}) - (0,181 * \text{T2}) + (0,600 * \text{CP}) - (0,0877 * \text{EDV}) + (0,186 * \text{ESV}) + (0,348 * \text{EF}).$$

APPENDIX C: Supplementary material, S2. Significant equations to predict the CMR parameters from a combination of cardiac mechanical properties.

- **T1 relaxation time:** 40% of T1 can be predicted ($r=0.63$) from a linear combination of mechanical properties (LVS, LVC, Pmax, Pmin, VAC and CWE), as follows:

$$T1 = 93,979 - (3,496 * LVS) - (38,562 * LVC) + (4,815 * Pmax) - (1,991 * Pmin) + (118,746 * VAC) + (688,611 * CWE)$$

- **CP:** 14% of CP can be predicted ($r=0.377$) from a linear combination of mechanical properties (LVS, LVC, Pmax, Pmin, VAC and CWE), as follows:

$$CP = 0,0863 + (0,0171 * LVS) - (0,0318 * LVC) + (0,00433 * Pmax) - (0,00289 * Pmin) - (0,0682 * VAC) - (0,00245 * CWE)$$

APPENDIX D: Supplement information: cardiac mechanical performance assessment at different levels of exercise in childhood acute lymphoblastic leukemia survivors.

TABLE.D. S1, Supplementary material. Clinical characteristics of childhood ALL survivors included in the analysis (N=63) and not included in the study (N=187).

Characteristics	Total (N=63)	Total (N=184)*	p-value
Gender, N (%)			
Male	28 (44.4)	96 (52.2)	0.274
Female	35 (55.6)	87 (47.3)	
Body Mass Index, kg/m²			
Mean (SD)	24.6 (4.7)	24.2 (5.3)	0.605
Median (range)	24.0 (17.1-39.0)	23.3 (15.2-47.1)	
Age at interview, years			
Mean (SD)	22.9 (6.9)	21.3 (6.1)	0.025
Median (range)	22.0 (12.0-38.0)	21.0 (8.0-40.0)	
Age at cancer diagnosis, years			
Mean (SD)	7.7 (5.2)	5.8 (4.3)	0.005
Median (range)	6.0 (0.9-18.0)	4.0 (1.0-18.0)	
Time from diagnosis, years			
Mean (SD)	15.6 (5.5)	15.4 (5.1)	0.696
Median (range)	15.3 (5.5-28.1)	14.7 (5.7-28.6)	
Risk groups, N (%)			
Standard risk	15 (23.8)	97 (52.7)	-
High risk with dexrazoxane	26 (41.3)	41 (22.3)	
High risk without dexrazoxane	22 (34.9)	46 (25.0)	
Treatment protocol, N (%)			
DFCI 87-01	7 (11.1)	19 (10.3)	-
DFCI 91-01	16 (25.4)	27 (14.7)	
DFCI 95-01	15 (23.8)	59 (32.1)	
DFCI 2000-01	17 (27.0)	60 (32.6)	
DFCI 2005-01	8 (12.7)	19 (10.3)	
Doxorubicin, mg/m²			
Mean (SD)	236.2 (103.1)	163.3 (120.0)	<0.001
Median (range)	276.9 (45.6-400.0)	61.9 (41.5-472.9)	
Dexrazoxane, N (%)			
Yes	26 (41.3)	41 (22.3)	0.174
No	37 (58.7)	143 (77.7)	
Radiation therapy, N (%)			
Yes	45 (71.4)	94 (51.1)	0.108
No	18 (28.6)	90 (48.9)	
Ejection fraction (biplane Simpson (%))			
Mean (SD)	55.4 (5.3)	55.7 (8.5)	0.744
Median (range)	55.9 (39.0-66.0)	57.1 (45.0-66.8)	
Heart rate at rest, bpm			
Mean (SD)	90.1 (13.8)	90.3 (14.2)	0.968
Median (range)	88.0 (63.0-126.0)	91.0 (58.0-127.0)	
Maximum heart rate during exercise test, bpm			
Mean (SD)	186.5 (13.9)	187.5 (10.5)	0.464
Median (range)	188.5 (136.0-206.0)	190.0 (155.0-210.0)	
$\dot{V}O_2$ peak during exercise test, mL·kg⁻¹·min⁻¹			
Mean (SD)	30.2 (7.6)	33.0 (8.6)	0.023
Median (range)	29.8 (14.1-47.3)	32.4 (15.5-57.8)	
Moderate to vigorous physical activity (min/day)			
Mean (SD)	23.2 (33.4)	29.3 (28.7)	0.166
Median (range)	11.8 (0.0-238.0)	22.7 (0.0-149.2)	

TABLE D.S2, Supplementary material. Childhood ALL survivors' Ees assessed during the CPET at different levels of exercise according to their prognostic risk groups.

	Prognostic risk groups	N	Mean	(SD)	95% Confidence Interval		p-value
					Lower Bound	Upper Bound	
Rest	SR	13	1.900	(0.175)	1.794	2.006	0.318
	HR+DEX	24	1.895	(0.216)	1.804	1.986	
	HR	21	1.818	(0.164)	1.743	1.893	
	Total	58	1.868	(0.190)	1.818	1.918	
Workload 1	SR	14	1.837	(0.163)	1.743	1.931	0.402
	HR+DEX	24	1.754	(0.192)	1.673	1.835	
	HR	19	1.784	(0.183)	1.696	1.872	
	Total	57	1.784	(0.182)	1.736	1.833	
Workload 2	SR	13	1.757	(0.191)	1.642	1.872	0.578
	HR+DEX	25	1.717	(0.226)	1.624	1.811	
	HR	19	1.678	(0.197)	1.583	1.773	
	Total	57	1.713	(0.207)	1.658	1.768	
Workload 3	SR	10	1.715	(0.241)	1.542	1.888	0.564
	HR+DEX	23	1.638	(0.216)	1.545	1.732	
	HR	17	1.627	(0.203)	1.523	1.731	
	Total	50	1.650	(0.215)	1.589	1.711	
Workload 4	SR	5	1.744	(0.223)	1.467	2.021	0.174
	HR+DEX	18	1.626	(0.268)	1.493	1.760	
	HR	12	1.496	(0.255)	1.334	1.658	
	Total	35	1.598	(0.265)	1.507	1.689	
Workload 5	SR	4	1.589	(0.119)	1.400	1.778	0.519
	HR+DEX	8	1.654	(0.270)	1.429	1.880	
	HR	4	1.457	(0.376)	0.858	2.056	
	Total	16	1.589	(0.269)	1.445	1.732	
Workload 6	SR	2	1.560	(0.155)	0.171	2.949	0.310
	HR+DEX	5	1.747	(0.267)	1.415	2.078	
	HR	2	1.442	(0.045)	1.035	1.848	
	Total	9	1.637	(0.240)	1.453	1.822	
Workload 7	SR	2	1.812	(0.413)	-1.895	5.518	0.932
	HR+DEX	2	1.791	(0.396)	-1.764	5.346	
	HR	1	1.630				
	Total	5	1.767	(0.296)	1.399	2.135	

APPENDIX E: Supplement information: assessing the feasibility and reliability of a new exercise cardiovascular magnetic resonance protocol for the characterization of cardiac function and mechanics.

