Myocardial Work –
Application and Clinical Characterization of a New Echocardiographic Tool

Myocardial Work –
Anwendung und klinische Charakterisierung einer neuen Echokardiographie-basierten Methode

Doctoral thesis for a doctoral degree

at the Graduate School of Life Sciences,

Julius-Maximilians-University Würzburg,

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Würzburg, 2021

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1 Summary

Left ventricular (LV) ejection fraction (EF) and global longitudinal strain (GLS) are the most commonly used measures of LV function. Yet, they are highly dependent on loading conditions since higher afterload yields lower systolic deformation and thereby a lower LVEF and GLS – despite presumably unchanged LV myocardial contractile strength. Invasive pressure-volume loop measurements represent the reference standard to assess LV function, also considering loading conditions. However, this procedure cannot be used in serial investigations or large sample populations due to its invasive nature. The novel concept of echocardiography-derived assessment of myocardial work (MyW) is based on LV pressure-strain loops, may be a valuable alternative to overcome these challenges, and may also be used with relative ease in large populations. As MyW also accounts for afterload, it is considered less load-dependent than LVEF and GLS.

The current PhD work addresses the application and clinical characterization of MyW, an innovative echocardiographic tool. As the method is new, we focused on four main topics:

(a) To establish reference values for MyW indices, i.e., Global Work Index (GWI), Global Constructive Work (GCW), Global Wasted Work (GWW), and Global Work Efficiency (GWE); we addressed a wide age range and evaluated the association of MyW indices with age, sex and other clinical and echocardiography parameters in apparently cardiovascular healthy individuals.

(b) To investigate the impact of cardiovascular (CV) risk factors on MyW indices and characterize the severity of subclinical LV deterioration in the general population.

(c) To assess the association of the LV geometry, i.e., LV mass and dimensions, with MyW indices.

(d) To evaluate in-hospital dynamics of MyW indices in patients hospitalized for acute heart failure (AHF).

For the PhD thesis, we could make use of two larger cohorts:

The **STAAB population-based cohort study** prospectively recruited and phenotyped a representative sample (5,000 individuals) of the general population of the City of Würzburg, aged 30-79 years and free from symptomatic heart failure at the time of inclusion. We focused on the first half of the study sample (n=2473 individuals), which fulfilled the anticipated strata regarding age and sex.

The **Acute Heart Failure (AHF) Registry** is a prospective clinical registry recruiting and phenotyping consecutive patients admitted for decompensated AHF to the Department of Medicine I, University Hospital Würzburg, and observing the natural course of the disease. The AHF Registry focuses on the pathophysiological understanding, particularly in relation to the early phase after cardiac decompensation, with the aim to improve diagnosis and better-tailored treatment of patients with AHF. For the current study, we concentrated on patients who provided pairs of echocardiograms acquired early after index hospital admission and prior to discharge.

The main findings of the PhD thesis were:

From the STAAB cohort study, we determined the feasibility of large-scale MyW derivation and the accuracy of the method. We established reference values for MyW indices based on 779 analyzable, apparently healthy participants (mean age 49 ± 10 years, 59% women), who were in sinus rhythm, free from CV risk factors or CV disease, and had no significant LV valve disease. Apart from GWI, there were no associations of other MyW indices with sex. Further, we found a disparate association with age, where MyW showed stable values until the age of 45 years, with an upward shift occurring beyond the age of 45. A higher age decade was associated with higher GWW and lower GWE, respectively. MyW indices only correlated weakly with common echocardiographic parameters, suggesting that MyW may add incremental information to clinically established parameters.

Further analyses from the STAAB cohort study contributed to a better understanding of the impact of CV risk factors on MyW indices and the association of LV geometry with LV performance. We demonstrated that CV risk factors impacted selectively on GCW and GWW. Hypertension appears to profoundly compromise the work of the myocardium, in particular, by increasing both GCW and GWW. The LV in hypertension seems to operate at a higher energy level yet lower efficiency. Other classical CV risk factors (Diabetes mellitus, Obesity,

Dyslipidemia, Smoking) – independent of blood pressure – impacted consistently and adversely on GCW but did not affect GWW. Further, all CV risk factors affected GWE adversely.

We observed that any deviation from a normal LV geometric profile was associated with alterations on MyW. Of note, MyW was sensitive to early changes in LV mass and dimensions. Individuals with normal LV geometry yet established arterial hypertension exhibited a MyW pattern that is typically found in LV hypertrophy. Therefore, such a pattern might serve as an early sign of myocardial damage in hypertensive heart disease and might aid in risk stratification and primary prevention.

From the AHF Registry, we selected individuals with serial in-hospital echocardiograms and described in-hospital changes in myocardial performance during recompensation. In patients presenting with a reduced ejection fraction (HFrEF), decreasing N-terminal pro-natriuretic peptide (NT-proBNP) levels as a surrogate of successful recompensation were associated with an improvement in GCW and GWI and consecutively in GWE. In contrast, in patients presenting with a preserved ejection fraction (HFpEF), there was no significant change in GCW and GWI. However, unsuccessful recompensation, i.e., no change or an increase in NT-proBNP levels, was associated with an increase in GWW. This suggests a differential myocardial response to de- and recompensation depending on the HF phenotype.

Further, GWW as a surrogate of inappropriate LV energy consumption was elevated in all patients with AHF (compared to reference values) and was not associated with conventional markers as LVEF or NT-proBNP. In an exploratory analysis, GWW predicted the risk of death or rehospitalization within six months after discharge. Hence, GWW might carry incremental information beyond conventional markers of HF severity.

2 Zusammenfassung

Die linksventrikuläre (LV) Ejektionsfraktion (EF) und der Global Longitudinal Strain (GLS) sind die am häufigsten verwendeten Maße der LV-Funktion. Sie sind jedoch stark von den jeweiligen Belastungsbedingungen abhängig, da eine höhere Nachlast zu einer geringeren systolischen Deformation und somit zu einer niedrigeren LVEF und GLS führt, trotz einer vermutlich unveränderten myokardialen Kontraktionsstärke. Intrakardiale Druck-Volumen-Schleifenmessungen stellen den Referenzstandard zur Beurteilung der LV-Funktion dar, da hiermit auch die umfassende Berücksichtigung der Lastbedingungen (Vorlast, Nachlast) möglich ist. Dieses Verfahren lässt sich jedoch aufgrund des invasiven Charakters nur schwer in Follow-up Untersuchungen oder großen Studienpopulationen einsetzen. Angelehnt an die Prinzipien dieser invasiven Technik, wurde vor kurzem das neuartige Konzept der Echokardiographie-abgeleiteten Beurteilung der Myokardarbeit (MyW) entwickelt. Dieser Ansatz wertet Druck-Strain-Schleifen aus und berücksichtigt den Einfluss der Nachlast, so dass MyW als weniger lastabhängig gilt verglichen mit LVEF und GLS. Die Analyse von MyW könnte deshalb eine wertvolle Alternative sein, um den o.g. Herausforderungen zu begegnen. Die Methode lässt sich in großen Stichproben, ggf. auch wiederholt, einsetzen.

Die hier vorgelegte Dissertation befasst sich mit der Anwendung und klinischen Charakterisierung von MyW, einer innovativen echokardiographischen Methode. Der Fokus lag auf vier Themenbereichen:

(a) Festlegung von Referenzwerten für MyW-Indizes, d. h. Global Work Index (GWI), Global Constructive Work (GCW), Global Wasted Work (GWW) und Global Work Efficiency (GWE); wir adressierten einen breiten Altersbereich und quantifizierten die Assoziation der MyW-Indizes mit Alter, Geschlecht und weiteren klinischen und echokardiographischen Parametern bei kardiovaskulär gesunden Normalpersonen.

(b) Untersuchung des Einflusses kardiovaskulärer Risikofaktoren auf die MyW-Indizes und die Charakterisierung einer subklinischen LV-Verschlechterung in der Allgemeinbevölkerung.

(c) Bewertung der Assoziation der MyW-Indizes mit der LV-Geometrie, insbesondere der LV-Masse und der LV-Dimensionen.

(d) Bewertung der Dynamik der MyW-Indizes im Krankenhaus bei Patienten, die wegen akuter Herzinsuffizienz (AHF) ins Krankenhaus aufgenommen wurden.

Im Rahmen der hier vorgelegten Dissertation wurden die Daten zweier größerer Kohorten herangezogen:

Die bevölkerungsbasierte STAAB-Kohortenstudie rekrutierte und phänotypisierte prospektiv eine repräsentative Stichprobe (5.000 Personen) der Allgemeinbevölkerung der Stadt Würzburg im Alter von 30-79 Jahren, die zum Zeitpunkt des Einschlusses keine vorbeschriebene Herzinsuffizienz hatten. Wir konzentrierten uns auf die erste Hälfte der Studienstichprobe (n=2473 Personen), welche die erwarteten Stratifizierung bezüglich Alter und Geschlecht erfüllten.

Das Acute Heart Failure (AHF) Register ist ein klinisches Register zur Rekrutierung und Phänotypisierung von konsekutiven Patienten, die wegen akut dekompensierter Herzinsuffizienz in die Medizinische Klinik I des Universitätsklinikums Würzburg aufgenommen wurden. Ziel dieser Studie ist es, das pathophysiologische Verständnis insbesondere in Bezug auf die Frühphase nach einer kardialen Dekompensation zu verbessern und damit die gezielte Diagnostik und Therapie von Patienten mit AHF zu verbessern. Wir fokussierten hier auf Patienten, bei denen im Krankenhaus zwei Echokardiogramme durchgeführt wurden: früh nach Aufnahme ins Krankenhaus und kurz vor der Entlassung.

Die wichtigsten Erkenntnisse der hier vorgelegten Dissertation sind:

Aus den Daten der STAAB-Kohortenstudie wurden Referenzwerte für MyW-Indizes etabliert, die auf Auswertungen von insgesamt 779 gesunden Normalpersonen (mittleres Alter 49 ± 10 Jahre, 59% Frauen) mit Sinusrhythmus beruhen. Diese Probanden wiesen gemäß der Ergebnisse einer umfangreichen Eingangsuntersuchung keine kardiovaskulären Risikofaktoren oder Erkrankungen auf und zeigten echokardiographisch keinen Hinweis auf eine LV-Klappenerkrankung. Mit der Ausnahme von GWI fanden sich keine Assoziationen der MyW-Indizes mit dem Geschlecht. Darüber hinaus zeigte sich eine Altersabhängigkeit der MyW-Indizes. Bis zum Alter von 45 Jahren wies MyW stabile Werte auf, jenseits des 45. Lebensjahres jedoch eine Aufwärtsverschiebung: dabei war eine zunehmend höhere Altersdekade mit mehr GWW bzw. weniger GWE verbunden. Die MyW-Indizes korrelierten

nur schwach mit üblichen echokardiographischen Parametern, was darauf hindeuten könnte, dass MyW zusätzliche Informationen jenseits klinisch etablierter Variablen beitragen kann.

Weitere Analysen aus der STAAB-Kohortenstudie trugen zu einem besseren Verständnis des Einflusses kardiovaskulärer Risikofaktoren auf die MyW-Indizes und der Assoziation der LV-Geometrie mit der LV-Leistung bei. Wir zeigten, dass kardiovaskuläre Risikofaktoren sich selektiv auf GCW und GWW auswirken. Hypertonie beeinträchtigte die Arbeit des Myokards zutiefst, insbesondere durch die Erhöhung sowohl des GCW als auch des GWW. Der LV arbeitet demnach bei Hypertonie auf einem höheren Energieniveau – jedoch mit geringerer Effizienz. Andere klassische kardiovaskuläre Risikofaktoren (Diabetes mellitus, Adipositas, Dyslipidämie, Rauchen), wirkten sich unabhängig vom Blutdruck durchweg negativ auf GCW aus, zeigten jedoch keinen Einfluss auf GWW. Darüber hinaus wirkten sich alle kardiovaskulären Risikofaktoren nachteilig auf GWE aus.

Jede Abweichung von einem normalen LV-Geometrie Profil war mit Änderungen der MyW verbunden. Bemerkenswert war, dass MyW empfindlich auf frühe Veränderungen der LV-Masse und -Dimensionen reagierte. Personen mit arterieller Hypertonie aber noch normaler LV-Geometrie zeigten ein myokardiales Arbeitsmuster, das ansonsten typischerweise bei LV-Hypertrophie zu finden ist. Somit könnte dieses Muster als frühes Zeichen einer Myokardschädigung bei hypertensiver Herzerkrankung dienen und bei der Risikostratifizierung und Primärprävention helfen.

Aus dem AHF-Register wählten wir Personen mit seriellen Echokardiogrammen im Krankenhaus aus und beschrieben Veränderungen der myokardialen Leistung während der Rekompensationsphase beschrieben. Als Surrogat einer Rekompensation zogen wir während der Hospitalisierung sinkende Spiegel von N-terminalem pro-natriuretischem Peptid (NT-proBNP) heran. Bei Patienten mit reduzierter Ejektonfraktion (HFrEF) waren fallende NT-proBNP Werte (i. S. einer erfolgreichen Rekompensation) mit einer Verbesserung von GCW und GWI und konsekutiv auch von GWE verbunden. Im Gegensatz dazu gab es bei Patienten, die eine erhaltene Ejektonfraktionsfraktion aufwiesen (HFpEF), keine signifikante Veränderung von GCW und GWI. Eine erfolglose Rekompensation, d. h. keine Veränderung oder ein potenzieller Anstieg von NT-proBNP, war jedoch mit einem Anstieg von GWW verbunden. Wir interpretierten dies als unterschiedliche myokardiale Reaktion auf De- und Rekompensation in Abhängigkeit vom Herzinsuffizienz-Phänotyp. Darüber hinaus war GWW

als Surrogat eines unangemessenen LV-Energieverbrauchs bei allen Patienten mit AHF erhöht (im Vergleich zu Referenzwerten) und korrelierte mit keinem der konventionellen Marker. In einer explorativen Analyse war GWW ein starker Prädiktor für das Risiko, im Verlauf der nächsten sechs Monaten nach Krankenhausentlassung zu sterben oder erneut hospitalisiert zu werden. Damit könnte die GWW zusätzliche Informationen enthalten, die über die konventionellen Marker für den Schweregrad der Herzinsuffizienz hinausgehen.

3 Introduction

3.1 Left ventricular function and cardiovascular risk factors

Cardiovascular (CV) disease remains the leading cause of mortality worldwide and a major contributor to disability (1, 2). The burden of CV disease is linked to well-established modifiable risk factors and harmful lifestyle (3). CV risk factors increase the risk of developing CV disease, i.e., by altering the metabolic environment and homeostasis, but also directly adversely affecting myocardial function (4, 5). In asymptomatic individuals with no clinically overt heart disease, the long-term presence of CV risk factors induces pathophysiological changes, i.e., accelerates ventricular and vascular aging, thus leading to alterations in left ventricular (LV) structure (remodeling) and/or function (6, 7). In contrast, LV structure and function remain better preserved in the absence of CV risk factors (3).

Assessment of LV function has a central role in the evaluation of cardiac disease and represents a cornerstone in any imaging examination (8). LV is the main and most researched chamber of the heart. The role and importance of LV are mainly related to the pumping of oxygenated blood throughout the body's vascular system as the main source of oxygen and energy (9). Thus, the assessment of LV structure and function, including wall thickness, wall motion, and LV volumes throughout the cardiac cycle is an essential part of the echocardiographic examination (10). LV myocardial performance depends on the electrical conduction, myocardial contractility, loading conditions (preload and afterload), ventricle geometry (shape and size), and function of the aortic and mitral valve (11). Deterioration of a single parameter might disrupt the homeostasis of synchronized myocardial contraction and relaxation.

The mechanistic and hemodynamic relationship of LV with other parts of the heart, i.e., left atrium and aorta, are complex. Compensatory mechanisms triggered by LV dysfunction lead to vascular, neurohumoral, and structural adaptions. They are also mirrored in energetics and function of the LV even at an early stage. LV dysfunction is caused through several mechanisms and might consecutively be followed by changes in structure and function and ultimately heart failure (HF) (12). The complexity of the cardiac pump system makes it almost impossible for a single metric to comprehensively characterize LV function, and thus it requires the use of

several measurements (13). However, advances in technology in the last decades made it possible to develop various non-invasively derived markers that provide robust information on global and regional LV function.

3.2 Myocardial function in heart failure patients

HF represents a complex syndrome, often regarded as a later stage of a large array of cardiovascular diseases, in which cardiac function (myocardial, valvular, and/or pericardial) is impaired. The impairment of LV myocardial function encompasses both the systolic and diastolic phases.

3.2.1 Heart failure – definition and classification

The European Society of Cardiology (ESC) defines *heart failure* as a clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) (14, 15). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise (14, 15).

HF is one of the leading causes of cardiovascular morbidity and mortality worldwide, with an overall prevalence rate of up to 3–4% (16, 17). In patients older than 65 years, HF is the leading cause of hospitalization in industrialized countries (18, 19).

The etiology of HF includes a wide range of causes, which frequently overlap (15):

1. Myocardial diseases (including ischemic heart disease, genetic cardiomyopathy, toxic /metabolic damages, and infections, i.e., viral myocarditis)
2. Abnormal loading conditions caused by valvular diseases, structural myocardial defects, hypertension, volume overload, and high output states.
3. Arrhythmias – ectopic beats or conduction disorders
4. Pericardial disease

HF is classified according to structural disease (ACC/AHA) (20) and symptoms – exercise intolerance – New York Heart Association (NYHA classification). According to current ESC guidelines from 2016 (15), HF is diagnosed in the presence of typical signs and symptoms, elevated natriuretic peptides, and based on LVEF. HF is classified into three categories: HF with reduced ejection fraction (HFrEF, LVEF <40%), HF with midrange ejection fraction (HFmrEF; LVEF 40–49%, later renamed as HF with mildly reduced ejection fraction (14)), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%) (15).

HFrEF is characterized by an impaired global LV pump function, i.e., LVEF <40%, usually accompanied by LV remodeling and dilation. HFrEF often presents a consequence of a myocardial injury, i.e., ischemic heart disease, exposure to cardiotoxins, or myocarditis, leading to reduced ventricular contraction. Studies found that male sex, LV hypertrophy, cardiac conduction disorders (bundle branch block), and previous myocardial infarction were more strongly associated with HFrEF compared to HFpEF (21).

In contrast, HFpEF is conventionally referred to as non-systolic or diastolic HF; however, its pathophysiology is still not well understood. Establishing the diagnosis of HFpEF is challenging since LVEF is normal and congestion due to elevated cardiac filling pressures is difficult to evaluate by non-invasive means (22). The diagnosis of HFpEF requires an increased plasma concentration of natriuretic peptides and proof of relevant structural heart disease and/or diastolic dysfunction (15). HFpEF patients likely account for more than 50% of the patients with HF (22, 23). These patients are usually of higher age, more often women, and have more often comorbidities such as arterial hypertension, diabetes, and obesity when compared to HFrEF (24, 25). Despite primarily suffering from diastolic dysfunction, patients with HFpEF frequently exhibit (subtle) concomitant systolic dysfunction (26). Thus, HF is pathophysiologically heterogeneous and covers a broad clinical spectrum.

HFmrEF is a newly introduced entity in 2016 Guidelines including patients in the ‘’gray’’ area of HF and with LVEF between 40-49% (15). The detailed profile of the HFmrEF entity is still under discussion and a matter of further characterization. This gray area was defined to endorse further research on a certain group of HF population. Here we find patients with HFpEF who had LVEF worsening over time, as well as patients with HFrEF, in whom LVEF improved over time. The latter was already defined in the last universal definition of HF as HF

with improved ejection fraction (HFimpEF) (27). A new definition can therefore be expected in the forthcoming guidelines. Thus, we focussed on HFrEF vs. HFpEF entities for the current PhD thesis.

Essential diagnostic work-up for HF includes detailed medical history, clinical examination, electrocardiography, laboratory examination (i.e., natriuretic peptides), and echocardiography. Natriuretic peptides BNP are secreted by the atrial and ventricular myocardium in response to wall stress such as volume expansion and pressure overload (28, 29). The upper limit in the non-acute setting is 35 pg/ml for BNP and 125 pg/ml for NT-proBNP, respectively (15). In the acute setting, higher thresholds apply, i.e., 100 pg/ml for BNP and 300 pg/ml for NT-proBNP.

Echocardiography provides crucial information regarding systolic and diastolic function, wall thickness, chamber volumes, valve function, and potential wall motion abnormalities (10, 15). Until now, LVEF has been used as a parameter to classify HF. However, in the case of HFpEF, the LVEF does not provide valuable information. Data from population-based studies showed that individuals with low-normal LVEF (EF 50-55%) had a greater mortality and morbidity risk compared to individuals with LVEF >55% (30, 31). Further, a study including nearly half a million echocardiography reports showed that an LVEF between 60–65% was associated with the lowest mortality risk in a median follow-up time of 4 years, whereas a deviation from these values was associated with a worse prognosis (32).

LV global longitudinal strain as a measure of global longitudinal systolic LV deformation is reduced in patients with HFrEF. In contrast, in most patients with HFpEF, LV longitudinal strain is still within the normal range. However, recent studies showed that even patients with HFpEF have impaired longitudinal function (26), suggesting a slight LV systolic dysfunction despite normal LVEF. The presence of hypertension, obesity, and atrial fibrillation in patients with HFpEF, might affect systolic and diastolic function. Since a decrease in longitudinal function is the first event in the process of deteriorating LV contraction, longitudinal strain analysis allows for an early detection of HF, but can also be useful in later HF for the assessment of LV synchrony (33). Additionally, the longitudinal strain was shown to be an early diagnostic and prognostic marker in HF (34). In order to get more insights on LV function and performance in patients with HFpEF, physiology-based methods such as MyW based on longitudinal strain and

estimated LV pressure seem promising and might offer new insights into pathophysiology and assessment of patients with HF. Further, indices of MyW, more specifically GCW was shown to be a better determinant of exercise capacity than GLS in patients with HFpEF (35).

3.2.2 Acute heart failure

Acute heart failure (AHF) is characterized by rapid onset or worsening of signs and/or symptoms of HF and thus represents a life-threatening condition that requires immediate medical attention (14, 15). Further, AHF indicates a vulnerable state associated with repeated episodes of decompensation requiring hospitalization and a poor prognosis, i.e., 17% mortality risk within 6 months (36-38).

AHF includes a wide spectrum of clinical conditions with various etiologies and triggers (15). The majority of AHF cases arise from deteriorated pre-existing HF, but it also may occur as an event for the first time (*de novo*) (15, 39, 40). The in-hospital mortality in acute decompensated HFpEF patients appears to be lower compared to HFrEF patients, but rehospitalization rates seem to be similarly high for both groups (41).

The complex syndrome of AHF involves a wide range of pathophysiological changes in cardiac structure and function, leading to a set of clinical signs and symptoms, mostly related to congestion and end-organ dysfunction (41). Echocardiography provides critical information regarding diagnosis, underlying causes, hemodynamics, treatment monitoring, and prognosis in AHF patients (42, 43). Further, echocardiographic data from patients with AHF demonstrate a high prevalence of structural and hemodynamic abnormalities (42). Most of the hemodynamic echocardiographic indices are load-dependent, and loading conditions vary considerably during acute de- and subsequent recompensation of HF. LVEF is a well-acknowledged risk predictor among AHF patients (44, 45), but as it is heavily dependent on loading conditions, it fails to provide information in nearly 50% of the HF population. Studies showed that LV longitudinal strain has a better prognostic value insofar as it is an independent predictor of HF readmissions after an AHF episode (46, 47).

Including information on afterload in the assessment of LV performance might give new insights into the pathophysiology and LV function in AHF patients. These assumptions will be discussed in more detail in the following chapters.

3.3 Echocardiographic assessment of LV function

Echocardiography is an indispensable tool in the diagnosis and treatment monitoring of heart diseases, including HF. Echocardiography provides real-time information on systolic and diastolic function, cardiac structure and volumes, hemodynamics, and valve pathologies (regurgitation or stenosis) (33). Current guidelines recommend the use of echocardiography even in severe cardiac disease, including *de novo* AHF or acutely decompensated HF in general (15, 20, 48).

Echocardiography in AHF can help confirm the diagnosis, identify underlying causes and associated pathophysiology, and monitor therapy response (42, 49). Echocardiography is the most practical and versatile method in terms of providing clinically relevant information (33). Besides that, the selection process and evaluation of patients for various assisted device therapies also heavily relies on echocardiographic assessment (33).

Further, echocardiography is widely available, easily repeatable, safe, and has better cost-effectiveness compared to all other modalities informing on LV morphology and structure. Poor acoustic windows, operator variability, and lower sensitivity are listed as the main disadvantages (50). Nevertheless, echocardiography is used at any stage of HF, and most recent developments in LV strain analysis are especially important to the recognition of subclinical deterioration in the early stages of HF. These were shown to have diagnostic, therapeutic, and prognostic implications (33). A major goal of echocardiographic assessment in HF is to evaluate the performance of the left ventricle, which depends not only on the contractile state but also on loading conditions. To address these issues, we can either correct standard measures for loading conditions or measure contractility independent of loading (33).

Over the years, several surrogate echocardiographic parameters have been introduced to evaluate LV function. In the following, we discuss the utility of the most widely used indexes of LV systolic function, such as LVEF and global longitudinal strain, including a recently introduced non-invasive method, i.e., measurement of myocardial work (MyW).

3.3.1 Left ventricular ejection fraction

LV volumes and LVEF were first described and used to assess LV function in the 1960s (51, 52). Folse and Braunwald used a radioisotope dilution technique to assess LV function (51) and laid the foundation of an echocardiographic parameter that has left its mark over the last 60 years of cardiovascular medicine. The reference standard for the assessment of LV volumes and performance is the invasive pressure-volume measurement. However, because of its invasive nature, there is a need for non-invasive surrogates using easy, safe, and accessible methods.

LVEF is the most widely used surrogate parameter to assess LV global systolic function. LVEF is defined as the proportion of the stroke volume (the difference between end-diastolic volume (EDV) and end-systolic volume (ESV) estimates) to the end-diastolic volume and is expressed in percent (10).

LVEF= (LVEDV –LVESV) / LVEDV

Current guidelines recommend the two-dimensional measurement of LVEF using Simpson's biplane method (tracking of the endocardial border in apical 4- and 2- chamber view) (10). According to current guidelines, normal LVEF values range from 52-72% in men and 54-74 % in women. Lower values are classified into mildly abnormal, moderately abnormal, and severely abnormal. Further, LVEF has become a key part of clinical guidelines in cardiology, i.e., determining HF classification, risk assessment, and therapy guide of different CV diseases (HF, ischemic, and valve disease) as well as the main selection criterion for the majority of HF clinical trials (15, 53). LVEF assessment by two-dimensional echocardiography is easy to apply, can be eyeball-estimated, and is useful for clinical decisions as it might identify patients to likely respond to HF medications and device therapy (54, 55).

LVEF as a dimensionless parameter reflects both cardiac function and remodeling (55). Further, LVEF remains one of the most important prognostic factors, especially in HF patients with reduced LVEF (LVEF <40%) (56, 57). Since half of the HF population consists of HF patients with preserved LVEF (LVEF ≥50%), LVEF is considered to have a lack of clinical utility in this subgroup. Beyond this threshold (LVEF ≥50%), significant systolic dysfunction may still be present, but changes in LVEF do not correlate with symptoms, inform on prognosis, or offer an effective guide to treatment (58, 59).

Thus, LVEF is not an appropriate marker for patients with HFpEF or early stages of HF with subclinical LV dysfunction (60).

The measurement of LVEF also has several intrinsic limitations. For a correct LVEF assessment, good image quality with no foreshortening of apical LV views is needed. LVEF is affected by LV geometry and is considered both preload- and afterload-dependent. LVEF is also influenced by valve disease and heart rate (54, 61). LVEF considers changes in LV volumes during a heart cycle but does not consider the myocardial mechanics of systole and diastole.

LVEF estimation does not take possible intraventricular dyssynchrony of contraction into account (55). Another limitation can be differences in delineation within and in between users. Studies have reported a wide range of intra- and inter-observer variability (62). However, this disadvantage may be expected to considerably decrease in the near future with the implementation of artificial intelligence for automated assessment.

Despite these limitations, LVEF remains the most commonly used cardiac imaging parameter in patients with HF and is utilized in clinical routine to guide therapy in patients with HFrEF (60). However, increased life expectancy and the thus observed higher incidence of underlying diseases such as hypertension, diabetes mellitus, and obesity in the general population seem to associate with subtle, subclinical myocardial impairment and LV dysfunction, – which evades conventional LVEF assessment (63).

Thus, a more comprehensive in-depth approach is needed.

3.3.2 Global and regional longitudinal strain

Myocardial strain measured by echocardiography was introduced in 1998 using Tissue Doppler data (64). Since then, there has been extensive research and immense development of the non-invasive angle-independent speckle-tracking strain echocardiography (STE) (65). Strain based on STE, using grayscale images, describes the most fundamental property of the myocardium, which is shortening and lengthening of the myocardium over the cardiac cycle as a measure of regional and global LV function (66).

Strain is a dimensionless measure of myocardial deformation and expressed in percent, where negative values indicate shortening and positive values indicate lengthening of the

myocardium. Thus, negative strain values represent a better muscle contraction and are considered healthier values.

In opposition to LVEF, strain allows studying the different spatial components of contractile function depending on the orientation of the fibers. As such, strain can be derived in a longitudinal, circumferential, or radial direction, yielding respective strain values for LS, CS, RS. These values can be inspected segmentally, regionally, or globally (59, 67). Up to now, CS and RS have not been introduced to clinical practice, mostly due to high user- and intervendor variability.

Longitudinal strain is measured in the apical long-axis view, using two-dimensional 4-, 3-, and 2-chamber views and calculating strain of respective LV segments (17 or 18 segments depending on the model used). The average of all segmental strain values yields the global longitudinal strain (GLS). A meta-analysis of 24 studies including 2597 individuals reported that normal values range from –15.9% to –22.1% (68). Women exhibited slightly more negative values (up to 1%) compared to men (69, 70). Importantly, this method depends on two-dimensional image quality and frame rate (should be between 50 to 80 s^{-1}) and differs between vendors. A potential foreshortening of LV apical views leads to false strain values. Further, strain values are affected by LV geometry and hemodynamic factors, i.e., loading conditions, inhomogeneous contractility, tissue characteristics, synchrony of contraction (67).

GLS provides added value in clinical practice as it is a simple, robust measure of LV long-axis function (71) and associates with NT-proBNP independently of other conventional indices of systolic and diastolic function (72). Of particular interest is the utility in patients with normal LVEF and subclinical LV dysfunction, i.e., preclinical phases of HF (33, 66). Work from several studies showed that patients with hypertension and diabetes mellitus frequently present with normal LVEF yet impaired LV longitudinal systolic function as, e.g., indicated by reduced GLS values (73, 74). Further, GLS was more compromised in patients with HFpEF compared to patients with hypertension but no symptoms of HF (59, 72), illustrating its potential to quantify the subtle differences between these two entities. Therefore, GLS has been promoted as a marker of early LV dysfunction that can identify individuals in the general population at higher risk for CV morbidity and mortality (75). In patients with HFpEF, approximately 50% show reduced GLS values, which are also predictive of future outcomes, including CV death or HF

hospitalization (26, 76, 77). Further, independent of LVEF, GLS was a predictor of outcome in patients with both stable or acutely decompensated HF (46, 78, 79).

In cardiac conditions other than HF, longitudinal strain was shown to be a better diagnostic and prognostic factor compared to LVEF in patients with an acute coronary syndrome without persistent ST-elevation or valvular heart disease (80-83). Further, longitudinal strain facilitated the evaluation of LV dyssynchrony (84), thus improving the selection process for cardiac resynchronization therapy (CRT). This is done by qualitatively and quantitatively assessing regional strain curves of the septum and lateral wall. Further, in oncological patients receiving chemotherapy, GLS permitted earlier detection of LV myocardial deterioration (85, 86). Thus, GLS has been increasingly advocated as a complementary metric to LVEF and as a new potential reference standard to recognize LV dysfunction (55). Considering all the benefits, the Food and Drug Administration of the United States decided in 2019 to incorporate and reimburse strain measurements in the newer echo machines based on the promise that additional measurement of GLS will improve risk assessment of the population and enable better phenotyping of patients with HF and other CV diseases (46).

3.3.3 Myocardial Work analysis

In recent years, there has been growing interest in novel non-invasive parameters to assess LV function. Assessment of strain by STE improved the diagnosis and risk assessment in patients with different CV diseases as detailed in 3.3.2. However, the sensitivity of strain measurement is limited, as a proportion of patients with HF symptoms exhibits GLS values within the normal range. Further, these markers reflect global and regional myocardial function, respectively. However, they do not reflect myocardial oxygen demand or work (87). As LVEF, GLS is also dependent on loading conditions and LV geometry: Increased pressure or volume overload mediate reduced systolic deformation and result in lower LVEF and GLS despite presumably unchanged LV myocardial contractile function (88-91). These characteristics compromise the specificity of GLS.

The concept to assess cardiac work by pressure-volume loops (Figure 1) dates from the 1970s, where the area covered by the pressure-volume curve reflects stroke work and the associated amount of oxygen consumption of the LV myocardium (92-94).

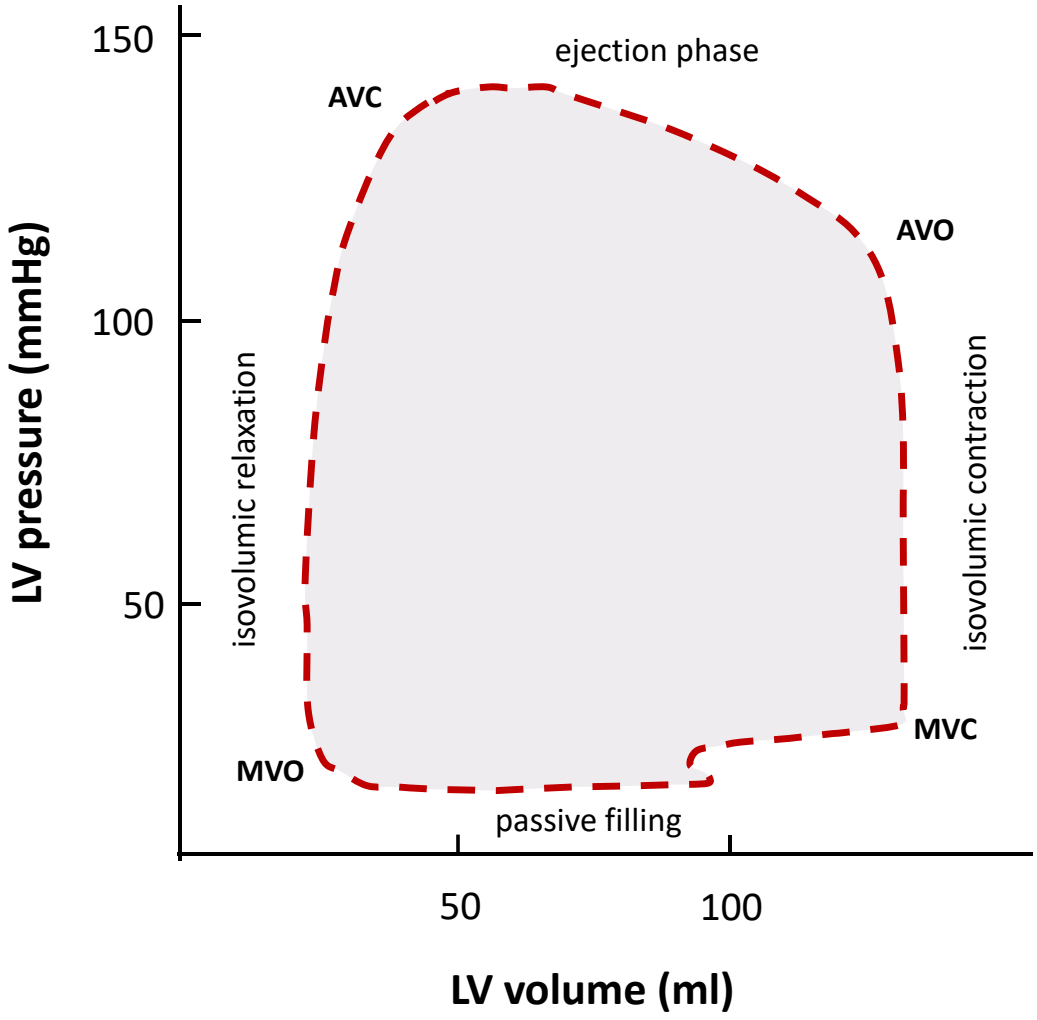


Figure 1. Pressure-volume loop depicting four phases of cardiac cycle: isovolumic contraction, ejection phase, isovolumic relaxation and, passive filling. MVC: mitral valve closure, AVO: aortic valve opening, AVC: aortic valve closure, MVC: mitral valve closure. Illustration designed by F.S

Invasive measurements using pressure-volume loops represent the reference standard that provides a real-time assessment of LV function, considering contractility and loading conditions (95). However, due to the risks and technical/professional preconditions associated with the investigation´s invasive nature, its use in clinical routine has been limited. Recent advances in cardiovascular imaging allow approximating the intrinsic and functional cardiac performance with satisfactory precision, also accounting for loading conditions (96). In 2012, the group of Otto A. Smiseth from Oslo, Norway, introduced a novel echocardiographic method, for which he coined the term "**Myocardial Work" (MyW)**. This method allows to non-invasively quantify LV active myocardial performance, including systole and early diastolic

phase of the cardiac cycle (87). Echocardiography-derived MyW is conceptualized to integrate information on myocardial deformation (speckle-tracking derived longitudinal strain) ***and*** afterload (blood pressure) expressed as a pressure-strain loop (PSL). The uniqueness of this method is that it allows to differentiate, segment by segment, between constructive work (energy contributing to blood ejection) and wasted work (energy not contributing to blood ejection) in relation to the phases of the cardiac cycle.

Further, by including deformation happening in the early phase of diastole, i.e., isovolumetric relaxation time (IVRT), MyW accounts for potential left ventricular dyssynchrony that may occur at this phase. IVRT represents a phase in which the myocardium is actively spending energy. The contraction (shortening) of myocardial segments against a closed valve leads to a waste of energy and a decrease in myocardial efficiency (97-99). Thus, MyW might allow more profound insights into regional LV performance and mechanics when compared to other non-invasive markers. Thus, MyW better reflects contractility in hemodynamic overload states, making it a more robust marker of systolic function of the LV (100).

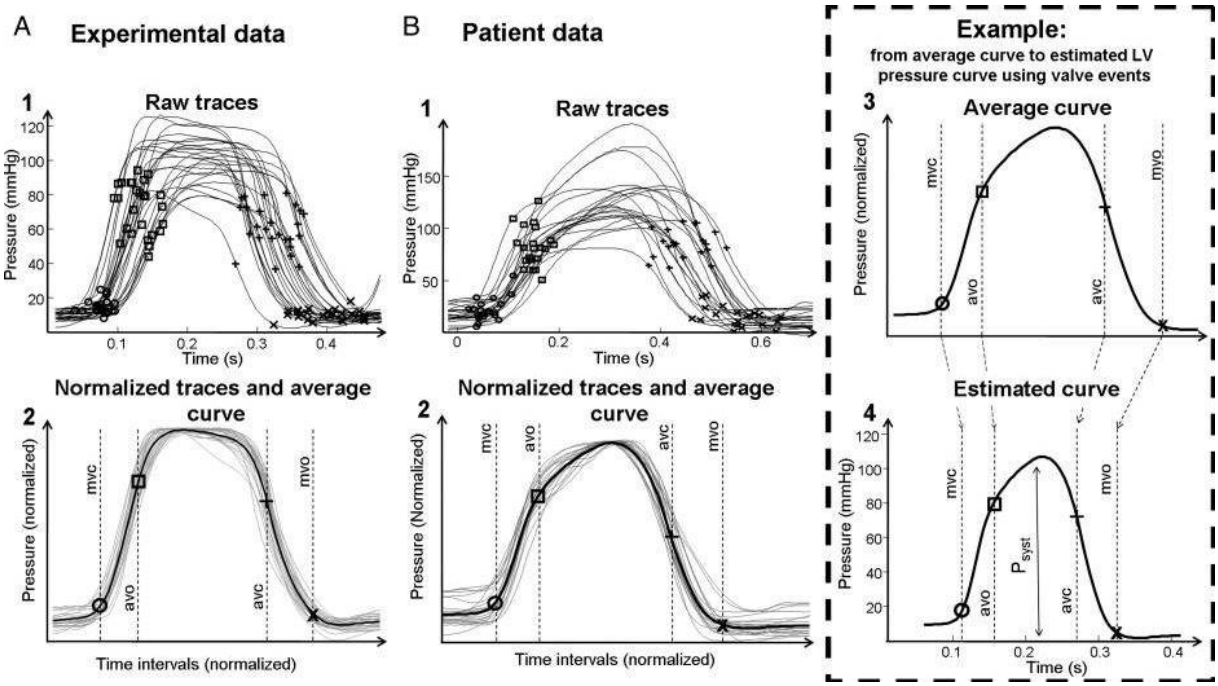


Figure 2. Estimation of left ventricular pressure reference curve from experimental and clinical data. Reprinted from "Russell K, Eriksen M, Aaberge L, Wilhelmsen N, Skulstad H, Remme EW, et al. A novel clinical method for quantification of regional left ventricular pressure-strain loop area: a non-invasive index of myocardial work. Eur Heart J. 2012;33:724–33. (87). Permission for reproduction was obtained from the Oxford University Press Journal.

The MyW method was validated in animal models (dogs) as well as in healthy subjects and patients with different cardiac pathologies (NYHA II-IV) (87, 101-103). In the validation study, the authors created a single reference pressure curve by pooling LV pressure traces of all interventions and normalized them by using the timing of valve events. In the next step, they stretched or compressed pressure traces along the time axis between individual valve events in order to make the valvular events coincide for all recordings (Figure 2) (87).

