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Summary, Conclusions and Future Perspectives
SUMMARY

Heart failure is a global epidemic, and despite significant advances in specific advanced heart disease-directed therapies and interventions over the past decade, outcomes following a diagnosis of clinically manifest cardiac dysfunction remain suboptimal. Specifically, adverse LV remodeling remains an all-too common negative outcome after STEMI and contributes to an ever-increasing burden of ischemic myocardial dysfunction despite the systematic use of primary percutaneous revascularization and guideline-directed optimal medical therapies. Accurate, early estimation of infarct size remains an essential component of assessing risk for later LV enlargement and systolic dysfunction. Additionally, determination of the degree to which the ischemic dysfunctional myocardium is reversible, and therefore viable with potential for recovery of function, carries significant prognostic importance for these patients. Finally, prompt detection of a residual or new ischemic substrate to avoid potentiation of myocardial impairment and improve outcomes is also clinically relevant in this population. For those with non-ischemic myocardial diseases such as sarcoidosis, accurately adjudicating disease load and associated clinical HF risk can be especially challenging. It is becoming increasingly apparent, primarily through the evolution of advanced imaging modalities, that CS, which carries a poor prognosis and can present with sudden cardiac death even in the absence of prior clinical manifestations, is more prevalent that previously thought. Therefore, determination of the true burden of myocardial involvement in sarcoidosis, subclinical and otherwise, across either or both ventricles, and how this involvement relates to overall disease course and future adverse outcome (including death and symptomatic HF) is of escalating clinical importance.

Meanwhile, both classification and risk stratification of this heterogeneous group of HF syndromes has up to now remained largely focused on one single surrogate parameter of LV radial function, LVEF. However, the limitations of LVEF as an absolute marker of the presence or absence of LV systolic dysfunction are being increasingly recognized, in parallel with the growing prevalence of HFP EF. Recent developments in echocardiographic technology have propelled the quantitative assessment of myocardial mechanics into the spotlight, enabling analysis of myocardial motion not only in radial, but also in longitudinal and circumferential directions and additionally allow quantification of rotational deformation. These global and regional indices of myocardial function are capable of providing information on myocardial contractility and tissue characterisation that is incremental to to standard 2D echocardiographic systolic and diastolic function parameters. Assessment of myocardial mechanics using STE can ultimately provide new and superior pathophysiological insights into the mechanisms of contractile dysfunction and
myofiber disruption in a wide range of ischemic and non-ischemic myocardial diseases. Furthermore, specific investigation into the physiological inhomogeneity of transmural myocardial mechanics in different myocardial disease substrates and under both resting and stress conditions can provide additional insights into the evolution and staging of cardiac dysfunction. Overall, this widely available, non-invasive and safe imaging modality has the ability to facilitate improved risk stratification across the diverse spectrum of HF.

The aim of the present thesis was to explore the role of myocardial mechanics, as assessed by 2D STE, in identifying subclinical cardiac dysfunction in non-ischemic myocardial disease (sarcoidosis) and determining the presence or absence of specific substrates (remodeling, ischemia, viability) in those with established ischemic myocardial dysfunction.

In the Part I of the thesis, biventricular longitudinal mechanics as assessed by STE were explored in sarcoidosis patients with and without overt cardiac involvement and related to future outcome. The potential role of LV GLS as a monitoring tool correlated to both myocardial and overall disease burden in sarcoidosis was also investigated.

Part II focused on risk stratification of patients after STEMI, and in particular determining early risk markers independently associated with the critical outcome of LV remodeling, including heart rate as a clinical marker and LV GLS as a potential indicator of infarct size. Specifically, the association between the degree of early impairment in longitudinal deformation and future adverse LV dilatation was assessed. Additionally, the relationship between BMI, LV GLS and all-cause mortality was systematically explored, affording the unique opportunity to provide further insight into the perplexing obesity paradox phenomenon. Finally, in Part III of the thesis, both longitudinal and rotational deformation parameters were studied in patients with ischemic myocardial dysfunction at both rest and during pharmacological stress, in order to determine the presence or absence of myocardial viability and/or new or residual ischemic substrates. The novel exploration of the feasibility, clinical applicability and potential incremental value of assessment of these parameters throughout DSE was also discussed extensively in a comprehensive review article.

Part I: Subclinical and Evolving Myocardial Dysfunction

Chapter Two detailed the assessment of LV GLS in 100 patients with extracardiac sarcoidosis, aiming to determine the prevalence of subclinical cardiac dysfunction, likely attributable to early, focal and/or patchy granulomatous inflammation and associated tissue disruption, in these patients. Despite having no clinical manifestations of cardiac involvement or evidence of structural heart disease
by conventional parameters, sarcoidosis patients had a significantly impaired LV GLS compared to matched control subjects. Furthermore, over a quarter of these seemingly low-risk patients went on to develop a cardiac event and/or evidence of CS on advanced imaging modalities over a median follow-up time of just under 3 years; LV GLS was found to be the only independent associate of this composite endpoint. Therefore, LV GLS may be an important new parameter for the early detection of CS and for improved risk stratification of sarcoidosis patients without manifest cardiac involvement.

