



The Potential of Oxygenation-Sensitive CMR in Heart Failure

Elizabeth Hillier^{1,2} · Matthias G. Friedrich^{1,3}

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Abstract

Purpose of Review Cardiac magnetic resonance imaging (CMR) use in the context of heart failure (HF) has increased over the last decade as it is able to provide detailed, quantitative information on function, morphology, and myocardial tissue composition. Furthermore, oxygenation-sensitive CMR (OS-CMR) has emerged as a CMR imaging method capable of monitoring changes of myocardial oxygenation without the use of exogenous contrast agents.

Recent Findings The contributions of OS-CMR to the investigation of patients with HF includes not only a fully quantitative assessment of cardiac morphology, function, and tissue characteristics, but also high-resolution information on both endothelium-dependent and endothelium-independent vascular function as assessed through changes of myocardial oxygenation.

Summary In patients with heart failure, OS-CMR can provide deep phenotyping on the status and important associated pathophysiology as a one-stop, needle-free diagnostic imaging test.

Keywords Myocardial oxygenation · Microvascular dysfunction · Heart failure · Oxygenation-sensitive CMR · OS-CMR · CMR

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by dyspnea or an exertional capacity limitation caused by impaired ventricular filling or emptying, or both [1]. Currently, an estimated 26 million people are diagnosed with heart failure (HF) worldwide [2]. It is a leading cause of hospitalization, and its prevalence is increasing. The increase in prevalence has been attributed to factors including an aging population, improvements in the long-term survival of patients with chronic HF, and a reduction in short-term mortality of other cardiovascular conditions known to cause HF [2, 3].

A recent joint consensus statement on the classification of HF has subcategorized HF based on functional and/or

structural abnormalities resulting in either a reduction in overall systolic function (LVEF \leq 40%, heart failure with reduced ejection fraction, HFrEF), preserved overall systolic function (LVEF \geq 50%, heart failure with preserved ejection fraction, HFpEF), an intermediate functional classification (LVEF 40–49%, heart failure with mildly reduced ejection fraction, HFmrEF), or a classification for functional improvement (LVEF \leq 40% at baseline and a \geq 10 point improvement on second measurement with an LVEF \geq 40%, heart failure with improved ejection fraction, HFimpEF) [4]. These HF phenotypes may display different clinical characteristics, comorbidities, outcomes, response to therapy, and prognoses [5–7]. There is a need for improved recognition of the specific causes of acute HF to establish an HF diagnosis, optimize therapy, and improve overall quality of life for HF patients [4, 8, 9].

Cardiac imaging is routinely used in the investigation of all HF phenotypes. Echocardiography is typically applied as the first-line imaging modality for HF. It is less expensive than other frequently used imaging modalities and widely available and can be used at the bedside. However, image quality and accuracy of quantitative results are inconsistent [4]. Importantly, echocardiography provides little information about the myocardial tissue [10] or coronary vascular function.

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✉ Matthias G. Friedrich
matthias.friedrich@mcgill.ca

¹ Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada

² Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada

³ Departments of Medicine and Diagnostic Radiology, McGill University, 1001 Decarie Blvd, Montreal, QC H4A 3J1, Canada

Cardiovascular magnetic resonance imaging (CMR) is the current gold standard for quantitative functional assessment of the heart. CMR is also able to provide detailed information on cardiac morphology and especially on the composition of myocardial tissue [11, 12]. This includes the identification of myocardial edema, fibrosis, or infiltration with amyloid, fat, or iron. Consequently, the use of CMR in patients with HF has significantly increased over the past decade to aid in diagnosis, risk stratification, therapeutic decision-making, and monitoring [13, 14]. CMR has been shown to more accurately classify HF patients into subgroups based on left ventricular ejection fraction (LVEF) when compared with echocardiography [15]. Additionally, studies have indicated that in patients with HFpEF, CMR often identifies new pathology in HFpEF patients and better establishes specific diagnoses than echocardiography [16, 17]. CMR is a versatile, comprehensive imaging diagnostic tool for the quantitative assessment of cardiac morphology, function, and tissue status in patients with HF [13].