At the same time, evaluating patient data, they scaled (normalized) the pressure vertically to have the same peak value (87). Further, the reference pressure curve was used for predicting LVP in a specific subject by measuring the actual valvular timing (mitral and aortic valve) and adjusting the duration of time intervals (isovolumic contraction (IVC), LV ejection, and isovolumic relaxation (IVR) phases) by stretching or compressing the time axis of the averaged LV pressure curve to match the measured time intervals (87). Blood pressure measured above the brachial artery by a sphygmomanometer is used to adjust the scale of the vertical amplitude of each pressure curve (87).

Estimated pressure-strain loop area by STE and estimated LV pressure through brachial artery cuff pressure showed an excellent correlation with invasive measurement of pressure-strain loops (r=0.96) and very good visual agreement (87, 101). In another study, performing pressure-volume analysis during transient occlusion of the inferior caval vein, preload-recruitable stroke work as a load-independent ‘gold-standard’ of LV contractility showed a strong correlation with echocardiography-derived MyW (r=0.70; P=0.001) (100).

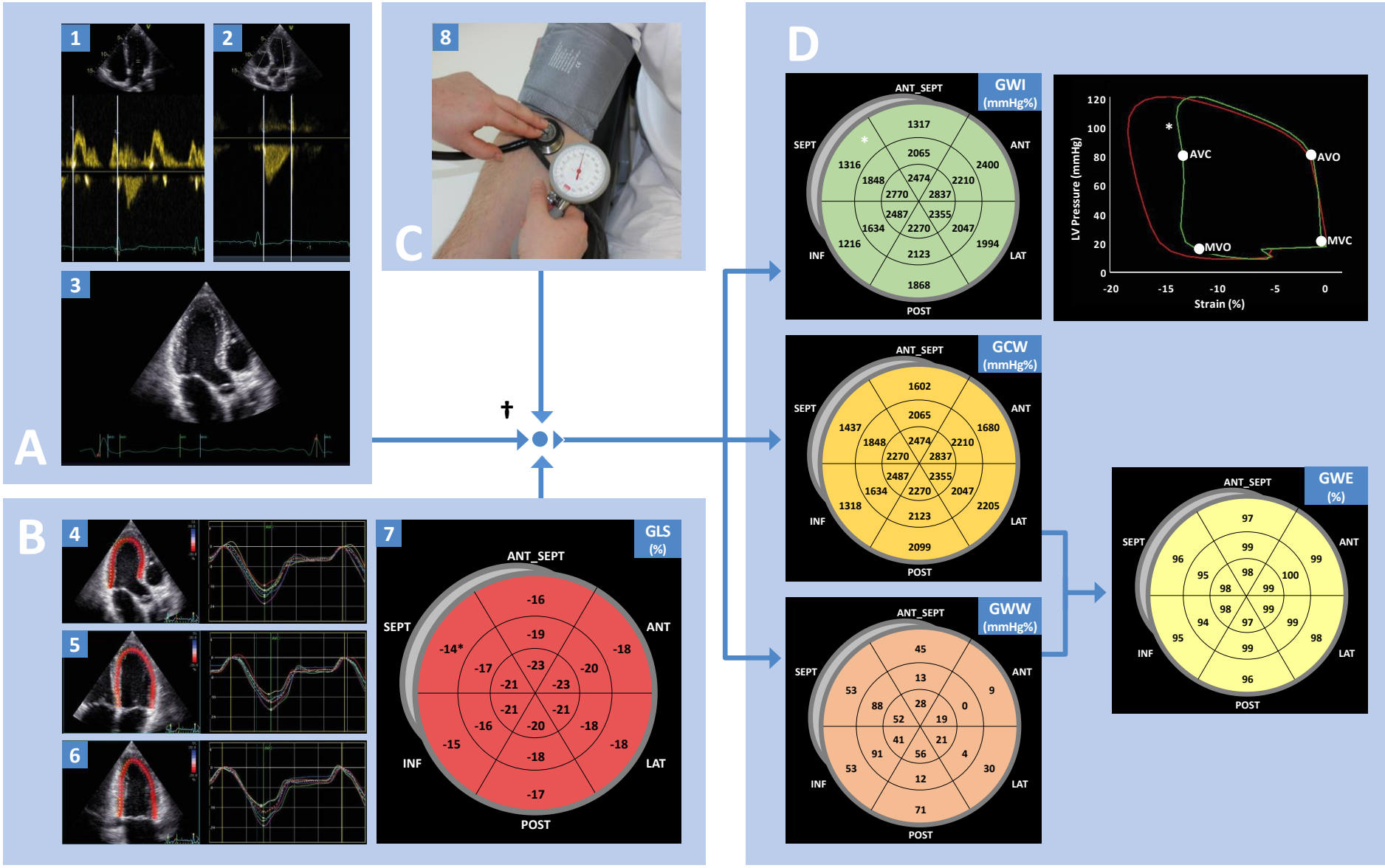
In a second work, the same authors showed in left bundle branch block patients that non-invasive MyW assessment was able to quantify the energy loss caused by uncoordinated left ventricular contractions (101). Consistently, the derived PSL area showed a strong correlation with cardiac glucose uptake measured by fluorodeoxyglucose-positron emission tomography (FDG-PET). This underscores that information derived from measurements of MyW might reflect regional and global myocardial metabolism and energetics (87).

In summary, MyW quantifying segmental and global LV performance in normal and HF patients holds promise to provide additional information regarding the pathophysiology and early phases of CV disease.

The assessment of MyW yields the following read-outs:

a) global constructive work (GCW; unit: mmHg%), i.e., work performed during shortening in systole and adding negative work during lengthening in isovolumic relaxation, also defined as work contributing to pump function;
b) global wasted work (GWW; unit: mmHg%), i.e., work performed during lengthening in systole or work performed during shortening (against a closed aortic valve) in isovolumic relaxation;
c) global work index (GWI; unit: mmHg%), i.e., the total amount of work within the pressure-strain loop area calculated from mitral valve closure to mitral valve opening;
d) global work efficiency (GWE; unit: %), i.e., GCW/(GCW+GWW).
   GWE represents an index of cardiac work expended from the respective LV segments during a cardiac cycle.

All indices are calculated as the mean of respective segmental values. The mathematical derivation of this method was given previously in detail (101, 104). Of note, global work efficiency defined by MyW analysis should be differentiated from the mechanical external efficiency assessed by PET (105). Thus, when presenting data, it is important to highlight the differences between these two methods. Nevertheless, a study in amyloidosis patients showed a fair relationship (R^2=0.48, p<0.0001) between MyW efficiency and mechanical external efficiency measured by ^{11}C-acetate PET (106). The physiological background of LV MyW analysis is depicted in Figure 3.


A
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LV Pressure (mmHg)
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GCW (mmHg%)
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2099
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GWE (%)
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Figure 3. Reprinted from Sahiti F, Morbach C, Cejka V, Albert J, Eichner FA, Gelbrich G, Heuschmann PU, Störk S – ``Left ventricular remodeling and myocardial work: Results from the STAAB cohort study'' Front Cardiovasc Med. 2021 Jun 11;8:669335. doi: 10.3389/fcvm.2021.669335. PMID: 34179134 (96). This is an open-access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Figure 1. Physiological background of LV myocardial work analysis

Section A – represents valvular times, mitral valve opening and close measured using pulse-waved Doppler and aortic valve opening and closure measured by continuous-wave Doppler

Section B – global longitudinal strain measured from 4, 3, and 2 chamber views.

Section C- estimated LV Pressure measured from brachial cuff pressure,

Section D, schematic presentation of segment-specific values of MyW indices, which later are expressed in global values. GCW and GWW are important physiological indices related to the shortening and lengthening of the LV segment. Work efficiency (GWE) is derived as the fraction of GCW and the sum of GCW and GWW

† at this stage, the collected information is used to inform the reference curve composed of LV pressure and valve opening/closure times (as constructed in the validation study by Russell 2012 (87) and depicted in Figure 2), and the pattern of the final loop is formed.

*indicates a segment-specific pressure-strain loop (in this case, we highlighted the septal basal segment.

The novelty of MyW lies in the fact that the LV pressure–strain loop area can now be estimated with an entirely non-invasive approach (i.e., by echocardiography only), using the estimated pressure curve in combination with strain by speckle tracking echocardiography and thus becomes widely applicable in larger study sample including screening situations.

Accounting for afterload (blood pressure), MyW is considered markedly less load-dependent than conventional measures, i.e., LVEF and GLS (87, 88, 91) and, therefore, proposed as a more suitable diagnostic marker overcoming the disadvantage of overestimating LV dysfunction in situations and disease entities with potentially associated fluctuations in loading conditions (40) (Figure 3). Considering physiological aspects of LV work and afterload adjustments, echocardiography-derived MyW might offer new insights into LV performance.

To date, the method of MyW has not yet been extensively tested as a general measure of LV systolic performance (107). However, there is ongoing research to investigate the advantages and potential use of the method in various fields of cardiology, such as

a) Cardiac resynchronization therapy: patient selection and response prediction (108-110),

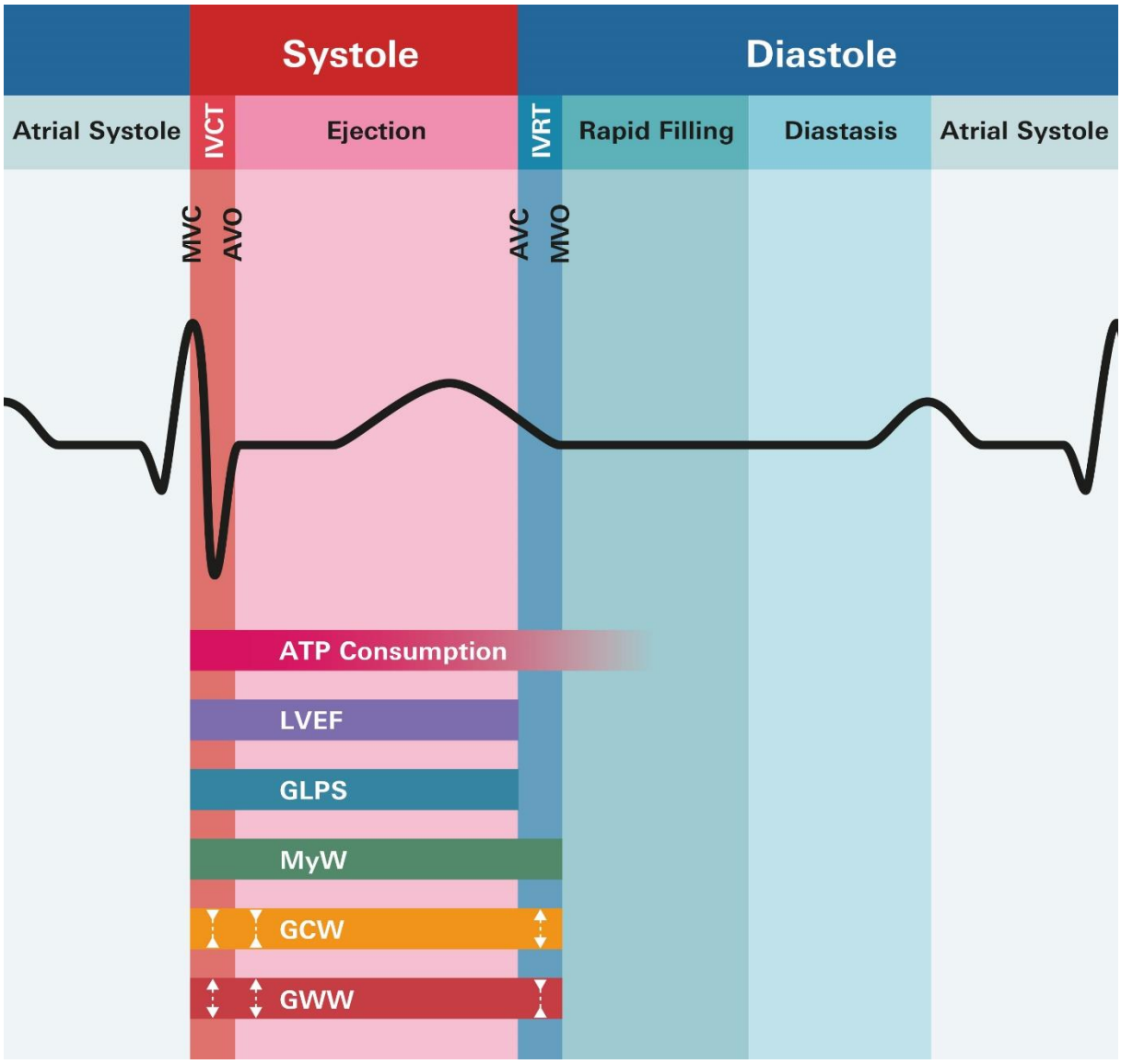
b) Earlier detection of acute coronary syndrome with non-ST elevation (89, 111),

c) Chronic HF (5, 35, 112)

d) Hypertension (5, 113, 114),

e) Hypertrophic cardiomyopathy (115, 116)

f) Amyloidosis (117).



Reprinted from Sahiti, F., Morbach, C., Cejka, V. et al. Impact of cardiovascular risk factors on myocardial work—insights from the STAAB cohort study. J Hum Hypertens (2021). https://doi.org/10.1038/s41371-021-00509-4, Nature Springer (5).

Figure 4. Surrogate measures of left ventricular function in relation to the cardiac cycle and ATP consumption. Myocardial work includes total active myocardial work and allows us to differentiate constructive from wasted work components.

LVEF, left ventricular ejection fraction; GLPS, global longitudinal peak strain; MyW, myocardial work; GCW, global constructive work; GWW, global wasted work; MVC, mitral valve closure; AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening; IVRT, isovolumic relaxation time; IVCT, isovolumic contraction time; ATP, adenosine triphosphate.

3.4 Invasive pressure-volume loops vs. echo-derived pressure-strain loops

Invasive measurement of LV function is performed by cardiac catheterization using conductance catheters, i.e., special catheters that allow simultaneous measurement of pressure and volume over multiple cardiac cycles generating pressure-volume (PV) loops. The assessment of LV function using the contemporary invasive PV analysis technique is challenging, but it provides a real-time assessment of LV contractility and loading conditions as well as surrogates of myocardial oxygen consumption (58, 95). The invasive pressure-volume analysis provides a reference for the assessment, diagnosis, and intervention monitoring of various CV diseases (i.e., myocardial damage, HF pathophysiology, valve heart disease) (11, 95). Further, invasive PV analysis provides accurate insights into the pathophysiology of the LV performance (11, 95).

In 1895, Otto Frank was the first to describe cardiac cycle and LV performance using pressure-volume loops (PVL) (95, 118). Further development in studies *in vivo* and *ex vivo* led to important insights into the mechanics and energetics of the LV (93, 95, 119-121). Nowadays, with contemporary PV analysis, it is possible to assess single-beat end-systolic and end-diastolic LV pressure-volume changes (ESPVR and EDPVR) (121, 122). The cardiac cycle is usually divided into two phases: the contraction phase, i.e., systole, and the relaxation and filling phase, i.e., diastole. However, with the help of PV diagrams (Figure 1), the cardiac cycle can be depicted into four phases, as follows: isovolumic contraction, ejection phase, isovolumic relaxation and, passive filling (11, 123).

The pressure-volume loop, as the analogously constructed pressure-strain loop, illustrates the cardiac cycle as a counter-clockwise loop. The right and left sides of the loop corresponding to the isovolumic contraction (mitral valve closure to mitral valve opening) and isovolumic relaxation phase (aortic valve closure to mitral valve opening), respectively. The upper segment, from aortic valve opening to aortic valve closure, represents the ejection phase, whereas the lower segment represents rapid filling and diastasis (time interval between mitral valve opening to mitral valve closure) (123, 124). These phases are included in the PV analysis, whereas pressure-strain loops do not take the rapid filling phase and diastasis into consideration. The area *within* the PV loop is referred to as the stroke work (SW) and represents the amount of energy imparted by the LV into the blood and can be expressed in

Joules or mmHg-ml (11). SW is estimated by the product of stroke volume (SV=EDV – ESV) and mean arterial pressure (MAP = DP + 1/3(SP – DP)) during ejection (SW= SV x MAP).

As mentioned previously, studies have shown that the pressure-volume area relates to the myocardial oxygen consumption (MVO2) (92, 95, 125); thus, it can be used to assess myocardial mechanical energetic efficiency (MEE = SW/MVO2) (92). The loop´s position and shape depends on the triad: preload, afterload, and contractile state (intrinsic contractile properties of the myocardium) (126). On the other side, the pressure-strain loop area represents the total amount of work calculated from mitral valve closure to mitral valve opening (expressed in mmHg%). The average global pressure-strain loop depends on the estimated LV pressure and deformation of the individual LV segments.

It is important to mention that echocardiography-derived MyW compared to the invasively measured pressure-volume loop, uses blood pressure measured from the brachial artery rather than central pressure Figure 3.

LV segmental dyssynchronies, e.g., observed in the left bundle branch block, often lead to deformation of the shape of individual segments. This is usually illustrated by distorted pressure-volume loops (a figure of eight and running out-of-phase in a counter-clockwise rotation (95)). Segmental dyssynchrony is further quantified by the percentage of time a segment moves in a direction opposite to the total volume change (95). This can also be illustrated in an accurate way using non-invasive pressure-strain loops, which are able to depict and quantify the work conducted by each LV segment. Further, non-invasive pressure-strain loops might be helpful in patient selection and prediction of response to CRT (108).

Given the invasive nature and related difficulties, invasive measurement of the pressure-volume relationship remains challenging and difficult to implement on a routine basis (121). Therefore, there is a need to develop and implement non-invasive concepts and methods such as MyW to assist in diagnosis, risk stratification, and treatment monitoring.

4 Aims

As MyW represents a recently introduced, innovative echocardiography-based tool, the work of the PhD thesis presented here aimed to assess the application and clinical utility of MyW in different study populations. The PhD thesis includes four manuscripts that dealt with complementary aspects of MyW:

Manuscript #1. Myocardial Work – Correlation patterns and reference values from the population-based STAAB cohort study (127)

Aims:

a) To establish normal reference values for MyW indices from the previously described sub-collective of healthy individuals (STAAB) and evaluate its associations with age, sex, and other echocardiographic measurements.

b) To determine MyW as a comprehensive correlate for active systolic and diastolic myocardial function using the new longitudinal strain-based echocardiographic method and non-invasively assess and quantify global and segmental constructive and wasted MyW.

Manuscript #2. Impact of cardiovascular risk factors on myocardial work – Insights from the STAAB cohort study (5)

Aim:

To assess the impact of cardiovascular risk factors and selected comorbidities on MyW and its derivatives in individuals free from heart failure (n=2473 participants).

Manuscript #3. Left ventricular remodeling and myocardial work: Results from the STAAB cohort study (96)

Aim:

To evaluate the association of different LV geometry patterns with MyW in individuals free from heart failure.

Manuscript #4. Dynamics of Left Ventricular Myocardial Work in Patients Hospitalized for Acute Heart Failure (AHF) (40)

Aims:

a) To characterize the in-hospital changes of LV function in AHF patients with either reduced or preserved LVEF using echocardiographic MyW analysis.

b) To determine changes in MyW in relation to changes in NT-proBNP from admission to discharge.

c) To evaluate associations of MyW parameters with established measures of LV myocardial function.

d) To assess the 6-month prognostic utility of MyW indices.

5 Methods

5.1 Study population

The concept of echocardiography-based MyW was presented and invasively validated by a research group in Oslo in 2012 (87, 101). This innovative method is still in its preclinical phase because many questions regarding methodology and clinical application have to be answered. In order to contribute to research in this area, we made use of clinical studies that were run at the Comprehensive Heart Failure Center in order to get insights into the use of the method in clinical practice.

5.1.1 STAAB cohort study

The Characteristics and Course of Heart Failure STAges A-B and Determinants of Progression (STAAB) program is an ongoing, prospective population-based cohort study. STAAB recruited and phenotyped a representative sample of the population of Würzburg, aged 30 to 79 years, which was free of symptomatic HF at the time of inclusion (128). STAAB is a joint initiative of the Comprehensive Heart Failure Center (CHFC) and the Institute of Clinical Epidemiology and Biometry (IKE-B) at the University and University Hospital Würzburg. It is funded by the German Ministry for Education and Research (BMBF 01EO1004 and 01EO1504) and led by Stefan Störk (CHFC) and Peter U Heuschmann.

The overarching aims of the STAAB program are a) to describe the prevalence and natural course of early (i.e., precursor) phases of HF in the general population, and b) to investigate the presence and relevance of CV risk factors and comorbidities in the early course of HF.

A total of n=5,000 residents of the City of Würzburg were recruited and comprehensively phenotyped for the STAAB cohort study. At the time of sampling, all participants had to be aged between 30 to 79 years. Data on inhabitants were obtained from the City Hall Registration Office, and – based on random sampling – 24,000 address data were drawn. Subsequently, potential participants stratified for age and sex (men to women ratio 1:1) were invited by mail to participate in the study. People with a previous diagnosis of HF, unable to give consent, or without sufficient knowledge of the German language were excluded. The study design and methodology have been published previously (128, 129). The baseline

examination of the whole cohort was conducted between December 2013 and November 2017. To establish normal reference values for MyW, we used data obtained from "apparently healthy" individuals, i.e., without CV risk factors or established CV disease.

Further criteria of "healthy "individuals were: sinus rhythm, LVEF above 50%, no regional wall abnormalities, or significant LV valve disease. N=953 met the definition of "apparently healthy". Of those, n=779 could be analyzed using MyW analysis (first manuscript (127)). In the second and third manuscript (5, 96)), we concentrated on data of the first half of the study population (i.e., the n=2473 individuals recruited between 12 December 2013 and September 2016), which had been pre-specified for a planned interim analysis (128).

Ethics and privacy

The STAAB study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, University of Würzburg (vote 98/13, J-117.605-09/13). Further, all participants provided written informed consent prior to any study-related examination. The personal data of the participants were pseudonymized, and the documentation was done in electronic Case Report Forms. All clinical data obtained were digitally stored in the campus-wide Data Warehouse for future data extraction.

Baseline examination

Patients were invited for a study examination at the Joint Survey Unit of the CHFC and IKE-B with dedicated space for the study visit, i.e., rooms for face-to-face interviews and physical examination, anthropometric measurements, echocardiography scans, and on-site processing, and temporary storage of biomaterials. Before the start of each examination, participants were informed about the purpose of the study and the examinations to be performed. We obtained information regarding demographic, economic, social factors, known CV risk factors, and CV disease during the face-to-face interview. Further, a number of questionnaires addressing lifestyle and psychoemotional health were filled in by participants themselves. All examinations were conducted by specially trained staff according to the Standard Operating Procedures (SOPs) (128).

Patients were requested to attend the Joint Survey Unit in a fasting state. During an average of 3.5 hours, participants underwent a structured and harmonized series of consecutive examinations.

Blood pressure was measured in a sitting position after 5 minutes of rest using brachial cuff measurement (Omron 705®). If the measured values between the first and second measurement (systolic and/or diastolic) differed by more than 10 mmHg, a third measurement was performed. Body height was measured using a digital stadiometer (SECA 274®), body weight was obtained from a bioelectrical impedance analysis (SECA mBCA 515®). Smoking habits and current medication were evaluated during the interview with the study physician (128).

Venous blood was collected from a cubital vein, and urine samples were taken. All laboratory measurements were performed on the same day at the Central Laboratory, University Hospital Würzburg, including fasting lipid profile, estimated glomerular filtration rate (eGFR), glycosylated hemoglobin (HbA1c), plasma glucose levels (5). Biomaterials for future analysis were aliquotted immediately and stored in the interdisciplinary bank for data and biomaterials Würzburg (ibdw) at – 80°C.

Echocardiography and quality assurance

All study participants underwent an extensive transthoracic echocardiographic examination performed by trained and internally certified sonographers using Vivid S6® with M4S Sector Array Transducer operating at 1.5-4.3 MHz (GE Healthcare, Horten, Norway) and Vivid E95 scanner with a M5SC-D transducer (1.5–4.6MHz; GE Healthcare, Horten, Norway) (69, 128). The pre-specified study protocol was set in the machine. Further, to ensure a good quality of the data obtained, the STAAB study runs a regular quality control program (128). The characteristics of performed measures of the echocardiography quality assurance program have been published previously (130). Three cardiac cycles were recorded for each view. Two-dimensional (2D) images were recorded with a frame rate between 50 to 80 frames/second and stored digitally. We measured LVEF using Simpson's biplane method, and from this measure, we derived LV end-diastolic and end-systolic volumes (10). Diastolic function was according to the latest guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging (131). Diastolic myocardial relaxation

velocities (s', e´, a') were assessed using tissue and PW-Doppler close to the septal and/or lateral mitral annulus. LA volume was assessed using biplane in apical four and two-chamber view, and left atrial volume index (LAVi) was calculated as LA volume indexed to body surface area. Valve regurgitation was assessed using color Doppler multiplane vena contracta and pressure half-time, and valve stenosis were assessed by evaluating maximal flow velocity by continuous-wave Doppler according to current recommendations (132, 133).

Using M-mode recording or 2D measurement in case of angulation, we derived LV measurements from the parasternal long-axis (10), i.e., interventricular end-diastolic septum thickness (IVSd), LV posterior wall thickness (LVPWd), and LV end-diastolic diameter (LVEDD). LV mass was calculated using the ASE corrected formula (10): LV mass (g) = 0.8 151 (1.04 [([LVEDD + IVSd +LVPWd] 3 - LVEDD3)]) + 0.6 as well. LV relative wall thickness (RWT) was calculated as: 2x posterior wall thickness / LV end-diastolic diameter (10, 134). LV mass index (LVMi) and LV end-diastolic volume index (LVEDVi) were calculated indexing LV mass and LV end-diastolic volume to body surface area, respectively. According to the latest guidelines), we classified the participants into four different subgroups according to their respective LV geometry pattern (10, 134) (Figure 5): a) normal LV geometry: LVMi ≤95 g/m^2 in women or ≤115 g/m^2 in men and RWT ≤0.42; b) concentric LV remodeling (CR): LVMi ≤95 g/m^2 in women or ≤115 g/m^2 in men and RWT >0.42; c) concentric LV hypertrophy (CH): LVMi >95 g/m^2 in women or >115 g/m^2 in men and RWT >0.42; d) eccentric LV hypertrophy (EH): LVMi >95 g/m^2 in women or >115 g/m^2 in men and RWT ≤0.42 (96).

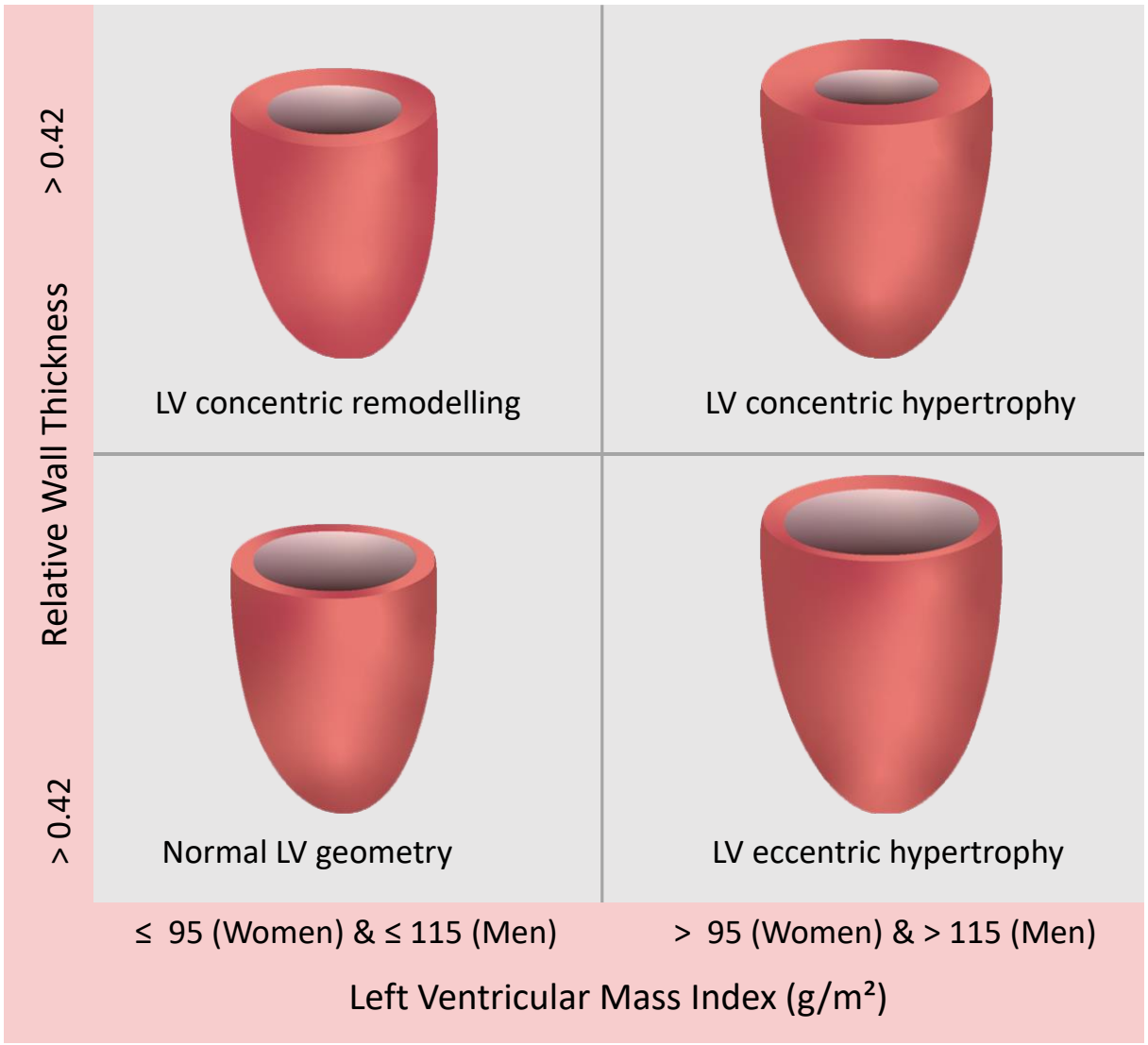


Figure 5. Sex-specific LV geometry patterns according to current guidelines (10). Illustration designed by F.S

5.1.2 AHF Registry

The Acute Heart Failure (AHF) Registry is a monocentric prospective follow-up study, an initiative of Comprehensive Heart Failure Center, University Hospital Würzburg, that comprehensively identifies and phenotypes consecutive adult patients admitted for AHF at the emergency department (24/7). The AHF registry aims to improve the pathophysiological understanding, diagnosis, and treatment of AHF, particularly in relation to the early phase after cardiac decompensation, potential worsening, progressive and advanced HF. Patients with high output HF, cardiogenic shock, or listed for high urgency transplant are excluded. The AHF registry runs entirely in a routine clinical setting, with no additional study-related procedures or any other interferences.

The diagnosis of AHF was made by physicians in-charge based on signs, symptoms, and the results of clinically indicated examinations and treated in a tertiary university clinical center according to the current guidelines (best clinical practice) of the time. The first (admission) and the last (discharge) echocardiography, laboratory tests, weight measurements were conducted in close temporal vicinity to admission and discharge, respectively. Further, patients were discharged based on the treating physician´s discretion based on clinical parameters and stability. Survival status and re-hospitalization (admissions to the hospital) were obtained after 6 months, either on the outpatient visit or by telephone follow-up or based on information from general practitioners, relatives, or registration authorities.

The population of the current analysis (40)

For the current work, we selected all patients admitted for AHF between August 2014 and December 2017 to the University Hospital Würzburg, who provided serial echocardiograms performed on hospital admission, and prior to discharge. We used prior to discharge estimated LVEF to stratify our study population according to guidelines from 2016 (15) into three categories: HF with reduced ejection fraction (HFrEF, LVEF <40%); HF with mildly reduced ejection fraction (HFmrEF; LVEF 40–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%). Laboratory measurements, including N-terminal prohormone B-natriuretic peptide (NT-proBNP) assay, were carried out at the Central Laboratory of the University Hospital.

Echocardiography

Echocardiography was performed on the clinical setting close after admission using Vivid 7, Vivid E9, and/or Vivid E95® (GE Healthcare, Horten, Norway). Images were obtained, and measurements were performed according to the current recommendations (10, 132, 133). Detailed information on how systolic and diastolic function echocardiographic parameters were determined is described in the previous echocardiographic section of the STAAB study (chapter 5.1.1). In patients not in sinus rhythm, representative cardiac cycles of similar length in all three apical views were selected, thus facilitating analysis of LV strain and MyW.

Surrogate of recompensation

Natriuretic peptides (NP) are well-established markers in AHF patients and are used to assess the severity of congestion (135). NT-proBNP, which is secreted by cardiac chambers and atria upon increased stretching of walls, is considered a robust and clinically useful marker of hemodynamic “stress” (136). Consequently, its measurement has adopted an essential role in the diagnosis, management, and prognosis of AHF patients (14, 137, 138). Further, studies found that the admission-to-discharge reduction of natriuretic peptides is an informative marker on treatment response and correlates with clinical and objective markers of decongestion (137, 139). We, therefore, utilized the in-hospital change in NT-proBNP as a surrogate of the efficiency of decongestive success. We operationalized the markers as a discharge-to-admission ratio, DAR: NT-proBNP at discharge divided by NT-proBNP at admission.

Ethics and privacy

The study protocol complies with the Helsinki Declaration and has received a positive vote (July 2014, ref. 55/14) from the Ethics Committee of Medical Faculty, University of Wurzburg, and the data protection officer of the University Hospital Würzburg. Recruited patients provided written informed consent. The patients had no risk of participating in the study.

5.2 Myocardial Work analysis – Step by step

In the introduction (Chapter 3.3.3), we explained in detail the physiological background of the assessment of MyW. Here, we will concentrate on practical steps on how to obtain a measure of MyW. MyW analysis was conducted off-line using commercially available software EchoPAC (Version 202, GE). Initially, using pulsed-wave Doppler through the mitral valve inflow and continuous-wave Doppler through the aortic valve, we determined valve closure and opening times for each participant (Figure 6a and 6b). Next, we assessed segmental longitudinal strain in apical three-, four-, and two-chamber views and derived the absolute value of global longitudinal strain (Figure 6c, 6d, 6e). Blood pressure, measured from the brachial cuff method, was then entered into the system (Figure 6f and 6g). The software calculations are based on a previously generated empiric normalized reference curve for LV pressure (87); see Chapter 3.3.3. This reference curve is then adjusted a) by aligning valvular times as assessed by echocardiography and b) by including blood pressure measured by cuff-manometer as a surrogate of peak systolic left ventricular pressure. After determining GLS and making the final adjustments of the valve times (if necessary) as well as entering blood pressure data (Figure 6g). MyW outputs are as seen in Figures 6h and 6i. The following indices are derived (Note: these indices were shown in Chapter 3.3.3, but for easier reading, we decided to mention them again):

a) global constructive work (GCW; unit: mmHg%), i.e., work performed during shortening in systole and adding negative work during lengthening in isovolumic relaxation, also defined as work contributing to pump function;
b) global wasted work (GWW, mmHg%), i.e., work performed during lengthening in systole or work performed during shortening against a closed aortic valve in isovolumic relaxation;
c) global work index (GWI; unit: mmHg%), i.e., the total amount of work within the pressure-strain loop area calculated from mitral valve closure to mitral valve opening;
d) global work efficiency (GWE; unit: %), i.e., GCW/(GCW+GWW);.

All indices are calculated as the mean of respective segmental values. MyW cannot be evaluated if more than one LV segment is unsuitable for speckle tracking, i.e., mostly due to suboptimal image quality.

5.2.1 Intra- and interobserver variability of the method

MyW analysis was performed by one researcher (FS). For the assessment of intra-observer variability used in manuscripts #1-3, 20 randomly selected scans, and for observer variability used in manuscript #4), 25 randomly selected scans were read by the same observer twice, two weeks apart. For the respective assessment of inter-observer variability, the same scans were read by a second person (CM) blinded to the previous results.

The results of the inter-and intraobserver variability regarding MyW parameters for the respective manuscripts (1-3) were previously published and were favorably low (5) (see manuscript #1, Table 2; manuscript #2, supplemental Table S1; manuscript #4, supplemental Table S1 (40).

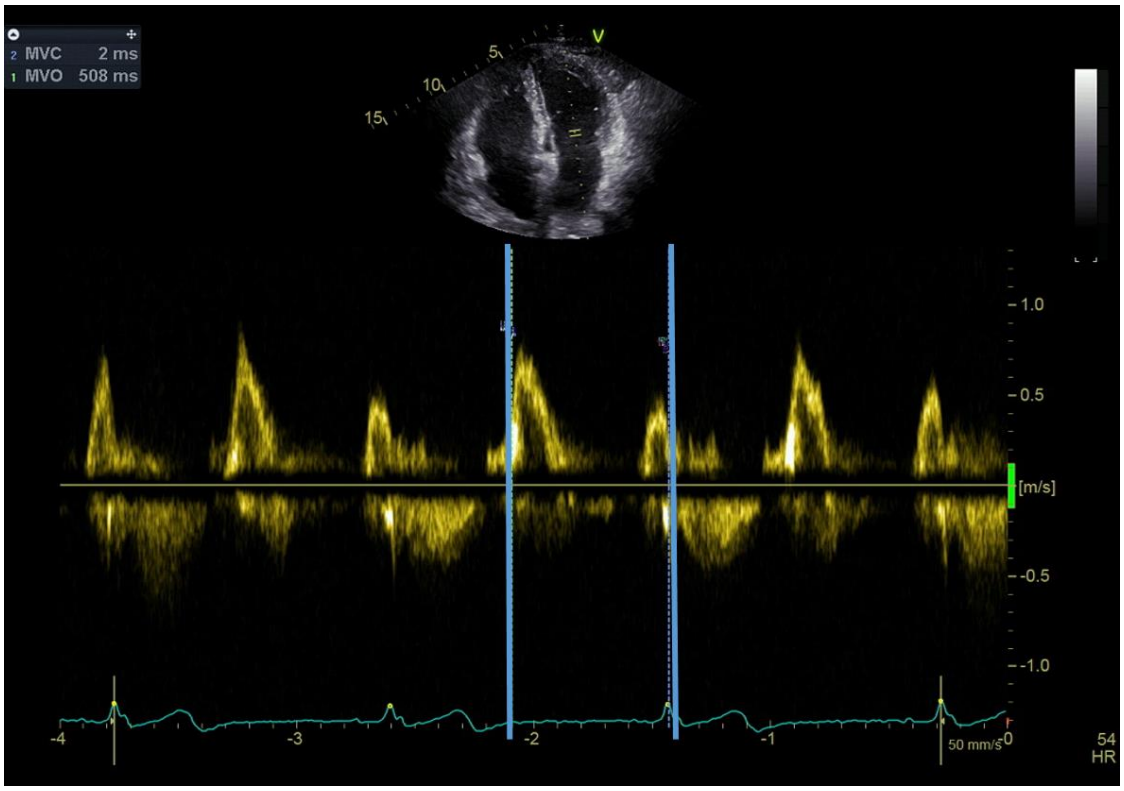


Figure 6a. First, using pulsed-wave Doppler in apical 4-chamber view, mitral valve closure and opening times are tracked.

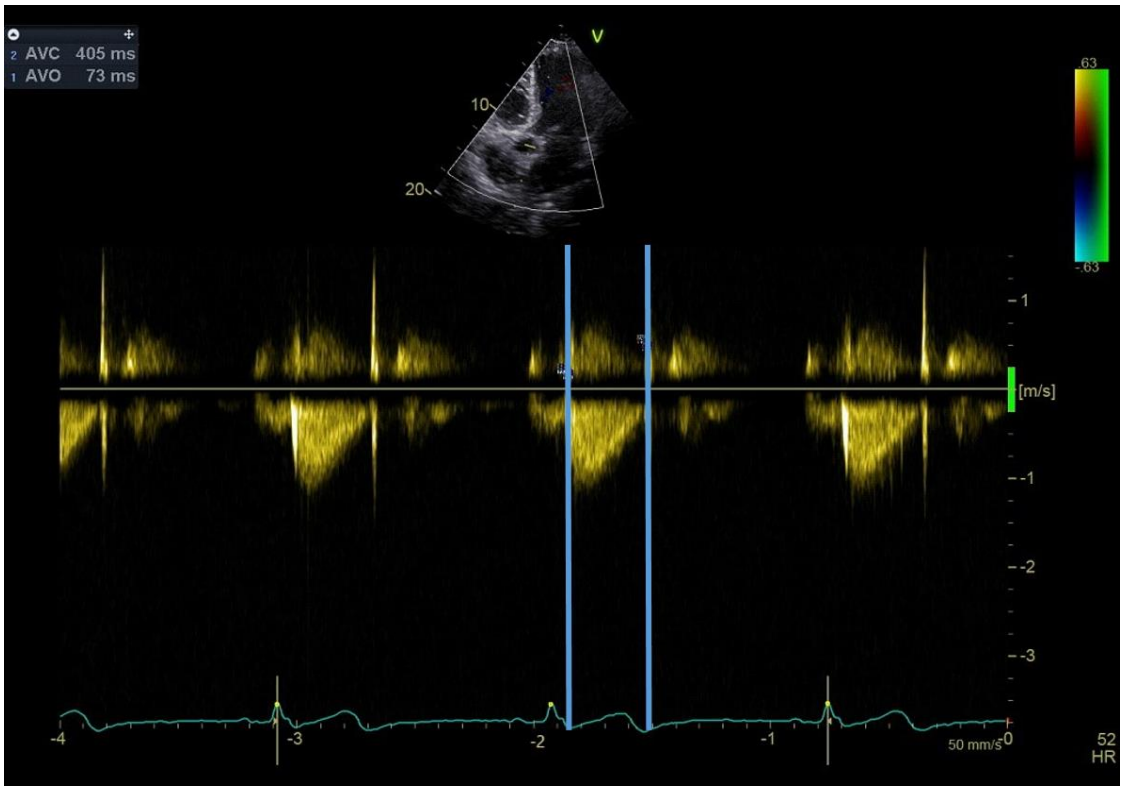


Figure 6b. Second, aortic valve closure and opening times are measured using continuous-wave Doppler in apical 5-chamber.