In Chapter Three the role of LV GLS in correlating with overall disease severity and monitoring evolution of (concealed and/or overt) myocardial involvement in a general sarcoidosis population with comprehensive baseline and follow-up data (n=60) was assessed. LV GLS identified worse intrinsic myocardial function at baseline in treated sarcoidosis patients, a more severe group by definition, and better myocardial function at follow-up echocardiography (a median of 3.4 years later) in patients showing general clinical disease improvement. Additionally, baseline LV GLS was independently associated with follow-up clinical improvement; a cut-off of ≤-17.5% identified those patients as more likely to improve in general and/or pulmonary disease characteristics over time. The ability to accurately monitoring the burden and course of disease in sarcoidosis, whether in the presence or absence of immunomodulatory therapy, is an exciting application of deformation imaging, particularly given the prevalence of implantable cardiac devices in confirmed sarcoid myocardial disease that prohibit follow-up CMR imaging, and the desire to avoid repeated exposure to ionizing radiation with PET imaging.

Chapter Four aimed to assess the prevalence of isolated RV contractile impairment using RV GLS and its correlates in sarcoidosis patients without manifest cardiac involvement or severe pulmonary hypertension, which has not been previously investigated despite the important position of the RV at the interface between cardiac, pulmonary and pulmonary vascular pathology. Quantitative RV function as assessed by RV GLS was feasible in 91% (n=88) of eligible patients and was found to be significantly impaired in this seemingly low-risk sarcoidosis population compared to a control population (n=50). Longitudinal RV mechanics were independently correlated with tricuspid annular plane systolic excursion, the current standard RV function parameter, but demonstrated superior ability, based on receiver-operating characteristics curve analysis, to relate to future adverse clinical outcome, defined as death or symptomatic HF. A previously defined cut-off for RV GLS of < or ≥-19% in a general RV myocardial dysfunction population identified sarcoidosis patients with impaired RV function as significantly more likely to experience worse clinical outcome. Regardless of whether the RV is involved through primary or secondary mechanism(s), the potential ability of RV GLS to
detect RV myocardial impairment at an earlier stage, prior to the development of reduced LVEF, clinical HF or irreversible pulmonary hypertension, may facilitate the targeting of specific anti-remodeling and pulmonary vasoactive therapies to these patients.

**Part II: Ventricular Remodeling**

**Chapter Five** evaluated the association between higher heart rates at time of discharge after STEMI, already established as a predictor of worse overall outcome in these patients, and later risk of adverse LV remodeling, as defined by a ≥20% increase in LV end-diastolic volume, in a large (n=964) contemporary STEMI population. This simple, easily accessible and targetable clinical marker was found to be independently associated with the development of unfavorable remodeling at 6 months. Specifically, a discharge heart rate higher than the median (69bpm) doubled the risk of showing LV remodeling at follow-up. The effects of higher discharge heart rate on later development of pathological LV dilatation were consistent across clinically relevant subgroups (including age, presence of diabetes, anterior territory infarction) and critically, irrespective of baseline LVEF. This study suggests that even in the modern era, incorporating primary percutaneous coronary intervention and evolving upstream antiplatelet and anti-remodeling therapies, heart rate is an as yet incompletely targeted pathophysiological biomarker.

In **Chapter Six**, LV GLS, proposed as a novel marker of infarct size, was measured in 1041 patients early after STEMI and tested for its association with LV dilatation over 3 and 6 months follow-up. Stratification of the study population according to median value of LV GLS(-15.0%) delineated a group of patients with more impaired myocardial function (>−15.0%) as significantly more likely to show increased LV dilatation during both follow-up time points. Notably, LV GLS provided incremental value to traditional infarct size assessment parameters, including wall motion score index and peak troponin level, for prediction of LV dilatation after STEMI. Moreover, LV GLS significantly reclassified additional patients for risk of adverse remodeling over and above known clinical and echocardiographic post-STEMI risk parameters. These results are particularly relevant given that this parameter provides a semi-automated, quantitative measure of LV systolic function that is quantifiable at rest and without requirement for expert observers, pharmacological stressors, expensive contrast media, or ionizing radiation. Therefore its future use as a real-world risk stratification tool in modern era STEMI patients is highly foreseeable.