Coronary vascular function plays an important role in HF, with a known role of endothelial dysfunction in HF patients with and without macrovascular ischemic heart disease [18, 19]. Coronary microvascular dysfunction (endothelial-dependent or endothelial-independent) is also associated with cardiovascular risk factors such as diabetes and hypertension and is considered an early marker of atherosclerosis [20]. Moreover, endothelial dysfunction has also been identified as a key part of the pathophysiology of HFrEF and HFpEF, associated with worse prognosis and increased rates of cardiovascular events [21, 22, 23••, 24]. Diagnostic techniques that can assess endothelium-dependent pathways may thus provide more meaningful clinical information for personalized therapeutic decision-making.

Over the past decade, oxygenation-sensitive CMR (OS-CMR) has emerged as a CMR imaging method capable of assessing endothelial dysfunction through monitoring changes of myocardial oxygenation without the use of exogenous contrast agents, based on the intrinsic magnetic properties of oxy- and deoxyhemoglobin [25, 26, 27•, 28–30]. The unique ability of OS-CMR to non-invasively monitor changes of myocardial oxygenation has been demonstrated in animal models, healthy volunteers, and in patients with macrovascular and microvascular disease states including coronary artery disease (CAD), ischemia with no obstructive coronary artery stenosis (INOCA), obstructive sleep apnea (OSA), hypertrophic cardiomyopathy (HCM), aortic stenosis, dilated cardiomyopathy (DCM), chronic heart failure, and post-transplantation [26, 27•, 31–34, 35••, 36].

We review OS-CMR and discuss its potential contributions to the investigation of patients with heart failure and introduce new imaging biomarkers to aid in the risk stratification and understanding of the underlying pathophysiology in heart failure patients.

The Blood Oxygen Level-Dependent (BOLD) Effect

The ability of magnetic resonance imaging (MRI) to harness the intrinsic magnetic differences of oxygenated vs deoxygenated hemoglobin in blood to visualize changes in oxygenation states was first demonstrated in 1990 [37]. Changes of the oxygenation state of hemoglobin in tissue result in changes of signal intensity in certain MRI images that are sensitive to the so-called blood oxygen level-dependent (BOLD) effect: Oxyhemoglobin has no unpaired electrons and no magnetic moment and does not significantly alter the peri-molecular magnetic field. Deoxyhemoglobin on the other hand has unpaired electrons with a destabilizing effect on surrounding protons, inducing its paramagnetic effect that results in an accelerated relaxation of surrounding protons. In MRI images that are “BOLD-sensitive” (typically T2*-weighted images), this effect leads to a decreased signal intensity of tissue with a higher concentration of deoxyhemoglobin [37]. Oxygenation-sensitive CMR (OS-CMR) can utilize the BOLD effect in clinical settings to monitor dynamic changes in deoxyhemoglobin concentrations as a marker for myocardial oxygenation. Such changes can be induced by vasoactive or other interventions that alter myocardial blood volume and blood flow or otherwise alter the balance between oxygen demand and supply [38–43].

Myocardial oxygen balance is subject to a complex coupling between myocardial ventricular function, myocardial oxygen consumption, and coronary blood flow. Under conditions of an increased myocardial work, healthy coronary vasculature will meet the additional oxygen demand by upregulating coronary blood flow through vasodilation [44]. Vasodilation without an associated increase of myocardial oxygen demand however results in a decrease in deoxyhemoglobin concentration (static demand, increase of supply). This change will lead to a reduction of the BOLD effect in myocardial tissue and thereby to an increase in BOLD-sensitive MRI signal intensity [38]. Vasoactive interventions can therefore be used to induce a detectable change of myocardial oxygenation. Dynamic changes of BOLD-sensitive MRI signal intensity during OS-CMR image acquisition in combination of vasoactive interventions can therefore be used as a marker for coronary vascular function.

Vasoactive Interventions for Assessing Coronary Vascular Function

Vasoactive stress can be induced through several different mechanisms including pharmacologic vasodilation (increase of blood/oxygen supply, no significant change of oxygen demand) or physical stress (increase of blood/oxygen supply with associated increase of oxygen demand). CMR stress

testing typically relies on pharmacologic vasodilators to induce a response from the myocardial vasculature. Endothelium-independent pharmacologic vasodilators such as adenosine act to uncouple myocardial blood flow from oxygen demand, inducing excess (above demand level) myocardial perfusion in healthy tissue. This intervention decreases deoxyhemoglobin concentration and results in an increased OS-CMR signal intensity [45]. Endothelium-dependent vasodilation through the use of respiratory maneuvers can be utilized to assess changes in myocardial oxygenation through the actions of carbon dioxide (CO₂), a known vasodilator [46]. An inadequate response of the coronary vasculature to an increased demand results in a higher concentration of deoxyhemoglobin. OS-CMR has been used to assess each of these different mechanisms, each with their own strengths and limitations for overall feasibility and ability to add information in the clinical context of heart failure.