Table E.1: End-diastolic volume measurements among 6 participants during rest and exercise

Participants EDV measurements	Rest	Handgrip-Valsalva	Cycle ergometer
P01 (ml)	154	153	130
P02 (ml)	147	155	136
P03 (ml)	155	161	119
P04 (ml)	120	95	119
P05 (ml)	129	130	125
P06 (ml)	176	180	124
Mean $\pm$ SD (ml)	146.83 $\pm$ 20.03	145.67 $\pm$ 29.55	123.4 $\pm$ 4.62

APPENDIX F: Supplement information: exercise stress cardiac magnetic resonance imaging in the assessment of induced cardiovascular responses in cardiac patients: a scoping review

Table 1. Summary of the study characteristics

Authors & year	Participant characteristics	Main objectives	Ex-CMR protocol	Cardiovascular responses to exercise		Other key findings
				Rest	Stress	
Backhaus et al., 2021 [104]	Participants: N=34 • Males N=9 • Females N=25 Age: 69.0 ± N/A yrs Disease: HFpEF	To examine free-breathing RT-CMR during physiologic exercise using a magnetic resonance-compatible ergometer	Supine cycle ergometer: • initial workload: increased by 5W until reaching a HR between 100-110 bpm Real time CMR methods: • rest, 3 min after surpassing HR=100 bpm	CI (RHC): 2.9 L/m ² LV total diastolic filling: 30.3 mL/m ² BSA LV early diastolic filling: 10.9 mL/m ² BSA LV mass: 57.0 g/m ² LVEDV: 68.3 mL/m ² LVSDV: 19.6 mL/m ² LVSV: 49.6 mL/m ² LVEF: 69.0 % RVEDV: 67.7 mL/m ² RVESV: 20.1 mL/m ² RVSV: 44.7 mL/m ² RVEF: 67.6 %	CI (RHC): 5.2 L/m ² LV total diastolic filling: 37.8 mL/m ² BSA LV early diastolic filling: 9.4 mL/m ² BSA	RT-CMR revealed significantly impaired LA total and early diastolic emptying in patients with HFpEF during exercise stress Total LV diastolic filling volumes increased significantly with exercise stress in HFpEF patients LA function identifies HFpEF more accurately compared with the LV functional counterpart at rest and during exercise stress
Brown et al., 2021 [117]	Participants: N=15 • Males N=N/A • Females N=N/A Age: 52.5 ± 14.0 yrs Disease: SSc	To simultaneously measure oxygen consumption and cardiac output using CMR-augmented CPET	Supine cycle ergometer: • initial workload: no resistance during the 1st minute, resistance increased at 0, 30 and 60 seconds and varied by stages: stages 1-3: 3W, stages 4-6: 5W, stages 7-8: 7W, stages 9-10: 9W and stages 11-12: 11W	CI: 3.1 ± 0.7 L/min/m ² SVi: 45.5 ± 7.7 ml/m ² HR: 69.5 ± 9.1 bpm RVEDVi: 70.2 ± 12.1 ml/m ² RVESVi: 24.5 ml/m ² RVSVi: 44.0 ± 7.2 ml/m ² LVEDVi: 67.7 ± 11.4 ml/m ² LVESVi: 23.7 ± 8.3 ml/m ² LVSVi: 44.1 ± 7.2 ml/m ² LVEF: 66.0 ± 8.0 % RVEF: 64.0 %	CI: 5.5 ± 1.2 L/min/m ² SVi: 44.8 ± 10.2 ml/m ² HR: 124.0 ± 16.5 bpm LVEF: 72.0 ± 12.0 % RVEF: 71.0 %	All patient groups had reduced peak iVO ₂ compared to healthy controls SSc and SSc-PAH had reduced peak ΔavO ₂ compared to healthy controls and NC-PAH patients SSc-PAH and NC-PAH patients had reduced peak CI compared to healthy controls and SSc patients

	Participants: N=15 • Males N=N/A • Females N=N/A Age: 59.7±8.4 yrs Disease: SSc-PAH		• workload was controlled by altering resistance depending on cadence CMR methods: • rest and after 90 seconds	CI: 3.0 ± 0.8 L/min/m ² SVi: 41.4 ± 9.7 ml/m ² HR: 72.5 ± 9.0 bpm RVEDVi: 71.7 ± 13.9 ml/m ² RVESVi: 27.7 ml/m ² RVSVi: 40.2 ± 9.4 ml/m ² LVEDVi: 63.7 ± 12.9 ml/m ² LVESVi: 22.9 ± 7.6 ml/m ² LVSVi: 40.8 ± 9.7 ml/m ² LVEF: 64.0 ± 9.0 % RVEF: 59.0 %	CI: 4.2 ± 1.0 L/min/m ² SVi: 41.6 ± 8.2 ml/m ² HR: 102.7 ± 14.0 bpm LVEF: 76.0 ± 8.0 % RVEF: 66.0 %	Higher hemoglobin was associated with higher peak ΔavO_2 independent of disease type Higher myocardial T1 was associated with lower peak SV CMR-CPET can help develop a better understanding of the causes of exercise dysfunction in different types of disease
	Participants: N=15 • Males N=N/A • Females N=N/A Age: 51.1 ± 18.1 yrs Disease: NC-PAH			CI: 3.0 ± 0.7 L/min/m ² SVi: 37.3 ± 10.1 ml/m ² HR: 80.6 ± 10.1 bpm RVEDVi: 69.7 ± 14.5 ml/m ² RVESVi: 29.1 ml/m ² RVSVi: 34.9 ± 9.0 ml/m ² LVEDVi: 54.7 ± 16.3 ml/m ² LVESVi: 19.6 ± 10.5 ml/m ² LVSVi: 35.1 ± 8.8 ml/m ² LVEF: 66.0 ± 10.0 % RVEF: 56.0 %	CI 4.3 ± 1.1 L/min/m ² SVi: 37.0 ± 9.7 ml/m ² HR: 118.4 ± 22.4 bpm LVEF: 78.0 ± 10.0 % RVEF: 59.0 %	
Claessen et al., 2018 [9]	Participants: N=9 • Males N=8 • Female N=1 Age: 44.0 ± 14.0 yrs Disease: mild DCM	To evaluate the cardiac response to dynamic exercise in ostensibly healthy endurance athletes with mildly reduced left ventricle ejection fraction as compared with a group of non-athletic subjects with mild or early DCM	Supine cycle ergometer Real time CMR methods: • rest, 25%, 50% and 66% maximal power	HR: 67.0 ± 8.0 bpm MAP: 90.0 ± 10.0 mmHg LVEDV: 99.0 ± 23.0 mL LVEF: 47.7 ± 5.5 %	HR: 142.0 ± 13.0 bpm MAP: 117.0 ± 15.0 mmHg LVEDV: 104.0 ± 26.0 mL LVEF: 52.8 ± 9.5 %	Our current results demonstrate that evaluation during exercise facilitates the differentiation between athlete's heart and pathological LV adaptation with considerable accuracy The findings of this study have clinical implications for subjects at risk for the development of DCM

Göransson et al., 2019 [109]	Participants: N=20 • Males N=7 • Females N=13 Age: 43.0 ± 12.0 yrs Disease: PAH	To describe cardiac response to exercise in PAH, as assessed with repeated Ex-CMR imaging assessments	Supine cycle ergometer (pedal) with remote-controlled resistance CMR methods: • rest and during 15-minutes of constant exercise	HR: 73.0 ± 8.0 bpm RVEDV: 233.0 ± 24.0 mL RVESV: 144.0 ± 24.0 mL RVSV: 90.0 ± 10.0 mL LVEDV: 132.0 ± 9.0 mL LVESV: 52.0 ± 6.0 mL LVSV: 80.0 ± 8.0 mL	HR: 109.0 ± 15.0 bpm RVEDV: 251.0 ± 23.0 mL RVESV: 161.0 ± 19.0 mL RVSV: 91.0 ± 14.0 mL LVEDV: 122 ± 14.0 mL LVESV: 42.0 ± 7.0 mL LVSV: 80.0 ± 12.0 mL	Cardiac response during exercise CMR is related to established measurements of morbidity and mortality, as demonstrated in RV dilation and reduced SV during exercise Reduced SV during exercise is a plausible factor to increased risk of decompensation SV response during exercise may be useful for future risk evaluation in patients with PAH
Groepenhoff et al., 2007 [118]	Participants: N=10 • Males N=5 • Females N=5 Age: 38.0 ± 16.0 yrs Disease: iPAH	To compare pulmonary blood flow per heart beat with SV determined with CMR imaging at rest and during exercise	Pulmonary function test + CPET Upright and supine cycle ergometer CMR methods: • rest, 40% maximal exercise and 100% maximal exercise	HR: 84.0 ± 13.0 bpm	HR: 155 ± 16 bpm Pulmonary blood flow per heart beat (upright position): 11.0 ± 17.0 mL Pulmonary blood flow per heart beat (supine position): -0.6 ± 8.0 mL	The iPAH patients were symptom limited in their maximal exercise tolerance as indicated by the significantly reduced maximal HR during CPET compared to the healthy controls A maximal exercise test is not needed to test the SV response to exercise