In **Chapter Seven**, the association between BMI, as stratified by standard World Heath Organisation categories, and early LV structural and functional changes, as determined by geometrical indices and longitudinal mechanics respectively,
was determined in a large (n=1604) contemporary post-STEMI population. GLS is particularly well-placed to study myocardial contractile dysfunction associated with obesity, where LVEF is compounded by the increased stroke volume associated with higher adiposity. Obese patients exhibited the most LV remodeling and the most impaired LV GLS at the time of admission for infarction compared to the leanest patients. However, despite the more hostile cardiac structural and functional profile of the highest BMI patients, and amid similar infarct characteristics, the lowest BMI patients showed the worst survival, in keeping with the obesity paradox frequently demonstrated in acute coronary syndrome populations. The ‘protective’ effect of higher BMI on post-STEMI outcome therefore appears to occur independently of, and indeed in spite of, underlying less favourable LV myocardial geometry and function. This study provides novel insight into this perplexing cardiovascular phenotype and suggests focusing on alternative mechanisms by which higher BMI might confer better prognosis after STEMI. However, while short- and medium-term risk of all-cause mortality may be lessened compared to lean patients, pre-obese and obese patients should continue to receive close follow-up and aggressive optimal pharmacological therapies after STEMI to modify longer-term risk of progressive myocardial dysfunction and development of clinical HF.

Part III: Ischemia and Viability

Chapter Eight leads the final part of the thesis with a detailed overview of established techniques such as contrast opacification and emerging advanced techniques such as quantitative deformation analysis designed to improve the diagnostic accuracy of stress echocardiography in its dual main roles of ischemia detection and viability assessment. Although DSE is a well-validated and cost-effective diagnostic and prognostic tool, its sensitivity and accuracy is challenged by limitations surrounding image quality, need for expert observers and lack of true quantification provided by conventional assessment methods. The use of contrast opacification to augment visualization in the absence of optimal image quality (involving ≥2 segments) is already recommended. The advent of deformation imaging meanwhile has the potential to improve the reliability and reproducibility of stress echocardiography by permitting quantification of regional myocardial function, reducing the dependence on expert observers. This review summarizes current evidence investigating the feasibility and clinical relevance of deformation parameters, derived by either tissue Doppler or STE methods, aimed at detecting the presence of significant CAD and/or stress-induced ischemia, as well as the identification and assessment of stunned, hibernating or scarred myocardium.

Chapter Nine investigated the feasibility and accuracy of several longitudinal deformation parameters during DSE, comparing their performance to conventional
visual analysis, for the identification of significant CAD and/or ischemia in patients after STEMI. A follow-up angiographic luminal diameter stenosis of >70% was used as the endpoint, which although a surrogate marker of ischemia, has been previously associated with severely reduced coronary flow reserve (≤1.5) in this population. Despite the demonstrated increased sensitivity of longitudinal mechanics for earlier stages of the ischemic cascade compared to wall motion analysis, they have not previously been systematically tested in the post-infarction population, in whom detection of a residual or new ischemic substrate has known significant prognostic benefit. Analysis of STE longitudinal strain parameters in 105 patients during full-protocol DSE was found to be feasible in the majority of patients after STEMI at peak-dose as well as at rest stage. At global level, the change in peak longitudinal systolic strain (PLSS) from rest to peak was independently associated with the presence of significant CAD at follow-up, unlike the change in wall motion score, with a cut-off of ≥1.9% showing high sensitivity (87%) to detect this endpoint. The change in segmental PLSS (using a sentinel segment approach) similarly demonstrated independent association with significant CAD in the corresponding coronary territory; this association persisted across key clinically relevant subgroups. This study highlights that the longitudinal deformation response to dobutamine – using several of these parameters known to be differentially affected in the presence of ischemia, prior infarction and/or severe CAD - might be particularly useful to characterize the complex ischemic substrate(s) in patients after STEMI. Furthermore, these findings provide additional evidence supporting the sentinel segment method for segmental myocardial deformation analysis on DSE, thereby minimizing the impact of signal noise and other technical factors that might otherwise limit widespread adoption of this approach.

In Chapter Ten, the novel association between stress-induced changes in LV twist throughout DSE and the later development of LV reverse remodeling, as a surrogate of myocardial viability, was evaluated in a group (n=82) of contemporary post-STEMI patients. Notably, although LV twist is emerging as a new parameter to define the global extent of contractile dysfunction after myocardial infarction, it has not been systematically evaluated previously during DSE, a test frequently performed to assess global myocardial functional capacity in this patient subset. LV twist measurement was feasible in 70% of patients, reassuringly within published limits of the feasibility of 1-stage LV twist measurements, given that this study required 3-stage optimal apical and basal short-axis images per patient. Overall, a significant increment in LV twist at ≥1 stages of DSE occurred in the majority of patients. Three main patterns of stress LV twist response - based on progressive increase or not throughout the test – were characterized. Both the pattern of progressive LV twist increase throughout DSE and the stress-induced
Increment in LV twist from rest to peak-dose were significantly associated with LV reverse remodeling at follow-up, suggesting a novel, clinical use for global LV twist as a marker of LV inotropic contractile reserve in post-infarction patients.