OS-CMR in Heart Failure

The diagnostic work-up of patients with suspected HF consists of an assessment of left ventricular systolic function and the determination of the presence or absence of ischemic disease [47].

Heart Failure: Ischemic vs Non-ischemic Cardiomyopathy

Coronary artery disease (CAD) accounts for approximately half of acute HF patients and half of HFrEF patients [48]. Given the therapeutic options of coronary revascularization and prevention treatment, the determination of the presence or absence of ischemic heart disease is critical to clinical decision-making in patients with HF. Coronary angiography is the current gold standard test to identify obstructive CAD, with fractional flow reserve (FFR) being a quantitative marker for the hemodynamic relevance of an observed coronary artery stenosis.

While first-pass perfusion stress CMR is currently not a first-line strategy for the investigation of patients with HF if non-ischemic etiology is suspected [1], its utility in suspected ischemic HF is however undisputable. Recent studies have demonstrated that stress CMR may not only be very accurate in identifying tissue subject to severe coronary artery stenoses, but also be part of the most cost-effective strategies to do that [49, 50]. Additionally, the clinical use of first-pass perfusion stress CMR has been associated with less coronary angiographies in patients with suspected CAD and in less revascularizations, even when compared to coronary angiography with FFR, all with similar clinical outcomes [51].

CMR first-pass perfusion is limited by the need for the intravenous application of gadolinium-based contrast agents and vasodilatory agents.

OS-CMR of coronary vascular function does not require contrast agents. In combination with adenosine, it can be used for assessing myocardial perfusion and oxygenation in a number of disease states [28]. In patients with CAD, adenosine OS-CMR could accurately detect regionally reduced myocardial perfusion and oxygenation in myocardial territories downstream of a significant coronary artery stenosis [52, 53]. Additionally, adenosine OS-CMR studies detected a regional myocardial perfusion and oxygenation dissociation in non-flow limiting CAD, indicating that perfusion deficits do not always indicate underlying oxygenation deficits [54–56].

A dissociation between myocardial perfusion and oxygenation may be an important pathophysiologic component in HF and therefore critical for our understanding of the pathophysiology of HF, with an impact on management strategies in both, ischemic and non-ischemic HF. This is particularly important in light of recent evidence that when comparing medical therapy to procedural intervention as a first-line treatment strategy, there were no significant changes in patient clinical outcomes [51, 57].

The endogenous contrast in OS-CMR that eliminates the need for gadolinium-based contrast agents represents a first important step in moving towards a needle-free CMR non-invasive stress test [52, 58]. An approach using vasodilatory agents however still requires an inconvenient and mildly risky administration of pharmacologic agents. Moreover, adenosine and analogues induce vasodilation through endothelium-independent mechanisms. A microvascular response to increased myocardial oxygen demand however may use endothelium-independent or endothelium-dependent mechanisms. However, endothelial-dependent dysfunction has significant prognostic value in HF and has been associated with an increased mortality risk in patients with HF [19, 59]. Endothelium-dependent interventions more accurately resemble physiological stress and may be more informative in terms of therapeutic consequences [60, 61].

Respiratory challenges, especially manipulations in blood carbon dioxide (CO₂) and oxygen levels, were explored due to their ability to act as endothelial-dependent vasoactive mechanisms. Inhaled gas and breathing maneuvers have been investigated based on the underlying principle that alterations in arterial carbon dioxide, and to a lesser extent oxygen, result in endothelial-dependent vascular changes similar to those obtained with physiologic stress [62]. Carbon dioxide (CO₂) is a significant modulator of vascular tone in the cerebral and coronary circulation, with hypercapnia resulting in vasodilation and hypocapnia resulting in vasoconstriction [46, 63].

OS-CMR studies have been performed by directly modulating the percentage of carbon dioxide in inhaled air through a face mask or nasal cannula, resulting in consistent and

reproducible changes in signal intensity [64–67]. Recently, OS-CMR with intermittent carbon dioxide was successfully used to perform a rapid, whole heart, free-breathing acquisition in an animal model [68]. Induced hypercapnia however is associated with often intolerable side effects related to the urge to breathe and associated anxiety [69].