Habert et al., 2018 [114]	Participants: N=11 • Males N=5 • Females N=6 Age: 36.3 ± 13.6 yrs Disease: RTOF	To assess the feasibility of Ex-CMR in RTOF To assess biventricular parameters and aortic rigidity in RTOF at rest and during Ex-CMR	Supine cycle ergometer (pedal): • initial workload: 25W, increased by 25W every 2 minutes • minimum duration was 10 minutes CMR methods: • rest and after exercise	HR: 69.6 ± 10.3 bpm RPP: 7731.0 ± 1568 mmHg/min SBP: 114.3 ± 16.2 mmHg DBP: 74.2 ± 9.3 mmHg MAP: 87.2 ± 10.1 mmHg RVEDVi: 179.5 ± 69.9 mL/m² RVESVi: 117.7 ± 53.3 mL/m² RVEF: 36.2 ± 8.3 % RVCOi: 4.1 ± 1.3 L/min/m² LVEDVi: 68.3 ± 17.6 mL/m² LVESVi: 31.5 ± 11.0 mL/m² LVEF: 53.8 ± 6.1 % LVCOi: 2.5 ± 0.5 L/min/m²	HR: 108.7 ± 18.8 bpm RPP: 15412.0 ± 4844.0 mmHg/min SBP: 143.1 ± 28.4 mmHg DBP: 84.1 ± 22.3 mmHg MAP: 103.2 ± 23.5 mmHg RVEDVi: 181.4 ± 73.6 mL/m² RVESVi: 118.6 ± 61.9 mL/m² RVEF: 37.2 ± 12.2 % RVCOi: 6.5 ± 1.9 L/min/m² LVEDVi: 65.9 ± 22.4 mL/m² LVESVi: 26.8 ± 14.0 mL/m² LVEF: 59.6 ± 10.4 % LVCOi: 4.1 ± 1.1 L/min/m²	This study shows the feasibility of performing an exercise test under CMR condition within a reasonable time frame Ex-CMR unmasked a reduced distensibility of the ascending aorta in RTOF, which may be an early sign of increased aortic rigidity
Hays et al., 2010 [62]	Participants: N=17 • Males N=8 • Females N=9 Age: 55.5 ± 6.8 yrs Disease: CAD	To measure noninvasively coronary endothelial function using clinical 3.0-T magnetic resonance imaging	Isometric handgrip exercise: • 4.5 min of continuous exercise at 30% max grip strength CMR methods: • before, during exercise, and during recovery	LVEF: 59.0 ± 11.2 %	HR: 12.6% increase RPP: 26.0% increase RPP: 11971.0 ± 2274.0 mmHg/min SBP: 12.5% increase	High-resolution magnetic resonance imaging combined with isometric handgrip stress provided a powerful new approach to the non-invasive assessment of endothelial-dependent coronary vasoreactivity

Hays et al., 2013 [113]	Participants: N=11 • Males N=8 • Females N=3 Age: 57.0 ± 6.0 yrs Disease: CAD	To assess coronary endothelial function using repeated isometric handgrip stress in CAD patients	Isometric handgrip exercise: • 4 min of continuous exercise at 30% max grip strength CMR methods: • before, during exercise (x2), and during recovery	RPP: 9087.0 ± 689.0 mmHg/min	RPP¹: 10917.0 ± 548.0 mmHg/min RPP²: 9385.0 ± 639.0 mmHg/min	Magnetic resonance imaging measures are unchanged during repeated isometric handgrip exercise tests in CAD patients These findings demonstrate the repeatability of non-invasive magnetic resonance imaging, coupled with repeated isometric handgrip exercise tests, of coronary endothelial function
Helsen et al., 2018 [119]	Participants: N=23 • Males N=17 • Females N=6 Age: 34.0 ± 7.0 yrs Disease: TGA-Mustard/Senning	To phenotype both TGA-Mustard/Senning and ccTGA patients by evaluating systolic sVR function and ventricular filling-related parameters at rest and during exercise	Upright cycle ergometer: • CPET: continuous ramp protocol Supine cycle ergometer	HR: 69.0 ± 10.0 bpm RVeDi: 127.1 ± 35.5 mL/m² RVeSVi: 78.0 ± 30.5 mL/m² RVSVi: 49.0 ± 9.7 mL/m² RVEF: 40.0 ± 7.0 % LVEDi: 69.2 ± 15.8 mL/m² LVeSVi: 25.9 mL/m² LVSVi: 40.6 ± 7.7 mL/m² LVEF: 63.0 % CI: 2.8 ± 0.4 L/min/m² SBP: 119.0 ± 12.0 mmHg	HR: 159.0 ± 21.0 bpm RVeDi: 113.3 ± 34.1 mL/m² RVeSVi: 68.6 ± 30.1 mL/m² RVSVi: 44.8 ± 10.0 mL/m² RVEF: 41.0 ± 9.0 % LVEDi: 58.4 ± 17.9 mL/m² LVeSVi: 17.9 mL/m² LVSVi: 37.4 ± 6.8 mL/m² LVEF: 69.0 % CI: 5.9 ± 0.9 L/min/m² SBP: 163.0 ± 21.0 mmHg	Despite similar sRV systolic function at rest and sRV contractility during exercise, there is a distinct difference in the contraction pattern (ventricular mechanics) of TGA-Mustard/Senning and ccTGA patients TGA-Mustard/Senning patients have an abnormal decrease in stroke volume during exercise, which is different from the increase observed in ccTGA patients The HRR of ccTGA patients was lower than that of TGA-Mustard/Senning patients
	Participants: N=10 • Males N=8 • Females N=2 Age: 45.0 ± 7.0 yrs Disease: ccTGA		CMR methods: • rest, 25% intensity, 50% intensity, and 66% intensity of maximal power exercise • Free breathing bicycle exercise at the abovementioned 4 exercise stages within the CMR	HR: 70.0 ± 13.0 bpm RVeDi: 126.8 ± 40.6 mL/m² RVeSVi: 76.1 ± 36.8 mL/m² RVSVi: 50.6 ± 9.0 mL/m² RVEF: 42.0 ± 10.0 % LVEDi: 68.1 ± 12.5 mL/m² LVeSVi: 27.3 ± 11.0 mL/m² LVSVi: 40.9 ± 7.1 mL/m² LVEF: 60.0 ± 6.0 % CI: 2.8 ± 0.4 L/min/m² SBP: 121.0 ± 15.0 mmHg	HR: 138.0 ± 38.0 bpm RVeDi: 130.2 ± 39.7 mL/m² RVeSVi: 71.6 ± 35.0 mL/m² RVSVi: 58.6 ± 13.6 mL/m² RVEF: 47.0 ± 11.0 % LVEDi: 70.9 ± 19.1 mL/m² LVeSVi: 23.8 ± 7.6 mL/m² LVSVi: 47.2 ± 13.0 mL/m² LVEF: 67.0 ± 5.0 % CI: 6.2 ± 1.4 L/min/m² SBP: 163.0 ± 29.0 mmHg	