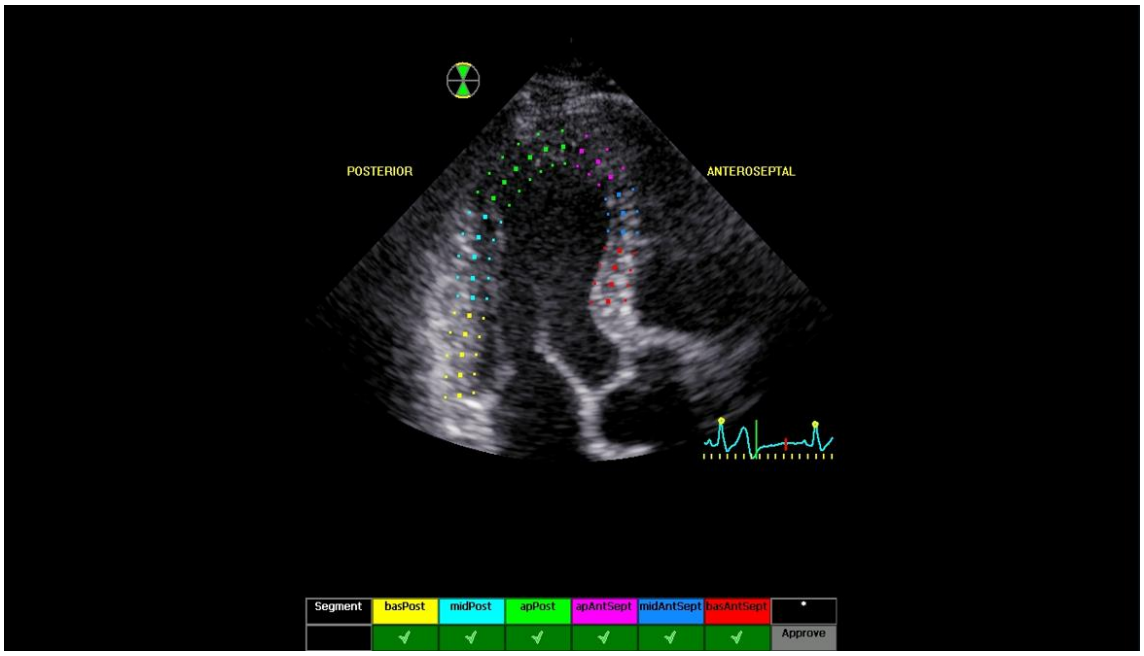


Figure 6c. Third, global longitudinal strain, starting with segmental strain measurements in 3-chamber view, is quantified. Adjustments in the automated speckle tracking contour are made if necessary.

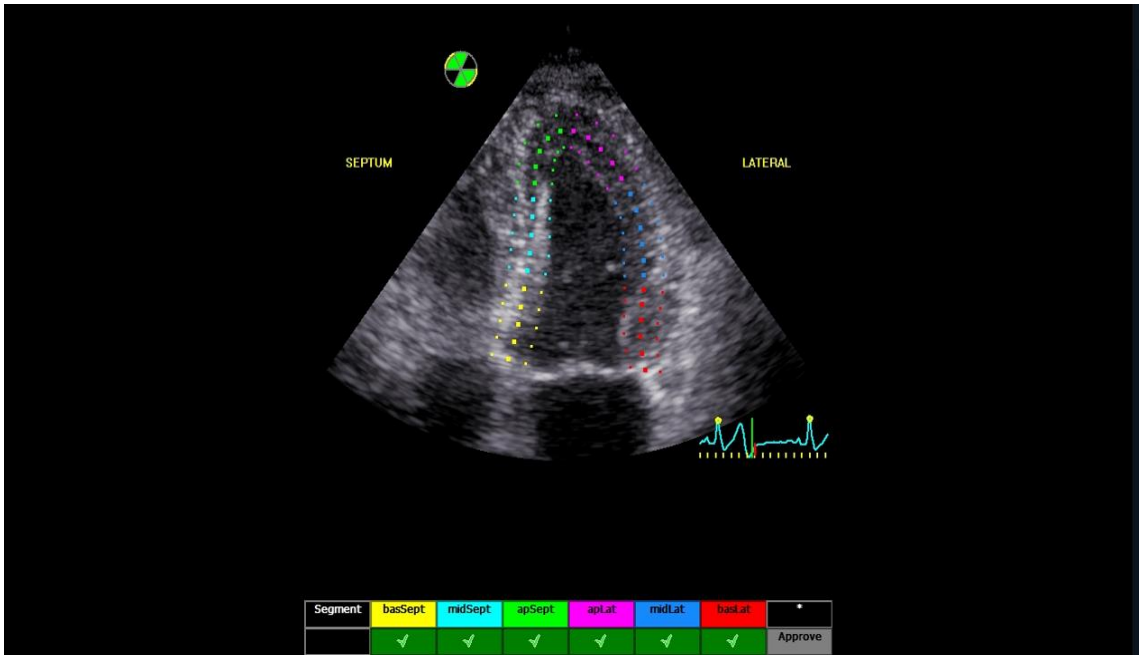


Figure 6d. Fourth, segmental strain in the apical 4-chamber view is quantified. Adjustments in the automated speckle-tracking contour are made if necessary.

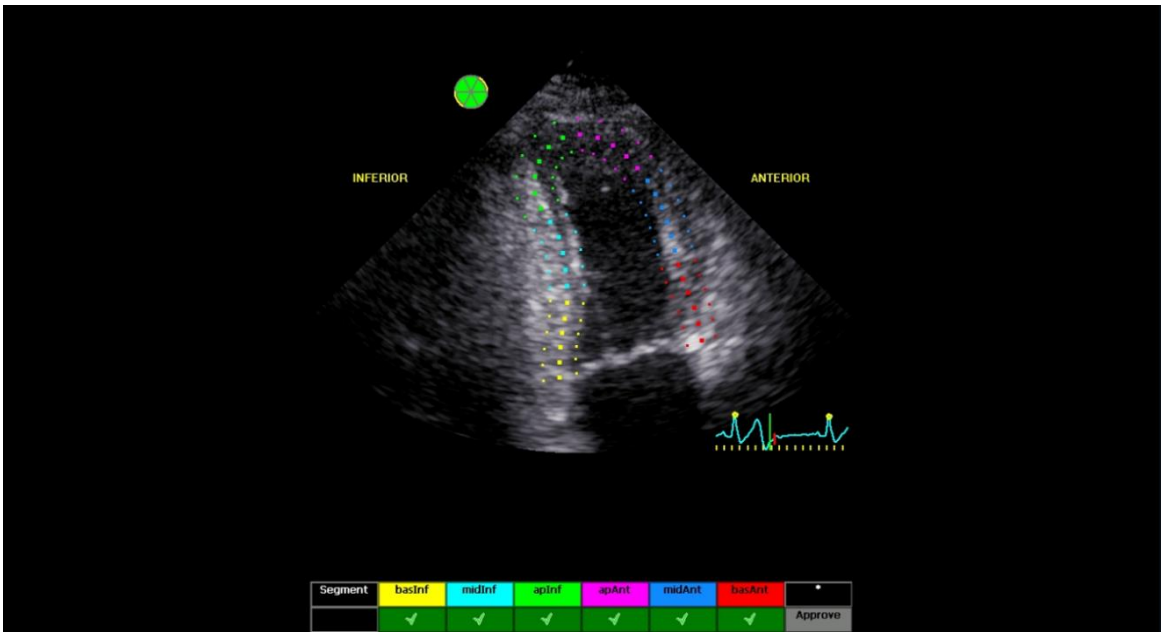


Figure 6e. Fifth, segmental strain in the 2-chamber view is measured. Adjustments in the automated speckle-tracking contour are made if necessary.

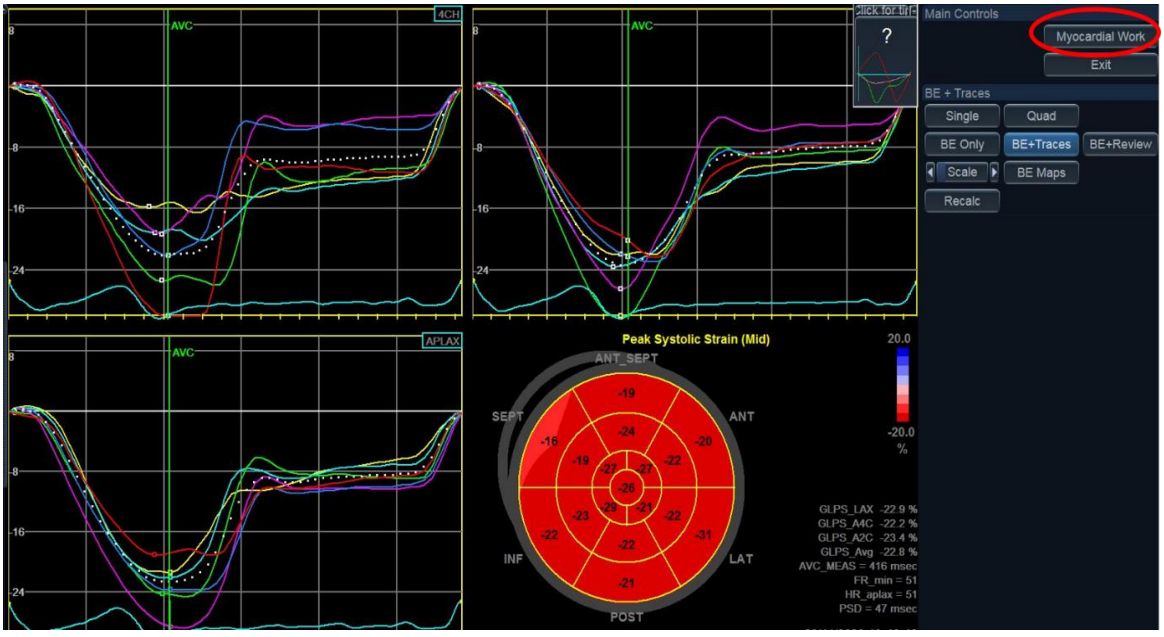


Figure 6f. Sixth, after estimating the respective segmental strain from three different apical views, the bull's eye scheme containing 17/18 segments (depending on the modality selected, respectively) is obtained. The next step is clicking the button on the right upper corner labeled “Myocardial Work”.

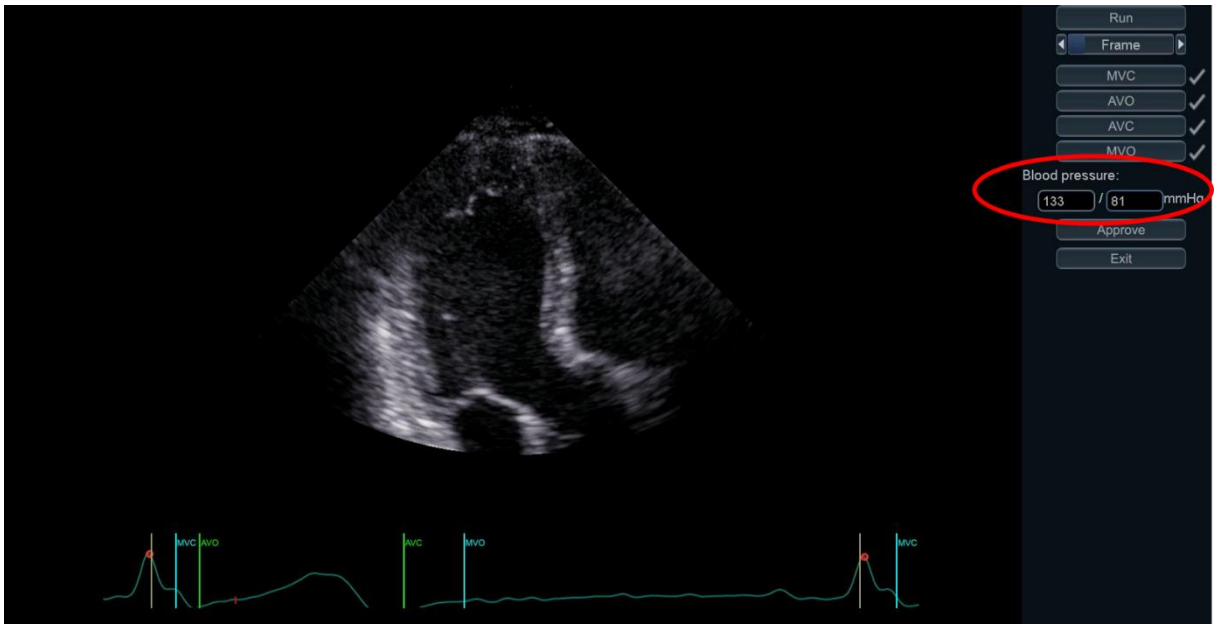


Figure 6g. Seventh, after selecting the myocardial work option, one is redirected again into the apical 3-chamber view. There, time points of valve events can be checked and adjusted, if necessary. Systolic and diastolic blood pressure values are entered in order to allow computation of segmental and global MyW values. This concludes the MyW assessment procedure.

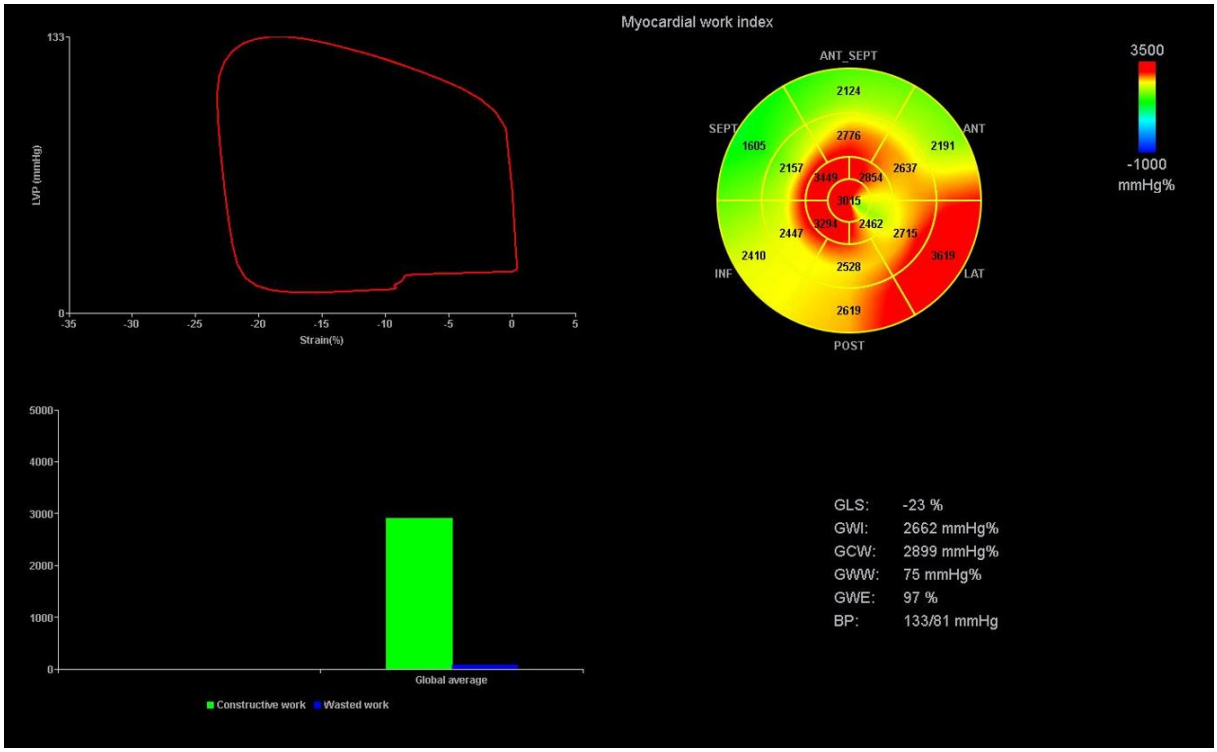


Figure 6h. Left: the global pressure-strain loop is presented, indicating the myocardial work index (i.e., the area within the loop). Right: the segmental myocardial work index values are shown in the bull's eye plot. MyW indices are calculated as a mean of the respective segmental values.

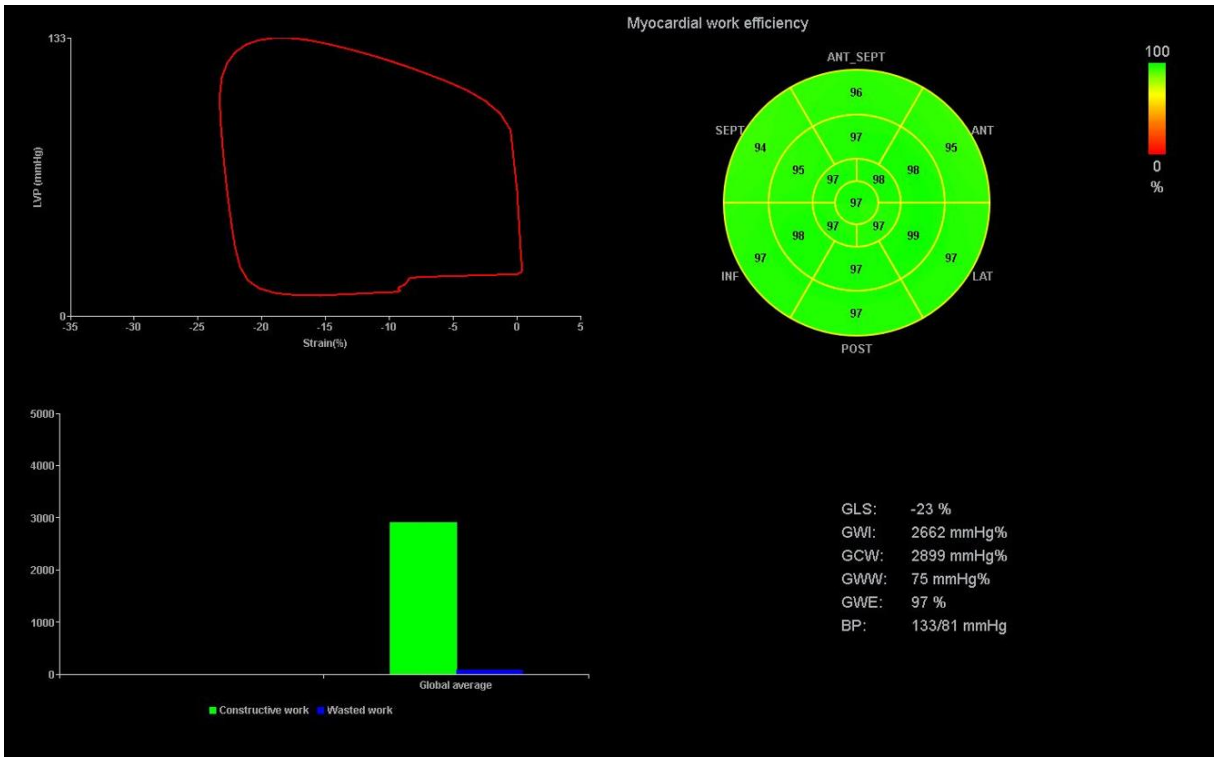


Figure 6i. Left: the global pressure strain loop is shown, indicating the MyW index (i.e., the area within the loop). Right: segmental work efficiency values are shown. MyW indices are calculated as a mean of the respective segmental values.

5.3 Statistical methods and data analysis

Statistical analyses were performed using SPSS (Version 22, 25 and 26, SPSS Inc., Chicago, USA) and R 3.6. Continuous variables are reported as mean with standard deviation (SD) or median with quartiles. Categorical variables are reported as frequencies with percentages. Data were tested for normality using the Shapiro-Wilk test. Normally distributed data were assessed using the Student´s t-test. Non-normally distributed data were compared using Mann-Whitney U-test or Kruskal-Wallis test, and categorical variables using the chi-square test. Additional statistical procedures used in each respective manuscript are described below.

Manuscript #1 (127). The Bland-Altman method with 95% limits of agreement was used to assess intra- and inter-observer variability (also in Manuscripts #2 and #3). Scatter diagrams of MyW indices with age were plotted with trend curves obtained from a locally weighted regression, and general linear models were computed(127). Kendall´s τ correlation coefficient was used to evaluate the associations of MyW indices with anthropometric and echocardiographic parameters in the subgroup of healthy individuals from the STAAB cohort.

Manuscript #2 (5). The association of CV risk factors with MyW indices was investigated through univariable linear regression analysis. In the second step, the multivariable models were run with adjustment for age and sex. As MyW is highly impacted by the current measurement of blood pressure, we additionally adjusted in separate models for systolic blood pressure.

Manuscript #3 (96). Univariable linear regression analysis was used to assess the association of LV geometry (LV mass and LV volumes) with MyW indices. Based on the results from univariable regression and physiological information behind these parameters, a model using the enter method was created, including age, sex, body mass index (BMI), LVEF, GLS, heart rate, LDL cholesterol, HbA1c, hypertension, LVMi, and LVEDVi. Further, to investigate trends in MyW indices, the Jonckheere-Terpstra was used.

Manuscript #4 (40). In patients hospitalized for AHF, the shape of the distribution of MyW indices was inspected using histograms and kernel density estimation. Scatter plots, and Pearson´s product-moment correlation coefficients (with 95% CI) were used to assess correlations between markers of LV systolic and diastolic function (log NT-proBNP, LVEF, mean e') with MyW indices. To quantify the direction and strength of association between the degree of NT-proBNP change reached during the in-hospital stay and the corresponding

change in MyW, we used a generalized linear model with gamma regression that allows modeling of skewed data(140). The ratio between discharge and admission, i.e., the discharge-to-admission ratio (DAR), was analyzed for all MyW parameters as a dependent variable. The DAR can be interpreted as “percent change”. Gamma rates were estimated using a multiplicative exponential model with terms for the LVEF category, NT-proBNP (also included as DAR), and their interaction term. Expected marginal mean gamma rates with 95% CI and p-values were estimated. Cox proportional hazard regression was used to explore the utility of MyW indices to predict time to death or all-cause re-hospitalization, and fixed adjustment for age and sex was employed in prognostic analyses. All tests were performed 2-sided. P-values <0.05 were considered statistically significant.

6 Results

6.1 Manuscript #1

Morbach C, Sahiti F, Tiffe T, Cejka V, Eichner FA, Gelbrich G, Heuschmann PU, Störk S – ''Myocardial Work – correlation patterns and reference values from the population-based STAAB cohort study'' PLoSONE 15(10):e0239684. Published online 2020 Oct 8. doi: 10.1371/journal.pone.0239684 PMID: 33031416.

6.1.1 Summary

A total of n=779 apparently healthy participants (49 ± 10 years, 59% women) in sinus rhythm, free from CV risk factors or disease and without significant LV valve disease, were derived from the total sample (n=4965) of the population-based STAAB cohort study, and MyW indices were assessed. The trend curves obtained from locally weighted regression showed a disparate association of MyW indices with age below vs. above the threshold of 45 years.

GCW residuals showed a normal distribution and an upward shift occurring at the age of 45 years. The reference for GCW in individuals younger than 45 years was determined at mean 2366 mmHg% (95% CI 2330; 2482) and in individuals older than 45 years at mean 2457 mmHg% (95% CI 2428; 2486).

As the data for GWW was non-normally distributed, we assessed non-parametric percentiles of residual distributions. Levels of GWW were also stable until the age of 45 years with reference values of median 68 mmHg% (quartiles 50, 90), but exhibited a slope of 6 points per age decade beyond the age of 45, with reference values of median 73 mmHg% (quartiles 52, 103).

Other than for GCW or GWW, GWI values were different between sexes, with higher values in women compared to men. Reference values below age 45 years for women were median 2206 mmHg% (quartiles 2003, 2409), and 2141 (quartiles 1938, 2344) for men. Reference values above age 45 years for women were 2252 mmHg% (quartiles 2049, 2455) and 2187

mmHg% (quartiles 1984, 2390) for men. GWE values were also stable up to age 45 years and not different between sexes. GWE decreased by 0.5% per increase in the age decade.

Further, the established reference values for each MyW index (Chapter 6.1.2, Table 3) serve to distinguish healthy from different disease entities.

Using Kendall´s τ correlation coefficient, we evaluated the association of MyW indices with anthropometric and echocardiographic markers. These markers were all within the normal range (as they were derived from healthy participants). Blood pressure was positively related to GWI, GCW, GWW and negatively to GWE. Systolic markers of LV function such as LV ejection fraction and global longitudinal strain were positively related to GWI, GCW, GWE, and negatively to GWW. Indicators of cardiac morphology (e.g., LV mass or LA volume) were positively related to GCW and GWW and inversely to GWE. E/e` as a marker of diastolic function was positively related to GCW and GWW and inversely to GWE. Body mass index, left ventricular end-diastolic volumes, stroke volume, and heart rate showed no significant correlation with MyW indices.

6.1.2 Manuscript (publication)

PLOS ONE

RESEARCH ARTICLE

Myocardial work - correlation patterns and reference values from the population-based STAAB cohort study

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☯ These authors contributed equally to this work.
¶ Membership of the STAAB consortium group is listed in the Acknowledgments.
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OPEN ACCESS

Citation: Morbach C, Sahiti F, Tiffe T, Cejka V, Eichner FA, Gelbrich G, et al. (2020) Myocardial work - correlation patterns and reference values from the population-based STAAB cohort study. PLoS ONE 15(10): e0239684. https://doi.org/10.1371/journal.pone.0239684

Editor: Elena Cavarretta, Universita degli Studi di Roma La Sapienza, ITALY

Received: May 16, 2020

Accepted: September 11, 2020

Published: October 8, 2020

Data Availability Statement: Data allowing the reproduction of our results are held in a public suppository: https://doi.org/10.6084/m9.figshare.12961976.v1.

Funding: The study is supported by the German Ministry of Research and Education within the Comprehensive Heart Failure Center, Würzburg (BMBF 01EO1004 and 01EO1504). There is no relationship with industry. SS and PUH received this funding. The funders had no role in study

Abstract

Background

Recently, *myocardial work* analysis as an echocardiographic tool to non-invasively determine LV work has been introduced and validated against invasive measurements. Based on systolic blood pressure and speckle-tracking derived longitudinal strain (GLS) during systole and isovolumic relaxation, it is considered less load-dependent than LV ejection fraction (LVEF) or GLS and to integrate information on LV active systolic and diastolic work.

Objectives

We aimed to establish reference values for global constructive (GCW) and global wasted work (GWW) as well as of global work index (GWI) and global work efficiency (GWE) across a wide age range and to assess the association with standard echocardiography parameters to estimate the potential additional information provided by myocardial work (MyW).

Methods

The *Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression* (STAAB) cohort study carefully characterized a representative sample of the population of the City of Würzburg, Germany, aged 30–79 years. We performed *myocardial work* analysis using the standardized, quality-controlled transthoracic echocardiograms of all individuals lacking any cardiovascular risk factor.

Results

Out of 4965 participants, 779 (49±10 years, 59% women) were eligible for the present analysis. Levels of GCW, GWW, and GWE were independent of sex and body mass index, and were stable until the age of 45 years. Thereafter, we observed an upward shift to further

design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: Caroline Morbach reports a research cooperation with the University of Würzburg and Tomtec Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany, speakers honorarium from Amgen, Alnylam and Tomtec, a travel grant from Orion Pharma and Alnylam, and participation in Advisory and Patient Eligibility Boards sponsored by AKCEA, Alnylam, Pfizer and EBR Systems outside the submitted work. Floran Sahiti has nothing to disclose Theresa Tiffe has nothing to disclose. Vladimir Cejka has nothing to disclose. Felizitas Eichner has nothing to disclose Götz Gelbrich reports a research cooperation with the University Hospital Würzburg and TomTec Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany, and a grant from the German Research Council (DFG) as the senior biometrician of the FIND-AF II trial outside the submitted work. Peter Heuschmann reports grants from German Ministry of Research and Education, European Union, Charité – Universitätsmedizin Berlin, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, Federal Joint Committee (G-BA) within the Innovationfond, University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo), grants from Charité – Universitätsmedizin Berlin (within Mondafis; Mondafis is supported by an unrestricted research grant to the Charité from Bayer), from University Göttingen (within FIND-AF randomized; FIND-AF randomized is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), outside the submitted work. Stefan Störk reports research grants from the German Ministry of Education and Research, European Union, University Hospital Würzburg; participation in Data Safety Monitoring or Event Adjudication in studies sponsored by Roche, Medtronic; participation in Advisory Boards for Novartis, Bayer, Boehringer Ingelheim, Thermo-Fisher, Boston Scientific; principal investigator in trials (co-) sponsored by Boehringer-Ingelheim, Novartis, Bayer, Lundbeck; speaker honoraria by Boehringer-Ingelheim, Servier, Novartis, Astra-Zeneca, Pfizer, Bayer, Thermo-Fisher, outside the submitted work. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

stable values of GCW and a linear increase of GWW with advancing age, resulting in lower GWE. Age-adjusted percentiles for GCW, GWW, GWI, and GWE were derived. Higher levels of blood pressure or LV mass were associated with higher GCW, GWI, and GWW, resulting in lower GWE; higher LVEF correlated with higher GCW and GWI, but lower GWW. Higher E/e´ correlated with higher GWW, higher e´ with lower GWW.

Conclusions

Derived from a large sample of apparently healthy individuals from a population based-cohort, we provide age-adjusted reference values for myocardial work indices, applicable for either sex. Weak correlations with common echocardiographic parameters suggest MyW indices to potentially provide additional information, which has to be evaluated in diseased patient cohorts.

Introduction

In-depth knowledge of the biomechanic properties of the left ventricle (LV) is a prerequisite for understanding the pathophysiology of left ventricular (LV) dysfunction. Invasive assessment of the intracardiac LV pressure-volume relationship is the gold standard to determine LV stroke work, a measure that comprehensively describes how "hard" the LV is working [1]. Only recently, an echocardiographic method to non-invasively determine LV stroke work, called *myocardial work*, has been introduced and validated against invasive measurements [2–4]. The method is based on speckle-tracking derived longitudinal strain and peripheral systolic blood pressure. As such, *myocardial work* is thought to be less load-dependent compared to LV ejection fraction or longitudinal systolic strain [5]. Further, the new method allows us to differentiate myocardial constructive from wasted work components, thus offering new insights into cardiac mechanics and the pathophysiology of cardiac disease states.

Estimation of pathologic conditions requires the definition of normal. Since the method has been introduced only recently, there is still insufficient information on the performance of *myocardial work* characteristics in healthy individuals. We therefore aimed 1) to establish reference values for *global constructive* and *global wasted myocardial work* of healthy individuals derived from a large, well characterized, population-based cohort and 2) to further characterize this new echocardiographic tool by assessing the association of constructive and wasted work with age, sex, anthropometry, and echocardiographic parameters.

Methods

Study population and recruitment

We present an analysis of the *Characteristics and Course of Heart Failure Stages A-B and Determinants of Progression* (STAAB) Cohort Study, based on consecutive participants from the general population of Würzburg, Germany, aged 30–79 years and stratified for age and sex. The detailed study design and methodology has been published [6]. All study related procedures are subjected to a rigid and regular quality control process [6]. The STAAB cohort study protocol and procedures received positive votes from the Ethics Committee of the Medical Faculty (vote 98/13) as well as from the data protection officer of the University of Würzburg (J-117.605-09/13). All participants provided written informed consent prior to any study examination.

Cardiovascular risk factors

History of arterial hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease (previous myocardial infarction, coronary artery disease, stroke, peripheral artery disease), and current pharmacotherapy was assessed by physician-led face-to-face interview. Assessment of smoking status, height, weight, and blood pressure (sitting position after five minutes rest), and an oral glucose tolerance test were performed according to standard operating procedures by trained and certified personnel [6]. Fasting lipid profile and glycosylated hemoglobin (HbA1c) were measured at the central laboratory of the University Hospital Würzburg. Cardiovascular risk factors were defined according to current recommendations as follows: hypertension [7], blood pressure $\geq$140/90 mmHg or anti-hypertensive pharmacotherapy; dyslipidemia, low density lipoprotein $\geq$190 mg/dl [8] or lipid-lowering pharmacotherapy; obesity [9], body mass index >30 kg/m^2; diabetes mellitus [10], HbA1c >6.5% or fasting plasma glucose >7.0 mmol/l or 2h-plasma glucose >11.1 mmol/l or anti-diabetic medication; smoking, current or ex-smoker.

Echocardiography

All patients underwent an extensive, pre-specified transthoracic echocardiography protocol performed by dedicated trained personnel that was internally certified and quality-controlled in 6-month intervals [11]. A Vivid S6 scanner with a M4S sector array transducer (1.5–4.3 MHz, GE Healthcare, Horten, Norway) or a Vivid E95 scanner with a M5SC-D transducer (1.5–4.6MHz; GE Healthcare, Horten, Norway) was used. A minimum of three cardiac cycles was recorded. Two-dimensional images from the LV apical four-, two-, and three-chamber views were recorded with a frame rate of 50 to 80 s^{-1} and stored digitally. We measured LV end-diastolic and end-systolic volumes and calculated LV ejection fraction (LVEF; Simpson´s biplane method). Valve regurgitation was determined integrating the color Doppler multiplane vena contracta method and the pressure half time method, and valve stenosis was quantified assessing maximal flow velocity by continuous-wave Doppler according to current recommendations [12, 13].

Myocardial work analysis

All *myocardial work* analyses have been performed by one single person (FS). To assess intra-observer variability, 20 random scans were read by one person (FS) twice, >2 weeks apart, for inter-observer variability, the same scans were read by a second person (CM) blinded to the previous results.

Fig 1 exemplifies the determination of myocardial work. For timing of aortic and mitral valve closure and opening, we used continuous-wave Doppler through the aortic valve and pulsed wave Doppler of the mitral valve inflow. As changes in heart rate during the examination might affect the loop area, we visually verified these time points in the apical three-chamber view and manually adjusted them, when necessary. LV apical four-, two-, and three-chamber views were analyzed off-line using integrated software (Automated Functional Imaging; EchoPAC®, Version 202, GE) to determine global longitudinal peak systolic strain (GLS). After entering brachial systolic blood pressure values the software calculates constructive and wasted work. Constructive work describes the net effect resulting from positive work (shortening) performed during systole plus negative work (lengthening) performed during isovolumic relaxation. Wasted work describes the net effect resulting from negative work (lengthening) performed during systole plus positive work (shortening) during isovolumic relaxation. By aggregating the segmental values for constructive and wasted work (18-segment model), the software calculates global constructive (GCW) and global wasted work (GWW) as mean of the

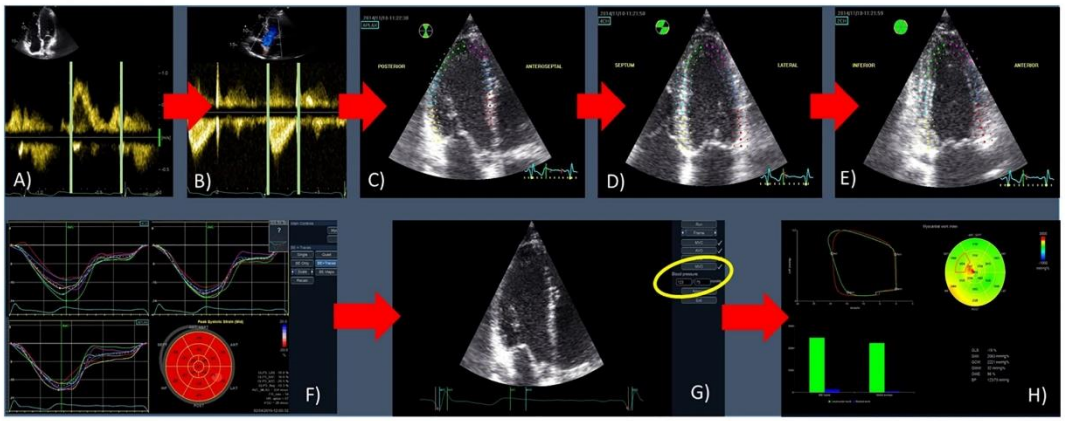

Fig 1. Determination of *myocardial work*. For exact timing, mitral valve opening and closure are determined using a pulsed-wave Doppler recording of the mitral inflow (A). Aortic valve opening and closure are determined using a continuous-wave Doppler recording through the aortic valve (B). Time points might be adjusted in the apical three chamber view (D), if necessary. Using *automated function imaging*, global longitudinal strain is determined in the apical three (C), four (D), and two (E) chamber views. The automated speckle tracking contour can be adjusted manually. After completion of strain determination (F), systolic and diastolic blood pressure levels have to entered (G) in order to determine global and segmental *myocardial work* (H).

https://doi.org/10.1371/journal.pone.0239684.g001

respective segmental values. For the current analysis, LV segments with poor tracking or suboptimal image quality were excluded as were subjects whose echocardiograms provided information on GLS and *myocardial work* in less than 17 segments. The software further provides a global work index (GWI = total work performed = area of the pressure-strain loop) and the global work efficiency (GWE = GCW/(GCW+GWW)).

The subgroup of the present analysis

For the determination of reference values, we defined a sub-sample of apparently healthy individuals, i.e., subjects free from cardiovascular risk factors and cardiovascular disease. We further excluded individuals with LVEF<50%, regional wall motion abnormalities, other than sinus rhythm or significant LV valve disease (any stenosis or > mild regurgitation of the mitral or aortic valve).

Data analysis

Statistical analysis was performed using SPSS (Version 25 and 26, SPSS Inc., Chicago, USA). Descriptives of quantitative data are provided as mean and standard deviation. Regarding the definition of cardiovascular risk factors, missing values were treated as pathologic findings (i.e., individuals with missing information did not enter the apparently healthy subgroup), except for individuals with one missing blood glucose value (fasting glucose, 2h glucose, or HbA1c) in case of two valid and normal values. P-values <0.05 were considered statistically significant. Observer variability was assessed using Bland-Altman 95% limits of agreement. The distributions of GCW and GWW were analyzed in an explorative manner. Scatter diagrams of GCW or GWW with age were plotted with trend curves obtained from locally weighted regression, and general linear models were computed. Standard deviations of residuals in subgroups were compared by Levene's test. Normality of residuals was examined by the Shapiro-Wilk test. Eventually, age-dependent percentiles were computed from the most

Table 1. Clinical characteristics of apparently healthy individuals with valid myocardial work analysis, and subgroups women vs men.

	Total	Men	Women	P
	N = 779	N = 322	N = 457	
Age [years], mean (SD)	49 (10)	49 (11)	49 (10)	0.87
Age groups [years], n(%)				
30-<39	128 (16)	55 (17)	73 (16)	
40-<45	146 (19)	61 (19)	85 (19)	
45-<50	167 (21)	70 (22)	97 (21)	
50-<55	118 (15)	45 (14)	73 (16)	
55-<60	83 (11)	32 (10)	51 (11)	
60 -<65	70 (9)	27 (8)	43 (9)	
65-<79	67 (9)	32 (10)	35 (8)	
BMI [kg/m^2], mean (SD)	23.7 (2.7)	24.4 (2.4)	23.3. (2.8)	<0.001
BSA [m^2], mean (SD)	1.82 (0.19)	1.98 (0.15)	1.71 (0.13)	<0.001
Systolic BP [mmHg], mean (SD)	119 (11)	124 (9)	115 (11)	<0.001
Diastolic BP [mmHg], mean (SD)	73 (8)	74 (8)	72 (8)	<0.001
Heart rate [min^{-1}], mean (SD)	63 (9)	60 (9)	64 (9)	<0.001
Total cholesterol [mg/dl], mean (SD)	200 (34)	197 (31)	202 (36)	0.09
LDL [mg/dl], mean (SD)	115 (32)	120 (29)	112 (34)	0.001
Fasting glucose [mmol/l], mean (SD)	5.29 (0.53)	5.35 (0.54)	5.25 (0.52)	0.01
2h glucose [mmol/l], mean (SD)	5.62 (1.24)	5.43 (1.26)	5.77 (1.20)	0.001
HbA1c [%], mean (SD)	5.32 (0.34)	5.30 (0.34)	5.33 (0.35)	0.33
Echocardiography				
LVEDVi [ml/m^2], mean (SD)	54 (11)	59 (12)	51 (10)	<0.001
LVMi [g/m^2], mean (SD)	68 (14)	76 (14)	62 (12)	<0.001
LAVi [ml/m^2], mean (SD)	22 (6)	23 (6)	21 (5)	0.003
LVEF [%], mean (SD)	61.1 (4.0)	60.8 (3.8)	61.4 (4.1)	0.06
E/e´, mean (SD)	6.7 (1.6)	6.5 (1.5)	6.9 (1.7)	0.001
E´, mean (SD)	11.1 (2.4)	10.8 (2.2)	11.3 (2.5)	0.002

Values are given as mean ± standard deviation (SD). P values refer to the comparison of men vs. women. Valid information for the respective parameters was >95% except for 2h glucose (n = 564, men n = 241, women n = 323), LVMi (n = 734, men n = 302, women n = 432), and LAVi (n = 643, men N = 265, women n = 378). BMI = body mass index, BSA = body surface area, BP = blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, HbA1c = hemoglobin A1c, LVEDVi = left ventricular enddiastolic volume index, LVMi = left ventricular mass index, LAVi = left atrial volume index, LVEF = left ventricular ejection fraction, E = early mitral inflow velocity, e´ = PW-Doppler derived early diastolic myocardial lengthening velocity (mean of septal and lateral wall).

https://doi.org/10.1371/journal.pone.0239684.t001

suitable model for the estimated mean GCW or GWW, adding the respective percentile of the residuals. The association of GCW and GWW with anthropometry and echocardiographic measures was assessed using Kendall´s τ correlation coefficient.

Results

The STAAB cohort study recruited an age- and sex-stratified population-based sample of 5011 participants. In 45 participants, the physician-led interview revealed a pre-existing heart failure, hence, these individuals had to be excluded from further study participation and did not enter any analysis. Further, one participant terminated the study participation and did not enter any analysis, too. Of the remaining 4965 participants, n = 779 were eligible for the present analysis (Table 1 & Fig 2). The inter- and intraobserver variability of myocardial work parameters was favourably low (Table 2).