Respiratory maneuvers such as hyperventilation and breath-holding have also been evaluated in humans for their ability to modify oxygen and carbon dioxide concentrations without the need for inspired gas manipulations or additional equipment [40, 70, 71].

A combination of hyperventilation with a subsequent breath-hold as a standardized breathing maneuver has emerged as an effective mechanism of inducing vasoactive stress [25, 67, 72, 73]. The standardized breathing maneuver consists of a 60-s period of paced deep breathing (hyperventilation) at 30 breaths per minute, inducing coronary vasoconstriction, followed by a voluntary maximal breath-hold, inducing coronary vasodilation (Fig 1) [26].

This maneuver in combination with OS-CMR has demonstrated breathing-induced changes in myocardial oxygenation (BMORE) in a healthy population [43, 74]. BMORE OS-CMR can detect blunted myocardial oxygenation in myocardial territories subtended by an angiographically significant coronary artery stenosis in both animal models and patients with CAD [26, 27]. Of note, BMORE OS-CMR may have a more significant effect on myocardial oxygenation changes than adenosine OS-CMR, with less side effects [45]. Used in conjunction with the endogenous contrast of OS-CMR, BMORE was shown to provide a safe, fast, non-invasive, and convenient method for assessing coronary vascular function, without the use of needles, exogenous contrast agents, radioactivity, or specialized additional equipment.

Heart Failure—Microvascular Dysfunction

Adenosine and OS-CMR have demonstrated to be feasible and accurately identify CAD through a regionally impaired