Jaijee et al., 2018 [110]	Participants: N=14 • Males N=4 • Females N=10 Age: 39.1 ± 9.4 yrs Disease: PAH	To determine the effect of elevated afterload on RV contractile reserved during normobaric hypoxia (which has been associated with transient acute pulmonary hypertension) and in chronic PAH before the RV becomes dilated or impaired	Supine cycle ergometer: • 40% of maximal CPET CMR methods: • rest and during exercise	HR: 63.4 ± 11.5 bpm CI: 2.9 ± 0.6 L/min/m² LVEDVi: 70.3 ± 14.6 mL/m² LVESVi: 25.7 ± 9.3 mL/m² LVSVi: 44.6 ± 6.7 mL/m² LVEF: 64.3 ± 6.2 % RVEDVi: 88.1 ± 2.5 mL/m² RVESVi: 40.1 ± 9.5 mL/m² RVSVi: 45.3 ± 2.6 mL/m RVEF: 53.6 ± 4.3 %	HR: 114.1 ± 15.6 bpm CI: 5.2 ± 1.2 L/min/m² LVEDVi: 67.2 ± 16.3 mL/m² LVESVi: 18.4 ± 8.8 mL/m² LVSVi: 48.9 ± 9.1 mL/m² LVEF: 73.7 ± 6.7 % RVEDVi: 93.2 ± 4.0 mL/m² RVESVi: 45.8 ± 15.9 mL/m RVSVi: 47.4 ± 2.6 mL/m² RVEF: 51.4 ± 10.7 %	Cardiac imaging during submaximal exercise demonstrates that patients with chronic PAH have depletion of contractile reserves despite preserved EF at rest Exercise imaging has the potential to unmask dysfunction in the RV before resting adaptations to PAH Data suggests that an impaired response to exercise may contribute to reduced LV preload and consequent underfilling
La Gerche et al., 2013 [116]	Participants: N=6 • Males N=N/A • Females N=N/A Age: 38.0 ± 26.0 yrs Disease: symptomatic ventricular arrhythmias	To validate a novel method of biventricular volume quantification by CMR imaging during maximal exercise	• Upright cycle ergometer: CPET at 50W+25W/min • Supine cycle ergometer CMR methods: • rest, 25% intensity, 50% intensity, and 66% intensity of maximal power exercise	HR: 61.0 ± 12.0 bpm LVEDV: 224.0 ± 29.0 mL LVESV: 102.0 ± 37.0 mL LVSV: 122.0 ± 25.0 mL LVEF: 55.0 ± 8.0 % RVEDV: 220.0 ± 34.0 mL RVESV: 101.0 ± 37.0 mL RVSV: 118.0 ± 20.0 mL RVEF: 55.0 ± 10.0 % CO: 7.2 ± 1.3 L/min	HR: 152.0 ± 27.0 bpm LVEDV: 226.0 ± 23.0 mL LVESV: 80.0 ± 36.0 mL LVSV: 145.0 ± 25.0 mL LVEF: 66.0 ± 8.0 % RVEDV: 226.0 ± 31.0 mL RVESV: 88.0 ± 39.0 mL RVSV: 139.0 ± 29.0 mL RVEF: 62.0 ± 14.0 % CO: 21.6 ± 5.7 L/min	During exercise, patients with arrhythmias experienced an increase in EF, while those with heart failure did not Although LVEDV at peak exercise remained the same as baseline values, LVESV decreased in arrhythmia patients, but not in those with heart failure
	Participants: N=3 • Males N=N/A • Females N=N/A Age: 63.0 ± 13.0 yrs			HR: 69.0 ± 5.0 bpm LVEDV: 132.0 ± 24.0 mL LVESV: 48.0 ± 13.0 mL	HR: 104.0 ± 16.0 bpm LVEDV: 142.0 ± 26.0 mL LVESV: 48.0 ± 14.0 mL	

	Disease: heart failure			LVSV: 83.0 ± 12.0 mL LVEF: 64.0 ± 4.0 % RVEDV: 141.0 ± 45.0 mL RVESV: 61.0 ± 44.0 mL RVSV: 80.0 ± 4.0 mL RVEF: 60.0 ± 16.0 % CO: 5.6 ± 0.3 L/min	LVSV: 94.0 ± 12.0 mL LVEF: 67.0 ± 4.0 % RVEDV: 148.0 ± 44.0 mL RVESV: 56.0 ± 34.0 mL RVSV: 90.0 ± 11.0 mL RVEF: 63.0 ± 11.0 % CO: 9.4 ± 1.2 L/min	
La Gerche et al., 2015 [105]	Participants: N=17 • Males N=N/A • Females N=N/A Age (patients without ICD): 39.0 ± 8.0 yrs Age (patients with ICD): 40.0 ± 9.0 yrs Disease: RV ventricular arrhythmias	To validate the pathophysiological concept of exercise-induced pro-arrhythmic remodeling in humans To develop a non-invasive clinical tool for differentiating healthy athletes from those with a propensity to serious arrhythmias	• Upright cycle ergometer: CPET at initial 50W+25W/min • Supine cycle ergometer CMR methods: • rest, 25% intensity, 50% intensity, and 66% intensity of maximal power exercise	HR: 61.0 ± 12.0 bpm LVEDV: 229.0 ± 24.0 mL LVESV: 100.0 ± 32.0 mL LVSV: 129.0 ± 22.0 mL LVEF: 56.8 ± 10.2 % RVEDV: 233.0 ± 34.0 mL RVESV: 108.0 ± 31.0 mL RVSV: 125.0 ± 21.0 mL RVEF: 54.1 ± 8.1 % CO: 7.7 ± 1.7 L/min	HR: 149.0 ± 25.0 bpm LVEDV: 224.0 ± 19.0 mL LVESV: 79.0 ± 28.0 mL LVSV: 145.0 ± 21.0 mL LVEF: 65.2 ± 10.0 % RVEDV: 237.0 ± 27.0 mL RVESV: 95.0 ± 30.0 mL RVSV: 142.0 ± 24.0 mL RVEF: 60.3 ± 10.4 % CO: 21.5 ± 5.1 L/min	CMR measures of RV function performed during exercise show promise in being able to differentiate healthy athletes from those with a propensity to serious ventricular arrhythmias
Latus et al., 2022 [120]	Participants: N=18 • Males N=14 • Females N=4 Age: 24.0 ± 3.0 yrs Disease: Fontan	To assess changes in V-A coupling and APC flow during exercise CMR	Supine cycle ergometer: • initial workload: increased by 15W every 5 minutes to achieve 60W CMR methods: • rest and during exercise	HR: 63.0 ± 9.0 bpm CI: 3.0 ± 0.5 L/min/m ² SBP: 112.0 ± 9.0 mmHg EDVi: 80.0 ± 17.0 mL/m ² ESVi: 32.0 ± 11.0 mL/m ² SVi: 48.0 ± 9.0 mL/m ² EF: 60.0 ± 7.0 %	HR: 96.0 ± 10.0 bpm CI: 5.2 ± 1.0 L/min/m ² SBP: 133.0 ± 16.0 mmHg EDVi: 84.0 ± 20.0 mL/m ² ESVi: 30.0 ± 11.0 mL/m ² SVi: 55.0 ± 12.0 mL/m ² EF: 65.0 ± 8.0 %	Fontan patients show in inefficient V-A coupling already at rest that is further aggravated during exercise primarily caused by a limited increase in ventricular contractility