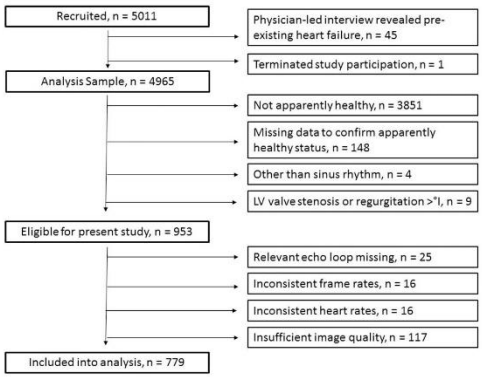

Fig 2. Study flow.

https://doi.org/10.1371/journal.pone.0239684.g002

Impact of age and sex on GCW and GWW

The plots of GCW and GWW by age are displayed in Fig 3A and 3B. Trend curves suggested altered dependencies around the age of 45 years. For further analysis we thus accepted the assumption of a modified association of age with myocardial work below vs above the threshold of 45 years. The respective numeric results are displayed in Table 3.

When proceeding analysis with a piecewise linear model for GCW (accepting a change in slopes occurring at 45 years), both slopes did not achieve significance. A respective threshold model, however, yielded significant differences of means. Equal standard deviations in both age groups were therefore accepted (Table 3). Including sex into the model had no effect. Residuals were approximately normally distributed, and normality was formally accepted after removing two outliers. Therefore, percentiles applicable for either sex were computed assuming a normal distribution and homogeneous standard deviation, with an upward shift occurring at the age of 45 years. The reference values for GCW are presented in Table 3A. The median (quartiles) for individuals younger than 45 years was 2366 mmHg% (2150; 2582), and was 2447 mmHg% (2241; 2673) for individuals older than 45 years, respectively.

Table 2. Observer variability for parameters describing myocardial work.

		Intra-observer variability		Inter-observer variability	
	Mean (SD)	**Mean difference (SD)**	**95%CI of differences**	**Mean difference (SD)**	**95%CI of differences**
GCW [mmHg%]	2532 (472.0)	26.4 (47.4)	4.2; 48.5	231.4 (199.8)	137.9; 324.9
GWW [mmHg%]	87.0 (44.2)	7.7 (18.5)	-1.0; 16.3	9.9 (49.4)	-33.0; 13.2
LVEF [%]	61.1 (4.8)	0.6 (3.2)	-0.9; 2.0	2.5 (5.2)	-0.0; 5.0
GLS [%]	-21.4 (2.3)	0.3 (0.3)	0.1; 0.5	1.9 (1.8)	1.1; 2.7

To assess intra-observer variability, 20 random scans were read by one person twice (FS), >2 weeks apart, for inter-observer variability, the same scans were read by a second person (CM) blinded to the previous results.

GCW = global constructive work: work performed during shortening in systole and adding negative work during lengthening in isovolumic relaxation.

GWW = global wasted work: negative work performed during lengthening in systole adding work performed during shortening in isovolumic relaxation.

SD = standard deviation, CI = confidence interval, LVEF = left ventricular ejection fraction, GLS = global longitudinal systolic strain.

https://doi.org/10.1371/journal.pone.0239684.t002

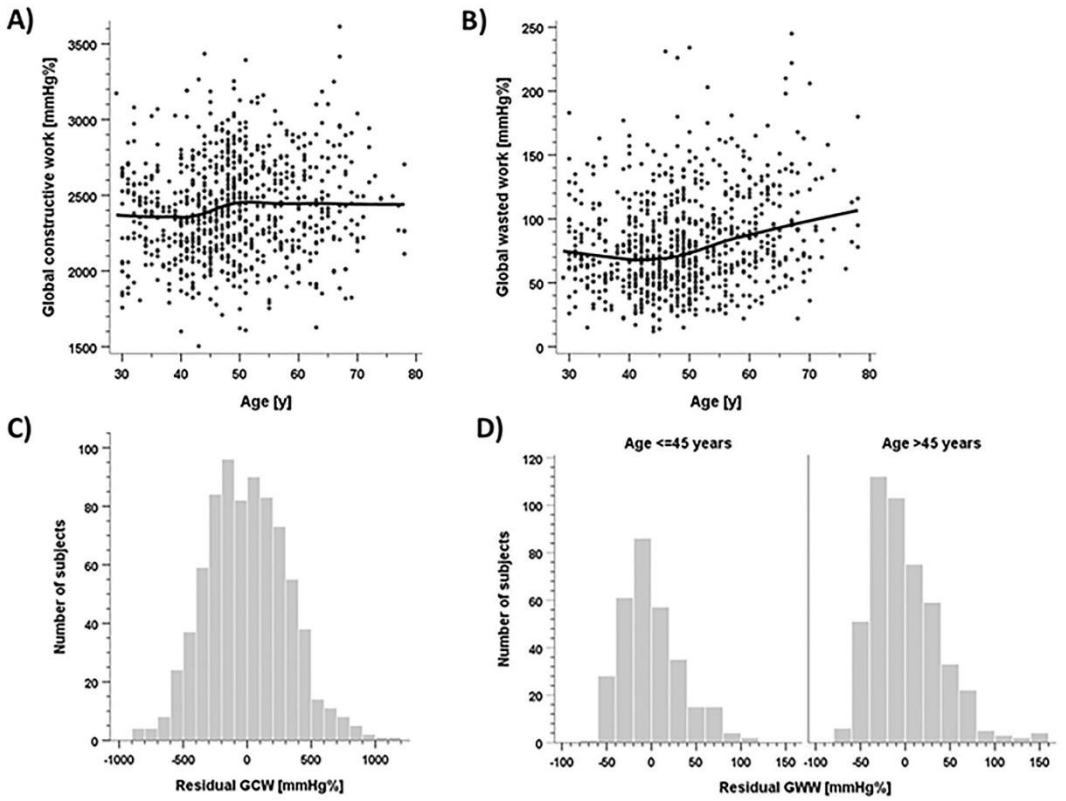

Fig 3. Association of global constructive (GCW, A) and global wasted (GWW, B) myocardial work with age and distribution of GCW (C) and GWW values (D). The curves were obtained from locally weighted regression analysis.

https://doi.org/10.1371/journal.pone.0239684.g003

The piecewise linear model for GWW yielded a significant slope beyond the age above 45 years, but not below 45 years. Therefore, the final model assumed the median GWW remaining constant up to the age of 45 years, and increasing linearly thereafter. The standard deviation of residuals was significantly higher in individuals older than 45 years. Again, no significant influence of sex on these associations was found. Normality of residuals was violated in both age groups. Therefore, percentiles applicable for both sexes were based on non-parametric percentiles of residual distributions. The reference values for GWW are presented in Table 3B. The median (quartiles) for individuals younger than 45 years was 68 (50; 90) mmHg%, and was 73 (52; 103) mmHg% for individuals aged 50 years, respectively. With each subsequent decade, the median GWW increased by 6 points (Table 3B, bottom).

GWI showed higher values (+46 mmHg%) in individuals >45 years, when compared to younger participants with no further increase with advancing age. Women had significantly higher values (+66 mmHg%), when compared to men. Therefore, we provide sex-specific percentiles for individuals ≤ and >45 years (Table 3C).

Table 3. Reference values for global constructive (GCW) and global wasted (GWW) myocardial work as well as for myocardial work index (GWI) and myocardial work efficiency (GWE).

		Age ≤45 years	**Age >45 years**			
		N = 304	**N = 475**			
A) Global constructive work (GCW) [mmHg%]						
Model with two slopes						
Mean at 45 years		2418				
Change per +10 years		+51	+25			
Test for slope		P = 0.11	P = 0.13			
Model with threshold at 45 years						
Mean		2366	2457			
95% CI		2330 to 2402	2428 to 2486			
Comparison of means		P<0.001				
SD of residuals		310	327			
Comparison of SDs		P = 0.11				
Common estimate of SD		320				
Test for sex difference		P = 0.16				
Normality of pooled residuals		P = 0.02				
2 outliers removed		P = 0.09				
Percentiles	**2.5**	**1739**	**1830**			
	10	**1956**	**2047**			
	25	**2150**	**2241**			
	50	**2366**	**2457**			
	75	**2582**	**2673**			
	90	**2776**	**2867**			
	97.5	**2993**	**3084**			
B) Global wasted work (GWW) [mmHg%]						
Model with two slopes						
Mean at 45 years		71				
Change per +10 years		−5	+14			
Test for slope		P = 0.15	P<0.001			
Model with one slope						
Estimated mean, ≤45 years		73				
Increase per 10 years, >45 years			+12			
95% CI of estimates		70 to 76	+9 to +16			
SD of residuals		33	38			
Comparison of SDs		P = 0.007				
Test for sex difference		P = 0.72				
Normality of residuals		P<0.001	P<0.001			
			50y	**55y**	**60y**	**65y**
Percentiles	**2.5**	**23**	**24**	**30**	**36**	**42**
	10	**35**	**36**	**42**	**48**	**54**
	25	**50**	**52**	**58**	**64**	**70**
	50	**68**	**73**	**79**	**85**	**91**
	75	**90**	**103**	**109**	**115**	**121**
	90	**119**	**131**	**137**	**143**	**149**
	97.5	**152**	**171**	**177**	**183**	**189**
C) Global work index (GWI) [mmHg%]		**Age ≤45 years**	**Age >45 years**			
Model with two slopes						

(*Continued*)

Table 3. (Continued)

		Age ≤45 years	Age >45 years			
		N = 304	N = 475			
Mean at 45 years (men/women)						
Men		2174				
Women		2241				
Change per +10 years		+32	+2			
Test for slope		P = 0.27	P = 0.88			
(adjusted for sex)						
Model with threshold at 45 years						
Means						
Men		2141	2187			
95% CI		2099 to 2183	2149 to 2224			
Women		2206	2252			
95% CI		2168 to 2245	2220 to 2284			
Comparison >45 vs. ≤45 years		+46 (+2 to +89) P = 0.04				
(adjusted for sex)						
Comparison women vs. men		+66 (+22 to +108) P = 0.003				
(adjusted for age group)						
Test for sex by age interaction		P = 0.64				
SD of residuals						
Men		287	293			
Women		307	311			
Comparison of 4 SDs		P = 0.34				
Common estimate of SD		301				
Normality of pooled residuals		P = 0.03				
2 outliers removed		P = 0.09				
Percentiles						
Men	2.5	1551	1597			
	10	1755	1801			
	25	1938	1984			
	50	2141	2187			
	75	2344	2390			
	90	2527	2573			
	97.5	2731	2777			
Women	2.5	1616	1662			
	10	1820	1866			
	25	2003	2049			
	50	2206	2252			
	75	2409	2455			
	90	2592	2638			
	97.5	2796	2842			
D) Global work efficiency (GWE) [%]		**Age ≤45 years**	**Age >45 years**			
Model with two slopes						
Mean at 45 years		96.5				
Change per +10 years		+0.2	−0.6			
Test for slope		P = 0.14	P<0.001			
Model with one slope						
Estimated mean, ≤45 years		96.4				

(*Continued*)

Table 3. (Continued)

		Age ≤45 years	Age >45 years			
		N = 304	N = 475			
Change per +10 years, >45 years			−0.5			
95% CI of estimates		96.3 to 96.5	−0.7 to −0.4			
SD of residuals		1.4	1.3			
Comparison of SDs		P = 0.01				
Test for sex difference		P = 0.42				
Normality of residuals		n.a.				
		Age ≤45 years	>45–60 years	>60 years		
Percentiles (raw)	2.5	93	92–93	91–92		
	10	94	93–94	92–93		
	25	95–96	94–95	93–94		
	50	96–97	95–96	95–96		
	75	96–97	96–97	96		
	90	97–98	97–98	96–97		
	97.5	98	97–98	97–98		

A) The trend curves of both GCW (cf. Fig 3A) and GWW (cf. Fig 3B) suggested changes of dependencies around the age of 45 years. The change in slopes at 45 years derived from a piecewise linear model for GCW was not significant. However, in a respective threshold model with the change of estimated mean GCW at 45 years, the difference of means was significant. Equal standard deviations in both age groups were thus accepted. Inclusion of sex into the model induced no significant changes of point estimates. Normal distribution of residuals was accepted after removing two outliers. Therefore, percentiles applicable for both sexes were computed assuming normal distribution and homogeneous standard deviations, with an upward shift occurring at the age of 45 years.

B) The change in slopes at 45 years derived from the piecewise linear model for GWW was significant. Therefore, the final model assumed a constant mean GWW until the age of 45 years, with a linear increase thereafter. The standard deviation of residuals was significantly higher in the age above 45 years. Again, no significant difference between sexes was found. As the assumption of normality of residuals was violated in both age groups, percentiles applicable for both sexes were based on non-parametric percentiles of residual distributions. Hence, these percentiles were different for age groups below and above 45 years with a continuous increase above the age of 45 years.

C) Like for GCW, the threshold model was adequate for GWI. In addition, women had significantly higher GWI values than men. As there was no significant interaction of sex and age group, the mean difference between sexes was assumed to be independent of age. The residuals were found to have homogeneous variances in the four groups defined by age and sex and to be normally distributed up to two outliers. Therefore, percentiles were derived from normal distributions.

D) Mean GWE was found to be constant up to the age of 45 years and then to decrease continuously. No significant difference between sexes was found. The variance was significantly higher in the younger subjects. Since the device provided only integer values of GWE, ranging from 91 to 99, the test for normality was not applicable, and percentiles were based on the raw data and not computed from a model. In order to reflect the decrease beyond 45 years, percentiles for two age groups in that range were presented.

https://doi.org/10.1371/journal.pone.0239684.t003

GWE was not different between men and women and was stable until the age of 45 years. Thereafter, we found decreasing values with increasing age (-0.5% per decade, p for slope <0.001), hence we provide age-specific percentiles applicable for either sex (Table 3D).

External factors affecting myocardial work indices

In a second step, we evaluated the association of GCW, GWW, GWI, and GWE with anthropometric and echocardiographic indices (Table 4). Because we had selected healthy individuals, these markers were all within normal ranges. Higher values of both systolic and diastolic blood pressure, but not of body mass index, were positively related with GCW, GWI, and GWW and negatively related with GWE. Higher LV ejection fraction and GLS were strongly associated with higher GCW, GWI, and GWE and with lower GWW. Further, higher LV mass was associated with both higher GCW and GWW, but lower GWE. Higher E/e´ was positively related to GCW and GWW, resulting in lower GWE, and e´ was inversely related to GWW,

Table 4. Association (Kendall's τ) of global constructive work (GCW), global wasted work (GWW), global work index (GWI), and global work efficiency (GWE) with anthropometrics and echocardiographic parameters of systolic and diastolic left ventricular function.

Variable	N	GCW		GWW		GWI		GWE	
		τ	P	τ	P	τ	P	τ	P
Measurements associated with criteria for "apparently healthy"									
Body mass index	779	0.00	0.99	−0.05	0.05	0.00	0.85	0.05	0.08
Systolic blood pressure	779	**0.38**	<0.001	**0.16**	<0.001	**0.35**	<0.001	**−0.09**	0.001
Diastolic blood pressure	779	**0.22**	<0.001	**0.12**	<0.001	**0.21**	<0.001	**−0.08**	0.001
Left ventricular ejection fraction	761	**0.13**	<0.001	**−0.12**	<0.001	**0.16**	<0.001	**0.18**	<0.001
Global longitudinal strain	779	0.44	<0.001	**−0.09**	<0.001	0.46	<0.001	0.22	<0.001
Left ventricular volume index	762	−0.01	0.57	0.04	0.13	−0.02	0.48	−0.04	0.16
Left ventricular mass index	739	**0.05**	0.04	**0.05**	0.03	0.02	0.50	**−0.06**	0.02
Left atrial volume index	643	**0.06**	0.02	−0.04	0.10	**0.06**	0.03	0.06	0.05
E/e' (average)	760	**0.05**	0.05	**0.07**	0.003	**0.08**	0.002	**−0.08**	0.003
e' (average)	761	0.01	0.68	**−0.15**	<0.001	**0.05**	0.04	**0.21**	<0.001
e' (lateral)	757	0.00	0.98	**−0.14**	<0.001	0.04	0.09	**0.20**	<0.001
e' (septal)	740	0.03	0.23	**−0.13**	<0.001	**0.07**	0.01	**0.19**	<0.001
Tricuspid regurgitation pressure gradient	288	**0.15**	<0.001	0.04	0.36	**0.17**	<0.001	−0.02	0.73
Stroke volume	761	0.02	0.51	−0.02	0.51	0.01	0.61	0.03	0.29
Heart rate	779	−0.01	0.72	0.03	0.15	−0.02	0.46	−0.03	0.20

E = pulsed-wave Doppler derived peak mitral inflow velocity, e´ = tissue Doppler and pulsed-wave Doppler derived mitral annular early diastolic relaxation velocity.

https://doi.org/10.1371/journal.pone.0239684.t004

consecutively, higher e´ correlating with higher GWE. Larger LA volumes were associated with higher GCW. Stroke volume and heart rate showed no significant correlation with myocardial work indices (Table 4).

Discussion

In a large sample of healthy individuals derived from a population-based cohort balanced for age and sex, we found myocardial work analysis an echocardiographic tool with good feasibility and a favorable intra- and inter-observer variability. GCW, GWW, and GWE were independent of sex and showed stable values up to the age of 45 years. Beyond that threshold, GCW and GWW behaved differently. Median GCW values showed a modest increment of about 4% around the age of 45 years, without major subsequent alterations at higher age groups. By contrast, GWW increased linearly with advancing age beyond the age of 45 years, resulting in decreasing GWE with advancing age. We here provided age-adjusted percentiles for both measures of myocardial work, which now may be used as reference for either sex. In contrast, GWI was higher in women when compared to men. In line with GCW, we found an increment in GWI around the age of 45 years with no further changes associated with advancing age.

As a consequence of the process of selecting participants for the current investigation, all anthropometric and echocardiographic measures were within normal ranges. Yet, we found disparate associations of anthropometry and LV geometry as well as of systolic and diastolic function with myocardial work indices. Higher LVEF and GLS were associated with higher GCW, GWI and GWE, and with lower GWW. Regarding diastolic function, we found higher E/e´ associated with higher GCW (trend), GWI, and GWW, but resulting in lower GWE, indicating that the increase in GWW with increasing filling pressure exceeds the increase in GCW. Further, higher e´ associated with lower GWW, which resulted in higher GWE, and larger LA

Table 5. Comparison of population under study: STAAB vs NORRE [5] vs University Hospital of Rennes [16].

Characteristics	STAAB	NORRE	Rennes
N, sites	1	22	1
Type of selection	Population-based, stratified for age and sex	Convenience sample	Healthy cohort of different ongoing studies
Inclusion criteria	• Age 30–79 years • Citizen of Würzburg	• Age ≥ 25 years • Normal ECG	• Age ≥ 18 years • Normal ECG and physical examination
Exclusion criteria	• Presence of CV risk factors (s) • History of CV disease and/or heart failure • Medical therapy with cardio-active drug • Significant LV valve disease (mitral valve and aortic valve)	• Presence of CV risk factor(s) • History of CV disease • Chronic exposure to excessive alcohol consumption • Medical therapy with cardio-active drug • Structural heart disease on echocardiogram	• Presence of CV risk factors • History of symptomatic cardiovascular or lung disease
Echo machine	GE Vivid S6 or E95	GE E9 or Philips IE33	GE, Vivid 7, Vivid E9, or E95
N, total sample	5000	734	N/A
N, healthy participants	779	734	N/A
N, female participants	457	320	N/A
N, male participants	322	414	N/A
Age, years	49 (10)	46 (13)	N/A
BMI, kg/m^2	24 (3)	24 (3)	N/A
BSA, m^2	1.8 (0.2)	1.8 (0.2)	N/A
Systolic blood pressure, mmHg	119 (11)	120 (13)	N/A
Diastolic blood pressure, mmHg	73 (8)	74 (9)	N/A
Glucose level, mmol/l	5.29 (0.53)	5.13 (0.67)	N/A
Total cholesterol, mg/dl	200 (34)	184 (31)	N/A
LVEDVi, ml/m^2	54 (11)	51 (11)	N/A
LVEF biplane, %	61 (4)	64 (5)	N/A
LAVi, ml/m^2	22 (6)	26 (6)	N/A

CV, cardiovascular; BMI- body mass index, BSA- body surface area, LVEDVi- left ventricular end diastolic volume index, LVEF- left ventricular ejection fraction biplane, LAVi- left atrial volume index (biplane).

https://doi.org/10.1371/journal.pone.0239684.t005

volume was associated with higher GCW and GWI. Higher LV mass, as well as higher blood pressure, were associated with higher GCW but also higher GWW, consecutively resulting in lower GWE. Body mass index was not associated with myocardial work. In conclusion, systolic LV function correlated with GCW and GWI, while diastolic function correlated with GWW, consecutively both, systolic and diastolic function correlating with GWE.

To our knowledge, this is the first report providing reference ranges for non-invasively determined myocardial work parameters from healthy individuals over a wide age range derived from a large, well-characterized population-based cohort balanced for age and sex. The detailed cardiovascular characterization allowed identifying individuals without cardiovascular risk factors or known cardiovascular disease. Quality controlled, standardized echocardiography permitted to exclude individuals with valvular disease. Given that valid analysis of myocardial work requires three apical views in good image quality, the feasibility in our cohort was good. The semi-automated analysis showed good inter- and intra-observer variability, rendering myocardial work a reliable diagnostic tool.

While LVEF and GLS as measures of LV systolic function are known to show slightly more favorable values in women [14] myocardial work parameters, which, in addition to GLS, take

Table 6. Comparison of individuals with valid myocardial work analysis: STAAB vs NORRE [5] vs University Hospital of Rennes [16].

	STAAB	NORRE	Rennes
Number of healthy participants with MyW analysis	779	226	115
Number of female participants	457	141	43
Number of male participants	322	85	72
Age, years	49 (10)	45 (13)	36 (13)
Individuals age group 20–40	128	95	<35 years n = 57
Male/ Female	55/73	N/A	N/A
Individuals age group 40–60	514	97	≥35 years n = 58
Male/ Female	208/306	N/A	N/A
Individuals age group ≥ 60	137	34	N/A
Male/ Female	59/78	N/A	
BMI, kg/m^2	24 (3)	23 (3)	23 (3)
BSA, m^2	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)
Systolic blood pressure, mmHg	119 (11)	116 (12)	121 (8)
Diastolic blood pressure, mmHg	73 (8)	73 (8)	73 (6)
Glucose level, mmol/l	5.29 (0.53)	5.05 (0.61)	N/A
Total cholesterol, mg/dl	200 (34)	182 (31)	N/A
GCW, mmHg%	2430 (351)	2232 (331)	2224 (229)
GWW, mmHg%	74 (54–101)	78.5 (52–122)	90 (61–123)
GWI, mmHg%	2209 (307)	1896 (308)	1926 (247)
GWE, %	96 (95–97)	96 (94–97)	96 (94–97)

BMI- body mass index, BSA- body surface area, GCW = global constructive work, GWW = global wasted work, GWI = global work index (total work performed = area of the pressure-strain loop), GWE = global work efficiency (GCW/(GCW+GWW)).

https://doi.org/10.1371/journal.pone.0239684.t006

systolic blood pressure into account, revealed no association with sex. This implies, that the real stroke work the myocardium has to perform, might be the same for either sex. Echocardiographic reference values are derived from healthy individuals and healthy women, who–as in our cohort–usually present with lower blood pressure values when compared to men [5]. Therefore, although the female myocardium appears to perform the same work but against a lower afterload, it might contract a little more, resulting in higher values of LVEF and more negative values of GLS. Thus, myocardial work might be the most reliable tool to study myocardial function independent of afterload conditions in either sex.

Interestingly, we found myocardial work stable until the age of 45 years. The moderate shift in GCW and GWI at higher age might be a result of changes in hormonal status with consecutive changes in blood pressure. Age-related changes in vascular function generally include deteriorating endothelial dysfunction and arterial stiffness, which is accompanied by increasing systolic blood pressure and pulse pressure even in individuals without cardiovascular risk factors. Below the age of 60 years, men compared to women exhibit a greater degree of endothelial dysfunction and worse arterial stiffness; beyond the age of 60, these vascular differences diminish. Below the age of 45 years, women have lower blood pressure than men, but blood pressure increases in the perimenopausal period. Subsequently, beyond the age of 64 years, the prevalence of hypertension is higher in women compared to men [15]. Regarding GWW, we found linearly higher values with higher age, potentially reflecting physiologic processes of healthy ageing like progressive fibrosis and modulation of cardiomyocytes. Consecutively, GWE decreased with advancing age.

Our results confirm but also extend previously published findings [5, 16]. Analyses from the EACVI Normal Reference Ranges for Echocardiography (NORRE) study [5] showed GCW higher in women when compared to men and higher in individuals >40 years when compared to younger adults. Regarding GWW, they found similar values for men and women and across all age groups [5]. Analyses from healthy study participants at the University Hospital of Rennes, France, showed higher GCW in women older than 35 years, but not in younger women when compared to men of same age. They further found no difference in GCW and GWW across the different age groups [16]. These incongruent findings might be due to sample size and the distribution of age and sex in the different cohorts (Tables 5 and 6). NORRE has the major strength of ethnic diversity of their study population which enables them to provide reference values valid for a large number of countries. On the other hand, a population based cohort study like STAAB with strict stratification for age and sex might due to its methodological approach be more appropriate to answer questions regarding sex- and age-dependency of echocardiographic measurements. Nevertheless, our results should be validated in different population-based cohorts from different countries and the evaluation of their physiological cause remains subject to further research.

Myocardial work indices were not associated with BMI and, taking afterload into account, are thought to be less load-dependent when compared to LVEF and GLS [5]. In addition to their sex-independency and their predictable age-dependency, this might make them a reliable and broadly applicable tool to assess myocardial function.

As expected, we found a positive association of GCW, GWI, and GWE and a negative association of GWW with LVEF. However, myocardial work indices also were associated with parameters of diastolic function. Integrating LV work during active relaxation in early diastole, myocardial work indices are the first, non-invasively obtained measures of almost total active LV work and might thus prove useful in the evaluation of the myocardial response to adverse cardio-metabolic conditions and cardiotoxicity. In addition, associations were only weak implying that MyW is likely to provide additional information beyond common echocardiographic parameters. The clinical and prognostic yield has to be evaluated in respective patient collectives.

Strengths and limitations

We present data from a cross-sectional single-center study with predominantly Caucasian participants. Hence, reference values might have to be adjusted in individuals of different descent. For calculcation of MyW, we utilized blood pressure readings derived from brachial measurements, which may be considered reliable in non-diseased subjects. In patients, precision of MyW measurements may be improved employing central blood pressure. Further, the prognostic implication of potentially abnormal values can currently not be determined and remains subject to further research. Nevertheless, our results are derived from a population-based cohort exactly meeting the strict stratification criteria for age and sex, and detailed assessment of cardiovascular risk factors allowed to identify an apparently healthy sub-cohort of substantial size. The ongoing STAAB follow-up with serial echocardiography and standardized assessment of cardiovascular events is likely to give detailed insights into the course of cardiac function and the prognostic implications of constructive and wasted myocardial work.

Conclusion

In healthy individuals from the general population, echocardiographically derived GCW, GWW, and GWE were independent from sex and BMI, but revealed a characteristic and disparate association with advancing age. In combination with its low load-dependency, high

feasibility and low observer variability, non-invasively assessed *myocardial work* holds promise as a reliable non-invasive diagnostic tool. *Myocardial work* integrates LV work performed in systole and isovolumic relaxation. It is thus the first measure of almost total active myocardial function and might aid the assessment of adverse cardio-metabolic states or cardiotoxicity. Further, the differentiation of myocardial active work in constructive and wasted work offers the opportunity to evaluate the impact of cardiovascular risk factors and diseases on different aspects of myocardial performance.

Acknowledgments

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6.2 Manuscript #2

Sahiti F, Morbach C, Tiffe T, Cejka V, Wagner M, Eichner FA, Gelbrich G, Heuschmann PU, Störk S – Impact of cardiovascular risk factors on myocardial work—insights from the STAAB cohort study. *J Hum Hypertens* (2021). https://doi.org/10.1038/s41371-021-00509-4).

6.2.1 Summary

From a total of n=2473 individuals included in the first planned interim analysis of the STAAB cohort study, n=1929 (mean age 54±12 years, 49.3% women) were eligible for MyW analysis. Based on the echocardiography and baseline control at the study visit, we had to exclude n=544 individuals. Reasons to exclude were: a) significant non-myocardial heart disease, n=47 (not in sinus rhythm, more than mild regurgitation, any stenosis of the mitral or aortic valve, symptomatic HF); b) missing blood pressure value, n=16; c) technical issues regarding the required views, n=143; d) suboptimal image quality, n=338. Excluded individuals were more often women, older, and had a slightly worse clinical CV risk profile compared to the individuals included in the analysis.

Four hundred thirty-nine individuals were free from CV risk factors defined as the “apparently healthy”`` subgroup. The 1490 individuals who exhibited at least one CV risk factor at the time of examination were older, were more often men, and had a higher body mass index compared to participants with no CV risk factors. Hypertension was the most prevalent CV risk factor in the total study sample, followed by smoking, obesity, and dyslipidemia.

In the current analysis, compared to individuals without any CV risk factor, individuals with ≥1 CV risk factor showed higher values of GCW and GWW, i.e., resembled the pattern of MyW in healthy individuals of advanced age. This observation was consistent with the concept of accelerated myocardial aging induced by the presence of CV risk factors. Differences in GCW and GWW between groups were not only significant but also large. In contrast, differences in GWI and GWE were subtle though statistically significant.

Men and women were of similar age, but women had lower body mass index, lower blood pressure, higher LV ejection fraction, and more negative GLS. Further, women had a lower prevalence of hypertension, diabetes, and dyslipidemia compared to men, yet there were no differences regarding smoking or obesity. Individuals in the group with ≥1 CVRF exhibited higher values for GWI, GCW, and GWW and lower values for GWE. Values for GCW were higher in women compared to men, whereas no sex difference was apparent regarding GWW.

In multivariable regression analysis adjusted for age and sex, arterial hypertension emerged as the risk factor with the most profound impact on MyW indices. Arterial hypertension was associated with higher values of GCW and GWI and was the only factor that was also associated with increased GWW. To a lesser degree also diabetes mellitus, obesity, dyslipidemia, and smoking affected MyW indices independent of blood pressure. They were associated with reduced GCW but not with GWW. All CV risk factors were associated with a decrease in GWE.

6.2.2 Manuscript and supplement (publication)

Journal of Human Hypertension
https://doi.org/10.1038/s41371-021-00509-4

ARTICLE

Impact of cardiovascular risk factors on myocardial work—insights from the STAAB cohort study

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Received: 24 September 2020 / Revised: 25 January 2021 / Accepted: 5 February 2021

Abstract
Myocardial work is a new echocardiography-based diagnostic tool, which allows to quantify left ventricular performance based on pressure–strain loops, and has been validated against invasively derived pressure–volume measurements. Myocardial work is described by its components (global constructive work [GCW], global wasted work [GWW]) and indices (global work index [GWI], global work efficiency [GWE]). Applying this innovative concept, we characterized the prevalence and severity of subclinical left ventricular compromise in the general population and estimated its association with cardiovascular (CV) risk factors. Within the Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression (STAAB) cohort study we comprehensively phenotyped a representative sample of the population of Würzburg, Germany, aged 30–79 years. Indices of myocardial work were determined in 1929 individuals (49.3% female, mean age 54 ± 12 years). In multivariable analysis, hypertension was associated with a mild increase in GCW, but a profound increase in GWW, resulting in higher GWI and lower GWE. All other CV risk factors were associated with lower GCW and GWI, but not with GWW. The association of hypertension and obesity with GWI was stronger in women. We conclude that traditional CV risk factors impact selectively and gender-specifically on left ventricular myocardial performance, independent of systolic blood pressure. Quantifying active systolic and diastolic compromise by derivation of myocardial work advances our understanding of pathophysiological processes in health and cardiac disease.

Introduction

Myocardial work (MyW) is a novel echocardiographic method allowing to noninvasively determine total active myocardial performance via its two components constructive and wasted MyW (Fig. 1) [1]. Following known concepts of estimation of left ventricular (LV) systolic function by afterload-adjusted parameters of fiber shortening [2], the derivation of MyW integrates information on myocardial deformation (by speckle-tracking longitudinal strain) and afterload by pressure–strain loops (PSL). As such, the energy-consuming phases of the cardiac cycle, i.e., systolic and early diastolic active MyW can be quantified (Fig. 1). This information can be derived segment-by-segment or expressed as a global value, i.e., global constructive and wasted MyW (GCW, GWW). Echocardiography-derived parameters of MyW showed a high correlation with invasive validation measurements [1, 3, 4]. MyW demands the imputation of systemic blood pressure; it is markedly less load-dependent compared to conventional measures of LV function as ejection fraction and global longitudinal strain (GLPS) [1, 5, 6], and might thus overcome the disadvantage of these measures of overestimating LV dysfunction in individuals with increased afterload [6, 7]. MyW might therefore be

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Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41371-021-00509-4.

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Published online: 02 March 2021

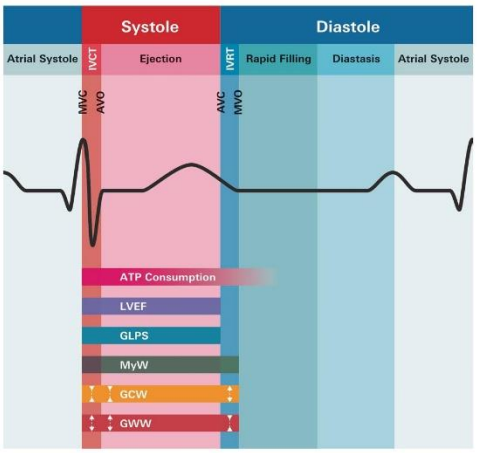

Fig. 1 Surrogate measures of left ventricular function in relation to the cardiac cycle and ATP consumption. Myocardial work includes total active myocardial work and allows us to differentiate constructive from wasted work components. LVEF left ventricular ejection fraction, GLPS global longitudinal peak strain, MyW myocardial work, GCW global constructive work, GWW global wasted work, MVC mitral valve closure, AVO aortic valve opening, AVC aortic valve closure, MVO mitral valve opening, IVRT isovolumic relaxation time, IVCT isovolumic contraction time, ATP adenosine triphosphate.

superior in detecting "real" subclinical LV dysfunction. Further, the derived PSL area was shown to reliably reflect the myocardial metabolic demand and oxygen consumption [1], thus, also providing insights into myocardial energetics.

Cardiovascular (CV) risk factors increase the risk to develop CV disease both indirectly, i.e., by altering the metabolic environment and homeostasis, or directly, i.e., by adversely affecting myocardial function [8]. As such, CV risk factors also associate with subclinical alterations in systolic and diastolic function and might accelerate conditions preceding heart failure with reduced and/or preserved ejection fraction [9–11]. Consistent with this view, changes of LV structure and function over time showed a more favorable pattern in the absence of CV risk factors [12].

Because the invasive assessment of pressure–volume loops is restricted to smaller patient samples due to the limited availability and the potential risks of an invasive procedure, echocardiography-based assessment of MyW is a readily available and noninvasive method. In the present analysis, we aimed to investigate the association between CV risk factors with MyW and its components in a large, well-characterized cohort derived from the general population.

Methods

Population

The Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression (STAAB) cohort study recruited and characterized a representative sample of the population of Würzburg, Germany, aged 30–79 years, free of symptomatic heart failure at inclusion. Details of the study design have been published previously [13]. The STAAB study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty, University of Würzburg (J-117.605-09/13). All participants provided written informed consent prior to any study examination. For the present analysis, we concentrated on the first half of the STAAB study population ($n = 2473$), which, due to a planned interim analysis [13], met sex and age stratification criteria of the total sample.

Baseline examination

Blood pressure (sitting position after 5 min of rest), body height and weight, smoking habits, and current medication were assessed according to standard operating procedures [13]. Laboratory measurements were performed at the Central Laboratory, University Hospital Würzburg, including fasting lipid profile, estimated glomerular filtration rate (eGFR), glycosylated haemoglobin (HbA1c), and plasma glucose levels.

CV risk factors included in the following analysis were *obesity* (body mass index > 30 kg/m^2) [14], *dyslipidaemia* (low-density lipoprotein [LDL] > 190 mg/dl [15], or on lipid-lowering medication), *diabetes mellitus* (HbA1c > 6.5%, or fasting plasma glucose > 7 mmol/l, or plasma glucose 2 h after oral intake of 75 g glucose > 11.1 mmol/l [16] or on antidiabetic medication), *hypertension* (blood pressure ≥ 140/90 mmHg [17] or on antihypertensive therapy), and *smoking* (current smoker or ex-smoker).

Echocardiography and quality assurance

All patients underwent standard transthoracic echocardiography using Vivid S6® (M4S Sector Array Transducer operating at 1.5–4.3 MHz, GE Healthcare, Horten, Norway). Two-dimensional images from the LV apical four-, two-, and three-chamber views were recorded with a frame rate of 50–80 s^{-1} and stored digitally. Image acquisition was performed by trained and certified sonographers on one echocardiography machine with consistent system presets according to a prespecified protocol. The characteristics and effectiveness of performance measures of the echocardiography quality assurance program have been published previously [18]. MyW analysis was performed by one

researcher (F.S.). For assessment of observer variability, 20 randomly selected scans were read by the same observer twice, 2 weeks apart, for interobserver variability, the same scans were read by a second person (C.M.) blinded to the previous results. The inter-and intraobserver variability regarding MyW parameters was favorably low (Supplemental Table S1).

Analysis of myocardial work

For MyW analysis, a previously generated empiric normalized reference curve for LV pressure was used [1]. This reference curve was adjusted (a) by aligning valvular times as assessed by echocardiography and (b) by including blood pressure measured by cuff manometer as a surrogate of peak systolic LV pressure. Aortic and mitral valve closure and opening times were assessed by CW Doppler through the aortic valve and PW Doppler of the mitral valve. However, as the changes in heart rate during the examination would possibly affect the loop area, these time points were visually verified in the apical three-chamber view and manually adjusted where necessary. Two-dimensional images from the LV apical four-, two-, and three-chamber views were analyzed off-line using Automated Functional Imaging (EchoPAC®, Version 202, GE) to determine GLPS. Once GLPS was determined, the final adjustments for valve opening and/or closure times were done. We further provided the program with blood pressure values, to facilitate the derivation of the following parameters: GCW-mmHg%, i.e., work performed during shortening in systole and adding negative work during lengthening in isovolumic relaxation, also defined as work contributing to pump function; global wasted work (GWW-mmHg%), i.e., work performed during lengthening in systole or work performed during shortening against a closed aortic valve in isovolumic relaxation; global work index (GWI-mmHg%), i.e., the total amount of work within the pressure-strain loop area calculated from mitral valve closure to mitral valve opening; GWE-%, i.e., GCW/(GCW + GWW). All indices were calculated as the mean of respective segmental values (18-segment model). Myocardial work was measured as detailed in a previous report of our research group [19]. We excluded subjects from further analysis if more than one LV segment was unsuitable for analysis due to poor tracking or suboptimal image quality. The latter was defined according to the American Society of Echocardiography as the inability to detect two or more contiguous segments in any of the three apical windows [20].

Data analysis

Statistical analysis was performed using SPSS (Version 25, SPSS Inc., Chicago, USA). Descriptives of continuous variables are provided as means (standard deviation), and categorical variables are presented as frequencies (percent). The variables were assessed for normality using the Shapiro–Wilk test. Differences in normally distributed variables were assessed using the t test. Non normal distributed variables were assessed using the Mann–Whitney U test. The relationship of MyW domains with sex, age, and CV risk factors was examined by analysis of covariance (ANCOVA). Chi-square tests were used to compare categorical variables. Observer variability was assessed using Bland–Altman 95% limits of agreement. First, a univariable model for each CV risk factor was built and in a second step adjusted for age and sex. Furthermore, to examine the association of the CV risk factors with MyW indices independent of blood pressure, we additionally adjusted for systolic blood pressure. Then, interaction for sex was tested, and, in case of statistical significance, respective values for men and women were reported. All tests were performed two-sided. P values < 0.05 were considered statistically significant.

Results

The sample of the first-planned interim analysis comprised 2473 individuals. A total of $n = 1929$ individuals (mean age 54 ± 12 years, 49.3% women) entered the present analysis. Reasons to exclude $n = 544$ participants were the following: significant non-myocardial heart disease, $n = 47$ (not in sinus rhythm, more than mild regurgitation, any stenosis of the mitral or aortic valve, symptomatic heart failure); missing blood pressure value, $n = 16$; technical issues regarding the required views, $n = 143$; suboptimal image quality, $n = 338$. Comparing analyzed vs. excluded participants in a sensitivity analysis showed that non-analyzable subjects were more often female, slightly older, and exhibited a slightly worse clinical CV risk profile across the entire spectrum (Supplemental Table S2).

A subgroup of 439 participants (23%) exhibited no CV risk factor. By contrast, 1490 participants (77%) had at least one CV risk factor. Compared to the subgroup of participants with no CV risk factors, participants with ≥1 CV risk factor were older, more often male, and had higher body mass index and less negative GLPS. There was no difference in LV ejection fraction (LVEF) between groups. Compared to women, men had lower LVEF and, consistently, less negative GLPS. Further, men exhibited higher body mass index, plasma glucose level, systolic blood pressure, and more often hypertension, diabetes, and dyslipidaemia. There was no sex-specific difference in the prevalence of smoking or obesity (Table 1).

Table 1 Baseline characteristics of the study population.