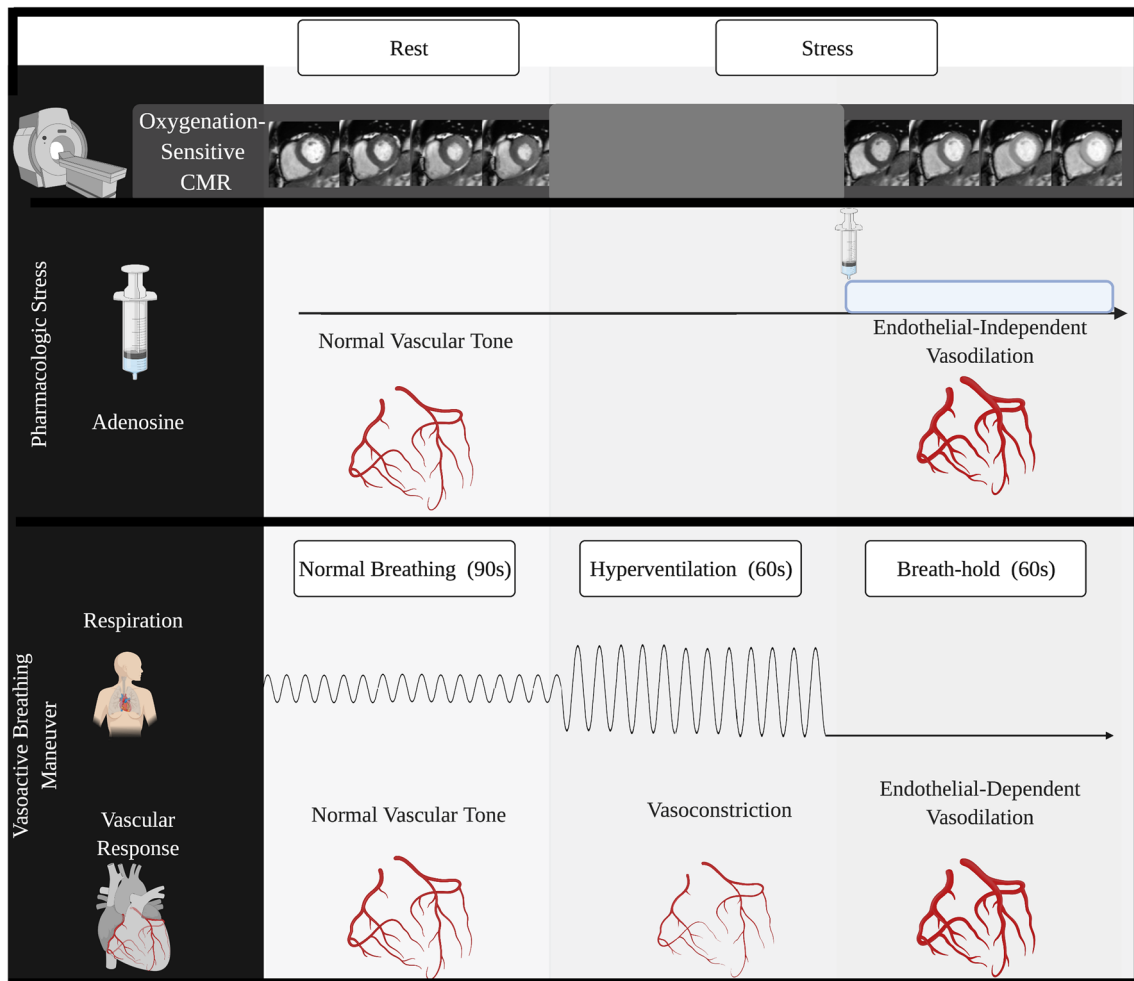


Fig. 1 Oxygenation-sensitive CMR (OS-CMR) scanning protocol with pharmacologic stress agent or using a standardized breathing maneuver. Hyperventilation leads to a coronary vasoconstrictive response through a decrease in arterial carbon dioxide, while the following breath-hold

increases arterial carbon dioxide and induces coronary artery dilatation. Myocardial signal intensity changes in OS-CMR images are measured at the end of the hyperventilation (maximal vasoconstriction) to the end of the breath-hold (maximal vasodilatation).

myocardial perfusion and oxygenation response in areas of macrovascular disease.

OS-CMR has also been used to assess microvascular disease and dysfunction.

Ischemia With No Significant Coronary Artery Disease

Reports estimate that up to half of patients who undergo a coronary angiography have no obstructive CAD, a clinical scenario that is especially prevalent in women [75, 76•]. Studies have demonstrated that over 50% of patients with ischemia with no obstructive coronary artery disease (INOCA) have microvascular dysfunction (MVD) [77].

An improved understanding of the underlying pathophysiology of INOCA would help guide personalized treatment strategies in these patients with a known increased risk of cardiovascular events and the development of HFpEF [76•, 77].

Adenosine stress perfusion CMR demonstrated subendocardial myocardial perfusion deficits in patients with INOCA [78]. However, these findings have not been replicated in subsequent studies utilizing adenosine stress perfusion CMR and OS-CMR [79]. Recently, novel biomarkers derived from BMORE OS-CMR images demonstrated regional heterogeneity in the myocardial oxygenation of INOCA patients without globally reduced oxygenation or perfusion abnormalities [35••] (Fig 2).

Regional myocardial deficits are consistent with previous observations of a maladaptive physiologic response to exercise and heterogenous flow in MVD, suggested to be a result of a variable combination of increased vasoconstriction and impaired vasodilation [80, 81]. These findings suggest a potential role of endothelium-dependent microvascular dysfunction in this patient population [35••], consistent with previously published evidence for heterogeneity of microvascular function [80].

Non-ischemic Heart Failure

Once significant CAD is excluded, the accurate identification of the etiology and associated pathomechanisms with HF often remains a significant clinical challenge. CMR has demonstrated increased diagnostic accuracy when compared to echocardiography in a non-ischemic HF population [16, 17]. Beyond the more accurate information on function including strain however, the potential of OS-CMR to investigate myocardial oxygenation and therefore provide additional insights on the individual underlying pathophysiology has been demonstrated in patients with non-ischemic HF.

OS-CMR has been used to investigate a number of microvascular disease states characterized by microvascular dysfunction. OS-CMR demonstrated a globally reduced

BMORE in patients with obstructive sleep apnea, especially when undergoing positive airway pressure therapy, and after heart transplantation even in the absence of cardiac allograft vasculopathy [34, 36]. Preliminary evidence from OS-CMR studies has demonstrated a reduced BMORE in HFrEF and with healthy aging [82, 83]. In a non-ischemic, dilated cardiomyopathy population, one study utilizing adenosine OS-CMR found a reduced myocardial perfusion response without a concomitant reduction in myocardial oxygenation, suggesting a dissociation between microvascular dysfunction and oxygenation [32]. Mahmood et al have demonstrated a reduced perfusion and oxygenation reserve in severe aortic stenosis without epicardial CAD, indicating coronary microvascular dysfunction [33]. The perfusion-oxygenation reduction seen in severe aortic stenosis with left ventricular hypertrophy is consistent with previous OS-CMR findings in a hypertensive left ventricular hypertrophy population [84]. In an overt hypertrophic cardiomyopathy (HCM) population, adenosine OS-CMR demonstrated an impaired myocardial perfusion/oxygenation. In HCM mutation carriers without overt left ventricular hypertrophy, a reduction in overall myocardial oxygenation was observed without a corresponding reduction in perfusion that was associated with a risk for arrhythmia [31, 85]. Impaired myocardial oxygenation and vasodilation was also observed in pulmonary hypertension with unobstructed epicardial coronary arteries likely reflecting microvascular dysfunction [86].