Le et al., 2020 [13]	Participants: N=13 • Males N=11 • Females N=2 Age: 43.0 ± N/A yrs Disease: DCM	To examine the diagnostic roles of Ex-CMR to distinguish between pathological DCM and physiological exercise-induced cardiac remodeling in patients with suspected DCM	Supine cycle ergometer: • initial 25W + 25W/min CMR methods: • rest and exercise	HR: 73.0 ± N/A bpm SBP: 116.0 ± N/A mmHg DBP: 76.0 ± N/A mmHg LV massi: 54.0 ± N/A g/m² LVEDVi: 102.0 ± N/A mL/m² LVESVi: 59.0 ± N/A mL/m² LVEF: 42.0 ± N/A % RVEDVi: 81.0 ± N/A mL/m² RVESVi: 45.0 ± N/A mL/m² RVEF: 49.0 ± N/A %	HR: 140.0 ± N/A bpm LVEF: 49.0% change	Ex-CMR has potential diagnostic and prognostic value in distinguishing between pathological DCM and physiological exercise-induced cardiac remodeling in patients with suspected DCM
Le et al., 2021[93]	Participants: N=60 • Males N=43 • Females N=17 Age: 59.0 ± 8.0 yrs Disease: CAD	To examine the diagnostic value of a multiparametric approach in patients with suspected CAD, compared with invasive fractional flow reserve	Supine cycle ergometer: • initial 25W + 25W/min CMR methods: • rest and exercise	HR: 73.0 ± 12.0 SBP: 139.0 ± 16.0 DBP: 79.0 ± 13.0 LV massi: 50.0 ± 12.0 g/m² LVEDVi: 76.0 ± 15.0 mL/m² LVESVi: 33.0 ± 12.0 mL/m² LVSVi: 43.0 ± 8.0 mL/m² LVEF: 57.0 ± 9.0 % RVEDVi: 77.0 ± 14.0 mL/m² RVESVi: 34.0 ± 10.0 mL/m² RVSVi: 42.0 ± 8.0 mL/m² RVEF: 56.0 ± 8.0 %	HR: 122.0 ± 19.0 SBP: 174.0 ± 26.0 DBP: 111.0 ± 29.0 CI: 6.2 ± 1.2 L/min/m² CI: 104.0% change SVi: 26.0% change LVEF: 21.0% change	Ex-CMR using supine cycle ergometer demonstrates feasibility in assessing multiple CMR parameters that in combination, have high accuracy in diagnosing significant CAD, as defined by invasive FFR

				CI: 3.1 ± 0.7 L/min/m ²		
Macdonald et al., 2018 [111]	Participants: N= 6 • Males N=1 • Females N=5 Age: 60.0 ± 9.0 yrs Disease: PAH	To examine the effects of PAH on aortic flow and stiffness in response to exercise with phase contrast MRI	Stepper ergometer: • beat of a metronome at the target exercise frequency • 30W for 3min CMR methods: • rest and exercise	HR: 69.0 ± 19.0 bpm SV: 67.0 ± 16.0 mL CO: 4.5 ± 1.4 L/min	HR: 116.0 ± 19.0 bpm SV: 90.0 ± 42.0 mL CO: 10.8 ± 5.7 L/min	Phase contrast MRI following a modest exercise challenge was capable of detecting differences in left heart dynamics likely induced from PAH Image quantification following exercise could likely be improved in future studies, through the implementation of free-breathing or real-time MRI acquisitions
Olsen et al., 2021 [112]	Participants: N=9 • Males N=4 • Females N=5 Age: $42.7 \pm N/A$ yrs Disease: PAH	To perform subject-specific computer simulations based on invasive measurements and CMR imaging, to investigate whole circulation properties in PAH at rest and exercise and determinants of exercise reserve	Supine cycle ergometer (pedal) with remote-controlled resistance • initial workload: 5-min warm-up, workload increase until patients achieved >13 out of 20 on the Borg Rating of Perceived Exertion Scale CMR methods: • rest and exercise	HR: 67.7 bpm CI: 2.6 L/min/m ² RVEDV: 211.3 mL RVESV: 130.2 mL RVEF: 39.2 % RV mass: 71.8 g LVEDV: 124.7 mL LVESV: 49.2 mL LVEF: 60.8 % LV mass: 99.3 g	HR: 107.3 bpm CI: 4.1 L/min/m ² RVEDV: 254.4 mL RVESV: 164.9 mL RVEF: 35.8 % LVEDV: 120.2 mL LVESV: 42.4 mL LVEF: 64.9 %	During exercise, PAH patients have an inadequate increase in RV myocardial contractile force coupled with severe increases in loading conditions

Petit et al., 2021 [106]	Participants: N=16 • Males N=7 • Females N=9 Age: 72.0 ± 2.0 yrs Disease: HFpEF	To evaluate RV performance at rest and during exercise using CMR in carefully selected symptomatic HFpEF patients with and without PH (i.e. Stage C heart failure) and in asymptomatic patients with subclinical LV diastolic dysfunction (i.e. Stage B heart failure)	Upright cycle ergometer: • CPET	HR: 69.0 ± 3.0 bpm SBP: 145.0 ± 5.0 mmHg LVEDVi: 66.0 ± 3.0 mL/m ² LVMI: 82.0 ± 18.0 gm/m ² LVEF: 61.7 ± 1.7 % RVEDVi: 69.0 ± 4.0 mL/m ² RVEF: 56.0 ± 2.0 % CI: 2.7 ± 0.1 L/min/m ²	HR: 104.0 ± 6.0 bpm SBP: 171.0 ± 9.0 mmHg LVEF: 66.1 ± 2.1 % RVEF: 52.8 ± 2.6 % CI: 4.1 ± 0.2 L/min/m ²	Exercise CMR identifies RV dysfunction and impaired RV-arterial coupling at an early stage of HFpEF
	Participants: N=7 • Males N=5 • Females N=2 Age: 66.0 ± 3.0 yrs Disease: LVCR		Supine cycle ergometer: • 25%, 50% and 66% of peak power achieved during CPET CMR methods: • rest and exercise	HR: 65.5 ± 5.0 bpm SBP: 159.0 ± 10.0 mmHg LVEDVi: 69.0 ± 6.0 mL/m ² LVMI: 86.0 ± 14.0 gm/m ² LVEF: 61.4 ± 1.9 % RVEDVi 65.0 ± 3.0 mL/m ² RVEF: 59.0 ± 1.0 % CI: 2.6 ± 0.3 L/min/m ²	HR: 109.0 ± 5.0 bpm SBP: 206.0 ± 15.0 mmHg LVEF: 64.1 ± 2.5 % RVEF: 58.9 ± 2.5 % CI: 4.8 ± 0.4 L/min/m ²	
Santens et al., 2023 [121]	Participants: N=44 • Males N=31 • Females N=13 Age: 25.0 ± 4.0 yrs Disease: patients who received ASO	To assess ventricular function by advanced echocardiography and CMR imaging at rest and during exercise	Upright cycle ergometer: • CPET Supine cycle ergometer Real time CMR methods: • rest, 25%, 50% and 66% maximal power	HR: 70.0 ± 13.0 bpm LVEDVi: 87.0 ± 18.0 mL/m ² LVESVi: 39.0 ± 13.0 mL/m ² LVEF: 57.0 ± 7.0 % RVEDVi: 84.0 ± 15.0 mL/m ² RVEF: 57.0 ± 8.0 % RVESVi: 38.0 ± 16.0 mL/m ² SVi LR: 48.0 ± 8.0 mL/m ² SVi RV: 47.0 ± 7.0 mL/m ² CILV: 3.0 ± 1.0 L/m ² CIRV: 3.0 ± 1.0 L/m ²	HR: 153.0 ± 21.0 bpm LVEDVi: 86.0 ± 18.0 mL/m ² LVESVi: 27.0 ± 11.0 mL/m ² LVEF: 70.0 ± 9.0 % RVEDVi: 83.0 ± 15.0 mL/m ² RVEF: 68.0 ± 11.0 % RVESVi: 30.0 ± 17.0 mL/m ² SVi LR: 59.0 ± 11.0 mL/m ² SVi RV: 55.0 ± 8.0 mL/m ² CILV: 9.0 ± 2.0 L/m ² CIRV: 8.0 ± 2.0 L/m ²	Subclinical myocardial LV and RV dysfunction was found, despite normal ventricular function on standard screening and normal levels of biomarkers The function of the subpulmonary RV at rest was associated with exercise capacity During exercise, the systemic LV function correlated with exercise capacity In ASO patients, maximal exercise capacity is impaired and seems to be linearly related to the CR of the LV and the RV Ex-CMR might play a role in detecting subclinical deterioration of ASO patients
	Participants: N=43 • Males N=20 • Females N=23	To document if Ex-CMR imaging could provide non-invasive characterization of	Supine cycle ergometer:	HR (RHC): 73 bpm CI (RHC): 3.1 L/m ²	HR (RHC): 108 bpm CI (RHC): 6.0 L/m ²	Latent PVD is a feature of HFpEF and is associated with impaired RV