	Total sample $n = 1929$	No CV risk factor $n = 439$	≥1 CV risk factor $n = 1490$	*P* value	Women $n = 951$	Men $n = 978$	*P* value
Female sex	951 (49.3)	248 (56.4)	703 (47.1)	0.001	–	–	–
Age [years]	54 (12)	49 (11)	55 (11)	<0.001	53 (11)	54 (12)	0.151
Body mass index [kg/m^2]	26 (4)	24 (3)	27 (4)	<0.001	25 (5)	27 (4)	<0.001
LVEF Simpson [%]	61 (4)	61 (4)	60 (5)	0.111	61 (4)	60 (4)	<0.001
GLPS [-%]	21 (3)	21 (2)	20 (4)	<0.001	22 (4)	20 (2)	<0.001
LVEDV	99 (25)	97 (25)	100 (25)	0.062	86 (19)	113 (23)	<0.001
LVESV	39 (11)	38 (10)	40 (12)	<0.001	33 (9)	45 (11)	<0.001
LV mass [g]	138 (39)	121 (32)	144 (39)	<0.001	116 (28)	160 (36)	<0.001
MV E wave [m/s]	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.011	0.74 (0.1)	0.67 (0.1)	<0.001
MV A wave [m/s]	0.6 (0.2)	0.5 (0.1)	0.6 (0.2)	<0.001	0.63 (0.2)	0.60 (0.2)	0.004
Mean E' [m/s]	0.09 (0.03)	0.11 (0.02)	0.09 (0.03)	<0.001	0.09 (0.02)	0.10 (0.3)	<0.001
E/E'	8 (3)	7 (2)	8 (3)	<0.001	8 (3)	7 (2)	<0.001
IVRT [ms]	94 (18)	89 (14)	95 (18)	<0.001	90 (15)	96 (19)	<0.001
Total cholesterol [mg/dl]	208 (38)	202 (34)	209 (39)	0.001	211 (39)	204 (37)	<0.001
LDL cholesterol [mg/dl]	122 (34)	117 (30)	124 (35)	<0.001	121 (35)	124 (33)	0.059
eGFR [mL/min]	87 (15)	90 (14)	86 (15)	<0.001	87 (15)	87 (14)	0.475
HbA1c [%]	5.5 (0.6)	5.3 (0.3)	5.5 (0.6)	<0.001	5.5 (0.6)	5.5 (0.6)	0.435
Glucose value [mmol/L]	5.5 (0.9)	5.2 (0.3)	5.6 (1.0)	<0.001	5.4 (0.8)	5.7 (1.0)	<0.001
Glucose value after 2 h [mmol/L]	6.0 (1.7)	5.6 (1.3)	6.1 (1.8)	<0.001	6 (1.6)	6 (1.8)	0.511
Systolic blood pressure [mmHg]	130 (18)	122 (11)	133 (18)	<0.001	127 (19)	134 (16)	<0.001
Diastolic blood pressure [mmHg]	78 (10)	75 (7)	80 (10)	<0.001	77 (10)	80 (9)	<0.001
Hypertension	849 (44)	–	849 (44)	–	369 (39)	480 (49)	<0.001
Diabetes	157 (8)	–	157 (8)	–	59 (6)	98 (10)	0.002
Smoking	376 (19)	–	376 (19)	–	170 (18)	206 (21)	0.075
Obesity	302 (16)	–	302 (16)	–	140 (15)	162 (17)	0.266
Dyslipidaemia	255 (13)	–	255 (13)	–	106 (11)	149 (15)	0.008

Data are *n* (%) or mean (SD) or median (interquartiles).

CV cardiovascular, *LVEF* left ventricular ejection fraction, *GLPS* global longitudinal peak strain, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *MV* mitral valve, *IVRT* isovolumic relaxation time, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate, *HbA1c* glycosylated haemoglobin.

Myocardial work indices

In the group with ≥1 CV risk factor we found markedly higher GWW, but only slightly higher corresponding GCW. Thus, the complementary ratios GWI and GWE were changed accordingly, i.e., increased GWI and decreased GWE, when compared to the subgroup with no CV risk factors. We observed significant yet minor differences between men and women, 3% for GCW and 5% for GWI, respectively. Further, in both subgroups with and without CV risk factors, women had significantly higher GWI when compared to men, whereas no such sex-related difference was apparent for GWW (Table 2).

Association of CV risk factors with myocardial work indices

Global constructive work

GCW was positively associated with systolic blood pressure, cholesterol, glucose level after 2 h, hypertension, and inversely associated with body mass index, obesity, and smoking (Table 3). After adjustment for age and sex, GCW

Table 2 Myocardial work characteristics of the study population according to risk factors and sex.

	Total sample $n = 1929$	No CV risk factor $n = 439$	≥1 CV risk factor $n = 1490$	*P* value	Women $n = 951$	Men $n = 978$	*P* value
GCW [mmHg%]	2505 (428)	2440 (334)	2526 (459)	<0.001	2550 (439)	2465 (427)	<0.001
GWW [mmHg%]	82 (58–119)	75 (54–109)	85 (60–123)	<0.001	83 (60–120)	82 (57–118)	0.685
GWI [mmHg%]	2277 (396)	2224 (310)	2293 (416)	0.001	2340 (408)	2216 (373)	<0.001
GWE [%]	96 (95–97)	96 (95–97)	96 (94–97)	<0.001	96 (95–97)	96 (94–97)	0.093

Data are *n* (%) or mean (SD) or median (interquartiles).

CV cardiovascular, *GCW* global constructive work, *GWW* global wasted work, *GWI* global work index, *GWE* global work efficiency.

Table 3 Quantitative impact of CV risk factors on global constructive work (GCW), measured in mmHg%.

	Univariable model		Interaction with sex	Adjusted for age and sex			Adjusted for age, sex, systolic blood pressure	
	Δ (95% CI)	*P* value	*P* value	Sex	Δ (95% CI)	*P* value	Δ (95% CI)	*P* value
Body mass index [kg/m^2]	−7 (−11 to −2)	0.004	0.005	M	−17 (−24 to −10)[a]	<0.001	−19 (−22 to −16)	<0.001
				F	−4 (−10 to +2)	0.154		
Systolic blood pressure [mmHg]	+17 (+16 to +17)	<0.001	0.376	All	+18 (+18 to +19)	<0.001	–	–
Total cholesterol [mg/dl]	+0.9 (+0.3 to +1)	0.001	0.466	All	+0.3 (−0.2 to +0.8)	0.296	–	–
LDL cholesterol [mg/dl]	+0.3 (−0.3 to +0.8)	0.319	0.420	All	−0.09 (−0.6 to +0.5)	0.758	–	–
HbA1c [%]	+11 (−24 to +45)	0.552	0.272	All	−59 (−95 to −23)	0.001	−97 (−122 to −72)	<0.001
Glucose level [mmol/L]	+4 (−15 to +24)	0.662	0.493	All	−11 (−31 to +9)	0.226	–	–
Glucose level after 2 h [mmol/L]	+36 (+23 to +49)	<0.001	0.685	All	+25 (+12 to +39)	<0.001	M: +3 (−9 to +16)	0.603
				All			F: −17 (−31 to −2)[b]	0.028
Diabetes	−13 (−83 to +57)	0.718	0.312	All	−80 (−150 to −11)	0.024	−161 (−210 to −113)	<0.001
Hypertension	+303 (+267 to +339)	<0.001	0.143	All	+290 (+250 to +331)	<0.001	–	–
Smoking	−186 (−234 to −139)	<0.001	0.968	All	−160 (−206 to −113)	<0.001	−69 (−102 to −36)	<0.001
Obesity	−99 (−151 to −46)	<0.001	0.527	All	−123 (−174 to −72)	<0.001	M: −137 (−185 to −89)[b]	<0.001
							F: −229 (−281 to −178)	<0.001
Dyslipidaemia	−16 (−73 to +40)	0.573	0.758	All	−98 (−155 to −41)	0.001	−94 (−134 to −54)	<0.001

Estimates were derived from ANCOVA models and report the strength of association of individual CV risk factors (per unit) on GCW as absolute difference with respective 95% confidence interval. E.g., a positive increment in body mass index of 1 kg/m^2 was associated with a 7 mmHg% decrement of GCW. Sex-specific associations are reported only ifinteraction with sex yielded a p value < 0.05.

[a]Interaction with sex was statistically significant after adjusting for age and sex.

[b]After adjustment for systolic blood pressure, there was a significant interaction with sex. *LDL* low-density lipoprotein, *HbA1c* glycosylated haemoglobin.

was associated with systolic blood pressure, glucose level, and hypertension. Higher body mass index, diabetes, smoking, obesity, and dyslipidaemia were significantly associated with lower GCW. After additional adjustment for systolic blood pressure, GCW remained inversely associated with body mass index, obesity, HbA1c, glucose level after 2 h, diabetes mellitus, smoking, and dyslipidaemia. Further, the association of GCW with obesity was more pronounced in women when compared to men.

Global wasted work

GWW was positively associated with systolic blood pressure, hypertension, cholesterol, dyslipidaemia, diabetes mellitus, and glucose level. After adjustment for age and sex, systolic blood pressure and hypertension remained associated with higher GWW (Table 4).

Global work index

GWI was inversely associated with body mass index, obesity, HbA1c, smoking, and positively associated with systolic blood pressure, hypertension, cholesterol, glucose level after 2 h (Table 5). After adjustment for age and sex, GWI was inversely associated with body mass index (men only), obesity, HbA1c, smoking, dyslipidaemia, and positively associated with glucose level after 2 h, systolic blood pressure, hypertension (the association was more pronounced in women). After additional adjustment for systolic blood pressure, an inverse association with body mass index

Table 4 Quantitative impact of CV risk factors on global wasted work (GWW), measured in mmHg%.

	Univariable model		Interaction with sex	Adjusted for age and sex		
	Δ (95% CI)	*P* value	*P* value	Sex	Δ (95% CI)	*P* value
Body mass index [kg/m^2]	+0.3 (−0.3 to +0.8)	0.329	0.558	All	−0.4 (−0.9 to +0.2)	0.165
Systolic blood pressure [mmHg]	+1.0 (+0.9 to +1.1)	<0.001	0.643	All	+0.9 (+0.8 to +1.0)	<0.001
Total cholesterol [mg/dl]	+0.09 (+0.03 to +0.1)	0.004	0.598	All	+0.01 (−0.05 to +0.07)	0.646
LDL cholesterol [mg/dl]	0.06 (−0.01 to +0.1)	0.099	0.608	All	−0.007 (−0.07 to +0.06)	0.826
HbA1c [%]	+11 (+6 to +15)	<0.001	0.785	All	+1 (−3 to +6)	0.537
Glucose level [mmol/L]	+5 (+3 to +7)	<0.001	0.283	All	+2 (−0.4 to +4)	0.107
Glucose level after 2 h [mmol/L]	+2 (+1 to +4)	0.003	0.379	All	0.8 (−0.7 to +2)	0.293
Diabetes	+13 (+5 to +21)	0.002	0.594	All	+2 (−7 to +10)	0.705
Hypertension	+29 (+25 to +33)	<0.001	0.671	All	+20 (+16 to +25)	<0.001
Smoking	−4 (−10 to +2)	0.175	0.115	All	−0.2 (−6 to +5)	0.935
Obesity	+6 (−0.2 to +12)	0.059	0.938	All	+2 (−4 to +8)	0.518
Dyslipidaemia	+12 (+5 to +18)	0.001	0.260	All	−1 (−8 to +6)	0.752

For interpretation of estimates and abbreviations please refer to the legend of Table 3.

Table 5 Quantitative impact of CV risk factors on global work index (GWI), measured in mmHg%.

	Univariable model		Interaction with sex	Adjusted for age and sex			Adjusted for age, sex, systolic blood pressure	
	Δ (95% CI)	*P* value	*P* value	Sex	Δ (95% CI)	*P* value	Δ (95% CI)	*P* value
Body mass index [kg/m^2]	−5 (−9 to −1)	0.019	0.002	M	−13 (−19 to −7)[a]	<0.001	−14 (−17 to −11)	<0.001
				F	−0.1 (−5 to +5)	0.968		
Systolic blood pressure [mmHg]	+14 (+14 to +15)	<0.001	0.877	All	+17 (+16 to +17)	<0.001	–	–
Total cholesterol [mg/dl]	+0.8 (+0.3 to +1)	0.001	0.862	All	+0.3 (−0.1 to +0.8)	0.163	–	–
LDL cholesterol [mg/dl]	+0.2 (−0.3 to +0.7)	0.481	0.794	All	−0.005 (−0.5 to +0.5)	0.984	–	–
HbA1c [%]	−2 (−34 to +30)	0.917	0.435	All	−46 (−79 to −12)	0.008	−80 (−104 to −56)	<0.001
Glucose level [mmol/L]	−3 (−21 to +16)	0.776	0.974	All	−8 (−27 to +10)	0.383	–	–
Glucose level after 2 h [mmol/L]	+31 (+18 to +43)	<0.001	0.985	All	+24 (+12 to +37)	<0.001	–	–
Diabetes	−20 (−84 to +45)	0.552	0.696	All	−53 (−118 to +12)	0.108	–	–
Hypertension	+253 (+219 to + 287)	<0.001	0.046	M	+240 (+190 to +288)[a]	<0.001	–	–
				F	+307 (+256 to +358)	<0.001		
Smoking	−160 (−204 to −116)	<0.001	0.827	All	−140 (−184 to −97)	<0.001	−58 (−90 to −26)	<0.001
Obesity	−82 (−131 to −34)	0.001	0.349	All	−95 (−143 to −48)	<0.001	M: −115 (−161 to −69)[b]	<0.001
							F: −184 (−233 to −134)	<0.001
Dyslipidaemia	−30 (−82 to +22)	0.256	0.908	All	−77 (−130 to −23)	0.005	−73 (−111 to −35)	<0.001

For interpretation of estimates and abbreviations please refer to the legend of Table 3.

[a]Interaction with sex was statistically significant after adjusting for age and sex.

[b]After adjustment for systolic blood pressure, there was a significant interaction with sex.

(either sex), HbA1c, obesity, dyslipidaemia, and smoking remained.

Global work efficiency

GWE was inversely associated with systolic blood pressure, hypertension, diabetes, HbA1c, glucose level, body mass index, obesity, cholesterol, and dyslipidaemia (Table 6). After adjustment for age and sex, inverse associations remained for systolic blood pressure, HbA1c, glucose level, diabetes mellitus, smoking, and obesity. This pattern was preserved after additional adjustment for systolic blood pressure.

Discussion

The current study investigated a well-characterized representative sample of the general population, aged 30–79 years, balanced for age and sex. We focused on the multifaceted associations of MyW, a novel echocardiographic approach quantifying active myocardial performance, with

Table 6 Quantitative impact of CV risk factors on global work efficiency (GWE), measured in %.

	Univariable model		Interaction with sex	Adjusted for age and sex		Adjusted for age, sex, systolic blood pressure	
	Δ (95% CI)	*P* value	*P* value	Δ (95% CI)	*P* value	Δ (95% CI)	*P* value
Body mass index [kg/m^2]	−0.02 (−0.04 to −0.002)	0.029	0.117	+0.003 (−0.02 to +0.02)	0.784	–	–
Systolic blood pressure [mmHg]	−0.02 (−0.03 to −0.02)	<0.001	0.125	−0.01 (−0.02 to −0.005)	<0.001	–	–
Total cholesterol [mg/dl]	−0.003 (−0.005 to 0)	0.021	0.869	0 (−0.003 to +0.002)	0.856	–	–
LDL cholesterol [mg/dl]	−0.002 (−0.004 to + 0.001)	0.080	0.769	0 (−0.002 to +0.003)	0.936	–	–
HbA1c [%]	−0.5 (−0.7 to −0.4)	<0.001	0.915	−0.2 (−0.4 to −0.04)	0.015	−0.2 (−0.4 to −0.02)	0.028
Glucose level [mmol/L]	−0.3 (−0.3 to −0.2)	<0.001	0.381	−0.1 (−0.2 to −0.03)	0.008	−0.1 (−0.2 to −0.02)	0.019
Glucose level after 2 h [mmol/L]	−0.04 (−0.1 to +0.02)	0.194	0.509	+0.02 (−0.04 to +0.08)	0.523	–	–
Diabetes	−0.8 (−1.1 to −0.5)	<0.001	0.742	−0.4 (−0.7 to −0.04)	0.028	–	–
Hypertension	−0.9 (−1.0 to −0.7)	<0.001	0.883	−0.5 (−0.6 to −0.3)	<0.001	–	–
Smoking	−0.2 (−0.5 to +0.001)	0.051	0.072	−0.4 (−0.6 to −0.1)	0.001	−0.4 (−0.6 to −0.2)	<0.001
Obesity	−0.4 (−0.7 to −0.2)	<0.001	0.944	−0.3 (−0.5 to −0.04)	0.020	−0.3 (−0.5 to −0.02)	0.038
Dyslipidaemia	−0.6 (−0.8 to −0.3)	<0.001	0.072	−0.08 (−0.3 to +0.2)	0.561	–	–

For interpretation of estimates and abbreviations please refer to legend of Table 3.

major CV risk factors and report three major findings. First, individuals exhibiting at least one risk factor had higher levels of all MyW domains except for work efficiency. This effect, compatible with a higher energy consumption during both the active systolic and early diastolic phase, was carried by an imbalanced increase in GWW resulting in lower work efficiency. Whereas GCW was higher in women compared to men, no such difference was found for GWW. Second, alterations in myocardial work were mainly induced by higher systolic blood pressure and pre-existing hypertension. In particular, hypertension showed the strongest association with all MyW domains and was the only risk factor with a pronounced and independent impact on GWW. Third, diabetes mellitus, obesity, dyslipidaemia, and smoking showed a pattern of isolated reduction in GCW and GWI, independent from systolic blood pressure, and did not affect GWW.

Hypertension

Systemic hypertension is known to induce LV hypertrophy, and ultimately heart failure. Experimental models of human hypertensive hypertrophy in rats showed that myocardial efficiency decreases over time, and the disease aggravates from compensated hypertrophy to heart failure [21]. In a large cohort of hypertensive participants, LV hypertrophy was associated with depressed myocardial mechano-energetic efficiency which, in turn, predicted adverse outcome [22]. Previous analyses of our cohort [10] suggested a sex-specific sensitivity of the myocardium to individual CV risk factors, such as hypertension and dyslipidaemia. The present analysis showed an adverse effect of hypertension on the GWI in either sex, which consistently was stronger in women when compared to men. Further, previous studies in smaller groups of patients with hypertension reported an increase in GCW and GWW but found no changes in GWE [23, 24]. Along these lines, the NORRE consortium [25] also found GWI and GCW to be associated with systolic blood pressure. Our results confirm that hypertension was associated with higher constructive and wasted myocardial work, but revealed an adverse impact on work efficiency. A lower myocardial work efficiency, in line with lower myocardial mechano-energetic efficiency as described previously [22], might be the underlying pathomechanism driving symptomatic heart failure in hypertensive heart disease.

Systolic blood pressure and hypertension were the only risk factor studied enhancing wasted work. GWW by itself is very intriguing comprising the myocardium's loss of energy during a heart cycle. This loss, according to Boe et al. [5], is an additional mechanical burden to the myocardium and may thus induce the accelerated development of heart failure. However, the exact mechanisms are not

well understood. Loading conditions seem to interfere on wall tension by increasing wall stress and stiffness [26] and subsequently by increasing wasted work. This translates into increased myocardial oxygen demand and successively cardiac work augmentation. Lam et al. [27] found that in the early stages of hypertension, the antihypertensive therapy reduced arterial and LV systolic stiffness and lowered the ventricular-arterial coupling ratio. Thus, although total cardiac work was reduced, efficiency improved. We consistently found hypertension associated with higher total myocardial work but lower efficiency, which was explained by a disproportional increase of wasted work. Consequently, we would expect antihypertensive therapy to lower total myocardial work and optimize GWE by reducing GWW. Detailed assessment of hypertensive patients using echocardiography derived MyW indices might further enlighten the pathophysiology of hypertensive heart disease and identify potential treatment targets.

Diabetes mellitus

Diabetes mellitus portends an increased risk for subsequent development of heart failure, and death [28]. Besides the development of CVD [28], diabetes mellitus seems also to directly affect the myocardium. Impaired GLS was found an early sign of diabetic heart disease [29], even in asymptomatic normotensive diabetes patients [30, 31], and was associated with adverse clinical outcomes [32]. In non-diabetic individuals, increased insulin resistance as a measure of glycaemic status was associated with impaired mechano-energetic efficiency [33]. In our study, diabetes mellitus and HbA1c were negatively associated with GCW and GWI. This association became even stronger after adjusting for systolic blood pressure, suggesting that diabetes and HbA1c affect systolic dysfunction independent of systolic blood pressure. After adjusting for blood pressure, we found an association of MyW efficiency with HbA1c but not with diabetes mellitus. MyW efficiency seems to be more affected by the level of chronic hyperglycemia as evidenced by HbA1c compared to the sole presence of diabetes mellitus. These findings emphasize the importance of enforcing blood sugar optimization to prevent cardiac damage in patients with diabetes mellitus.

Obesity, dyslipidaemia, and smoking

Obesity, dyslipidaemia, and smoking are established risk factors for CV disease and heart failure [34–36]. Obesity, like diabetes mellitus, is associated with subtle systolic dysfunction [37]. Further, both entities are associated with poor glycaemic control and hyperinsulinemia, which may lead to changes in myocardial metabolism and fibrosis [38, 39]. Smoking is interrelated with inflammation, lipid abnormalities, and arterial stiffness which are prone to contribute to alterations in LV structure and function [40]. In our analysis, they revealed similar patterns of myocardial alteration by lowering GCW and GWI but without significant affection of GWW, independent from systolic blood pressure. Further, previous analyses of our cohort [10] found obesity adversely associated with myocardial deformation in either sex. In contrast, after adjustment for systolic blood pressure, myocardial work indices appeared more severely affected by obesity in women when compared to men. Further, these results strengthen the concept of sex-specific sensitivity of the myocardium to respective risk factors and should trigger further research in this field. The presence of CV risk factors in a sample of the general population free from heart failure seems to impact LV performance as assessed by MyW and reduce work efficiency through different pathways. MyW may potentially give new insights into the pathophysiology of different cardiac diseases, help to identify early abnormalities in LV function, and establish a more sensitive index for early stage dysfunction that opens the way to early preventive interventions.

Strengths and limitations

To the best of our knowledge, this study is the first to provide a comprehensive assessment of the association of CV risk factors with echocardiography-based MyW indices, derived from a large, well-characterized representative sample of the general population. Within the STAAB cohort study, blood pressure was measured in a sitting position after 5 min of rest during the same 3-h study visit, in agreement with international recommendations [17]. Ideally, for this analysis, blood pressure should have been measured during the echocardiographic examination. Hypertension as a major risk factor, had a key impact in this analysis, given its high prevalence and the haemodynamic impact on LV function, performance, and contractility. MyW method relies on the indirect measurement of brachial cuff pressure as a surrogate of invasively measured pressure, which might affect the accuracy of the estimation of the various work domains. However, the approach used in the present study was reported to yield good agreement with invasive measurements [1].

Conclusion

Individual CV risk factors selectively impact on constructive and wasted active myocardial function as measured by MyW domains. In particular, the heart in hypertension appears to operate at higher energy levels as indicated by both increased GCW and GWW, which results

in lower work efficiency. This pathomechanism may drive the development of symptomatic heart failure in hypertensive heart disease. The other CV risk factors also adversely impact on GWE, predominantly by reducing GCW independent of systolic blood pressure. Quantifying active systolic and diastolic compromise by derivation of MyW holds promise to improve our understanding of pathophysiological processes in cardiac disease. Further studies are needed to evaluate the value of selected MyW parameters or a respective pattern of MyW indices to assess the current health status of an individual patient.

Summary

What is known about the topic

- Left ventricular ejection fraction and longitudinal strain are load-dependent and might thus overestimate left ventricular dysfunction. The reference standard to quantify ventricular dysfunction requires invasive haemodynamic assessment.
- "Myocardial work" represents a novel validated approach, which allows quantifying active myocardial performance by means of non-invasively derived echocardiographic pressure–strain loops.
- The components and indices of myocardial work are viewed as reliable surrogates of appropriate or disproportionate myocardial energy consumption.

What this study adds

- Cardiovascular risk factors adversely affect myocardial work, independent from systolic blood pressure, individually, cumulatively, and in a sex-specific manner.
- Hypertension profoundly compromises myocardial work, in particular by increasing global wasted work. The heart in hypertension appears to operate at higher energy levels, yet lower efficiency.
- Quantifying active systolic and diastolic domains by means of myocardial work holds promise to improve our understanding of pathophysiological processes in cardiac disease.

Acknowledgements We cordially thank the STAAB Consortium. Further, we greatly appreciate the time of all STAAB participants and their willingness to provide data to the study. We also thank the Mayor of the City of Würzburg and the local registration office for their sustained support of our study. We thank the entire study team, study nurses, technicians, data managers, and students for their efforts on the STAAB study. We also thank M. Ertl, G. Fette, and F. Puppe from the CHFC DataWarehouse, Institute of Informatics VI, University of Würzburg, as well as T. Ludwig, ICE-B, for diligent data management.

Funding The study is supported by the German Ministry of Research and Education within the Comprehensive Heart Failure Center, Würzburg (BMBF 01EO1004 and 01EO1504). Floran Sahiti is supported by an MD/PhD fellowship of the Interdisciplinary Center for Clinical Research (IZKF) of the Medical Faculty, University of Würzburg. Open Access funding enabled and organized by Projekt DEAL.

Author contributions *Floran Sahiti* analysis and interpretation of data, drafting of the paper, final approval of the paper submitted. *Caroline Morbach* analysis and interpretation of data, revising the manuscript critically for important intellectual content, final approval of the paper submitted. *Vladimir Cejka* analysis and interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. *Theresa Tiffe* analysis and interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. *Martin Wagner* analysis and interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. *Felizitas Eichner* analysis and interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. *Götz Gelbrich* conception and design, analysis and interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. *Peter U Heuschmann* conception and design, interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. *Stefan Störk* conception and design, interpretation of data, revising the paper critically for important intellectual content, final approval of the paper submitted. We agree to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. We fully disclose any relationship with industry.

Compliance with ethical standards

Conflict of interest Floran Sahiti receives financial support from Interdisciplinary Center for Clinical Research (IZKF) Würzburg (MD/PhD program scholarship). Caroline Morbach reports a research cooperation with the University of Würzburg and Tomtec Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany, speakers honorarium from Amgen and Tomtec, a travel grant from Orion Pharma and Alnylam, participation in Advisory and Patient Eligibility Boards sponsored by AKCEA, Alnylam, Pfizer and EBR Systems outside the submitted work. Vladimir Cejka none. Theresa Tiffe none. Martin Wagner none. Felizitas Eichner none. Götz Gelbrich reports a research cooperation with the University Hospital Würzburg and TomTec Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany, a grant from the German Research Council (DFG) as the senior biometrician of the FIND-AF II trial outside the submitted work. Peter Heuschmann reports research grants from German Ministry of Research and Education, European Union, Charité—Universitätsmedizin Berlin, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, Federal Joint Committee (G-BA) within the Innovationfond, University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo), grants from Charité—Universitätsmedizin Berlin (within Mondafis; Mondafis is supported by an unrestricted research grant to the Charité from Bayer), from University Göttingen (within FIND-AF randomized; FIND-AF randomized is supported by an unrestricted research grant to the University Göttingen from Boehringer-Ingelheim), outside the

submitted work. Stefan Störk reports research grants from the German Ministry of Education and Research, European Union, University Hospital Würzburg; participation in Advisory Boards for Astra-Zeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Novartis, Pfizer, Thermo-Fisher; principal investigator in trials (co-) sponsored by Bayer, Boehringer-Ingelheim, Novartis, Pfizer; speaker honoraria by Astra-Zeneca, Bayer, Boehringer Ingelheim, Novartis, Pfizer, Servier, outside the submitted work

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Supplemental Data

Impact of cardiovascular risk factors on myocardial work – Insights from the STAAB cohort study

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Supplemental Data

Supplemental table S1: Observer variability for parameters describing myocardial work.

	Mean (SD)	Intra-observer variability		Inter-observer variability	
		Mean difference (SD)	95% CI of differences	Mean difference (SD)	95% CI of differences
GCW [mmHg%]	2532 (472)	26.4 (47.4)	4.2; 48.5	231 (200)	138; 325
GWW [mmHg%]	87.0 (44.2)	7.7 (18.5)	–1.0; 16.3	–9.9 (49.4)	–33.0; 13.2
GWI [mmHg%]	2269 (413)	20.2 (52.1)	–4.2; 44.6	186 (152)	115; 257
GWE [%]	95.5 (1.6)	–0.15 (0.49)	–0.38; –0.01	0.6 (1.86)	–0.2; 1.4

To assess intra-observer variability, 20 random scans were read by one person twice (FS), more than 2 weeks apart. To assess inter-observer variability, the same scans were read by a second person (CM) blinded to the previous results. GCW = global constructive work, GWW = global wasted work, GWE = global work efficiency, GWI= global work index, SD = standard deviation, CI = confidence interval

Supplemental table S2. Sensitivity analysis comparing subjects with feasible vs non-feasible myocardial work (MyW) derivation

	Total sample (n=2473)	MyW analysis possible (n=1929)	MyW not possible (n=544)	P-value
Female sex	1269 (51.3)	951 (49.3)	318 (58.4)	**<0.001**
Age, years	54 (12)	54 (12)	56 (12)	**<0.001**
LV ejection fraction, %	60 (5)	61 (5)	58 (5)	**<0.001**
e/e' mean	8 (3)	8 (3)	8 (3)	**<0.001**
LDL cholesterol, mg/dl	123 (35)	122 (34)	124 (36)	0.411
HbA1c, %	5.5 (0.6)	5.6 (0.6)	5.7 (0.7)	**<0.001**
eGFR, ml/min	86 (15)	87 (15)	84 (16)	**0.002**
Heart rate, beats/min	68 (10)	67 (10)	70 (12)	**<0.001**
Body mass index, kg/m^2	27 (5)	26 (4)	28 (7)	**<0.001**
Diabetes mellitus	238 (10)	157 (8)	81 (15)	**<0.001**
Hypertension	1124 (45)	849 (44)	275 (51)	**0.007**
Smoking	463 (18.7)	376 (19.4)	87 (15.9)	0.069
Obesity	485 (19.6)	302 (15.6)	183 (33.6)	**<0.001**
Dyslipidaemia	347 (14.0)	255 (13.2)	92 (16.9)	**0.005**

Data are n (%) or mean (SD).
LV, left ventricular; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin

6.3 Manuscript #3

Sahiti F, Morbach C, Cejka V, Albert J, Eichner FA, Gelbrich G, Heuschmann PU, Störk S – ``Left ventricular remodeling and myocardial work: Results from the STAAB cohort study'' Front Cardiovasc Med. 2021 Jun 11;8:669335. doi: 10.3389/fcvm.2021.669335. PMID: 34179134;

6.3.1 Summary

Based on the data from the first pre-planned interim analysis of the STAAB cohort study, 1926 individuals (49.3% women, mean age 54±12 years) were eligible for MyW analysis. These individuals were in sinus rhythm, had an LV ejection fraction ≥ 50%, and had no significant LV valve disease. Based on the current recommendations (10, 134), study participants were allocated to 4 groups depending on their pattern of LV geometry: n=1789 individuals (93%) had normal LV geometry, n=100 (5%) exhibited concentric remodeling, n=31 (1.6%) eccentric hypertrophy, and n=6 (less than 1%) concentric hypertrophy.

Participants with abnormal LV geometry patterns were older, had higher levels of BMI, blood pressure, NT-proBNP, LDL cholesterol, and HbA1c compared to participants with normal LV geometry. Further, markers of systolic function (LV ejection fraction, stroke volume, and GLS) and diastolic function, although still within normal ranges, were more favorable in normal LV geometry compared to abnormal LV geometry patterns.

Alterations in MyW were apparent with an abnormal LV geometry pattern. GCW and GWI values were highest in concentric hypertrophy. A deviation from normal LV geometry was associated with higher values of GWW and lower GWE, respectively. In multivariable regression analysis adjusted for age, sex, BMI, heart rate, LV ejection fraction, LDL cholesterol, HbA1c, and hypertension, higher LV volume was associated with higher GWW (+0.5 mmHg% per mL/m^2, $p<0.001$) and lower GWE (–0.02% per mL/m^2, $p<0.01$).
In comparison, higher LV mass was associated with higher GWW (+0.45 mmHg% per g/m^2, $p<0.001$) and GCW (+2.05 mmHg% per g/m^2, $p<0.01$), and lower GWE (–0.015% per g/m^2,

p<0.001). These associations were dominated by the impact of blood pressure level and were also observed in hypertensive participants with still normal LV geometry.

6.3.2 Manuscript and supplement (publication)

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 11 June 2021
doi: 10.3389/fcvm.2021.669335

Left Ventricular Remodeling and Myocardial Work: Results From the Population-Based STAAB Cohort Study

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Cardiovascular Imaging, a section of the journal Frontiers in Cardiovascular Medicine

Received: 18 February 2021
Accepted: 06 May 2021
Published: 11 June 2021

Citation:
Sahiti F, Morbach C, Cejka V, Albert J, Eichner FA, Gelbrich G, Heuschmann PU and Störk S (2021) Left Ventricular Remodeling and Myocardial Work: Results From the Population-Based STAAB Cohort Study. Front. Cardiovasc. Med. 8:669335. doi: 10.3389/fcvm.2021.669335

Introduction: Left ventricular (LV) dilatation and LV hypertrophy are acknowledged precursors of myocardial dysfunction and ultimately of heart failure, but the implications of abnormal LV geometry on myocardial function are not well-understood. Non-invasive LV myocardial work (MyW) assessment based on echocardiography-derived pressure-strain loops offers the opportunity to study detailed myocardial function in larger cohorts. We aimed to assess the relationship of LV geometry with MyW indices in general population free from heart failure.

Methods and Results: We report cross-sectional baseline data from the Characteristics and Course of Heart Failure Stages A-B and Determinants of Progression (STAAB) cohort study investigating a representative sample of the general population of Würzburg, Germany, aged 30–79 years. MyW analysis was performed in 1,926 individuals who were in sinus rhythm and free from valvular disease (49.3% female, 54 ± 12 years). In multivariable regression, higher LV volume was associated with higher global wasted work (GWW) (+0.5 mmHg% per mL/m^2, $p < 0.001$) and lower global work efficiency (GWE) (−0.02% per mL/m^2, $p < 0.01$), while higher LV mass was associated with higher GWW (+0.45 mmHg% per g/m^2, $p < 0.001$) and global constructive work (GCW) (+2.05 mmHg% per g/m^2, $p < 0.01$) and lower GWE (−0.015% per g/m^2, $p < 0.001$). This was dominated by the blood pressure level and also observed in participants with normal LV geometry and concomitant hypertension.

Conclusion: Abnormal LV geometric profiles were associated with a higher amount of wasted work, which translated into reduced work efficiency. The pattern of a disproportionate increase in GWW with higher LV mass might be an early sign of hypertensive heart disease.

Keywords: myocardial work, myocardial work efficiency, left ventricular geometry, left ventricular mass, LV dilatation, left ventricular geometric abnormality, left ventricular remodeling

INTRODUCTION

The constant exposure to cardiovascular risk factors and/or adverse hemodynamic conditions induces complex changes in left ventricular (LV) geometry, often starting as a physiological compensatory response (1, 2). Alterations in LV geometry such as LV dilatation and LV hypertrophy are acknowledged precursors of myocardial dysfunction and ultimately of heart failure (3–6), but the mechanisms are still not well-understood. Invasive recording of pressure-volume loops as the reference standard provides real-time assessment of LV loading conditions, contractility, and myocardial oxygen consumption (7). However, its (repeated) use in clinical routine is limited due to the investigation's invasive nature. Recent advances in imaging methods allow to approximate the intrinsic and functional cardiac performance with satisfactory precision, also accounting for loading conditions. A novel echocardiographic method has been introduced and validated against invasive measurements that non-invasively quantifies active myocardial function, i.e., systolic and early diastolic active myocardial work (MyW) (8). This approach allows differentiating constructive from wasted MyW, with the latter not contributing to LV output. The concept of MyW measurement is based on speckle-tracking derived longitudinal strain and systolic blood pressure and is widely applicable, including situations of screening. However, echocardiography-derived MyW has to be differentiated from the puristic definition of cardiac work derived from invasive pressure-volume loops, expressed in Joule or Centijoule (9). MyW approximates the work contributing to LV output, i.e., constructive work, and quantifies energy loss due to uncoordinated left ventricular contractions resulting in stretching of individual LV segments by the contraction of other LV segments, i.e., wasted work (10). Further, MyW might allow profound insights into LV performance and, given the strong correlation with cardiac glucose uptake as measured by positron emission tomography, might also serve as surrogate of regional and global myocardial metabolism (8, 10). LV geometry patterns have been shown to be of prognostic relevance in community studies (11, 12) and depend, i.e., on exposure to modifiable cardiovascular risk factors, such as hypertension and obesity (4, 13, 14). Thus, the detailed evaluation of MyW in relation to LV geometry might further advance the pathophysiological understanding of functional changes associated with abnormal LV geometry. Therefore, we aimed to assess the association of LV geometry with myocardial work in a well-characterized population-based sample of individuals free from heart failure.

Abbreviations: LV, left ventricle/ventricular; LVMi, left ventricular mass index; LVEDVi, left ventricular end diastolic volume index; CR, concentric remodeling; CH, concentric hypertrophy; EH, eccentric hypertrophy; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GCW, global constructive work; GWW, global wasted work; STAAB, The Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression Cohort Study.

METHODS

Population

Within the Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression (STAAB) prospective cohort study, we recruited and comprehensively phenotyped a representative sample of the population of Würzburg, Germany, aged 30–79 years, $n = 5{,}000$, free of symptomatic heart failure. The study design and baseline characteristics have been published previously (15, 16). The STAAB study complies with the Declaration of Helsinki and was approved by the ethics committee, University of Würzburg (J-117.605-09/13). All participants provided written informed consent prior to any study-related examination. For the present analysis, we evaluated cross-sectional data of the baseline examination from the first half of the STAAB study population ($n = 2{,}473$). This group had been included between December 12, 2013, and September 2, 2016, was pre-specified for a planned interim analysis (15), and therefore met the sex and age stratification criteria of the total sample.

Baseline Examination

Participants were evaluated at the Joint Survey Unit of the Comprehensive Heart Failure Center and the Institute for Clinical Epidemiology and Biometry, University of Würzburg. Routine laboratory measurements were performed at the central laboratory of the University Hospital Würzburg, including fasting lipid profile, estimated glomerular filtration rate (eGFR), glycosylated hemoglobin (HbA1c), and NT-proBNP levels. Blood pressure (in a sitting position after 5 min of rest), body height and weight, hypertension history, and current anti-hypertensive pharmacotherapy were assessed according to standard operating procedures (14). According to ESC guidelines, the presence of hypertension was defined as blood pressure $\geq$140/90 mmHg or on anti-hypertensive pharmacotherapy (17). We further sub-classified our sample according to blood pressure into four groups as recommended by current guidelines (17): (a) optimal blood pressure, i.e., systolic blood pressure (SBP) $<$120 mmHg; (b) normal blood pressure, SBP 120–129 mmHg; (c) high-normal blood pressure, SBP 130–139 mmHg; and (d) grade 1 hypertension or higher, SBP $\geq$140 mmHg.

Echocardiographic Analysis and LV Geometry

Image acquisition was performed by trained and certified sonographers employing one echocardiography machine (Vivid S6® with M4S Sector Array Transducer operating at 1.5–4.3 MHz, GE Healthcare, Horten, Norway) with presets maintained according to a pre-specified protocol. The utility of performance measures of the echocardiography quality assurance program has been published previously (18). A minimum of three cardiac cycles was recorded. Two-dimensional images from the LV apical four-, two-, and three-chamber views were recorded with a frame rate of 50–80 s^{-1} and stored digitally. We derived end-diastolic interventricular septum thickness (IVSd), LV posterior wall thickness (LVPWd), and LV end-diastolic diameter (LVEDD)

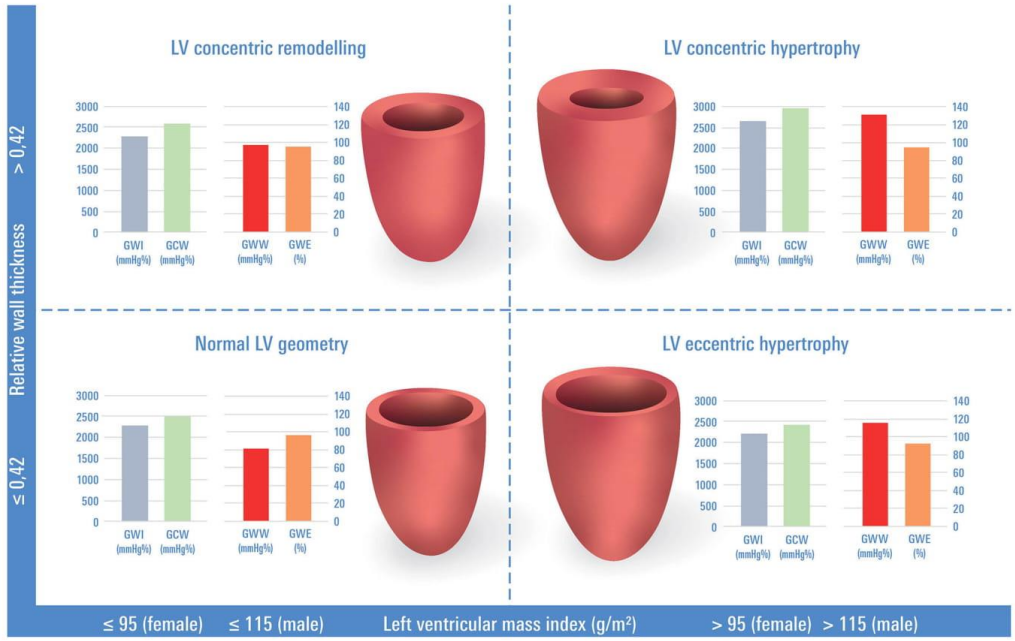

FIGURE 1 | Classification of left ventricular geometry based on the left ventricular mass index and relative wall thickness and myocardial work indices. Columns with myocardial work indices represent the mean or median values of our study sample. GWI, global work index; GCW, global constructive work; GWW, global wasted work, GWE, global work efficiency.

in the parasternal long-axis from an M-Mode recording, or—in case of suboptimal angulation—from a 2D measurement (19). We calculated LV mass using the corrected American Society of Echocardiography method (19): LV mass (g) = 0.8 (1.04 [([LVEDD + IVSd +LVPWd]^3 - LVEDD^3)]) + 0.6 as well. LV relative wall thickness (RWT) was calculated as: (2 * posterior wall thickness)/LV end-diastolic diameter (1, 19). We further measured LV ejection fraction (LVEF) and LV end-diastolic volume using Simpson's biplane method (19). Early diastolic myocardial relaxation velocity (e') was assessed using tissue and PW-Doppler close to the septal and/or lateral mitral annulus. LA volume was measured biplane in apical four and two-chamber view and left atrial volume index (LAVi) was calculated as LA volume indexed to body surface area. Valve regurgitation was determined by the color Doppler multiplane vena contracta method, and valve stenosis was quantified by continuous-wave Doppler measurements (15). LV mass index (LVMi) and LV end-diastolic volume index (LVEDVi) were calculated, indexing LV mass and LV end-diastolic volume to body surface area, respectively. According to the latest guidelines (1, 19), we classified the participants into four different subgroups according to their respective LV geometry pattern (**Figure 1**): (a) normal LV geometry, LVMi ≤95 g/m^2 in women or ≤115 g/m^2 in men and RWT ≤0.42; (b) concentric LV remodeling (CR), LVMi ≤95 g/m^2 in women or ≤115 g/m^2 in men and RWT >0.42; (c) concentric LV hypertrophy (CH), LVMi >95 g/m^2 in women or >115 g/m^2 in men and RWT >0.42; (d) eccentric LV hypertrophy (EH), LVMi >95 g/m^2 in women or >115 g/m^2 in men and RWT ≤0.42.