The impaired myocardial oxygenation response in these populations is consistent with our current understanding of a higher oxidative stress, reduced nitric oxide production, and endothelial dysfunction in these populations [34].

OS-CMR provides information on myocardial oxygenation and can obtain quantitative markers of myocardial ischemia and microvascular dysfunction across a number of disease states (Fig 3).

Table 1 provides an overview of studies on myocardial oxygenation in patients with heart failure.

OS-CMR and Myocardial Strain

While LVEF has been widely used for subclassifying HF phenotypes, it is not a sensitive marker of more subtle changes in myocardial function. Therefore, measuring myocardial deformation, or strain, using imaging has received more and more attention as a useful approach for detecting subclinical changes in myocardial function with better risk stratification than LVEF [4, 87, 88]. Strain imaging can evaluate strain in the three distinct layers of myocardial muscle fibers, i.e., endo-, mid-, and epicardium [89]. Strain is reported as deformation in three different directions, radial (concentric wall thickening), longitudinal (shortening of the ventricular long axis), and circumferential (tangential/rotational deformation)

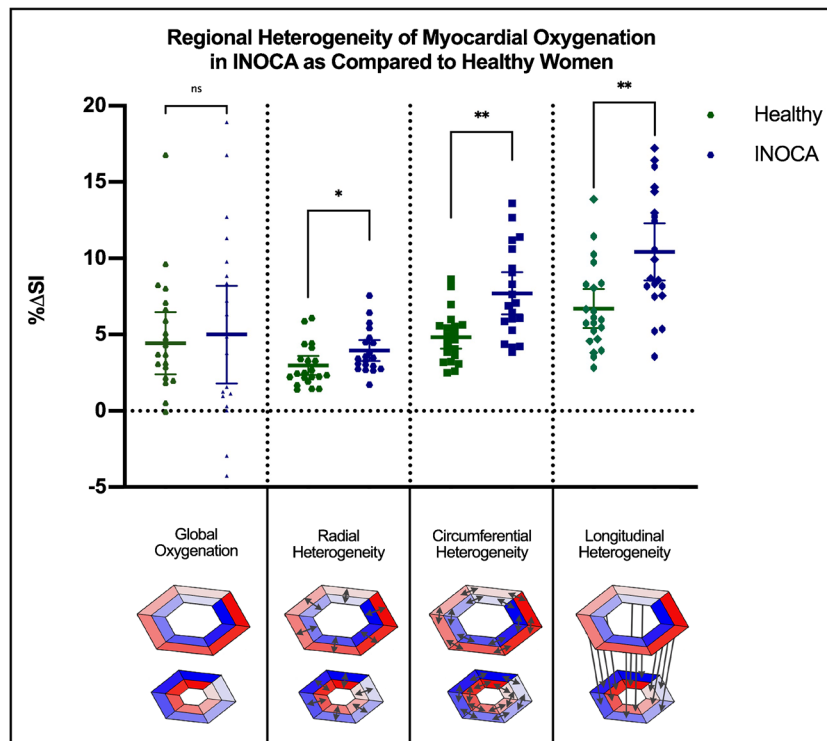


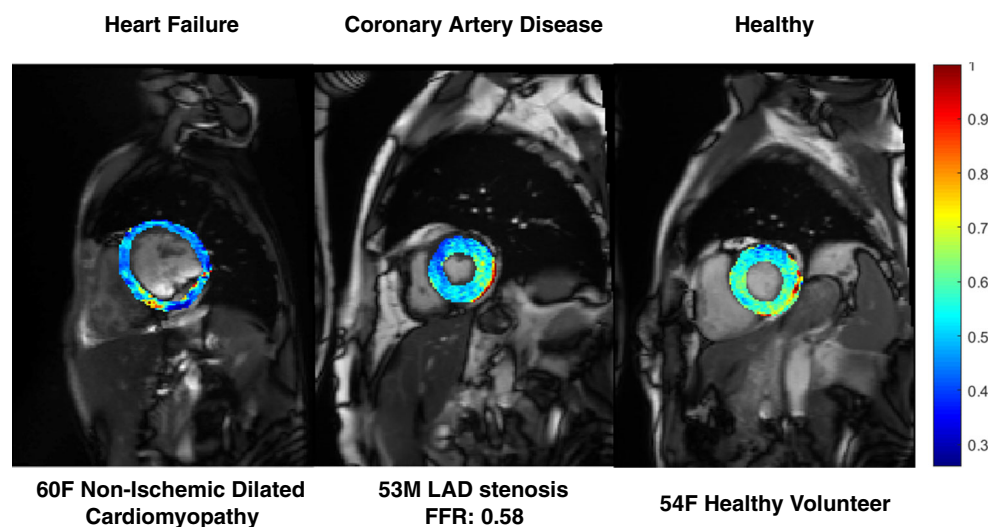
Fig 2 The impact of the breathing maneuver induced changes in myocardial oxygenation reserve on the myocardium and associated heterogeneous myocardial oxygenation changes as reflected by a change of signal intensity in OS-CMR images in the 3 spatial dimensions. Regional heterogeneity in myocardial oxygenation in women with INOCA compared with healthy volunteers. Schema demonstrating the determination of regional variability in signal intensity using radial, circumferential, and longitudinal differences. Radial differences were defined as the sum of the absolute differences between the endo- and

epicardium in each of the myocardial segments. Circumferential differences were the sum of the absolute differences between myocardial segments within the endo- and epicardium. Longitudinal differences were the sum of the absolute differences within the endo- and epicardium for corresponding segments of each slice acquired. INOCA, ischemia with no obstructive coronary artery disease; OS-CMR, oxygenation-sensitive cardiac magnetic resonance imaging; SI, signal intensity; * $P < 0.05$; ** $P < 0.01$ (figure modified from Elharram, Circulation, 2021)

[89]. Longitudinal strain can be used to predict LVEF change and HF phenotype as persistent HF_rEF or HF_{imp}EF [90] and appears to be a more accurate predictor of decompensation and mortality in both acute and chronic heart failure patients than LVEF [91–93]. Global longitudinal strain has therefore