Schuster et al., 2023 [107]	Age: 67 ± N/A yrs Disease: HFpEF with no PVD	cardiac and pulmonary physiology to identify HFpEF patients who could potentially benefit from IASD implantation	CMR methods: • rest and during exercise 3 minutes after reaching a plateau (between 100-110 bpm)			functional reserve, global diastolic filling and LV-CI
	Participants: N=24 • Males N=4 • Females N=20 Age: 70 ± N/A yrs Disease: HFpEF with latent PVD			HR (RHC): 67 bpm CI (RHC): 2.5 L/m ²	HR (RHC): 102 bpm CI (RHC): 4.1 L/m ²	CMR can quantified and be used to identify patients likely to benefit from IASD implantation
Seemann et al., 2023 [108]	Participants: N=1 • Males N=N/A • Females N=N/A Age: N/A Disease: HFpEF	To develop and CMR method to quantify time-resolved lung water dynamics during rest and exercise stress	Supine cycle ergometer (pedal) • initial workload: 60W, increased by the scanner operator if needed	HR: 49.0 bpm LVEF: 54.0 % CO: 6.2 L/min LVEDV: 245.0 mL LVESV: 118.0 mL	N/A	This method was capable of depicting and quantifying lung water dynamics in patients with compensated HF during supine exercise stress
	Participants: N=1 • Males N=N/A • Females N=N/A Age: N/A Disease: HFrEF		CMR methods: • rest and exercise	HR: 74.0 bpm LVEF: 27.0 % CO: 4.3 L/min LVEDV: 214.0 mL LVESV: 157.0 mL	N/A	
Steinmetz et al., 2021 [115]	Participants: N=33 • Males N=16 • Females N=17 Age: 35.6 ± 11.3 yrs Disease: cTOF	To elucidate the underlying mechanisms of exercise tolerance in cTOF patients using a comprehensive CPET and real-time CMR exercise testing protocol in a prospective case-control study	Upright cycle ergometer: • CPET: increased by 20W/min Supine cycle ergometer • initial workload: 15W, increased by 5/min Real time CMR methods: • rest and exercise after steady workload (50, 70 and 90W) of 5 minutes each	HR: 75.0 ± 11.0 bpm	HR: 122.0 ± 20.0 bpm	cTOF patients exhibited significantly impaired exercise tolerance in CPET compared with healthy controls (lower maximum oxygen uptake, lower performance) CMR-ET revealed a significantly lower contractile reserve in RV and LV function for cTOF patients compared with healthy controls Correlation analysis of CPET parameters and CMR-ET cardiac functional parameters did not reveal a significant impact of pulmonary RF, RV-EDVi, or RV-EF on overall exercise capacity. Lower LV-EF at 90W CMR-ET was correlated with good exercise capacity in cTOF patients
	Participants: N=8 • Males N=8 • Females N=0 Age: 72.5 ± 9.3 yrs	To evaluate rest and exercise hemodynamics in patients	Custom-built MRI-compatible exercise cycle • seated lower limb exercise	HR: 73.0 ± 13.0 bpm	HR: 94.0 ± 14.0 bpm	Mild exercise provides changes in hemodynamic conditions that may provide benefits in cardiovascular

Tenforde et al., 2010 [122]	Disease: AAA	with AAA and peripheral occlusive disease using PC-MRI	• Workloads were adjusted on patients' ability level and to increase HR (up to 150% resting HR)			health for individuals with advanced vascular disease Abdominal aortic hemodynamic changes due to lower extremity exercises can be quantified in patients with AAA and peripheral occlusive disease using PC-MRI
	Participants: N=6 • Males N=6 • Females N=0 Age: 62.3 ± 10.3 yrs Disease: peripheral occlusive disease			HR 68.0 ± 11.0 bpm	HR 92.0 ± 16.0 bpm	
von Knobelsdorff-Brenkenhoff et al., 2016 [21]	Participants: N=12 • Males: N=10 • Females: N=2 Age: 62.0 ± 14.0 yrs Disease: AS	To identify abnormalities of myocardial velocities in patients with left ventricular pressure overload using MRI tissue phase mapping at rest and exercise	Isometric handgrip exercise • 6 min of continuous exercise at 30% max grip strength	HR: 66.0 ± 9.0 bpm SBP: 136.0 ± 20.0 mmHg DBP: 75.0 ± 13.0 mmHg	HR: 75.0 ± 11.0 bpm SBP: 160.0 ± 28.0 mmHg DBP: 89.0 ± 19.0 mmHg LVEF: 65.0 ± 5.0 % LVEDV: 155.0 ± 52.0 mL LVEDi: 75.0 ± 22.0 mL/m ² LV MASS: 155.0 ± 58.0 g LV MASSi: 75.0 ± 26.0 g/m ²	Ex-CMR provided detailed information about the functional state of the LV in presence of preserved EF
	Participants: N=7 • Males: N=6 • Females: N=1 Age: 58.0 ± 19.0 yrs Disease: HYP			HR: 61.0 ± 9.0 bpm SBP: 131.0 ± 22.0 mmHg DBP: 77.0 ± 11.0 mmHg	HR: 73.0 ± 7.0 bpm SBP: 164.0 ± 13.0 mmHg DBP: 96.0 ± 15.0 mmHg LVEF: 62.0 ± 6.0 % LVEDV: 177.0 ± 35.0 mL LVEDi: 83.0 ± 13.0 mL/m ² LV MASS: 151.0 ± 45.0 g LV massi: 72.0 ± 22.0 g/m ²	