Myocardial Work Analysis

MyW analysis was performed off-line based on the stored echocardiography images and blood pressure measurements. Aortic and mitral valve closure and opening times were assessed by CW Doppler of the aortic valve and PW Doppler of the mitral valve. However, as potential changes in heart rate during the examination might affect the loop area, these time points were visually verified in the apical three-chamber view and manually adjusted where necessary. LV apical four-, two-, and three-chamber views were analyzed off-line using Automated Functional Imaging (EchoPAC®, Version 202, GE) to determine global longitudinal strain (GLS). Provision of peripheral blood pressure allowed the derivation of the MyW parameters as detailed by others (8, 10, 20).

A) Global constructive work [GCW (mmHg%)], i.e., the sum of positive work performed during shortening in

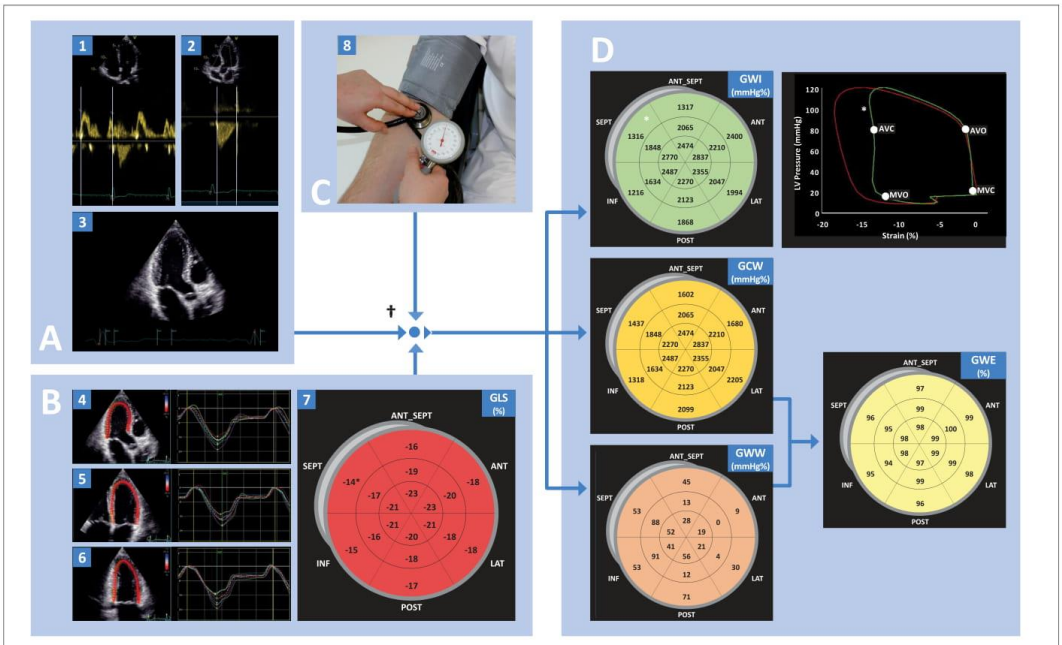

FIGURE 2 | Illustrative physiological background of LV myocardial work analysis. **(A)** Represents valvular times, with mitral valve opening and close measured using pulse-waved Doppler derived mitral inflow and aortic valve opening and closure measured by continuous-wave Doppler derived transaortic outflow. **(B)** Global longitudinal strain measured from 4, 3, and 2 chamber view. **(C)** Estimated LV Pressure measured from brachial cuff pressure. **(D)** Schematic presentation of segment-specific values of MyW indices, which later are expressed in global values. GCW and GWW are important physiological indices related to the shortening and lengthening of the LV segments. Work efficiency (GWE) is derived as the fraction of GCW and the sum of GCW and GWW. † Empiric reference curve of LV pressure as suggested in the validation study by Russell et al. (8). * indicates a segment-specific pressure-strain loop (in this case, we highlighted the septal basal segment).

systole and adding negative work during lengthening in isovolumic relaxation;

B) Global wasted work [GWW (mmHg%)], i.e., the sum of negative work performed during lengthening in systole plus work performed during shortening against a closed aortic valve in isovolumic relaxation;

C) Global work index [GWI (mmHg%)], i.e., the total work performed from mitral valve closure to mitral valve opening.

D) Global work efficiency [GWE (%)], i.e., GWE= GCW / (GCW + GWW).

All indices were calculated as the mean of respective segmental values (18-segment model). We excluded subjects from further analysis in whom >1 LV segment was unsuitable for analysis due to poor tracking or suboptimal image quality. Determination of MyW, as well as quality assurance measures, have been published previously (21). **Figure 2** illustrates step by step the approach to LV myocardial work analysis.

Data Analysis

Continuous variables are described as mean (standard deviation) and categorical variables as frequency (percent). Normal distribution was checked using the Shapiro-Wilk test. Normal distributed variables were compared using the *t*-test, non-normal distributed variables using the Mann-Whitney *U*-test, and categorical variables using the chi-square test, respectively. Differences between groups were tested using the Kruskal-Wallis test, median test, and chi-square test. To test the relationship between LV geometry and MyW, we first ran a univariable linear regression analysis for each of MyW indices. Because we wanted to describe the relative contribution of systolic blood pressure, this variable was also tested, despite the fact that it is part of the derivation of myocardial work indices. In subsequent multivariable models, however, systolic blood pressure was omitted. Models were based on results of univariable regression and their physiological context. Thus, the multivariable model included age, sex, body mass index (BMI), LVEF, GLS, heart rate, low-density lipoprotein (LDL), glycosylated hemoglobin (HbA1c), hypertension, and measures of LV geometry such as LVMi and LVEDVi. The Jonckheere-Terpstra test was used for trend analysis. All tests were performed 2-sided. P-value < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (Version 26, SPSS Inc., Chicago, USA).

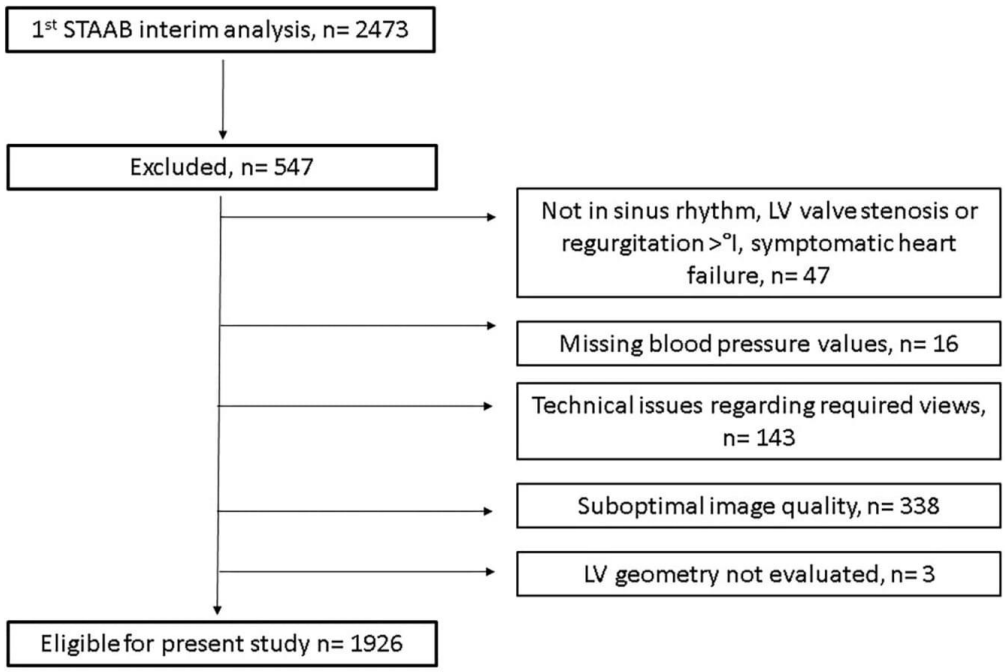

FIGURE 3 | Study flow.

RESULTS

For the pre-planned interim analysis of the STAAB cohort study, 2,473 individuals were considered. Of those, a total of $n = 547$ participants were excluded from the current analysis for different reasons including technical issues regarding required views, poor tracking or suboptimal image quality, or missing blood pressure values (for details, see **Figure 3**). Therefore, a total sample of $n = 1{,}926$ individuals was included (49.3% women, with mean age 54 ± 12 years). Ninety-three percent of those had normal LV geometry, and 5% exhibited CR, 2% had EH, and <1% had CH, respectively. **Table 1** presents the clinical and echocardiographic characteristics for the total sample and stratified for groups defined by LV geometry.

Participants with normal LV geometry were younger and had lower BMI, SBP, NT-proBNP, LDL cholesterol, and HbA1c compared to abnormal geometric LV patterns (**Table 1**). Accordingly, participants with normal LV geometry exhibited less often obesity, hypertension, diabetes mellitus, or dyslipidemia. In contrast, coronary heart disease and anti-hypertensive treatment was more prevalent in individuals with abnormal LV geometry patterns. Even though still within the normal range, LVEF and GLS were more favorable in normal LV geometry when compared to CR and EH (**Table 2**). LVEDV index was lower in CR and higher in EH participants. Diastolic function in abnormal LV geometry patterns was significantly less favorable when compared to normal LV geometry. MyW characteristics are shown in **Table 2**. When compared to normal LV geometry, we found higher values of GCW and GWI in CH, as well as of GWW in CR and EH. These effects resulted in compromised GWE with any type of abnormal LV geometry.

In multivariable linear regression analysis including age, sex, BMI, heart rate, LVEF, LDL, HbA1c, hypertension, LVMi, and LVEDVi, we found that higher LV muscle mass was associated with a higher GCW, but also with higher GWW, thus resulting in reduced GWE. In contrast, higher LV volume was associated with higher GWW only, which also resulted in lower GWE (**Table 3**). In a further step, we analyzed patients with normal LV geometry according to the presence of hypertension (**Table 4**). Individuals with hypertension were more often male, were older, and had higher BSA and BMI. They showed similar LV volumes but significantly higher LV mass and LA volume and less favorable measures of systolic and diastolic function. Individuals with hypertension revealed significantly higher GCW and GWI, but also GWW, resulting in lower GWE. A sensitivity analysis focusing on the current blood pressure category showed

TABLE 1 | Baseline characteristics in the total sample and according to left ventricular (LV) geometry.

	All subjects (*N* = 1,926)	LV normal geometry (*N* = 1,789)	LV concentric remodeling (*N* = 100)	LV concentric hypertrophy (*N* = 6)	LV eccentric hypertrophy (*N* = 31)
Age [years]	54 (12)	53 (12)	61 (10)*	69 (16)*	61 (9)*
Sex, women	950 (49.3)	879 (49.1)	48 (48.0)	4 (66.6)	19 (61.2)
BSA [m^2]	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.9 (0.3)	1.9 (0.2)
BMI [kg/m^2]	26.0 (4.3)	25.9 (4.1)	28.3 (4.7)*	30.1 (9.0)	28.1 (5.0)*
Heart rate [beats/min]	67 (10)	67 (10)	69 (10)*	60 (5)*	65 (12)
SBP [mmHg]	130 (18)	130 (17)	141 (18)*	148 (12)*	139 (23)*
DBP [mmHg]	78 (10)	78 (10)	81 (8)*	79 (13)	78 (14)
NT-proBNP [pg/ml]	52 (24, 97)	51 (24, 94)	52 (29, 108)	87 (63, 245)	154 (58, 305)*
LDL cholesterol [mg/dl]	122 (34)	122 (34)	126 (34)*	113 (27)	124 (44)*
HbA1c [%]	5.5 (0.6)	5.5 (0.5)	5.9 (1.0)*	5.8 (0.5)	6.1 (1.1)*
eGFR [ml/min]	87 (15)	87 (15)	83 (15)	85 (19)	86 (17)
Hypertension	848 (44.0)	735 (41.1)	79 (79.0)*	6 (100)*	28 (90.3)*
Diabetes	155 (8.0)	124 (6.9)	20 (20.0)*	3 (50.0)*	8 (25.8)*
Obesity	301 (15.6253)	253 (14.1)	33 (33.0)*	2 (33.3)	13 (41.9)*
Dyslipidemia	254 (13.2)	222 (12.4)	19 (19.0)	2 (33.3)	11 (35.5)*
Coronary heart disease	70 (3.6)	53 (2.9)	8 (8.0)*	1 (16.6)	8 (25.8)*
Peripheral artery disease	25 (1.3)	21 (1.2)	2 (2.0)	0 (0)	2 (6.5)*
Anti-hypertensive therapy	522 (27.1)	436 (24.4)	59 (59.0)*	5 (83.3)*	22 (70.9)*
ACEi/ARB	382 (19.8)	318 (17.7)	45 (45.0)*	5 (83.3)*	14 (45.2)*
Beta-blocker	242 (12.6)	200 (11.2)	26 (26.0)*	3 (50.0)*	13 (41.9)*
Diuretics	99 (5.1)	81 (4.5)	11 (11.0)*	2 (33.3)*	5 (16.1)*

**Explorative comparison with individuals with normal LV geometry (two-sided $p < 0.05$).*
Data are n (%), mean (SD), or median (quartiles).
BSA, body surface area; BMI, body mass index; NT-proBNP, N-terminal-pro Brain Natriuretic Peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate, ACEi, angiotensin converting enzyme inhibitor, ARB, angiotensin II receptor type 1 blocker. Medications history was obtained in n = 1,914 individuals.

a consistent pattern, i.e., higher GCW, GWI, and GWW with increasing blood pressure but lower GWE (**Table 5**). The strength of the association for the trends observed in **Tables 4**, **5** was maintained when adjusting for age.

DISCUSSION

The current study investigated the association of altered LV geometry with MyW indices in a large, population-based sample. Three major findings emerged. First, while the majority of individuals studied exhibited a normal LV geometry, a relevant proportion of participants revealed an abnormal LV geometry; these subjects were older and presented with a less favorable profile of cardiovascular risk factors. Second, both LV enlargement and LV hypertrophy were adversely associated with GWE, predominantly through increasing the amount of GWW. Third, when compared to participants without hypertension, individuals with normal LV geometry and concomitant hypertension exhibited larger LV mass and LA volume and less favorable measures of systolic and diastolic function. Their MyW pattern was characterized by higher GCW and GWW and thus lower GWE, comparable to the pattern found in LV hypertrophy.

Altered LV geometry, including its components LV mass and LV volume, constitute pivotal information of the standard echocardiography report (1), as they reliably indicate maladaptation due to adversely regulated hemodynamics (22). Such conditions trigger myocardial responses that aim at maintaining a normal cardiac output despite compromised energetics (23–25). When left untreated, these adaptive changes induce early, subclinical changes in LV geometry, advance toward subclinical impairment in LV function (1), and ultimately cause functional capacity loss (26). This complex configuration is mainly driven by changes at the histological and metabolic level, e.g., myocyte hypertrophy, apoptosis, and energy consumption (27). Not surprisingly, deteriorating LV geometry was shown to predict incident heart failure (28, 29).

An increased hemodynamic load, induced either by pressure, e.g., in hypertension, or by volume, e.g., in valvular disease, or by a combination of both stimuli, contributes to LV hypertrophy and/or dilation, resulting in different geometric adaptations (1, 2). Recently, changes in LV chamber geometry, i.e., an increase in LV mass and/or LV size, were reported to relate to impaired GLS (30). LV mass and LV volume further impact on electric conduction times resulting in prolonged QRS duration and potential consecutive LV dyssynchrony (31–34), which, in turn,

TABLE 2 | Baseline echocardiographic characteristics including myocardial work according to the LV geometry classification.

	All subjects (*N* = 1,926)	LV normal geometry (*N* = 1,789)	LV concentric remodeling (*N* = 100)	LV concentric hypertrophy (*N* = 6)	LV eccentric hypertrophy (*N* = 31)
IVSd [mm]	9 (1)	9 (1)	10 (1)*	11 (1)*	9 (1)*
LVPWd [mm]	8 (1)	8 (1)	10 (1)*	11 (1)*	11 (1)*
LVEDd [mm]	48 (5)	48 (5)	44 (4)*	51 (4)	55 (4)*
RWT	0.34 (0.05)	0.33 (0.05)	0.45 (0.04)*	0.44 (0.02)*	0.35 (0.04)*
LVM [g]	138 (39)	136 (37)	153 (36)*	219 (43)*	219 (42)*
LVMi [g/m^2]	72 (16)	71 (15)	78 (15)*	113 (13)*	112 (10)*
LVEDV [mL]	99 (25)	99 (25)	93 (22)*	100 (33)	123 (29)*
LVEDVi [mL/m^2]	52 (10)	52 (10)	47 (9)*	52 (16)	64 (14)*
LAV [mL]	46 (15)	46 (15)	47 (16)	54 (12)	55 (17)*
LAVi [mL/m^2]	24 (7)	24 (7)	25 (8)	28 (7)	29 (9)*
E prime lateral	11 (3)	11 (3)	9 (2)*	7 (2)*	8 (3)*
E prime septal	9 (2)	9 (2)	7 (2)*	5 (1)*	6 (2)*
LVEF [%]	61 (4)	61 (4)	60 (4)*	59 (3)	58 (7)*
Stroke volume [ml]	60 (15)	60 (15)	55 (14)*	58 (16)	70 (16)*
GLS [–%]	21 (3)	21 (3)	20 (2)*	21 (1)	19 (3)*
GCW [mmHg%]	2,506 (428)	2,501 (424)	2,575 (457)	2,965 (240)*	2,445 (526)
GWW [mmHg%]	83 (59, 119)	81 (58, 118)	98 (68, 133)*	130 (80, 191)	117 (90, 158)*
GWI [mmHg%]	2,278 (396)	2,276 (392)	2,311 (424)	2,670 (315)*	2,207 (502)
GWE [%]	96 (95, 97)	96 (95, 97)	95 (94, 97)*	94 (91, 96)	94 (93, 95)*

**Significantly different when compared to LV normal geometry (two-sided $p < 0.05$).*
Data are n (%), mean (SD), or median (quartiles).
LVEF, left ventricular ejection fraction; GLS, global longitudinal strain, IVSd, interventricular septum diameter; LVPWd, left ventricular posterior wall diameter; LVEDd, left ventricular end-diastolic diameter; RWT, relative wall thickness; LVM, left ventricular mass; LVMi, left ventricular mass index; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LAV, left atrial volume; LAVi, left atrial volume index, GCW, global constructive work; GWW, global wasted work; GWI, global work index; GWE, global work efficiency.

TABLE 3 | Univariable and multivariable regression analysis of myocardial work indices and different echocardiographic parameters.

	GCW [mmHg%]		GWW [mmHg%]		GWI [mmHg%]		GWE [%]	
	Mean 2,506, SD 428		Median 83, quartiles 59, 119		Mean 2,278, SD 396		Mean 96, SD 2	
	Univariable analysis	Multivariable analysis†	Univariable analysis	Multivariable analysis†	Univariable analysis	Multivariable analysis†	Univariable analysis	Multivariable analysis†
Sex [Women]	+87.3***	ns	−0.5	+10.9***	+124***	+68.8***	+0.2*	−0.4***
Age [years]	+7.9***	+4.5***	+1.2***	+0.8***	+4.9***	+1.6*	−0.05***	−0.03***
BMI [kg/m^2]	−6.5**	−10.1***	+0.3	−1.3***	−4.9*	−5.7**	−0.02*	+0.05***
LVEF [%]	+19.4***	+11.0***	−2.1***	−1.4***	+21.9***	+13.1***	+0.1***	+0.08***
GLS [–%]	+50.4***	+51.4***	−2.5***	−1.2**	+50.9***	+48.4***	+0.2***	+0.1***
Heart rate [beats/min]	−4.9***	ns	+0.3**	+0.4***	−5.5***	−2.6**	−0.02***	−0.02***
Systolic BP [mmHg]	+16.6***	–	+1.1***	–	+14.3***	–	−0.02***	–
LDL-C [mg/dl]	+0.3	ns	+0.06	ns	+0.2	ns	−0.002	ns
HbA1c [%]	+10.5	−35.7*	+10.6***	ns	−1.7	ns	−0.5***	ns
LVEDVi [mL/m^2]	−2.0*	ns	+0.3**	+0.5***	−2.0*	ns	−0.02***	−0.02***
LVMi [g/m^2]	+2.4***	+2.0**	+0.7***	+0.4***	+1.1*	+1.5**	−0.03***	−0.01***
IVSd [mm]	+21.9**	–	+6.7***	–	+10.6	–	−0.3***	–
LVPWd [mm]	+16.6*	–	+6.1***	–	+4.3	–	−0.3***	–
LVEDd [mm]	−3.1	–	+0.6*	–	−4.8*	–	−0.03**	–
RWT	+539**	–	+109***	–	+351*	–	−4.5***	–
Hypertension	+304***	+343***	+29.2***	+19.4***	+253***	+316***	−0.9***	−0.3**

(–) indicates that the variable was not considered in the multivariable regression analysis.
*GCW, global constructive work, GWW, global wasted work; GWI, global work index; GWE, global work efficiency; BMI, body mass index; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain, LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; IVSd, interventricular septum diameter; LVPWd, left ventricular posterior wall diameter; RWT, relative wall thickness; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. †Multiple adjustment includes: sex, age, BMI, LVEF, GLS, heart rate, LDL, HbA1c, hypertension, LVEDVi, LVMi.*

TABLE 4 | Echocardiographic patterns in participants with LV normal geometry according to the presence of hypertension.

	Total sample	Without hypertension	With hypertension	*p*
N (%)	1,789	1,054 (59)	735 (41)	
Women	879 (49)	572 (54)	307 (42)	<0.001
Age, years	53 (12)	49 (10)	59 (10)	<0.001
BSA [m^2]	1.9 (0.2)	1.87 (0.21)	1.94 (0.23)	<0.001
BMI [kg/m^2]	26 (4)	25 (4)	27 (4)	<0.001
SBP [mmHg]	130 (17)	121 (11)	142 (17)	<0.001
DBP [mmHg]	78 (10)	75 (7)	83 (10)	<0.001
LVEF [%]	61 (4)	61 (4)	60 (5)	<0.001
GLS [–%],	21 (3)	21 (4)	20 (2)	<0.001
E prime lateral (cm/s)	11 (3)	12 (3)	10 (3)	<0.001
E prime septal (cm/s)	9 (2)	9 (2)	8 (2)	<0.001
LAV [ml]	46 (15)	43 (14)	50 (17)	<0.001
LAVi [ml/m^2]	24 (7)	23 (6)	26 (8)	<0.001
LVEDVi [mL/m^2]	52 (10)	52 (11)	52 (10)	0.256
LVMi [g/m^2]	71 (15)	67 (13)	76 (15)	<0.001
GCW [mmHg%]	2,501 (424)	2,372 (310)	2,687 (491)	<0.001
GWW [mmHg%]	81 (58, 118)	74 (53, 100)	97 (67, 136)	<0.001
GWI [mmHg%]	2,276 (392)	2,167 (294)	2,431 (457)	<0.001
GWE [%]	96 (95, 97)	96 (95, 97)	96 (94, 97)	<0.001

Data are n (%), mean (SD), or median (quartiles).
BSA, body surface area; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LAV, left atrial volume; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVMi, left ventricular mass index; GLS, global longitudinal strain; GCW, global constructive work; GWW, global wasted work; GWI, global work index; GWE, global work efficiency.

is also known to adversely affect GLS (30, 35). Echocardiography-based determination of MyW parameters now offers the possibility to non-invasively study the different components of active myocardial function and to apply this method to larger collectives. Covering both the impairment of longitudinal LV function and a potential LV dyssynchrony induced by conduction delays, MyW might advance our mechanistic understanding of the myocardial function and subsequent adaptive changes in individuals with abnormal LV geometry. We determined three pathological groups (see **Figure 1**), which serve as examples of a (well-acknowledged) disease paradigm characterizing the gradual alteration of LV morphology over time given certain risk constellations (1, 19).

Concentric LV Remodeling and Concentric Hypertrophy

CR dominated in our study sample, followed by EH and CH. CR is considered a late-stage response of the LV to adverse hemodynamic circumstances and is predominantly caused by pressure overload as induced by increased afterload (36) due to arterial hypertension or aortic stenosis (37), or volume overload (1). CR is associated with adverse LV function (38, 39) and an adverse prognosis when compared to normal LV geometry (4, 40, 41). In our sample, participants with CR were older and showed a less favorable risk factor and comorbidity profile and lower values of GLS when compared to participants with normal LV geometry. The more detailed analysis of LV myocardial function revealed a trend toward an increase in GCW and GWI (**Figure 1**), which might be a consequence of increased myocardial muscle power in LV hypertrophy, and was even more pronounced in CH. In addition to this increase in constructive myocardial work, participants with CR and CH exhibited significantly higher levels of GWW when compared to participants with normal LV geometry. The lower values of global work efficiency suggest that the proportionate increase in GWW exceeds the increase in GCW with progressing LV hypertrophy might be one explanation for impaired exercise capacity in individuals with LV hypertrophy and abnormal LV geometry (42). Further, these findings were even more pronounced in individuals with CH. As this subgroup was small in our study sample, we did not perform further statistical analyses. However, the CH pattern is of high clinical relevance, and further dedicated studies in hypertensive patients need to provide additional insights.

Arterial hypertension is one of the most prevalent cardiovascular risk factors and a major contributor to long-term changes in LV geometry (36, 37, 43, 44). A higher prevalence of hypertension was seen with a deviation from normal LV geometry. However, even in participants with measures of LV geometry within a normal range, we found notable differences in LV structure and function in individuals with and without hypertension. Among subjects with normal LV geometry, those with hypertension presented with equal LV size but with higher LV mass when compared to subjects without hypertension (**Table 4**). The LV myocardium of those with hypertension performed a higher amount of work, constructive (GWI, GCW) and wasted work, at a lower efficiency level. A detailed analysis of LV structure and function according to the current blood pressure during the study visit showed a similar pattern (**Table 5**). Higher SBP values were associated with higher LV mass though still within the normal range. Participants with normal and high-normal BP had higher LV mass when compared to participants with optimal BP. Further, normal and high-normal blood pressure were associated with significantly higher values of work performed by the myocardium, including wasted work, when compared to optimal blood pressure (**Table 5**). As part of the adaptation process, it appears that the LV hypertrophies to perform a higher amount of work. Due to a disproportionate increase in wasted work, work efficiency seems to be affected already in individuals with high-normal blood pressure, hence in a very early stage of disease (**Table 5**). Our results give a glimpse of mechanistic insights into the pathophysiology of hypertensive heart disease and highlight the importance of early and consistent treatment of arterial hypertension to reach optimal treatment goals.

Eccentric Hypertrophy

This phenotype is characterized by increased LV size (i.e., LV dilatation) in the presence of normal wall thickness. EH is typically found in states of chronic volume overload, such as significant mitral regurgitation (which was excluded from

TABLE 5 | MyW indices in individuals with normal LV geometry according to blood pressure category.

	Blood pressure categories					
	All individuals (*N* = 1,789)	**Optimal SBP <120 (*N* = 570)**	**Normal SBP 120–129 (*N* = 398)**	**High-normal SBP 130–139 (*N* = 355)**	**Hypertensive SBP ≥140 (*N* = 466)**	***P* for trend**
Women	879 (49)	383 (67)	164 (41)	142 (40)	190 (41)	<0.001
Age [years]	53 (12)	49 (10)	50 (11)	56 (11)	59 (10)	<0.001
LVEF [%]	61 (4)	61 (4)	61 (4)	60 (4)	60 (5)	0.010
GLPS [–%]	21 (3)	22 (5)	21 (3)*	20 (2)	20 (3)	<0.001
SBP [mmHg]	130 (17)	112 (7)	125 (3)	134 (3)	152 (12)	<0.001
GCW [mmHg%]	2,501 (424)	2,224 (276)	2,406 (302)	2,545 (299)	2,888 (444)	<0.001
GWW [mmHg%]	81 (58, 118)	68 (49, 92)	77 (55, 110)	87 (62, 120)	105 (77, 149)	<0.001
GWI [mmHg%]	2,276 (392)	2,038 (267)	2,193 (286)	2,310 (289)	2,611 (425)	<0.001
GWE [%]	96 (95, 97)	96 (95, 97)	96 (95, 97)	96 (95, 97)	96 (94, 97)	<0.001
LVMi [g/m^2]	71 (15)	65 (14)	70 (14)	73 (14)	77 (15)	<0.001
LVEDVi [ml/m^2]	52 (10)	51 (10)	52 (10)	53 (11)	52 (10)	0.056
RWT	0.33 (0.05)	0.31 (0.05)	0.32 (0.05)	0.33 (0.04)	0.34 (0.05)	<0.001

Data are n (%), mean (SD), or median (quartiles).
P for trend (Jonckheere Terpstra trend test and Chi-square test, as appropriate).
BP, blood pressure; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; SBP, systolic blood pressure, GCW, global constructive work, GWW, global wasted work; GWI, global work index; GWE, global work efficiency; LVMi, left ventricular mass index; LVEDVi, left ventricular end-diastolic volume index; RWT, relative wall thickness.

our study sample), but also as an early manifestation of a cardiomyopathic process (1, 36). Further, previous work from our population-based cohort reported a higher proportion of increased LV volumes in individuals with structural heart disease with no clinical HF symptoms and absent CV risk factors known as the B-not-A group of HF (16). Participants with EH were older, more often female, had higher NT-proBNP levels, and a higher prevalence of hypertension, diabetes, and dyslipidemia when compared to normal LV geometry or CR. GCW and GWI were normal among individuals with EH, but GWW was markedly enhanced and GWE compromised. Of note, GWW and GWE were predominantly determined by larger LV volumes, potentially as a consequence of increased wall stress in larger LV volumes (45). Our results extend first analyses from NORRE (46), a multinational study to generate normal values for echocardiographic measures, where mild univariate associations between LV size and MyW indices were found that vanished in multivariable analysis, possibly due to issues of sample size and selection criteria. In contrast to a concentric increase in LV mass, an increase in LV size without an increase in LV wall thickness seems to be associated with an increase in GWW only, and lower GWE.

Cardiomyopathies are characterized by heterogeneous patterns of LV hypertrophy and progressive LV enlargement leading to myocardial dysfunction (47–49) and, on a histological level, by cardiomyocyte hypertrophy, myocardial disarray, and interstitial fibrosis (49). Recent work in patients with cardiomyopathy showed impaired MyW indices when compared to healthy controls (48, 50, 51). MyW analysis was hypothesized to reveal the effect of chronic remodeling on myocardial function in patients with cardiomyopathies, unmasking, i.e., a low capacity to adjust to an increased workload (52). Chan et al. (50) suggested that wasted work may be related to the increased myocardial wall stress against a higher afterload. Likewise, wasted work results to be of great interest as a potential factor reducing LV work efficiency and ultimately might contribute to LV remodeling. LV remodeling and consecutive functional changes reflect myocardial glucose metabolism and energetics (53), which was shown to correlate with non-invasive echocardiography-derived MyW indices (8). Our results show additional insights into the relationship of LV mass and size with myocardial work and might contribute to the elucidation of pathophysiological processes in cardiomyopathies.

Limitations and Strengths

In this large population-based sample, cardiovascular risk factors were comprehensively and carefully assessed according to standard operating procedures. In particular, echocardiography was performed by well-trained and internally certified and quality-controlled sonographers (18). However, the current cross-sectional analysis cannot inform on longitudinal alterations and causal inferences. The size of the three subgroups emerging with an abnormal LV geometry was relatively small. Nevertheless, due to the representative mode of sampling, they mirror the frequencies of these abnormalities in the population free of heart failure. For the derivation of MyW parameters, ideally, blood pressure should be measured during the echocardiographic examination. In STAAB participants, blood pressure was measured in a sitting position after 5 min of rest in a separate room but immediately prior to the echocardiographic examination. Hence, the thus introduced imprecision is likely to be small. Technically and physiologically, information on MyW should not be regarded as the exact equivalent to investigations on pressure-volume loop recordings (10, 45, 54). As discussed elsewhere in detail, MyW does not account for radial, and circumferential LV function nor wall stress since LV radial

curvature and wall thickness are not part of its derivation from pressure-strain loops (45, 54). Comparison of MyW, particularly of GWW, between different hearts, however, is considered a valid measure since it is a relative measure that compensates for limited information about local geometry and consecutive potential differences in wall stress (10). Further, MyW integrates LV systolic longitudinal strain, blood pressure, and time intervals, thus comprehensively accounting for potential impairment (a) in LV longitudinal contraction and (b) and in cardiac conduction induced by abnormal LV geometry as apparent, e.g., in patients with heart failure.

CONCLUSION

MyW analysis is a non-invasive, echocardiography-based method facilitating new insights into the relationship of LV geometry and myocardial performance in this population-based cohort free from heart failure. Any deviation from a normal LV geometric profile was associated with an alteration of MyW. While LV dilation was associated with solely higher GWW, concentric remodeling and hypertrophy were associated with both higher GCW and GWW. A disproportionately higher GWW resulted in lower GWE. These altered MyW patterns were already present in hypertensive individuals with normal LV geometry and might thus serve as an early sign of incipient hypertensive heart disease. Longitudinal studies are needed to test this hypothesis and improve our understanding on the mechanisms of hypertensive heart disease and the time course of its evolvement.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Faculty of Medicine, University of Würzburg (vote #98/13) and data protection officer of the University of Würzburg (#J-117.605-09/13). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FS, CM, GG, PH, and SS concepted and designed the study. FS, CM, VC, JA, FE, GG, PH, and SS analysis and interpretation of data. FS drafted the manuscript. CM, VC, JA, FE, GG, PH, and SS revised the manuscript critically for intellectual content. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the German Ministry of Research and Education within the Comprehensive Heart Failure Center, Würzburg (BMBF 01EO1004 and 01EO1504). FS was supported by an MD/PhD fellowship of the Interdisciplinary Center for Clinical Research (IZKF) of the Medical Faculty, University of Würzburg.

ACKNOWLEDGMENTS

STAAB Consortium consists of: Frantz (Department of Medicine I, Division of Cardiology, University Hospital Würzburg); C. Maack (Comprehensive Heart Failure Center, University Hospital and University of Würzburg); G. Ertl (University Hospital Würzburg); M. Fassnacht (Department of Medicine I, Division of Endocrinology, University Hospital Würzburg); C. Wanner (Department of Medicine I, Division of Nephrology, University Hospital Würzburg); R. Leyh (Department of Cardiac & Thoracic Surgery, University Hospital Würzburg); J. Volkmann (Department of Neurology, University Hospital Würzburg); J. Deckert (Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, University Hospital Würzburg); H. Faller (Department of Medical Psychology, University of Würzburg); R. Jahns (Interdisciplinary Bank of Biomaterials and Data Würzburg, University Hospital Würzburg). We greatly appreciate the time of all STAAB participants and their willingness to provide data to the study. We also thank the Mayor of the City of Würzburg and the local registration office for their sustained support of our study. We thank the entire study team, study nurses, technicians, data managers, and students for their efforts on the STAAB study. We also thank M. Ertl, G. Fette, and F. Puppe from the CHFC DataWarehouse, Institute of Informatics VI, University of Würzburg, as well as T. Ludwig, ICE-B, for diligent data management.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6.4 Manuscript #4

Sahiti F, Morbach C, Henneges C, Stefenelli U, Scholz N, Cejka V, Albert J, Heuschmann PU, Ertl G, Frantz S, Angermann CE, Störk S. Dynamics of Left Ventricular Myocardial Work in Patients Hospitalized for Acute Heart Failure. (40) J Card Fail. 2021 Dec;27(12):1393-1403. doi: 10.1016/j.cardfail.2021.07.004. Epub 2021 Jul 29. PMID: 34332057.

6.4.1 Summary

Based on the data collected for the Acute Heart Failure (AHF) Registry between August 2014 and December 2017, n=185 participants hospitalized for AHF had two echocardiograms on admission and prior to discharge, respectively. Of those, n=126 (mean age 73±12 years, 37% women) could be evaluated using MyW analysis and were included in the study. Echocardiographic examinations were conducted within a median time of 43 hours (quartiles 19, 69) after admission and within 72 hours prior to discharge.

The majority of these patients (83%) suffered from chronic HF, and only 17% exhibited *de novo* HF. On admission, most patients reported symptoms compatible with NYHA functional class III or IV, respectively. Based on the measurements at discharge, 51 patients (40.5%) had a LVEF <40% (HFrEF), n=8 patients (6.3%) LVEF 40-49% (HFmrEF), and n=67 (53.2%) LVEF ≥50% (HFpEF). Patients with HFrEF were younger, less often women, had lower blood pressure values, and had fewer comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia when compared to patients with HFpEF. In addition, HFrEF patients presented with higher LV volumes and LV mass. From admission to discharge, we found no major shifts between HF categories. Strain values and absolute values of MyW indices such as GCW, GWI, and GWE, were significantly lower in HFrEF compared to patients HFpEF. GWW was the only parameter that did not differ between the two groups of patients. Further, using Pearson`s correlation coefficient, we found that all MyW indices except for GWW were associated with markers of LV function, i.e., NT-proBNP, LVEF, and e'.

During a median hospital stay of 12 days (quartiles 8, 12), patients lost a median weight of 3 kg (quartiles 1, 7), paralleled by a decrease in NT-proBNP of 1815 pg/ml (quartiles 5173, 366). Even though absolute levels of NT-proBNP were higher in HFrEF than HFpEF, the relative in-

hospital change of NT-proBNP was of similar magnitude in both subgroups, with most patients experiencing a marked decrease.

Changes occurring in MyW indices during the in-hospital stay were then related to changes in NT-proBNP. In patients with HFrEF, a significant improvement in GCW, GWI, and GWE was apparent in HFrEF patients that was associated with decreasing NT-proBNP levels. No such association was found for GWW. In patients with HFpEF, a different pattern emerged as no relevant in-hospital changes in GCW, GWI and, GWE ratios were found. However, in patients in whom NT-proBNP levels failed to drop, GWW increased.

During six months of follow-up, 90 events of the combined endpoint death or hospitalization occurred (18 deaths, 72 patients with at least one rehospitalization). In Cox proportional hazards regression adjusted for age and sex, GWW (HR 1.035 per 10 mmHg% increment, 95%CI 1.005-1.065; p=0.020) and GWE (HR 0.967, 95%CI 0.939-0.996; p=0.024) measured at discharge predicted the 6-month risk for the combined endpoint re-hospitalization or death.

6.4.2 Manuscript and supplement (publication)

Journal of Cardiac Failure Vol. 27 No. 12 2021

Dynamics of Left Ventricular Myocardial Work in Patients Hospitalized for Acute Heart Failure

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ABSTRACT

Background: The left ventricular ejection fraction (LVEF) is the most commonly used measure describing pumping efficiency, but it is heavily dependent on loading conditions and therefore not well-suited to study pathophysiologic changes. The novel concept of echocardiography-derived myocardial work (MyW) overcomes this disadvantage as it is based on LV pressure−strain loops. We tracked the in-hospital changes of indices of MyW in patients admitted for acute heart failure (AHF) in relation to their recompensation status and explored the prognostic utility of MyW indices

Methods and Results: We studied 126 patients admitted for AHF (mean 73 ± 12 years, 37% female, 40% with a reduced LVEF [<40%]), providing pairs of echocardiograms obtained both on hospital admission and prior to discharge. The following MyW indices were derived: global constructive and wasted work (GCW, GWW), global work index (GWI), and global work efficiency. In patients with HF with reduced ejection fraction with decreasing *N*-terminal prohormone B-natriuretic peptide levels during hospitalization, the GCW and GWI improved significantly, whereas the GWW remained unchanged. In patients with HF with preserved ejection fraction, the GCW and GWI were unchanged; however, in patients with no decrease or eventual increase in *N*-terminal prohormone B-natriuretic peptide, we observed an increase in GWW. In all patients with AHF, higher values of GWW were associated with a higher risk of death or rehospitalization within 6 months after discharge (per 10-point increment hazard ratio 1.035, 95% confidence interval 1.005−1.065).