been found to add incremental value and have greater prognostic value than LVEF [92]. These findings have led some authors to suggest the standard use of strain parameters in all HF patients to assess both systolic and diastolic dysfunction [4, 94, 95].

Fig 3 Oxygenation-sensitive CMR (OS-CMR) in a heart failure patient demonstrating a globally impaired myocardial oxygenation reserve, in a patient with coronary artery disease with a significant left anterior descending (LAD) lesion with a fractional flow reserve of 0.58 demonstrating regionally impaired myocardial oxygenation, and a healthy volunteer demonstrating a globally increased myocardial oxygenation response to a combined vasoactive breathing maneuver.



Strain imaging has traditionally been assessed by speckle tracking echocardiography.

CMR strain techniques such as fast strain-encoded CMR (fSENC), feature tracking (FT), or tissue tracking (TT) have emerged as convenient and readily available techniques that can accurately and reproducibly obtain strain parameters [96–98]. CMR FT-derived longitudinal strain recently demonstrated good correlation to echocardiography in the setting of acute myocardial infarction [99]. Combined CMR fSENC with standardized breathing maneuvers can yield a high diagnostic accuracy (95% sensitivity) for the detection of patients with suspected CAD, with significantly shorter acquisition times than established methods [100••].

In contrast to fSENC, CMR FT/TT does not need additional images as it can measure strain in routine cine images as used for ventricular volumes [101, 102]. Stress longitudinal strain from CMR FT with vasodilator stress was an incremental and independent predictor of adverse cardiac events in patients with known or suspected CAD [103]. In the context of HF, CMR reveals a transmural strain gradient from endocardium (highest strain) to epicardium (lowest strain values) that is blunted in patients with HF and lower ejection fraction (HFmEF and HFrEF) [101]. CMR FT has been suggested as having potential to be the new gold standard for assessment of systolic function [104]. Additionally, abnormal longitudinal strain has been found to be a useful prognostic marker in patients with HFpEF and in patients with dilated cardiomyopathy, incremental to LVEF [57, 105•, 106]. The observed longitudinal strain impairment reflects LV stiffness and impaired relaxation, causes for the observed “diastolic dysfunction” in HFpEF [94, 105•, 107]. However, although diastolic dysfunction plays a fundamental role in the pathophysiology of HFpEF, worsening of diastolic dysfunction is associated with other cardiometabolic comorbidities and even physiological aging [108]. Therefore, strain parameters should be used in a proper clinical context and in conjunction with other imaging parameters.