Abbreviations: AAA, abdominal aortic aneurysms; APC, aortopulmonary collateral; AS, aortic stenosis; ASO, arterial switch operation; BPM, beats per minute; BSA, body surface area; CAD, coronary artery disease; ccTGA, congenitally corrected transposition of the great arteries; CI, cardiac index; CILV, cardiac index left ventricle; CIRV, cardiac index right ventricle; CMR, cardiac magnetic resonance; CMR-CPET, cardiac magnetic resonance-cardiopulmonary exercise test; CO, cardiac output; CPET, cardiopulmonary exercise test; CR, contractile reserve; cTOF, correction of tetralogy of Fallot; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; EDVi, end diastolic volume index; EF, ejection fraction; ESVi, end systolic volume index; Ex-CMR, exercise cardiac magnetic resonance; FFR, fractional flow reserve; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HRR, heart rate recovery; HYP, arterial hypertension; IASD, interatrial shunt device; ICD, implantable cardiac defibrillator; iPAH, idiopathic pulmonary arterial hypertension; iVO₂, oxygen consumption indexed to weight; LA, left atrial; LV, left ventricle; LVCOi, left ventricular cardiac output index; LVCR, left ventricular relaxation due to concentric remodeling; LVEDV, left ventricular end diastolic volume; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVESVi, left ventricular end systolic volume index; LV mass, left ventricular mass; LV Massi, left ventricular mass index; LVMI, left ventricular mass index; LVSV, left ventricular stroke volume; LVSVi, left ventricular stroke volume index; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NC-PAH, non-connective tissue disease pulmonary hypertension; PAH, pulmonary arterial hypertension; PC-MRI, phase contrast magnetic resonance imaging; PH, pulmonary hypertension; PVD, pulmonary vascular disease; RHC, right heart catheterization; RPP, rate pressure product; RT-CMR, real-time cardiac magnetic resonance; RTOF, repaired tetralogy of Fallot; RV, right ventricle; RVCOi, right ventricular cardiac output index; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end diastolic volume; RVEDVi, right ventricular end diastolic volume index; RVESV, right ventricular end systolic volume; RVESVi, right ventricular end systolic volume index; RV MASS, right ventricular mass; RVSV, right ventricular stroke volume; RVSVi, right ventricular stroke volume index; SBP, systolic blood pressure; SSc, systemic sclerosis; SSc-PAH, systemic sclerosis associated pulmonary arterial hypertension; sRV, systemic right ventricle; SVi, stroke volume index; SV, stroke volume; SViLV, stroke volume index left ventricle; SViRV, stroke volume index right ventricle; TGA, transposition of the great arteries; V-A, ventricular arterial; W, watt; YRS, years; Δ avO₂, arteriovenous oxygen content gradient.

Table 2. Reported Ex-CMR testing advantages and limitations

Authors & Year	Ex-CMR testing protocols	Reported Ex-CMR testing advantages	Reported Ex-CMR testing limitations
Backhaus et al., 2021 [104]	Supine cycle ergometer	• RT-CMR allows highly accurate identification of HFpEF during physiologic exercise and qualifies as a suitable noninvasive diagnostic alternative. • The RT-CMR method used in this study allows CMR stress testing during actual exercise with live image reconstruction, good image quality, and good temporal and spatial resolution, which makes this test a potentially valid non-invasive to RHC. • Results of the HFpEF-Stress trial demonstrate the feasibility and higher accuracy of RT-CMR as a non-invasive method for clinical detection of HFpEF. • The addition of physiologic exercise RT-CMR in the diagnostic workup of patients with HFpEF offers several advantages. These include the ability to live RT physiology assessment during actual exercise with temporal resolution comparable with echocardiography in modern scanners. There are benefits from the standpoint of conventional CMR imaging such as higher spatial resolution and absence of imaging plan restrictions. Moreover, RT-CMR renders the need for breath-holding during imaging obsolete and enables the implementation of exercise stress during imaging, the importance of which has been well established for RHC within major guideline recommendations. • Our results demonstrate feasibility of exercise RT-CMR in the clinical setting. • The high spatial resolution enabled detailed and reliable analysis of changes in cardiac volumes and longitudinal shortening during the cardiac cycle. Exercise stress does not negatively affect image quality in RT-CMR. This represents a substantial advantage over echocardiography, which has impaired data reliability during physiologic exercise.	• More detailed evaluation of early diastolic filling/emptying during exercise stress using mathematical approaches is limited by the temporal resolution of RT-CMR, especially at relatively high heart rates of 100 to 110 bpm.
Brown et al., 2021 [117]	Supine cycle ergometer	• The CMR measurements of cardiac output are considered gold-standard, eliminating some of the assumptions made by other non-invasive methods (e.g. Doppler echocardiography). • All subjects successfully completed the exercise protocol and no subjects required medical intervention. • The benefit of CMR-augmented CPET to investigate exercise dysfunction is a novel technology allowing simultaneous quantification of peak $\dot{V}O_2$ and cardiac index and subsequent calculations of $\Delta a\dot{V}O_2$.	• Achieving true peak-exercise using a supine exercise protocol is challenging. • The long time interval between clinical measures (i.e., lung function tests) and CMR-CPET may affect the robustness of correlations between these markers.
Claessen et al., 2018 [9]	Supine cycle ergometer	• To date this is the only study to compare exercise measures in EAs and DCM patients.	• Image quality and through-plane movement during exercise provide limitations in feasibility and reproducibility.

Göransson et al., 2019 [109]	Supine cycle ergometer	• The repeated measurements approach in our study also adds information on associated cardiac changes with change in exercise response. • CMR imaging at rest has the advantage of assessing RV structure and function with high reproducibility in PAH. As SV and RV volumes could be considered the strongest predictors of morbidity and mortality in PAH, the SV and RV responses during exercise possibly reveal the degree of right heart adaptation to increased output.	• Exercise testing before exercise CMR imaging would have provided a more comprehensive assessment but also complicated the general applicability of the method indicated. Image quality was lower during exercise than during rest.
Groepenhoff et al., 2007 [118]	Supine cycle ergometer	• The intra-beath method was originally developed to calculate the TLCO during a constant exhalation. The advantage of such a technique is that it can be performed during exercise. • To validate the intra-breath method, we used MRI to measure SV since this method is non-invasive, clinically accepted and can be used during exercise.	Not reported.
Habert et al., 2018 [114]	Supine cycle ergometer	• An exercise stress CMR took more or less the same time to perform as exercise echocardiography.	• In this setting, the patient exercised first and is moved to the examination table immediately after completion of the exercise phase. However, with this protocol, a lot of time was lost installing the patient on the CMR table and even more so in debilitated patients with right ventricular dysfunction. • Exercise in the supine position did not develop the same power as on a treadmill. • Exercise stress CMR requires caution as a stress test, it entails the same risks as an electrocardiographic exercise test or single photon emission computed tomography. • Another limitation was the fact that the image acquisitions were not carried out during exercise but less than a minute after pedaling stopped and with a short breath hold.
Hays et al., 2010 [62]	Isometric exercise	handgrip • Isometric handgrip exercise is well suited to the MRI environment as it requires no vascular access and has been used safely in subjects with CAD.	Not reported.
Hays et al., 2013 [113]	Isometric exercise	handgrip Not reported.	Not reported.
Helsen et al., 2018 [119]	Supine cycle ergometer	• The main advantage of our supine bicycle protocol is that we test during physiological stress, maintain preload during exercise (in contrast to dobutamine stress).	Not reported.
Jaijee et al., 2018 [110]	Supine cycle ergometer	• Ex-CMR using ungated continuous imaging is considered the “gold standard” for ventricular volume measurements during high intensity exercise and shows close agreements with invasive assessment.	• Exercise CMR accuracy depends on adequate temporal and spatial resolution to avoid underestimating SV at high HRs.
La Gerche et al., 2013 [116]	Supine cycle ergometer	• The excellent reproducibility (interobserver and repeated tests) of exercise CMR was demonstrable despite the fact that there was a number of analysis stages each with the potential to increase variability.	• Slightly less time is required for analyzing gated images at rest but at higher levels of exercise, difficulties in identifying the endocardium make this at least as time consuming, if not impossible.