Conclusions: Our results suggest differential myocardial responses to decompensation and recompensation, depending on the HF phenotype in patients presenting with AHF. The GWW predicted the 6-month prognosis in these patients, regardless of LVEF. Future studies in larger cohorts need to confirm our results and identify determinants of short-term and longer term changes in MyW. (*J Cardiac Fail 2021;27:1393−1403*)

Key Words: Acute heart failure, myocardial work, recompensation, echocardiography.

Acute heart failure (AHF) is defined as "rapid onset or worsening of symptoms and/or signs of heart failure requiring urgent evaluation and treatment, typically leading to hospital admission."[1] These iterative episodes of decompensation in AHF are associated with a 12-month mortality risk of 17%,[2,3] yet treatment is solely symptom directed.[1] The lack of specific therapy might be, at least in parts, due to the limited mechanistic knowledge on myocardial function during decompensation and recompensation. In patients with HF, echocardiography provides critical information regarding diagnosis, underlying causes, hemodynamics, monitoring of treatment effects, and prognosis.[1,4,5] The left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) are common measures of LV function in AHF.[6] However, both measures are highly dependent on loading conditions, since higher afterload causes lower systolic deformation and results in lower LVEF and GLS despite presumably unchanged LV myocardial contractile strength.[7,8] The reference standard is invasive evaluation of the pressure−volume relationship, which is more sensitive[9] and allows a detailed assessment of the mode and severity of heart failure and current loading conditions. However, this approach is difficult to apply in serial investigations.

Recently, a novel echocardiographic method to noninvasively assess myocardial work (MyW) based on pressure−strain loops has been introduced,[10,11] which

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Manuscript received April 27, 2021; revised manuscript received June 30, 2021; revised manuscript accepted July 13, 2021.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2021.07.004

accounts for blood pressure and is thus considered less load-dependent. MyW represents a comprehensive measure of LV active myocardial function covering systolic contraction and early diastolic active relaxation and has been shown to mirror myocardial glucose consumption.[10] Therefore, assessment of MyW might hold advantages over LVEF measurements when studying disease entities characterized by fluctuations in loading conditions and might facilitate the understanding of pathophysiological processes. Previous work suggested that MyW is more sensitive[12] and might reflect the mechanistic properties of the heart with similar accuracy as the invasive hemodynamic assessment and is thus likely to provide incremental information on myocardial performance in patients with AHF beyond that of LVEF and GLS.[8,10,11,13,14]

The present study aimed to characterize in-hospital changes of LV function in patients with AHF with either reduced or preserved LVEF using echocardiographic MyW analysis, to evaluate associations of MyW parameters with established measures of LV myocardial function, determine changes in MyW in relation to changes in *N*-terminal pro-hormone B-natriuretic peptide (NT-proBNP) and assess their 6-month prognostic significance.

Methods

For the current secondary analysis, we considered all patients admitted for AHF between August 2014 and December 2017 to the University Hospital Würzburg, who consented to participate in the AHF Registry and had pairs of echocardiograms obtained on hospital admission and prior to discharge. The AHF Registry is a monocentric prospective follow-up study that comprehensively identifies and phenotypes consecutive patients admitted for AHF at the emergency department with the aim to capture the natural progression of this condition. AHF was diagnosed by the emergency room physician in charge based on signs, symptoms, and the results of clinically indicated diagnostic tests. Exclusion criteria were high output heart failure, cardiogenic shock, acute myocardial infarction, or active listing as a heart transplant candidate. Patients were treated according to current guidelines (best clinical practice), and the time of discharge was determined based on the treating physician's discretion. Survival status and rehospitalizations (admission to the hospital) were assessed after 6 months either during an outpatient visit or by telephone interview, or based on information retrieved from the general practitioner, relatives, or registration authorities. The study complied with the Declaration of Helsinki and was approved by the local Ethics Committee. Each patient provided written informed consent. Based on the last in-hospital LVEF assessment, patients were stratified according to current guidelines[1] into 3 categories: HF with reduced ejection fraction (HFrEF, LVEF<40%), HF with midrange ejection fraction (HFmrEF; LVEF 40%−49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%). Laboratory measurements, including an NT-proBNP assay, were carried out at the Central Laboratory of the University Hospital.

Echocardiography and Assessment of MyW

Echocardiography was performed using Vivid 7 and/or Vivid E9 (GE Healthcare, Horten, Norway). Images were obtained and measurements were performed according to the latest guidelines.[15] The LVEF was determined using Simpson's biplane method. In patients not in sinus rhythm, representative cardiac cycles of similar length in all 3 apical views were selected, thus facilitating analysis of LV strain and MyW. If no suitable cycles could be selected, the MyW analysis was omitted. Early diastolic myocardial relaxation velocity (e′) was assessed using tissue and pulsed-wave Doppler imaging close to the septal and/or lateral mitral annulus. For MyW analysis, a previously generated empiric normalized reference curve for LV pressure is used.[10] This reference curve is adjusted by aligning valvular times as assessed by echocardiography and secondly by including blood pressure measurements. Aortic and mitral valve closure and opening times were assessed by continuous-wave Doppler through the aortic valve and pulsed-wave Doppler on the mitral valve inflow. However, because changes in the heart rate during examination might affect the loop area, these time points were visually verified in the apical 3-chamber view and manually adjusted where necessary. LV apical 4-, 2-, and 3-chamber views were analyzed off-line using Automated Functional Imaging (EchoPAC, Version 202, GE) to determine global longitudinal peak systolic strain. Once the GLS was determined, the final adjustments for valve opening and/or closure times were done. Blood pressure values were entered into the EchoPAC system, using the measurement with the closest time distance to the echocardiography scan. Blood pressure was determined after several minutes of rest using a brachial cuff. Then, the following indices were derived: global constructive work (GCW [mmHg%]), i.e., work performed during shortening in systole and adding negative work during lengthening in isovolumic relaxation; global wasted work (GWW [mmHg%]), i.e., work performed during lengthening in systole or work performed during shortening against a closed aortic valve in iso-volumic relaxation; global work efficiency (GWE [%]), i.e., calculated as the sum of constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments (GCW/[GCW+ GWW]); and the global work index (GWI [mmHg%]), i.e., total work from mitral valve closure to the mitral valve opening. All indices were calculated as the mean of respective segmental values (18-segment model). A summary on how measures of MyW are derived has been published recently.[16−18] Accordingly, MyW measurements based on pressure−strain loops yield an estimate of cardiac work and should not be regarded as its precise equivalent. The best approximation of true cardiac work and, therefore, the current reference standard is facilitated via cardiac catheterization using conductance catheters. Stroke work is derived using pressure−volume loops, and it represents the amount of energy imparted by the LV into the blood. It is expressed in Joules or mmHg−mL,[19] and is the analogy

parameter to the global MyW index (representing the area within pressure−strain loop). However, stroke work does not provide information on a segmental basis. Further, myocardial external efficiency quantified by positron emission tomography yields information about oxidative metabolism, and should be differentiated from efficiency assessed through echo-derived MyW, which is calculated as the ratio between constructive work and the sum of wasted and constructive work. Of note, a study in amyloidosis patients showed a fair relationship between these 2 related concepts ($R^2 = 0.48$, $P < .0001$).[20]

The MyW analysis was performed by 1 person (FS) who was blinded to the outcomes. For assessment of observer variability, 25 randomly selected scans were read twice by the same observer, 1 week apart, for quantification of interobserver variability, the same scans were read by a second person (CM) blinded to the previous results. The interobserver and intraobserver variability regarding MyW parameters was favorably low (Supplemental Table S1).

Surrogate of Recompensation

Based on the assumption that successful recompensation after AHF is accompanied by a decrease in NT-proBNP, we used the change in NT-proBNP (Roche, Roche/Cobas reagents) levels during hospitalization as a surrogate for the efficiency of decongestive efforts (discharge to admission ratio [DAR] = NT-proBNP at discharge/NT-proBNP at admission). For the present analysis, we considered a decrease in NT-proBNP during the in-hospital stay (DAR of <1) as an indicator of recompensation, whereas a respective increase or unchanged value (DAR of ≥1) was considered as an indicator of unsuccessful recompensation.

Data Analysis

Continuous variables are reported as mean (standard deviation) or median (quartiles), and categorical variables as frequency (percent). MyW parameters were first analyzed for the shape of their distribution on admission and discharge using histogram and kernel density estimation. The band-width was selected by unbiased cross-validation. Correlations between log NT-proBNP, LVEF, and mean e' were analyzed using scatter plots and Pearsońs product-moment correlation coefficients with 95% confidence intervals. The strength of correlation was considered weak with a coefficient <0.3, moderate with a coefficient ≥0.3 and <0.6, and strong with a coefficient ≥0.6.

To quantify the direction and strength of association between the degree of NT-proBNP change reached during the in-hospital stay and the corresponding change in MyW, we used a generalized linear model with gamma regression that allows modeling skewed data. The DAR was analyzed for all MyW parameters as a dependent variable. The DAR can be interpreted as percent change. Gamma rates were estimated using a multiplicative-exponential model with terms for the LVEF category, NT-proBNP, and their interaction term. NT-proBNP was also included as DAR. Expected marginal mean gamma rates with 95% confidence intervals and P values were estimated. Cox proportional hazard regression was used to explore the usefulness utility of MyW indices to predict time to death or all-cause rehospitalization. Fixed adjustment for age and sex was used in prognostic analyses. A P value of less than .05 indicated an exploratory significant finding. All statistical analyses were performed using R 3.6 and SPSS 22.

Results

A total of 185 patients had 2 echocardiograms performed during their in-hospital stay. Of them, 59 were excluded due to suboptimal image quality or due to required views missing or recorded with too different heart rate. We included 126 patients in the present analysis: mean age 73 ± 12 years, 46 women (37%). Of those, 21 (17%) had de novo HF, and 75 (60%) patients were in New York Heart Association functional class IV on admission (Table 1). Echocardiography was performed within a median of 43 hours (quartiles 19, 69) after admission and within 72 hours before discharge. Patients were hospitalized for a median of 12 days (quartiles 8, 16). The median interecho time was 9 days (quartiles 5, 12). At discharge, 51 patients (40.5%) had an LVEF of less than 40%, 8 (6.3%) had an LVEF of 40%−49%, and 67 (53.2%) had an LVEF of 50% or greater. During their hospital stay, the median weight loss in these patients was 3 kg (quartiles 1, 7), and the median change in NT-proBNP was −1815 pg/mL (quartiles −5173, −366). In a sensitivity analysis, we found no significant difference in baseline characteristics between the patients with and without serial echocardiograms (Supplemental Table S2).

Owing to their low number ($n = 8$) and because this intermediate group might yield inconclusive results regarding MyW analyses, we excluded patients with HF with mid-range ejection fraction from the comparative analyses, thus focussing on the comparison of patients with HFrEF vs HFpEF. Absolute NT-proBNP levels both at admission and discharge were higher in patients with HFrEF compared with HFpEF, but the relative change was similar (Table 1): the median DAR for NT-proBNP was 0.53 (quartiles 0.33, 0.90) in patients with HFrEF, and 0.58 (quartiles 0.29, 0.75) in patients with HFpEF, respectively. Patients with HFpEF, when compared with patients with HFrEF, were more often female, older, had lower NT-proBNP levels, and higher systolic blood pressure on admission and at discharge, respectively Further, patients with HFrEF presented with a higher internal diameter and LV volumes and lower GLS (Table 1). There were no major shifts between LVEF categories in most of the patients from admission to discharge (Supplementary Table S3). Further, the majority of patients received enforced diuretic therapy, complemented by beta-blockers and angiotensin-converting enzyme inhibitors (Table 1). The baseline MyW characteristics of the study population are described in Table 2. GLS as well as absolute values of MyW parameters such as GCW, GWI, and

Table 1. Baseline characteristics according to LVEF category

Characteristics	All Patients ($n = 126$)		LVEF <40% ($n = 51$)		LVEF ≥50% ($n = 67$)	
	Admission	Discharge	Admission	Discharge	Admission	Discharge
Age (years)	73 (12)	-	66 (14)	-	78 (8)	-
Female	46 (37)	-	14 (27)	-	29 (43)	-
De novo heart failure	21 (17)	-	9 (18)	-	12 (18)	-
Chronic heart failure	105 (83)	-	42 (82)	-	55 (82)	-
Systolic BP (mmHg)	125 (19)	123 (19)	120 (19)	117 (19)	130 (19)	128 (18)
Diastolic BP (mmHg)	69 (14)	69 (13)	73 (16)	70 (15)	67 (13)	68 (12)
Body weight (kg)	84 (18)	80 (17)	85 (18)	81 (16)	83 (18)	78 (17)
LVEF (%)	44 (18)	48 (17)	25 (7)	30 (5)	59 (7)	62 (7)
NYHA functional class III	44 (35)	52 (41)	18 (35)	22 (43)	24 (36)	27 (40)
NYHA functional class IV	75 (60)	5 (4)	29 (57)	2 (4)	40 (60)	3 (4)
NT-proBNP (pg/mL)	5717 (2262, 10,522)	2345 (945, 5278)	6386 (4150, 12,919)	3046 (1659, 6799)	4924 (1331, 8783)	1749 (637, 4895)
eGFR (mL/min)	49 (22)	48 (21)	51 (20)	51 (23)	47 (23)	45 (20)
History of hypertension	101 (80)	-	34 (67)	-	59 (88)	-
Diabetes mellitus	51 (41)	-	18 (35)	-	31 (46)	-
Nonsinus rhythm	58 (46)	.	25 (49)	-	28 (42)	-
Past myocardial infarction	32 (25)	-	15 (29)	-	13 (20)	-
LVEDV (mL)	98 (73, 142)	93 (75, 146)	148 (119, 183)	152 (115, 200)	80 (64, 99)	79 (60, 92)
LVESV (mL)	49 (31, 102)	43 (28, 94)	115 (85, 148)	107 (75, 145)	32 (26. 43)	29 (22, 38)
Stroke volume (mL)	43 (17)	47 (17)	37 (13)	45 (14)	48 (19)	50 (18)
MCF	23 (15)	25 (11)	16 (6)	20 (6)	29 (19)	30 (12)
IVSd (mm)	10 (2)	10 (2)	9 (2)	10 (2)	11 (2)	11 (2)
LVPWd (mm)	10 (2)	10 (2)	10 (2)	10 (2)	10 (1)	10 (1)
LVEDd (mm)	54 (10)	54 (10)	62 (9)	62 (8)	49 (7)	48 (7)
LVMi (g/m^2)	110 (92, 130)	109 (87, 132)	119 (102, 146)	121 (105, 142)	100 (77, 119)	100 (776, 120)
E-wave (m/s)	1.0 (0.8, 1.2)	1.0 (0.7, 1.2)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)	1.1 (0.9, 1.3)	1.1 (0.8, 1.3)
A-wave (m/s)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)	0.4 (0.3, 0.7)	0.4 (0.3, 0.7)	0.7 (0.5, 0.9)	0.8 (0.5, 1.1)
e' (m/s)	0.06 (0.04, 0.08)	0.06 (0.05, 0.08)	0.05 (0.04, 0.06)	0.05 (0.05, 0.06)	0.07 (0.06, 0.9)	0.08 (0.06, 0.09)
E/e'	16 (12, 20)	15 (11, 21)	17 (13, 30)	18 (11, 23)	15 (12, 20)	14 (11, 20)
TR maximal velocity	3.1 (0.6)	3.0 (0.5)	3.0 (0.6)	2.9 (0.5)	3.1 (0.6)	3.0 (0.5)
Medication, *n* (%)						
Diuretics	123 (98)	119 (94)	49 (96)	49 (96)	66 (99)	62 (93)
Beta-blocker	99 (79)	103 (82)	44 (86)	48 (94)	48 (72)	48 (72)
ACEi/ARB	71 (56)	82 (65)	28 (55)	34 (67)	39 (58)	42 (63)
Calcium channel blocker	41 (33)	33 (26)	8 (16)	5 (10)	32 (48)	28 (42)
Glycosides	39 (31)	34 (27)	20 (39)	15 (29)	17 (25)	17 (25)

Data are n (%), mean (SD), or median (quartiles), as appropriate.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor type 1 blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate according to the CKD-EPI formula; HbA1c, glycosylated hemoglobin; IVSd, interventricular septum diameter; LVEDd, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index; LVPWd, left ventricular posterior wall diameter; MCF, myocardial contraction fraction; NYHA, New York Heart Association; TR, tricuspidal regurgitation.

Eight patients in the heart failure with midrange ejection fraction group are not shown here.

GWE, were significantly lower in patients with HFrEF when compared with patients with HFpEF. GWW was the only parameter not differing between both patient groups (Table 2).

GWI, GCW, and GWE were correlated negatively with NT-proBNP and positively with LVEF and e'. By contrast, GWW was not correlated with any of these parameters (Table 3). From admission to discharge, there was an improvement in GLS in all patients with AHF and an improvement in GCW, GWI, and GWE in patients with an LVEF <40%. Sixteen patients showed no in-hospital decrease in NT-proBNP. In the whole subgroup of patients with an LVEF ≥50%, all indices of MyW remained unchanged during the hospitalization (Table 2). However, when respective changes were inspected dependent on the alteration of NT-proBNP, important differences emerged (Fig. 1 and Supplemental Table S4). The GCW improved slightly in patients exhibiting a reduction in NT-proBNP during hospitalization, whereas patients with increasing levels of NT-proBNP exhibited an increase in GWW. With in-hospital decrease in NT-proBNP levels, we found a significant increase in GWE in patients with HFrEF, but not in patients with HFpEF (Figure 1). An illustrative example of how MyW pressure−strain loops derived on admission and prior to discharge may be typically altered according to the HF phenotype is given in Fig. 2.

During 6 months of follow-up, 18 patients (14%) died and 72 patients (57%) were rehospitalized at least once, resulting in an overall rate of the composite end point death or first hospitalization of 90 events. To better magnify the association of GWW with the outcome, we expressed GWW by 10 mmHg% increments. In Cox proportional hazards regression adjusted for age and sex, GWE (hazard ratio 0.967, 95%CI 0.939−0.996, $P = .024$) and GWW (HR 1.035, 95%CI 1.005−1.065; $P = .020$) and measured at discharge predicted the 6-month risk for the combined end

Table 2. MyW Indices on Admission and Discharge by LVEF Category*

MyW Indices	All Patients ($N = 126$)	LVEF <40% ($n = 51$)	LVEF ≥50% ($n = 67$)
GLS (%)			
Admission	12.7 (6.9, 17.1)	6.5 (5, 7.9)	16.6 (14.3, 19.6)
Discharge	14.2 (8.7, 18.3)	8.5 (6.5, 10.4)	18.1 (16.2, 21.0)
Change†	1.4 (0.4, 3.5)	1.5 (0.5, 3.5)	1.4 (0.5, 3.1)
GCW (mmHg%)			
Admission	1401 (778, 2087)	752 (525, 1012)	2012 (1614, 2441)
Discharge	1627 (926, 2243)	915 (714, 1144)	2229 (1787, 2502)
Change†	166 (−36, 399)	172 (2, 343)	162 (−114, 466)
GWW (mmHg%)			
Admission	126 (77, 200)	127 (90, 204)	118 (62, 190)
Discharge	111 (69, 170)	97 (74, 210)	111 (63, 155)
Change†	−18 (−71, 25)	-20 (−70, 20)	−17 (−89, 32)
GWI (mmHg%)			
Admission	1161 (643, 1863)	580 (443, 854)	1815 (1443, 2173)
Discharge	1381 (830, 2002)	789 (590, 977)	1960 (1585, 2296)
Change†	134 (−43, 368)	203 (19, 333)	140 (−106, 458)
GWE (%)			
Admission	88 (80, 94)	80 (74, 86)	92 (89, 96)
Discharge	91 (86, 94)	86 (79, 91)	94 (91, 96)
Change†	2.0 (0.0, 6.0)	4.0 (0.0, 9.0)	1 (−1.0, 5)

Data are median (quartiles).
*LVEF value for categorization derived prior to discharge.
†Change is defined as discharge minus admission value. GCW, global constructive work; GLS, global longitudinal strain; GWI, global work index; GWE, global work efficiency; GWW, global wasted work; MyW, myocardial work. Other abbreviations as in Table 1.

Table 3. Correlation of Myocardial Work Indices With (Bio)-Markers of Left Ventricular Function

Myocardial Work Indices	NT-proBNP* ($n = 108$)	LVEF (%) ($n = 126$)	E' wave ($n = 118$)
GLS (%)			
Admission	−0.41 (−0.55, −0.24, $P < .001$)	0.87 (0.83, 0.91, $P < .001$)	0.47 (0.03, 0.60, $P < .001$)
Discharge	− 0.33 (−0.48, −0.16, $P < .001$)	0.89 (0.85, 0.92, $P < .001$)	0.42 (0.26, 0.55, $P < .001$)
GCW (mmHg%)			
Admission	−0.39 (−0.54, −0.22, $P < .001$)	0.82 (0.76, 0.87, $P < .001$)	0.37 (0.20, 0.52, $P < .001$)
Discharge	−0.36 (−0.50, −0.18, $P < .001$)	0.86 (0.81, 0.90, $P < .001$)	0.36 (0.18, 0.50, $P < .001$)
GWW (mmHg%)			
Admission	0.06 (−0.12, 0.25, $P = .51$)	−0.14 (−0.31, −0.03, $P = .11$)	−0.11 (−0.29, 0.06, $P = .19$)
Discharge	0.06 (−0.12, 0.24, $P = .51$)	−0.15 (−0.32, 0.01, $P = .07$)	−0.17 (−0.34, 0.01, $P = .053$)
GWI (mmHg%)			
Admission	−0.37 (−0.52, −0.20, $P < .001$)	0.83 (0.76, 0.88, $P < .001$)	0.37 (0.20, 0.52, $P < .001$)
Discharge	−0.35 (−0.50, −0.18, $P < .001$)	0.86 (0.81, 0.90, $P < .001$)	0.35 (0.20, 0.51, $P < .001$)
GWE (%)			
Admission	−0.21 (−0.38, −0.02, $P = .02$)	0.64 (0.53, 0.73, $P < .001$)	0.33 (0.15, 0.48, $P < .001$)
Discharge	−0.22 (−0.39, −0.04, $P = .01$)	0.62 (0.50, 0.67, $P < .001$)	0.28 (0.10, 0.43, $P = .002$)

Data are Pearson's product-moment correlation coefficients with 95% confidence interval and P values.
*Log transformed.
Correlations are considered weak if <0.3, moderate if between 0.3 and <0.6, and strong if ≥0.6. NT-proBNP, amino-terminal prohormone of brain natriuretic peptide. Other abbreviations as in Tables 1 and 2.

point of rehospitalization or death. Regarding GWW, further adjustment for NT-proBNP or LVEF did not materially alter the assocation (Supplemental Table S5).

Discussion

In the present study, we quantified the myocardial response to decongestive treatment during hospitalization for AHF using noninvasively derived indices of MyW. We report 4 major findings. First, in the whole cohort, GCW, GWI, and GWE correlated with parameters of HF severity, LVEF, and NT-proBNP, whereas GWW did not show such an association. Second, GCW, GWI, and GWE improved with an in-hospital decrease of NT-proBNP levels in patients with HFrEF, but not in patients with HFpEF. Third, the GWW showed no in-hospital change in patients with HFrEF, but was an indicator of nonresponse in HFpEF. Fourth, of all the MyW parameters, only the GWW predicted the risk of death or rehospitalization within the first 6 months after discharge in all patients with AHF, regardless of LVEF.

Echo-derived MyW is still refined to the research setting, where it could become valuable in exploring the mechanisms of altered LV performance against the background of various stressors and disease entities. This report is the first to apply noninvasive MyW analysis to patients with AHF and to provide detailed insights into the in-hospital changes of MyW parameters corresponding to changes in NT-

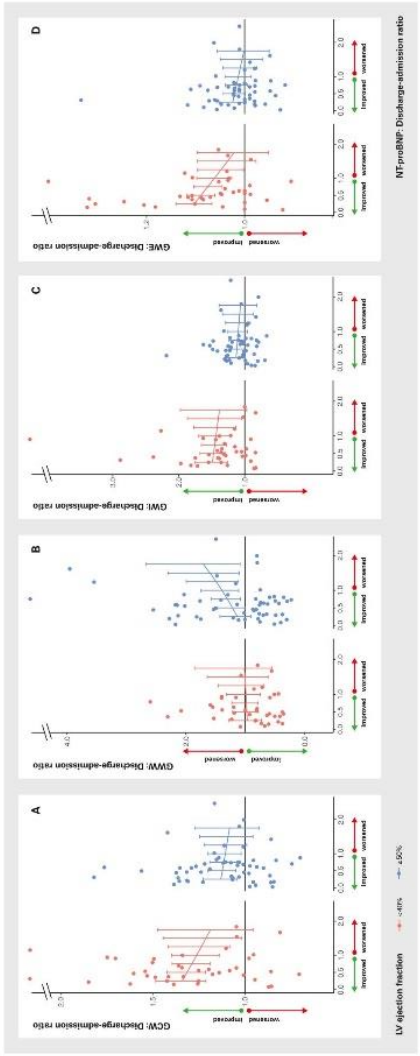

Fig. 1. Association between in-hospital changes in natriuretic peptide level and changes in myocardial work (MyW) indices. (A) Global constructive work (GCW). (B) Global wasted work (GWW). (C) Global work index (GWI). (D) Global work efficiency (GWE). *x*-Axis: N-terminal pro-hormone B Natriuretic Peptide (NT-proBNP). Discharge to admission ratio (DAR). *y*-Axis: respective MyW domain DAR. In-hospital changes are operationalized as the DAR. The association between DAR of NT-proBNP and DAR of MyW indices according to the left ventricular ejection fraction (LVEF) category is shown in scatter plots. Expected marginal mean gamma rates with 95% confidence intervals were derived from gamma regression adjusted for the LVEF category, NT-proBNP, and their interaction term (for details, see Methods). On the *x*-axis, if NT-proBNP on admission is 4000 pg/mL and decreases to 2000 pg/mL prior to discharge (i.e., after decongestive treatment), the DAR equals 0.5. Hence, an improvement is expressed as a DAR <1, a worsening as a DAR >1. Please note that, on the *y*-axis, worsening and improvement is different for GWW vs the other 3 MyW indices.

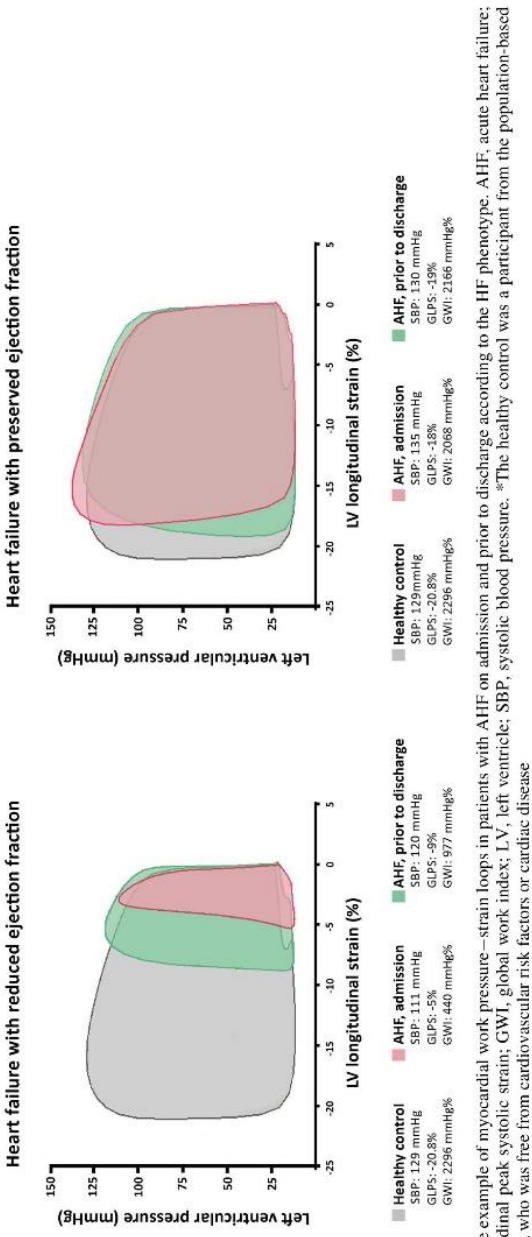

Fig. 2. An illustrative example of myocardial work pressure–strain loops in patients with AHF on admission and prior to discharge according to the HF phenotype. AHF, acute heart failure; GLPS, global longitudinal peak systolic strain; GWI, global work index; LV, left ventricle; SBP, systolic blood pressure. *The healthy control was a participant from the population-based STAAB cohort study, who was free from cardiovascular risk factors or cardiac disease

proBNP. The decrease in natriuretic peptide levels is considered a reasonable marker of treatment response to HF-related therapy that correlates well with clinical and objective markers of decongestion and may serve as a surrogate of recompensation in either HF phenotype.[21,22] Moreover, NT-proBNP is a robust indicator of hemodynamic stress,[23] and plays an essential role in the diagnosis, management, and prognosis of patients with AHF.[22,24,25]

As the sampling strategy aimed at including consecutive patients presenting with AHF regardless of etiology and severity, the study sample covered the complete spectrum of patients hospitalized with moderate to severe AHF. The analysis had to be restricted to patients undergoing echocardiography twice in the desired time windows and having sufficient image quality. In the overall cohort, patients benefited from recompensation strategies during hospitalization as indicated by a median weight loss from admission to discharge of 3 kg and a concomitant marked decrease in NT-proBNP levels. Further, we found that patients with HFpEF also exhibited mild systolic dysfunction as assessed by strain analysis on admission, which improved during hospitalization.

We observed marked differences in MyW indices on admission and prior to discharge between the 2 HF groups. These differences might be influenced by differential ventricular−vascular coupling, which is altered in HFrEF, but usually preserved in HFpEF. GCW is a measure of LV work contributing to ejection and is supposed to globally reflect LV mechanics and performance,[26] whereas the GWI expresses the total amount of work performed by the LV. Consistently, both the GCW and the GWI showed a strong correlation with LVEF, as previously reported in healthy volunteers,[17,26] and a moderate correlation with NT-proBNP levels. Because patients with HFrEF suffer from compromised myocardial performance, their overall workload as expressed by the GCW and GWI was decreased to a greater extent (on admission) compared with patients with HFpEF. Of note, compared with healthy participants, patients with HFpEF showed only a mildly decreased GCW.[17,27]

The GWW quantifies the amount of work performed by the myocardium but not contributing to LV ejection. In patients with AHF, the GWW was the only index of MyW not differing between patients with HFrEF and patients with HFpEF, although the values were much higher than observed in healthy individuals.[17,27] Accordingly, the GWW was not related to any of the parameters of HF severity. A higher GWW prior to discharge and consecutively lower GWE before discharge provided prognostic information regarding the 6-month risk of rehospitalization or death in models adjusted for age and sex. In particular, GWW retained its prognostic utility after extended adjustments (supplemental, Table S5), which is compatible with an incremental prognostic utility of GWW over and above the conventional markers of LV function and congestion.

The GWE, which is calculated from segmental constructive and wasted work values, is an estimate of cardiac efficiency and was weakly correlated with NT-proBNP levels and strongly with LVEF. The current knowledge on the impact of myocardial efficiency beyond the individual measurements GCW and of GWW in cardiac disease and its prognostic implications are scarce.[28] A recent study showed that different cardiac pathologies associate with different levels of compromised MyW efficiency.[29] Our results are in line with this finding; we observed a marked difference in GWE in both HF groups, with values that were much lower than expected in nondiseased subjects.[17,27] Thus, MyW might add information in the diagnostic pathway complementary to the LVEF, as the latter is not immediately responsive to recompensation. However, the clinical utility of MyW needs to be evaluated in future studies. MyW using pressure−strain loops has already been investigated in patients with heart failure,[30] mainly to identify positive cardiac resynchronization responders,[31] and in patients with hypertrophic cardiomyopathy.[32] Up to now, indices of MyW have been reported in small samples of patients with chronic HFrEF,[29,33,34] yet information on in-hospital changes following acute cardiac decompensation remains scarce. An analysis of the MyW might offer new insights into the myocardial response to the recompensation process, including possible differences between HFrEF and HFpEF. The bimodal distribution of the LVEF among patients with HF and the associated patient characteristics suggests a distinct pathophysiology in the 2 types of HF.[35,36] Previous studies found no differences in clinical signs and echocardiography-derived indices of peripheral and cardiac congestion (inferior vena cava diameter, systolic pulmonary artery pressure, left and right atrial area, and E/e′) between patients with HFrEF and patients with HFpEF, despite higher levels of natriuretic peptides in patients with HFrEF.[37] Recent studies reported improvement in the LVEF during hospitalization in patients with HFpEF as well,[38,39] and clinical and hemodynamic markers of congestion were found to uniformly improve during hospitalization both in patients with HFrEF and patients with HFpEF,[40] despite no or only minimal alteration of cardiac chamber dimensions.[39] In line with these observations, both the LVEF and GLS improved during hospitalization. Extending these concepts, the less load-dependent MyW indices revealed a differential response to Decompensation and recompensation in patients with HFrEF and patients with HFpEF. We found an improvement in the GCW, GWI, and GWE in the total sample of patients with HFrEF, which was associated with a decrease in NT-proBNP, wheras the GWW remained unchanged (Fig. 1). In contrast, in the total sample of patients with HFpEF, there was no significant change in the GCW, GWI, or GWE. However, in the subgroup with no decrease or an eventual increase in NT-proBNP levels, we observed an increase in the GWW (Fig. 1). Changes associated with recompensation in HFpEF might be revealed only during longer term follow-up. However, this finding might also indicate that chronic deterioration and/or acute decompensation in HFpEF is not solely related to impairment in cardiac function and should trigger further research regarding extracardiac causes and comorbidities.

Limitations

We acknowledge the relatively small sample size resulting from the necessity to restrict analyses to patients providing pairs of echocardiograms with sufficient image quality. Hence, our findings should be considered hypothesis generating and await confirmation in future studies. Further, due to logistic reasons in an emergency setting, the median time from admission to the first comprehensively documented echocardiogram was more than 24 hours. Future studies in larger cohorts are needed to confirm our results and to identify determinants of short-term and longer term changes in MyW. There is no generally accepted reference standard describing the level of recompensation after AHF. However, the change in NT-proBNP levels is an accepted surrogate of response to decongestive treatment, although it may depend on additional factors that we could not fully account for in our dataset. This includes changes in renal function, although mean changes from admission to discharge were minor per subgroup. Diuresis and subsequent loss of body weight are typically higher in decompensated patients with HFrEF compared with HFpEF. Further, using a noninvasive estimated central blood pressure might improve the precision of MyW calculation. Finally, MyW is not a direct measurement, rather a derived estimate of cardiac work and efficiency.[10]

Conclusions

To the best of our knowledge, this study is the first to evaluate indices of MyW in patients with AHF across the total spectrum of LVEF, both in the acute setting and after recompensation. In patients with HFrEF, decreasing NT-proBNP as a surrogate of successful recompensation was associated with an improvement in GCW and GWI and consecutively in GWE. In contrast, in patients with HFpEF, there was no significant change in GCW and GWI, but unsuccessful recompensation was associated with an increase in GWW. This finding suggests a differential myocardial response to decompensation and recompensation, depending on the HF phenotype. Further, wasted work as a surrogate of inappropriate LV energy consumption was increased in all patients with AHF. However, it did not correlate with other established surrogates of LV function, but predicted the risk of death or rehospitalization within 6 months after discharge. These results encourage the use of echocardiography-derived MyW in HF research to gradually better understand the differential mechanistic concepts determining treatment response and ultimately prognosis.

Declaration of Competing Interest

Floran Sahiti receives financial support from IZKF Würzburg (MD/PhD program scholarship). Caroline Morbach reports a research cooperation with the University of Würzburg and Tomtec Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany, speakers honorarium from Amgen and Tomtec, a travel grant from Orion Pharma and Alnylam, and participation in Advisory and Patient Eligibility Boards sponsored by AKCEA, Alnylam, Pfizer, and EBR Systems outside the submitted work. Carsten Henneges has nothing to disclose. Ulrich Stefenelli has nothing to disclose. Nina Scholz has nothing to disclose. Vladimir Cejka has nothing to disclose. Judith Albert has nothing to disclose. Peter U. Heuschmann reports grants from the German Ministry of Research and Education, European Union, Charité – Universitätsmedizin Berlin, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, Federal Joint Committee (G-BA) within the Innovationfond, University Hospital Heidelberg (within RASUNOA-prime; RASUNOA-prime is supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer-Ingelheim, Daiichi Sankyo), grants from Charité – Universitätsmedizin Berlin (within Mondafis; Mondafis is supported by an unrestricted research grant to the Charité from Bayer), from University Göttingen (within FIND-AF randomized; FIND-AF randomized is supported by an unrestricted research grant to the University Göttingen from Boehringer Ingelheim), outside the submitted work. Georg Ertl reports significant honoraria for trial leadership from Abbott, and Novartis; has been a consultant for Abbott, Boehringer Ingelheim, Novartis, ResMed, and Vifor (modest); and received significant grant support from Boehringer Ingelheim, Thermo Fisher, Siemens Healthineers, Vifor, and Federal Ministry of Education and Research. Stefan Frantz reports research grants from the German Ministry of Education and Research. He received honoraria from and was on advisory boards for AMGEN Europe, AstraZeneca, Bayer Vital, Boehringer Ingelheim, Bristol-Meyers Squibb GmbH, Daiichi Sankyo, MSD, Novartis, Pfizer, Sanofi, Servier, Vifor. Christiane Angermann reports honoraria for trial leadership from Abbott, Boehringer Ingelheim, and Novartis; has been a consultant for Abbott, Boehringer Ingelheim, Novartis, ResMed, Springer, and Vifor; and received significant grant support from Boehringer Ingelheim, Thermo Fisher, Siemens Healthineers, Vifor, Competence Network Heart Failure, Würzburg, and the Federal Ministry of Education and Research. Stefan Störk reports research grants from the German Ministry of Education and Research, European Union, University Hospital Würzburg; participation in Data Safety Monitoring or Event Adjudication in studies sponsored by Roche and Medtronic; participated on Advisory Boards for Novartis, Bayer, Boehringer Ingelheim, Thermo-Fisher, and Boston Scientific; principal investigator in trials (co-) sponsored by Boehringer Ingelheim, Novartis, and Bayer; and received speaker honoraria from Boehringer Ingelheim, Servier, Novartis, Astra-Zeneca, Pfizer, Bayer, and Thermo-Fisher, outside the submitted work.

Acknowledgments: The athors greatly appreciate the time of all participants with acute heart failure and their willingness to provide data to the study. We thank the entire study team, study nurses, technicians, data managers, and students for their efforts on the acute heart failure study.

Funding: Supported by an unrestricted grant from Boehringer Ingelheim and the German Ministry of Research and Education within the Comprehensive Heart Failure Center, Würzburg (BMBF 01EO1004 and 01EO1504).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2021.07.004.

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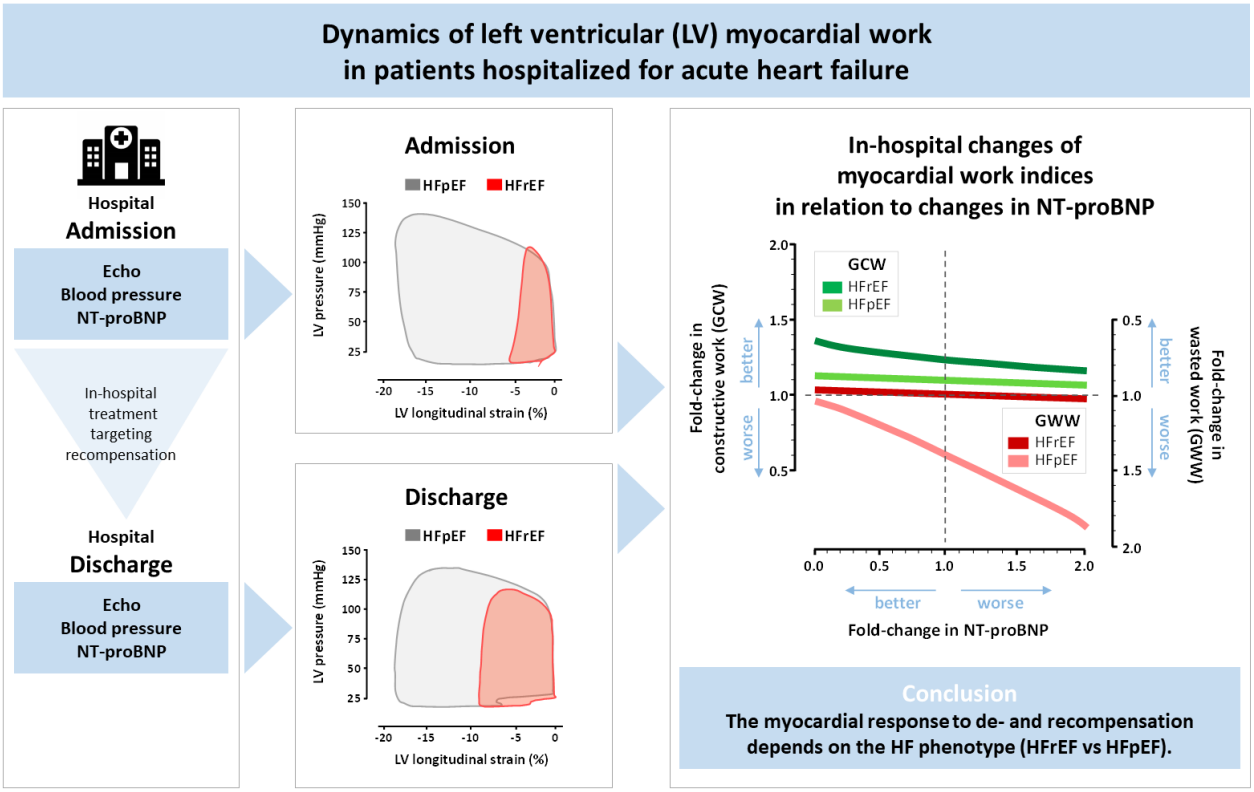

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SUPPLEMENTAL MATERIAL

Dynamics of left ventricular myocardial work in patients hospitalized for acute heart failure

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Supplemental Table S1. **Observer variability for parameters describing myocardial work.**

		Intra-observer variability		Inter-observer variability	
	Mean (SD)	Mean difference (SD)	95% CI of differences	Mean difference (SD)	95% CI of differences
GWI [mmHg%]	1749 (880)	26.2 (45.5)	7.5; 45.0	163 (164)	95; 231
GCW [mmHg%]	1973 (935)	20.0 (43.3)	2.1; 37.9	165 (179)	91; 239
GWW [mmHg%]	108 (54)	3.8 (16.3)	–2.9; 10.5	–21.7 (46.9)	–41.1; –2.33
GWE [%]	90.6 (8.4)	–0.16 (0.69)	–0.44; 0.12	1.5 (3.7)	–0.02; 3.06

To assess intra-observer variability, 25 random scans were read by one person twice (FS), more than a week apart. To assess inter-observer variability, the same scans were read by a second person (CM) blinded to the previous results. GCW = global constructive work, GWW = global wasted work, GWE = global work efficiency, GWI= global work index, SD = standard deviation, CI = confidence interval

Supplemental table S2. Sensitivity analysis comparing subjects with feasible vs non-feasible myocardial work (MyW) derivation

	Total sample (n=185)	MyW analysis possible (n=126)	MyW not possible (n=69)	P-value
Female sex	70 (38)	46 (37)	24 (35)	0.586
Age, years	73 (12)	73 (12)	74 (11)	0.651
Body weight, kg	81 (19)	80 (17)	883 (24)	0.077
Body mass index, kg/m^2	48 (16)	28 (5)	29 (8)	0.398
LV ejection fraction, %	44 (19)	49 (16)	46 (16)	0.268
NT-proBNP, pg/ml	2327	2345	2274	0.959
	(1000, 5159)	(944, 5278)	(1073, 4080)	
LDL cholesterol, mg/dl	96 (39)	97 (39)	93 (399	0.528
HbA1c, %	6.4 (0.9)	6.4 (0.9)	6.5 (1.0)	0.700
eGFR, ml/min	47 (20)	49 (21)	45 (19)	0.363

Data are n (%) or mean (SD) or median (quartiles).
LV, left ventricular; LDL, low-density lipoprotein; HbA1c, glycosylated haemoglobin; eGFR, estimated glomerular filtration rate; Measures are analyzed at discharge.