Finally, in Chapter Eleven the principle of using rotation mechanics under pharmacological stress conditions to provide incremental value for assessment of the presence or absence of myocardial viability was further explored. The novel aim of the current study was to investigate the pathophysiological concepts underlying the different LV sublayer-based consequences of myocardial infarction by assessing the response of each sublayer to dobutamine stress in post-STEMI patients with persistent regional ischemic myocardial dysfunction. Specifically, it was hypothesized that in post-STEMI patients (n=69) with baseline resting wall motion abnormalities, recruitment in LV subepicardial twist throughout DSE would reflect contractile reserve, as defined by improvement in LV function at 6 month follow-up. LV sublayer twist measurement at rest and peak-dose stages of DSE was feasible in more than two-thirds of DSE studies. Accordingly, the response of LV subepicardial twist (and not LV subendocardial twist) on full protocol DSE was found to be independently associated with improvement in LVEF at follow-up. Furthermore, the change in LV subepicardial twist was the only parameter in addition to the change in LVEF during DSE to provide significant incremental value over a baseline model composed of relevant clinical parameters for the prediction of LVEF improvement. These findings support and extend known pathophysiological concepts surrounding the layer-specific components of the transmural disease burden by suggesting preserved LV subepicardial function (identified by recruitment on DSE) reflects greater extent of viable myocardium. Differential analysis of LV sublayer twist mechanics on DSE may therefore provide a novel method of assessing myocardial viability in patients after STEMI.

Conclusions and Future Perspectives
Ameliorating the burden of HF will require a multi-faceted approach, and ultimately will need to include more sophisticated screening and monitoring tools to better reflect the actual degree of myocardial contractile impairment and related myofiber disruption, and its potential reversibility, at each stage of the disease process. Specifically, preventing progression of myocardial disease from Stage A to Stage B necessitates earlier detection of subclinical disease in patients with cardiovascular risk factors and/or potentially cardiotoxic systemic diseases. Halting further progression of disease from Stage B to Stage C necessitates more precise estimation of the already manifest damage and determination of factors associated with increased risk. This thesis set out to address the use of emerging echocardiographic techniques capable of reflecting the underlying aberrant
myocardial mechanics at both of these potential transition stages in non-ischemic and ischemic disease states. Clearly, in the clinical research settings studied, assessment of intrinsic rather than surrogate myocardial contractility using speckle-tracking derived deformation parameters succeeded in facilitating 1) earlier identification of subclinical and/or focal disease in systemic disease-associated myocardial dysfunction and 2) incremental risk stratification including assessment of ischemia and viability in established ischemic myocardial dysfunction.

However, for this parameter to fulfill its potential in the day-to-day “real-world” arena as well as it has done in this and other research settings, several obstacles need to be addressed and overcome. Firstly, enhancements of the current generation of speckle-tracking technology should result in standardization in how measurements are performed, in tandem with the promised upcoming intervendor standardization aiming to ensure accurate interpretation of deformation data irrespective of vendor. Secondly, echocardiographic protocols need to be designed for prospective acquisition of images optimal for deformation analysis, and should take into account simultaneous assessment of loading conditions in order to ensure studies are interpreted in the light of this potential further source of variation. Finally, additional studies are promptly required in multicenter and prospective settings to better establish the feasibility, reproducibility and diagnostic accuracy of the various parameters across multiple disease states.

While GLS is poised to emerge from the echocardiography laboratory into the clinical arena with an already extensive and ever-growing evidence platform in both ischemic and non-ischemic cardiac dysfunction, it is important that other parameters, either in isolation or combined with longitudinal assessment, are not left trailing behind. As illustrated in the present thesis, it is the combination of parameters arising from different sublayer components, specifically the demonstration of a subendocardial-to-subepicardial gradient, that may provide the most useful pathophysiological, and ultimately clinically relevant, information. These echocardiographic innovations allow an unparalleled insight into the transmural heterogeneity of myocardial contractility, free of the medical contraindications and economic and feasibility limitations associated with CMR imaging. With further evolution in techniques and processing as described, the unique pathobiological insights into myocardial dysfunction provided by systematic use of this novel echocardiographic modality alongside conventional parameters, under resting and/or stress conditions, is destined to result in improved outcomes across the phenotypic spectrum of HF.