La Gerche et al., 2015 [105]	Supine cycle ergometer	Real-time CMR performed during free breathing and strenuous exercise has been rigorously validated and has the advantage of providing simultaneous comparisons between LV and RV function. Thus, confidence can be placed in the divergence of ventricular function observed in EA-VAs during exercise.	- Despite the expectation of more accurate quantification of RV function with exercise CMR, it did not prove better than echocardiography at identifying athletes with subtle RV dysfunction and arrhythmias. Given the widespread availability and cost-effectiveness of echocardiography, this is an important finding. - High-quality images can be acquired by Ex-CMR in virtually all subjects but the technique remains expensive and confirmed to few specialized centres. - Although these areas under the ex-CMR ROC curves seemed inferior to those of echocardiography, direct comparison is limited by the fact that athletes with an ICD had to be excluded from CMR measurements.
Latus et al., 2022 [120]	Supine cycle ergometer	Physical exercise occurring with the cycle ergometer activates muscle pump function of the legs and thereby creates a different physiological haemodynamic situation than dobutamine with a greater extent of blood returning from the lower extremities.	- The chosen CMR exercise levels were not adapted to the results of the CPET study, nor were the levels gender, or age-matched. - Due to imaging artifacts that occurred with body movement at higher exercise levels, analysis of both blood flow and cine images was challenging and, according to our experiences, may not be reliable at a workload exceeding 60W. - Although the participants were asked to exercise until subjective maximal exertion, the presented values at highest cycle intensity may not represent individual maximal exercise capacity. - The limited temporal and spatial resolution of the used RT-CMR sequences may also affect our results.
Le et al., 2020 [13]	Supine cycle ergometer	- For the first time, the diagnostic value and prognostic implications of exercise stress imaging were demonstrated in patients with suspected DCM. - Exercise stress coupled with imaging has theoretical advantage to rest-based imaging. - CMR is widely considered the gold standard for the assessment of cardiac function and LV mass. Moreover, the strength of myocardial characterization with gadolinium contrast in CMR is unparalleled in other conventional imaging modalities. For these reasons, we used the recently developed exercise stress CMR to examine the role of exercise stress imaging in DCM. - Unlike cardiopulmonary exercise tests or echocardiography, exercise stress CMR can assess cardiac function, myocardial mass, tissue characterization and exercise capacities in the single modality. - Unlike exercise LVEF and other imaging parameters, peak exercise CI is a measure that incorporates a physiological parameter (heart rate) in the assessment of exercise capacity.	Although echocardiography remains the mainstay of cardiac imaging, it has limitations in distinguishing overlapping phenotypes between DCM and exercise-induced cardiac remodeling.
Le et al., 2021[93]	Supine cycle ergometer	Stress CMR has evolved as a highly accurate non-invasive and prognostic test that provides cost-effective imaging-based strategy to guide coronary revascularization in patients with stable CAD.	Free-breathing exercise stress perfusion image acquisition at high HR remains challenging to achieve optimal spatial and temporal resolution due to breathing

		• It is the first study to examine the potential of a multiparametric in-scanner ExCMR protocol to diagnose significant CAD, when compared to the gold standard invasive FFR. • Instead of relying on one parameter, the novel ExCMR protocol combines different diagnostic strengths of regional wall motion abnormalities, perfusion defects, LGE and exercise capacity in a single stress modality to improve diagnostic confidence in detecting significant CAD.	and cardiac motion. This would affect stress perfusion imaging quality and result in difficulty in the interpretation of imaging and lower interobserver agreement of perfusion assessment as compared to RWMA and LGE.
Macdonald et al., 2018 [111]	Stepper ergometer	• Total examination time was less than an hour, including set-up and take-down of the exercise equipment. Subjects typically spent less than 30 min in the scanner bore.	• Despite the advantages MRI could offer over existing exercise imaging modalities in assessing pulmonary hypertension, exercise MRI is challenging because of the relatively slow acquisition speed and the narrow confinements of the magnet bore. • The harness used to reduce chest motion was not entirely effective at preventing subject movement, as demonstrated with the two subjects who moved out of their prescribed scanned planes. Motion such as this probably lead to shifts of rotations in scanned plans in the other subjects which would impact the accuracy of flow and vessel cross-sectional area measurements.
Olsen et al., 2021 [112]	Supine cycle ergometer	Not reported.	Not reported;
Petit et al., 2021 [106]	Supine cycle ergometer	• The exercise CMR technique enabled us to clearly demonstrate an impaired increase in ventricular contractility during exercise in patients without any signs or symptoms of heart failure, but with early diastolic dysfunction (i.e. Stage B heart failure). • Studying both functional (LV and RV exercise haemodynamics) and structural (extracellular volume measurement) parameters using CMR might identify earlier stages of the disease (i.e. in asymptomatic patients), which are better responsive to targeted interventions.	Not reported
Santens et al., 2023 [121]	Supine cycle ergometer	Not reported	• Ex-CMR did not document on average abnormal changes in ventricular dimension and function
Schuster et al., 2023 [107]	Supine cycle ergometer	• CMR exercise stress testing enables quantification of RV functional reserved, PVR and left heart interplay in HFpEF. • The role of exercise stress CMR imaging in HFpEF provides firstly early detection of HFpEF, secondly general prognostic assessment, and thirdly a gatekeeper function regarding referral for invasive characterization. • The present data highlight the potential role of RT-CMR exercise stress testing as a novel non-invasive approach for individual patient selection for IASD treatment.	Not reported
Seemann et al., 2023 [108]	Supine cycle ergometer	• The consistent increase in LWD in human subjects when transitioning from rest to exercise, and decrease when transitioning from exercise to rest, further validates the ability to measure lung water dynamics. • MRI offers the advantages of being noninvasive, quantitative, and free from ionizing radiation during long exercise studies. Moreover,	Not reported

most patients with heart failure routinely undergo cardiac MRI exams for assessment of cardiac volumes, function, and tissue characterization.			
Steinmetz et al., 2021 [115]	Supine cycle ergometer	Impaired RV function, pulmonary flow and LV function became apparent during exercise-stress real-time CMR and were not visible at rest.	- The participants terminated CMR-ET before reaching their maximal exercise level because the exercise was performed within the MR scanner and because they were wrapped with the receiver coil. - The scanner array was uncomfortable and more strenuous than upright standard CPET outside the scanner.
Tenforde et al., 2010 [122]	Custom-built MRI-compatible exercise cycle	Not reported.	Not reported
von Knobelsdorff-Brenkenhoff et al., 2016 [21]	Isometric handgrip exercise.	CMR imaging allows the quantification of the LV motion using TPM	A highly accelerated TPM sequence with image acquisition during one breath-hold was used to enable imaging during peak stress, with the drawback of prolonged temporal resolution. True peak velocities may have been underestimated.

Abbreviations: BPM, beats per minute; CAD, coronary artery disease; CI, cardiac index; CMR, cardiac magnetic resonance; CMR-ET, cardiac magnetic resonance exercise testing; CPET, cardiopulmonary exercise test; DCM, dilated cardiomyopathy; EA, endurance athletes; EA-VA, endurance athletes ventricular arrhythmias; Ex-CMR, exercise cardiac magnetic resonance; FFR, fractional flow reserve; HHpEF, heart failure with preserved ejection fraction; HR, heart rate; IASD, interatrial shunt device; ICD, implantable cardiac defibrillator; iVO₂, oxygen consumption indexed to weight; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; LWD, lung water density; MR, magnetic resonance; MRI, magnetic resonance imaging; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; ROC, receiver operating characteristics; RT-CMR, real-time cardiac magnetic resonance; RT, real time; RV, right ventricle; RWMA, regional wall motion abnormalities; SV, stroke volume; TLCO, transfer factor for carbon monoxide; TPM, tissue phase mapping; W, watt; Δ avO₂, arteriovenous oxygen content gradient.