In recent studies, myocardial oxygenation as measured by OS-CMR and MORE parameters correlated with echocardiography-derived LV strain parameters in patients with aortic stenosis. These impairments were shown to be reversible with improved myocardial perfusion, oxygenation, and strain parameters 8 months post aortic valve replacement [33]. In a CAD population, post-stenotic hyperoxia-induced myocardial oxygenation deficits were found to be accompanied by reduced diastolic strain [109]. As OS-CMR is mostly performed using slightly modified regular cine sequences, one set of images yields data on both myocardial oxygenation and myocardial strain. Importantly, this can be done in a dynamic setting. Preliminary evidence utilizing OS-CMR images to derive strain response to stress demonstrated the ability of the technique to assess myocardial strain in young adults born pre-term before and after exercise intervention [110].

Strain CMR imaging studies have highlighted the ability of OS-CMR to obtain dynamic information on myocardial oxygenation and function providing both functional and vascular information in one acquisition. OS-CMR markers in combination with CMR strain parameters to investigate HF on an individual basis may then allow for a more robust, personalized imaging evaluation.

Limitations of OS-CMR

The limitations of both CMR and OS-CMR include a lack of access to scan time, cost, inability to image patients with specific contraindications such as claustrophobia, issues between subspecialties, and a lack of local expertise [111]. OS-CMR with breathing maneuvers may however help alleviate some of these issues, as it does not require contrast agents, specialized equipment, or the presence of a trained physician at the scanner. Local expertise will be necessary only in training patients in deep, paced breathing. However, the need for specific strategies and software algorithms and to analyze the dynamic changes related to tissue oxygenation and strain evaluation remain a significant limitation of OS-CMR. CMR software is costly and can be a barrier to widespread implementation where manual annotation and analysis is time-consuming and can introduce human error.

Conclusion

In patients with heart failure (HF), CMR offers a wide range of quantitative markers that provide important diagnostic and prognostic information. The addition of oxygenation-sensitive CMR (OS-CMR) will further improve clinical decision-making by novel insights into the role of coronary vascular function in this context. This includes the differentiation of ischemic from non-ischemic etiology of HF (by identifying regional abnormalities of coronary vascular function, but also by providing information on the regional integrity and homogeneity of vascular function). Importantly, the use of breathing maneuvers in combination with OS-CMR allows for assessing endothelium-dependent function.

OS-CMR has already been applied in multiple studies of patients with various cardiac diseases associated with HF, such as cardiomyopathies, valvular heart disease, arterial hypertension, and patients with microvascular dysfunction in the absence of coronary artery stenosis.

Comprehensive CMR scans can therefore be used to quantitatively study markers of cardiac morphology, volumes, gross function, strain, myocardial tissue composition, and vascular function, all as part of a safe, needle-free scan. The multiparametric approach that uses oxygenation-sensitive cine imaging for function and vascular function allows for short, cost-efficient scan protocols.

Future OS-CMR studies should focus on validation in larger populations and comparative analyses of its clinical utility in various etiologies. Furthermore, the use of deep learning techniques will allow for identifying novel biomarkers for an improved personalized risk stratification and management strategies in patients with heart failure.

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Author Contribution EH and MGF contributed to the idea, design, and editing of the manuscript. EH performed the literature search and drafted the manuscript.

Declarations

Conflict of Interest MGF is a shareholder and consultant of Circle Cardiovascular Imaging Inc. Dr Friedrich is listed as a holder of United States Patent No. 14/419,877: Inducing and measuring myocardial oxygenation changes as a marker for heart disease; United States Patent No. 15/483,712: Measuring oxygenation changes in tissue as a marker for vascular function; United States Patent No 10,653,394: Measuring oxygenation changes in tissue as a marker for vascular function - continuation; and Canadian Patent CA2020/051776: Method and apparatus for determining biomarkers of vascular function utilizing bold CMR images. EH is listed as a holder of Canadian Patent CA2020/051776: Method and apparatus for determining biomarkers of vascular function utilizing bold CMR images. The other authors report no conflicts.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- Of major importance

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