Supplemental Table S3. **Change in left ventricular ejection fraction category during the in-hospital stay**

		Discharge		
	LVEF	**<40%**	**40-49%**	**≥50%**
Admission	**<40%**	49	---	1
	40-49%	2	7	1
	≥50%	---	1	65

Data are counts of AHF patients (n=126).

Supplemental Table S4: **Association between the discharge-to-admission ratio (DAR, with 95% confidence intervals) of NT-proBNP and DAR of myocardial work indices according to left ventricular ejection fraction category***

	Discharge-to admission ratio (DAR) of myocardial work parameter at DAR of NT-proBNP of …	LVEF <40% N=51	LVEF ≥50% N=67
GCW (mmHg%)	0.25	1.34 (1.21, 1.48)	1.13 (1.04, 1.23)
	0.50	1.31 (1.21, 1.42)	1.12 (1.05, 1.20)
	0.75	1.29 (1.19, 1.39)	1.11 (1.04, 1.19)
	1.00	1.26 (1.14, 1.40)	1.11 (1.02, 1.20)
	1.25	1.24 (1.08, 1.42)	1.10 (0.99, 1.22)
	1.50	1.21 (1.02, 1.44)	1.09 (0.96, 1.24)
	1.75	1.19 (0.96, 1.48)	1.08 (0.92, 1.27)
GWW (mmHg%)	0.25	0.97 (0.73, 1.28)	1.14 (0.90, 1.43)
	0.50	0.97 (0.78, 1.22)	1.22 (1.01, 1.47)
	0.75	0.98 (0.79, 1.23)	1.30 (1.08, 1.57)
	1.00	0.99 (0.74, 1.32)	1.39 (1.11, 1.75)
	1.25	1.00 (0.68, 1.46)	1.49 (1.11, 1.99)
	1.50	1.01 (0.62, 1.64)	1.60 (1.11, 2.30)
	1.75	1.01 (0.55, 1.86)	1.71 (1.09, 2.67)
GWI (mmHg%)	0.25	1.49 (1.26, 1.76)	1.13 (0.99, 1.29)
	0.50	1.47 (1.29, 1.68)	1.12 (1.00, 1.25)
	0.75	1.45 (1.28, 1.66)	1.11 (0.99, 1.24)
	1.00	1.44 (1.21, 1.70)	1.10 (0.96, 1.25)
	1.25	1.42 (1.13, 1.77)	1.09 (0.92, 1.29)
	1.50	1.40 (1.05, 1.87)	1.08 (0.87, 1.34)
	1.75	1.38 (0.97, 1.97)	1.07 (0.82, 1.39)
GWE (%)	0.25	1.10 (1.07, 1.14)	1.02 (1.00, 1.05)
	0.50	1.09 (1.06, 1.12)	1.02 (1.00, 1.04)
	0.75	1.08 (1.05, 1.10)	1.02 (0.99, 1.04)
	1.00	1.06 (1.03, 1.10)	1.01 (0.99, 1.04)
	1.25	1.05 (1.00, 1.10)	1.01 (0.98, 1.04)
	1.50	1.03 (0.98, 1.10)	1.01 (0.96, 1.05)
	1.75	1.02 (0.95, 1.10)	1.00 (0.95, 1.06)

*LVEF measured at discharge used for categorization.
The table provides the corresponding point estimates with 95% confidence intervals of the figure, derived from gamma regression adjusted for the LVEF category, NT-proBNP, and their interaction term.
DAR, discharge-to-admission ratio; LVEF, left ventricular ejection fraction; GCW, global constructive work; GWW, global wasted work; GWI, global work index; GWE, global work efficiency

Supplemental table S5. **Prognostic utility of Global Wasted Work (GWW) regarding 6-month risk for the combined end-point rehospitalization or death**

	p-value	Hazard Ratio	95% Confidence Interval
Age, per year	0.685	0.995	(0.973, 1.018)
Sex, male	0.168	1.447	(0.856, 2.446)
Discharge GWW, per 10 mmHg%	0.037	1.034	(1.002, 1.068)
Discharge LVEF (biplane), per %	0.569	0.994	(0.975, 1.014)
Discharge NT-proBNP per SD	0.151	1.143	(0.952, 1.371)

Prediction of the combined end-point rehospitalization or death using Cox regression adjusted for age, sex, global wasted work measured at, LVEF measured at discharge and NT-proBNP measured at discharge.
GWW, global wasted work; LVEF, left ventricular ejection fraction; SD, standard deviation, NT-proBNP (N-terminal prohormone of brain natriuretic peptide)

7 General Discussion

In the current doctoral thesis, I characterized and systematically investigated the application of a novel echocardiography-based approach, i.e., the non-invasive assessment of MyW.

We established age-adjusted normal reference values for MyW indices from healthy individuals of the general population and showed that derivation of MyW is a robust tool with favorable intra-and interobserver variability. We obtained in-depth, innovative insights into the relationship of MyW with CV risk factors and components of LV geometry, i.e., LV mass and LV volumes. Finally, we shed light onto the in-hospital dynamics of MyW indices in patients with AHF across the whole spectrum of LVEF.

Echocardiography-derived MyW is an invasively validated approach that allows to determine constructive and wasted left ventricular work from pressure-strain loops and to obtain serial measurements from larger groups of patients (96). Compared to other echocardiographic measures, MyW has two major advantages: 1) it is considered less dependent from loading conditions than LV ejection fraction (LVEF) and longitudinal strain, and 2) it covers the majority of energy-depleting LV function components, i.e., systolic contraction and early diastolic active relaxation. These properties render MyW a promising method for future applications in research and clinical practice.

In the following sections, the findings of the current PhD work are highlighted in the context of the published literature regarding 1) reference values of MyW indices 2) the relationship of myocardial function with CV risk factors, especially of hypertension, and potential pathophysiological insights in various CV diseases as well as the characterization of LV subclinical changes using MyW, and 3) the serial application of MyW in patients hospitalized for AHF.

7.1 Reference values

By integrating LV work during systole and active relaxation in early diastole, non-invasive MyW indices capture the majority of components comprising “active LV work”, i.e., requiring energy. For any given marker, reference values derived from healthy individuals serve as a mean to differentiate between normal (physiological) conditions and pathological ones. Thus,

studies regarding reference values are essential. At the time point when the research proposal was written and approved by the thesis committee, there was no study yet reporting on reference values of MyW. In the meantime, results from two smaller studies from adult populations were published (141, 142). Extending these reports from convenient samples, the main strength of a population-based sample like ours is that the distribution of (apparently) healthy individuals, those with certain risk profiles, and subjects with established disease, occurs in group sizes that ideally approximate “real-world” (i.e., given the sampling strategy was correct) and avoids sampling bias. Valid results and conclusions may be derived if the sample size is large enough and statistical analyses are applied correctly. STAAB was designed by a multidisciplinary team of experts, and the design was extensively reviewed by an international expert panel prior to funding (the methods have been published) (128).

The NORRE study (Normal Reference Ranges for Echocardiography) was a multi-centric study, comprising 22 collaborating centers, and was the first to publish reference values for MyW (141, 143). Regarding MyW analysis, NORRE evaluated 226 self-reported healthy volunteers of different ethnicities, 62% women, mean age 45 (13) years. Further, at the University Hospital Rennes, France, a convenient sample of 115 individuals, 32 women, mean age 36 (13) years, was studied with respect to MyW reference values (142). In contrast, in our population-based sample balanced for age and sex, 779 healthy individuals, 59% women, mean age 49 (10) years, were investigated (127). This comprises four to seven times more healthy individuals compared to other published studies (127). In contrast to the former studies, STAAB used a rigid methodological approach to yield representativeness, as studied subjects were derived from the general population, strictly stratified for age decade and sex (127). The larger sample size results in more precise point estimates and increases statistical power in analyses.

GWI and GCW values in our cohort were higher compared to the two other studies but were closer to ideal reference values calculated mathematically. This might be partially explained by a better characterization of the status “healthy”, where GLS values were mean -21.4 (-2.3) %, and systolic blood pressure values were mean 119 (19) mmHg. Further, in a normal healthy heart, LV segments are supposed to contract in a synchronous manner against a given blood pressure, and ideally, the work efficiency should be close to 100%. Thus, one would expect a healthy heart to work at optimal efficiency without losing work, as “work lost” is considered a burden for the LV. In our study sample, the median GWW was lower compared to the other

cohorts but not zero, suggesting that even in healthy individuals, a certain amount of cardiac work is “wasted”. However, this can be potentially explained by the presence of post-systolic shortening, which was present even in healthy participants (99, 144). In contrast, in patients with left bundle branch block (LBBB) and cardiomyopathies, there are segments that lengthen during systole or contract against a closed aortic valve, thereby grossly increasing the amount of wasted work. These observations highlight the importance of MyW as a sensitive marker detecting work being lost even in normally contracting ventricles (145). Of note, MyW reference values at young adolescents did not differ much from adults (146).

One advantage of this new method is that it is non-invasive. However, not every echocardiographic image is evaluable as a certain level of image quality is needed to trace the entire LV in all three apical views. In the STAAB cohort study, we found MyW analysis with high but not excellent feasibility (feasibility 78 to 80%). It takes an experienced reader approximately 2-3 minutes to fully read one MyW analysis off-line.

Our results extend the previously published data (127, 141, 142). MyW indices apart for GWI were shown to be independent of sex and body mass index, respectively. Similar to LVEF and GLS, MyW index was slightly higher in women compared to men. Owing to the geometry of the women's heart, women exhibit more favorable contractility. Prior to menopause, blood pressure is considerably lower (10) compared to the postmenopausal period when humoral changes pose women at similar risks of hypertension and myocardial infarction as men (147). Thus, MyW considering afterload might be a more reliable tool to assess LV performance in response to changes in hemodynamic/cardiometabolic conditions across the lifespan.

Our results showed a disparate association of MyW with advancing age. Levels of MyW indices were stable until the age of 45 years. Further, we identified a slight increment at the age of 45 for GCW and GWI with an upward shift to again stable values beyond this age. In contrast with advancing age, we observed a linear increase in GWW and a linear decrease in GWE, respectively. The increase in MyW indices and decrease in work efficiency with advancing age might be explained by ventricular-vascular aging and the increased prevalence of hypertension and other CV risk factors. These changes might potentially reflect progressive fibrosis and remodeling of cardiomyocytes as a physiological process of aging (69, 127).

Further, MyW indices were associated with parameters of systolic and diastolic function. However, these associations were weak (127). More specifically, MyW indices were associated

with LVEFand GLS but showed weak correlation with LVEF (Kendall's τ –0.12 to 0.18) and weak to moderate correlation for GLS (Kendall's τ –0.09 for GWW; +0.22 for GWE; +0.44 for GCW; +0.46 for GWI), suggesting that indices of MyW are likely to offer additional information beyond LVEF and GLS and to contribute to a more comprehensive assessment of LV performance.

Clinical implications

Based on the results of the current PhD thesis, we can recommend the use of decade-specific MyW values in order to differentiate healthy aging from accelerated aging fueled by risk factors. The novel echocardiographic MyW indices (apart from GWI) were independent from sex and provided incremental information on LV performance beyond LVEF and GLS.

7.2 Hypertension and Myocardial Work

The presence of the modifiable risk factors and comorbidities and the lack of proper and timely control lead to local and systemic changes in the body organs. In the beginning, these changes are considered an adaptive response. Further, non-modifiable risk factors such as age, sex, and genetic profile also play an important role in influencing the CV system (148). Hemodynamic and non-hemodynamic factors mainly affect the morphology and function of the cardiac chambers, especially the LV.

LV cardiac remodeling is defined as a spectrum of molecular, cellular, and interstitial alterations affecting all components of the heart, i.e., myocytes, vasculature, and extracellular matrix (149, 150). The clinical manifestation of these alterations are changes in cardiac morphology and function of the heart – usually after a cardiac trauma, e.g., in the context of myocardial infarction (149-151). On the other hand, progressive remodeling occurs mainly due to increased hemodynamic load, either induced by pressure as in hypertension or by other conditions, e.g., valvular disease (96, 134, 152). If left untreated, these conditions lead to systolic and diastolic dysfunction (153, 154). Thus, LV remodeling (i.e., hypertrophy and dilation) are the fundamental precursors of clinically overt HF (155, 156). These changes are associated with adverse cardiovascular events, although the exact mechanisms are still incompletely understood (156, 157). In this project (Manuscripts #2 and #3), we used different

approaches to characterize MyW and elucidate LV performance. Firstly, we evaluated the impact of individual CV risk factors on LV performance. Secondly, we approached from the structural side and analyzed the association of LV geometry (LV mass and dimensions) and its changes, i.e., remodeling, with LV performance. We were well aware that cardiac work is a result of the co-existence and interaction of both cardiac structure and function. However, all the parameters available to date, except for invasive measurements, have failed to provide a clear picture on the performance of the heart during states at risk.

Data from the sample included in the MyW analysis (i.e., n=1929 individuals from the first pre-planned interim analysis of population-based STAAB study) showed a high prevalence of modifiable CV risk factors. 77% of the individuals exhibited at least one CV risk factor, with a marked predominance of arterial hypertension, followed by smoking and obesity. Further, the majority of our study participants showed a normal LV geometry. This is in line with results from other population-based studies investigating the clinical relevance of LV geometry, including mainly hypertensive populations (150, 158). Individuals with a history of HF were not eligible for the STAAB cohort study. Further, individuals with significant valve disease or individuals not in sinus rhythm were excluded from the MyW analysis. These factors might also have contributed to the high prevalence of individuals with normal LV geometry.

We found that the presence of individual CV risk factors was associated with altered MyW indices. Hypertension showed the strongest association with impaired MyW and was the only CV risk factor associated with increased wasted work. Hypertension was associated with higher amounts of expended work overall (GWI), which was consistently stronger in women compared to men. The same applied for the physiology-based indices, i.e., constructive and wasted work, which were higher in hypertensive compared to healthy individuals (5). Our results are in line with reports from other recently published studies (115, 159). However, these studies showed a preserved GWE in the population with hypertension.

In contrast, we observed an adverse impact of CV risk factors and especially hypertension on MyW efficiency. This also applied to changes in LV geometry components, which, even though not as strong, were significantly associated with MyW alterations and lower cardiac work efficiency. These initially subtle alterations very well might turn long-term into a major pathophysiologic driver of hypertension-induced changes and ultimately symptomatic HF (5). Other CV risk factors than blood pressure were associated with a different but consistent MyW pattern, i.e., lower constructive and unchanged wasted work. This implies that CV risk factors

might weaken the heart and reduce the cardiomyocyte's contractility without increasing dyssynchrony and wasted work. The reasons for this are not obvious so far but might be based on subtle disturbances in the interplay of electrical excitation, pumping processes, and the function of the heart valves, as well as by promoting adverse remodeling and cardiovascular disease. (5, 96). The planned STAAB follow-up will shed light on long-term changes associated with CV risk factors.

In the following, we concentrated on the discussion on the most commonly observed CV risk factor, arterial hypertension, exhibiting a prevalence of 44%. Hypertension is a predominant CV risk factor and causes LV hypertrophy. American Guidelines on HF consider hypertension and LV hypertrophy as parameters defining HF precursor stages A and B, respectively, thereby emphasizing the progressive nature of the HF syndrome and the importance of HF prevention (20). There is growing evidence that the changes in LV geometry occur already at the early stages of hypertension and are also associated with slight impairments in LV function (154). Prevention of these structural changes or regression of LV hypertrophy was seen with blood pressure control either by employing lifestyle changes or antihypertensive treatment, leading to lower outcomes rates (160-163). With the rapid technological advancements and new echocardiographic methods, echocardiography remains the first-line imaging tool for the assessment of cardiac function in the hypertensive population (134, 164-166). The assessment of LV strain has been recommended as a routine parameter to assess LV remodeling and function in the hypertensive population (134, 166). However, both LVEF and GLS are considered load-dependent, thus not as well suited for tracking changes in LV function related to changes in loading conditions (114) and subsequently to understand the pathophysiology of LV remodeling related to hypertension.

Our findings revealed that all MyW indices apart from global work efficiency were significantly higher in individuals with hypertension compared to apparently healthy individuals. Further, hypertension also had the strongest impact on MyW, “draining the heart energetically” and wasting its work, i.e., the only risk factor with a major influence on GWW. In contrast, other CV risk factors had no impact on GWW but only decreased GCW and GWE. Importantly, this effect was independent of systolic blood pressure.

Thus, we suggest that different CV risk factors might follow different pathways of myocardial alteration. As mentioned earlier, other studies failed to demonstrate differences in GWW and GWE in patients with hypertension compared to controls (115, 159, 167). Further, Mansour

et al. found that peak GLS and SBP above 180 mmHg appeared to be independent predictors of abnormal GWW (168). However, these studies were limited in the selection process of defining healthy control groups and included small sample sizes, causing limited statistical power.

Previous studies, most of them using invasively derived indices of myocardial contractility as stroke work or end-systolic elastance (EES) or arterial elastance (EA), showed similar results, with higher values in hypertensive patients compared to patients with optimal blood pressure (169). This was also confirmed in our study using echo-derived measures, where we showed that patients with hypertension conducted significantly higher amounts of work (increased GWI and GCW) compared to healthy controls (5, 96). In normal subjects, when LV faces higher afterload to eject the blood, there is a compensatory response of the LV maintaining stroke volume and LVEF (170). LV function increases to higher energy levels that are necessary to maintain homeostasis and match the arterial afterload (115, 145, 167). A potential increase in afterload has been proven to decrease GLS, which often may lead to misinterpretation of the true contractile function (90, 91, 115). Higher GWI, which refers to the amount of work performed from the LV, was inversely associated with peak oxygen consumption and positively with functional capacity independently of LV structure and function in all hypertensive participants (115). On the other side, prolonged exposure to hypertension which is followed by adverse remodeling and increased LV stiffness was associated with reduced blood flow that may decrease of coronary flow reserve (171-174) and an altered cardiac reserve, which is unable to increase myocardial performance in situations of stress (174). This may partially explain why the hypertrophied segments with pronounced tissue fibrosis in cardiomyopathies are unable to increase cardiac work during acute changing loading conditions and typically result in lower values of MyW indices (114, 115, 145).

Hypertension was more present in altered patterns of LV geometry. We observed that even in patients with normal LV geometry, 41% of individuals presented with hypertension, which represents a significant amount of comorbidity, considering normal LV geometry. Compared to the individuals within normal LV geometry and without hypertension. The observation that hypertension closely interacts and correlates with muscle mass is well established, and several studies have found that patients with hypertension undergo cardiac changes (175, 176). We observed that a higher blood pressure throughout different categories was associated with higher LV mass and dimensions and, subsequently, alterations in the systolic performance of

the LV. This was observed even for subtle changes in LV mass and dimensions within normal current cut-off values of blood pressure and before end-organ damage, i.e., LV hypertrophy.

Previous studies reported similar findings suggesting that LV geometry change might occur before the onset of overt hypertension and/or progresses concurrently (156, 177-179), confirming the relationship between LV remodeling and blood pressure (176, 180-182). However, differences in conventional contractility indices between patients with optimal blood pressure and in the prehypertension stage were not significant (179). These subtle LV structural-functional changes may be detected with the help of new methods in echocardiography (87, 89, 96, 183). Compared to other studies, which found a significant increase in wasted work only in patients with SBP above 180 mmHg, we found a significant linear increase in wasted work and a trend towards a decrease in work efficiency even in pre-hypertension (SBP between 120-139 mmHg). The group of high normal blood pressure (130-139 mmHg) showed higher values of wasted work compared to healthy controls (96, 127). The American Guidelines (184) have set a lower limit of SBP ≥130 mmHg to define hypertension and advocate for stricter blood pressure control. In contrast, the European Guidelines refer to a systolic blood pressure value ≥140 mmHg (164, 166). Our results tend to support the American recommendations and emphasize the importance of early examination of LV mass/dimensions and blood pressure since early changes within formally normal LV geometry were already associated with alterations in LV performance. A more optimal and stricter control of blood pressure can potentially help to control and prevent changes in LV structure and performance.

Regarding alteration in cardiac structure, we defined three groups of individuals exhibiting abnormal LV geometry, which might be considered small. Yet, our main intention was not to statistically compare potential differences between these groups. Rather, the three pathological groups (see Figure 5) served as examples of the (well-acknowledged) disease paradigm (134), characterizing the gradual alteration of LV morphology over time given certain risk constellations (i.e., hypertension) (96). As expected, we found representative frequencies of these constellations in the cross-sectional STAAB sample. We then contrasted the myocardial function of these three pathological groups with the non-pathological group. When we characterized MyW, an innovative surrogate of LV performance, fairly large differences emerged between these four groups (see Manuscript #3, Figure 1). We observed

that across the entire spectrum of hypertrophy, MyW is gradually and specifically altered, providing additional information on LV performance.

Another major finding, however, related to the “normal group”. Still, within the range of normal LV mass and dimensions, individuals with hypertension already exhibited the same MyW pattern, even though less pronounced, that can be found in individuals with LV hypertrophy. We concluded that this pattern might constitute an early sign of myocardial alteration by hypertension, thus potentially aiding in risk stratification and primary prevention strategies. MyW might be considered a sensitive parameter of early myocardial alteration, and further studies are needed to assess the diagnostic and prognostic utility of this novel imaging tool as well as its potential role in the assessment of treatment response.

Clinical implications

Our studies showed that echo-derived MyW is a tool with high feasibility which provides incremental information regarding LV performance beyond LVEF and GLS in both the population at large and in selected samples of individuals with hypertension. Our results suggest an alteration in myocardial performance associated with hypertension which can be found already in hypertensive individuals with preserved LV geometry. Thus, MyW might become a valuable, sensitive imaging tool for preventive and therapeutic strategies.

7.3 Heart failure and Myocardial Work

HF is a progressive disorder frequently originating acutely from an index event damaging the heart muscle or long-term gradually from exposure to adverse factors, i.e., “risk factors” (41). Conceptually, HF is characterized by two disparate hemodynamic patterns occurring with a similar frequency associated with either volume overload (e.g., following myocardial infarction or advanced valvular insufficiency) or pressure overload (e.g., in undertreated chronic hypertension or advanced valvular stenosis). In either condition, the assessment of the LV function in patients with HF is paramount. The bi-modal distribution of LVEF among patients with HF and their related patient characteristics suggest distinct pathophysiology in the two types of HF (40, 185, 186).

In patients with a reduced LVEF (i.e., HFrEF), the LV contractile force during systole is compromised, usually aggravated by overexpression of biologically active molecules exerting deleterious effects on the heart and circulation (41, 187). In patients with HFpEF, relaxation in the diastolic phase is predominantly compromised, usually reflected by pathologically increased LV mass and myocardial and/or vascular stiffness (150, 188-190). Whereas systolic compromise is fairly easy to diagnose, quantification of diastolic impairment in patients with HFpEF remains a major challenge for both research and clinical routine. It adds to the complexity of the HFpEF syndrome that an additional alteration of LV longitudinal systolic function appears to play a complementary albeit significant role (26, 72). Currently, two algorithms are clinically used to establish a diagnosis of HFpEF (191, 192). If the respective score suggests an intermediate likelihood of HFpEF (“gray area”), stress echocardiography or stress right heart catheterization is required to make the final diagnosis (191, 192).

Technological developments in imaging tools, especially in strain imaging, have made it possible to better understand the intricate diverse aspects of systolic function. E.g., measures considering changes in afterload such as pressure-strain derived MyW offer more physiological information regarding LV function. The application of MyW has been refrained to research up to now, and its clinical utility is largely unexplored. MyW has been shown to be more sensitive than LVEF and GLS to detect significant coronary artery disease in patients with Non-ST-Elevation Myocardial Infarction (NSTEMI) (89) – even in patients with no regional wall motion abnormalities and a normal LVEF (111). This indicates that MyW might better reflect the mechanistic properties of the heart, thus advancing our understanding of the

pathophysiological processes accompanying cardiac disease (5). However, up to now, there are few studies investigating the utility of MyW in patients with chronic HF. These studies mainly focused on patients undergoing cardiac resynchronization therapy (CRT), trying to better identify patients responding to CRT treatment (108, 109, 193, 194). Importantly, studying and applying MyW revealed new features of myocardial function in HF (195). Aalen *et al.* showed how mechanical factors impact abnormal septal motion, i.e., the "septal flash", frequently observed in patients with HFrEF and left bundle branch block (91). Further, Chan *et al.* suggested that the estimation of MyW might allow a better understanding of the relationship between LV remodeling and wall stress considering loading conditions (115).

Knowledge on determinants and patterns of potential in-hospital changes of myocardial function in patients with AHF are scarce in general and absent with respect to MyW. In acute conditions like AHF, echocardiography represents the imaging method that is most easily and readily available and offers essential information to triage the patient. In the acute setting, both HF phenotypes (HFrEF and HFpEF) have similar clinical presentation (i.e., signs and symptoms) and trigger similar treatment strategies. A better understanding of the processes underlying both decompensation and recompensation is needed to advance a personalized treatment approach.

Recent studies reported that clinical and hemodynamic markers of congestion improve uniformly during hospitalization in both HFrEF and HFpEF (196, 197). Previous echocardiographic studies in AHF found no differences in echocardiography-derived indices of peripheral and cardiac congestion (inferior vena cava diameter, sPAP, left and right atrial area, E/e' ratio) between HFrEF and HFpEF (198). LVEF is the most commonly used parameter, which depends but does not adjust for loading conditions and is therefore not ideal to study pathophysiological processes. In a clinical condition like AHF, where loading conditions play a dominant role, MyW should offer advantages to better capture LV performance.

The presented work here is first to apply and analyze the novel MyW in patients hospitalized for AHF. We investigated the effects of recompensation on MyW by analysis of serial echocardiograms of AHF patients and estimated the changes in myocardial performance occurring during decongestion. Patients with acute decompensated HFrEF featured a decreased GLS and MyW index and strongly impaired work efficiency at admission. Further, during the in-hospital stay, we observed an increase in LVEF and GLS, as well as in GWI and GCW, as a measure of work contributing to ejection (127, 143). However, wasted work in these

patients was significantly increased and showed no significant change during the hospital stay. By contrast, patients with HFpEF (i.e., normal LVEF values) had slightly decreased GLS values, which improved during the in-hospital stay. Further, they showed slightly decreased GWI, GCW, and GWE at admission. However, similarly as in HFrEF, higher amounts of wasted work were observed and remained unchanged during hospitalization.

Our study sample covered a wide spectrum of patients with different forms of HF and sets of comorbidities. In AHF patients, the duration of hospitalization depends not only on the severity of HF but also on the responsiveness to diuretic therapy and the management of comorbidities or complications. Hence, the duration of hospitalization is only a limited surrogate of disease severity and recompensation stage. We assumed that the time-point of discharge from the hospital might serve as the “best possible recompensation” that can be achieved for an individual patient. For the “level of success” of recompensation, however, we chose NT-proBNP and its changes as a parameter of fluid management. Thus, we described the dynamics of in-hospital changes in MyW indices in AHF patients in relation to changes in NT-proBNP as a surrogate marker of decongestive efforts. NT-proBNP is one the most well-established markers of hemodynamic stress, congestion, and decongestion (29, 40, 136, 137, 139). We observed an immense alteration at admission and a remarkable change between admission in a decompensated status and discharge after a median of 12 days of hospitalization. On average, patients lost 3 kg of body weight, with no difference between HF phenotypes. Similarly, no differences were found regarding the change in NT-proBNP between the HF groups. However, 16 patients showed no in-hospital decrease in NT-proBNP (40).

With recompensation (as indicated by lowered NT-proBNP), we found an improvement in GCW, GWI, and GWE in HFrEF patients, while GWW remained unchanged. In contrast, in HFpEF patients, there was no significant change in global constructive work or work efficiency. However, unsuccessful recompensation (i.e., absence of a decrease in NT-proBNP from admission to discharge) was associated with an increase in GWW. These findings suggest a differential myocardial response to recompensation depending on the HF phenotype (40).

A similar pattern of improvement in MyW was found in patients with chronic HFrEF treated with sacubitril/valsartan (199, 200). These patients showed reverse remodeling and improvement in global constructive work and MyW efficiency during 1 year of follow-up. There, wasted work also showed no significant change even in patients with chronic HFrEF (199, 200). These studies included only patients with HFrEF and did not relate changes in MyW

to changes in NT-proBNP or any other measure of recompensation. However, we suggest that the pattern of recompensation in patients with acute HFrEF is similar to the one with chronic HFrEF by improving GCW, work contributing to LV ejection, as the main parameter responsive to therapy in patients with acute and chronic HFrEF.

On the other side, changes associated with recompensation in HFpEF might be revealed during longer-term follow-up and with a better classification of HFpEF according to the underlying etiology. Another reason might be that chronic deterioration and/or acute decompensation in HFpEF is not solely related to impairment in cardiac function and should trigger further research regarding extra-cardiac causes and comorbidities.

In patients with HFrEF, Hedwig *et al.* showed a strong correlation between GWI and NT-proBNP, peak oxygen consumption during cardiopulmonary exercise, and LVEF (201). GWI <500 mmHg% was a predictor of severely impaired LV function, inadequate cardiopulmonary exercise, and increased NT-proBNP levels, all of which are markers of poor prognosis (201). Further, Wang *et al.* investigated the utility of MyW in 508 chronic HFrEF patients (112). They showed that GWI was a better prognostic factor compared to LVEF and GLS regarding all-cause death and HF-related rehospitalization (112). In our study sample, GCW, GWI, and GWE correlated with parameters of HF severity, LVEF, and NT-proBNP, whereas GWW did not show such an association. Interestingly, as mentioned above, GWW showed no in-hospital change in patients with HFrEF but indicated non-response to recompensation efforts in HFpEF. Hence, GWW, quantifying the amount of work performed by the myocardium but not contributing to LV ejection, might carry additional information beyond LVEF and GLS in AHF patients.

Exploring the prognostic utility of MyW indices, we found that higher GWW prior to discharge and consecutively lower GWE prior to discharge predicted the 6-month risk of rehospitalization or death in models adjusted for age and sex. GWW retained its prognostic utility even after extended adjustment for markers like LVEF and NT-proBNP, compatible with an incremental prognostic utility of GWW beyond conventional markers of LV function and congestion. However, due to the limited sample size, our data should be considered hypothesis-generating. Nevertheless, they should encourage further research regarding the role of MyW in AHF to get better insights overall into the pathophysiology of the disease and to determine the prognostic utility of MyW.

Clinical implications

In patients hospitalized for AHF, components of MyW were unfavorably altered and showed a disparate response to recompensation depending on the type of HF (HFrEF vs. HFpEF). Further, GWW was unrelated to other measures of LV function but predicted the risk of death or rehospitalization within six months after discharge. Determination of MyW in larger AHF cohorts might further enhance the pathophysiological understanding of congestion and decongestion in patients with HFrEF and HFpEF. Further, GWW might evolve as a valuable parameter to estimate the patients´ prognosis.

7.4 Strengths and limitations

MyW integrates LV systolic and early diastolic longitudinal strain and blood pressure, thus comprehensively accounting for potential impairment in LV longitudinal contraction and cardiac conduction (96). As already acknowledged by the inventors of the method, echo-derived MyW represents regional and global cardiac work *estimates* and not a direct measure of cardiac work. However, this method has been invasively validated in animals and patients with different cardiac pathologies (87, 101, 102), yielding good agreement with invasive measurements. We applied the MyW method as already established and validated, using a commercially available program (GE EchoPAC, Version 202). Limitations of the method are that the LV radial curvature and wall thickness are not part of the derivation algorithm from pressure-strain loops (101). Further, it is important to note that the information obtained from non-invasive MyW should not be considered as the exact equivalent to investigations on pressure-volume loop recordings (87, 96, 202, 203). However, the comparison of wasted work between different hearts is considered a valid measure since it is a relative measure that compensates for limited information about local geometry and consecutive potential differences in wall stress (96, 101).

This indicates that another prospective validation of the method in different cardiac disease entities would be useful and enrich the current literature. When assessing individual patients, MyW indices should be carefully assessed at the same time together with other conventional bioassays of LV function and performance, preferably also including measures of energy-consumption as, e.g., nuclear-medicine approaches.

A major strength of our work is the well-defined study sample derived from the population-based STAAB cohort study, primarily investigating early phases of HF in the general population, as well as the well-characterized sample of AHF patients derived from the prospective AHF Registry Würzburg, which comprehensively phenotypes consecutive patients admitted for AHF in the Emergency Department of the University Hospital Würzburg. The STAAB cohort included a representative sample of the population of Würzburg (predominantly Caucasian), stratified for age decade and sex. Standardized operating procedures were used fostering a comprehensive characterization of the study sample, including a healthy sub-cohort of substantial size (127), allowing to identify the impact of CV risk factors and other determinants onto the development of symptomatic HF in the general population (129, 130, 204). On the other side, the AHF Registry offers a unique possibility to study the mechanisms contributing to de- and recompensation and potentially affecting the outcome. We made use of the only suitable imaging method, i.e., echocardiography, which is suitable in the critical situation of acute decompensation. Nevertheless, good image quality is necessary for correct pressure-strain analysis. Despite rigidly defined quality control processes, not all patients undergoing echocardiographic examination were suitable for MyW analysis (130). However, our findings showed that this method is feasible, can thus be used in large population cohorts (5), and might potentially serve as a screening tool. Further, a sensitivity analysis including healthy and diseased individuals showed encouraging results on the reproducibility of the measures employed (5, 40, 127).

In agreement with international recommendations (164), we used brachial cuff pressure measurements. Ideally, for this analysis, blood pressure should have been measured during the echocardiographic examination(96). The precision of MyW measurements may be improved by using central blood pressure, which was more closely related with LV mass compared to brachial systolic blood pressure (205). As the most prevalent and hemodynamically relevant risk factor, hypertension had a key impact on this analysis. At this point, a further limitation is the cross-sectional design of the STAAB study, which does not allow to inform on longitudinal alterations and causal relationships. However, the planned follow-up is expected to reveal causality and deeper insights into the dynamics of LV performance using MyW in the general population.

To the best of our knowledge, our study is the first to evaluate MyW indices in AHF patients across the full spectrum of LVEF, both in the acute setting and after recompensation. The data

present real-world data of a severe clinical condition, which often presents a clinical and logistical burden for clinicians and scientists. A limitation of the current study sample from the AHF registry is its modest sample size, especially when categorizing patients in different subgroups according to their HF phenotype. This was mostly affected by the (non)-presence of the second, pre-discharge echocardiography scan. Another limitation is the time to first echocardiography examination, which occurred after a median of 47 hours. Knowing that AHF is a dynamically fast-changing condition, ideally, the first echocardiogram should have been obtained within 24 hours of hospital admission. The majority of the patients (98%) received intensive diuretic therapy, i.e., furosemide and torasemide subsequently, followed by beta-blockers and angiotensin-converting enzyme inhibitors. Due to the heterogeneity in pharmacotherapy and the limited sample size, we omitted further analyses regarding individual drug classes or substances. Thus, we are aware that our current study is not powered to judge on this granularity as this was beyond the scope of the current work. Regarding prognosis, our findings should be considered hypothesis-generating and await confirmation in future studies

8 Conclusion

The projects of the current PhD thesis evidenced that the novel concept to quantify MyW non-invasively by echocardiographic measurements is a feasible tool that can easily be applied in large study populations and in diseased patients. In view with its favorable characteristics of low load-dependency and observer variability, MyW appears to be a robust non-invasive diagnostic tool. We established normal reference values for MyW indices from healthy individuals of the population-based STAAB cohort study, i.e., largest study sample published to date. MyW indices, apart from GWI, in a healthy population were independent of sex and body mass index. Further, MyW showed a disparate association with advancing age, emphasizing the use of decade-specific MyW values to differentiate healthy from CV risk factors induced accelerated aging.

The current work contributes to a better understanding of the impact of CV risk factors and the LV geometry on LV performance measured by MyW. CV risk factors selectively affected constructive and wasted active myocardial function as measured by MyW domains. Hypertension appeared to profoundly compromise MyW, in particular by increasing both constructive and wasted work. The left ventricle in hypertension seems to operate at a higher energy level, yet lower efficiency, i.e., draining its energy and wasting its work (5). Other CV risk factors, independent of blood pressure, showed a different but consistent pattern of lower constructive work and work efficiency without affecting wasted work (5).

Across the spectrum of LV geometry, we could show that any deviation from a normal LV geometric profile was associated with gradual alterations of MyW. More specifically, changes in LV mass and dimensions were associated with selective changes in individual MyW indices. Further, MyW appeared to be sensitive to early changes in LV mass and dimension, i.e., LV remodeling. The major new finding is that even individuals with normal LV geometry and present hypertension exhibited a MyW pattern that can also be found in LV hypertrophy. Thus, this pattern might serve as an early sign of myocardial damage in hypertensive heart disease and might aid in risk stratification and primary prevention.

Further, we were the first to apply MyW to patients admitted for AHF. Regardless of the HF phenotype (HFrEF vs. HFpEF), decompensation in AHF was associated with reduced GWE. In

addition to assessing the acute and recompensated phase, we described in detail the in-hospital changes in myocardial performance in patients with AHF during recompensation.

Another important finding was the different myocardial responses to de- and recompensation depending on HF phenotype. More specifically, in patients with HFrEF, decreasing NT-proBNP as a surrogate of successful recompensation was associated with an improvement in GCW and GWI and consecutively in GWE. In contrast, in HFpEF patients, there was no such change in GCW and GWI; however, unsuccessful recompensation signified by no change or even a potential increase in NT-proBNP was associated with an increase in GWW. Further, wasted work as a surrogate of inappropriate LV energy consumption was elevated in all patients with AHF. Although GWW did not correlate with any conventional marker, it predicted the risk of death or rehospitalization within six months after discharge.

The differentiation of GCW and GWW offers new insights and more sensitive measures to LV remodeling and the presence of CV risk factors, and it holds promise to improve our understanding of the pathophysiological process in different CV diseases. Our results encourage the further use of MyW in HF research and better understand the differential mechanistic concepts determining treatment response and ultimately prognosis, especially in the HFpEF population. Future studies on antihypertensive medications and sodium-glucose transport inhibitors (SGLT2), and MyW might offer new insights and knowledge into LV performance. Further research and controlled clinical studies are required to investigate whether MyW will prove a more sensitive tool than LVEF and GLS. We believe that our data are a valid and a good basis to inform future studies in healthy and diseased subjects.

9 References

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10 Appendix

10.1 Abbreviations

AHF - acute heart failure

CV - cardiovascular

CR - concentric remodeling

CH - concentric hypertrophy

EH - eccentric hypertrophy

GCW - global constructive work

GLS - global longitudinal strain

GWW - global wasted work

GWE - global work efficiency

GWI - global work index

HFpEF - heart failure with preserved ejection fraction

HFrEF - heart failure with reduced ejection fraction

LV - left ventricle/ventricular

LVEF - left ventricular ejection fraction

LVMi - left ventricular mass index

LVEDVi - left ventricular end-diastolic volume index

MyW - myocardial work

PSL - pressure-strain loop

STAAB - The Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression Cohort Study

10.2 Presentation of the authors` contribution to the manuscripts

Dissertation Based on Several Published Manuscripts

10.2.1 Statement of author contributions and legal second publication rights

Publication (complete reference): **Sahiti F**, Morbach C, Cejka V, Tiffe T, Wagner M, Eichner FA, Gelbrich G, Heuschmann PU*, Störk S*. Impact of cardiovascular risk factors on myocardial work-insights from the STAAB cohort study. J Hum Hypertens. 2021 Mar 2. doi: 10.1038/s41371-021-00509-4. Epub ahead of print. PMID: 33654241.
*equally contributed

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	FS	CM, STS	PUH, GG		
Data Collection	FS	CM, STS	PUH, GG	TT, VC	MW, FAE
Data Analysis and Interpretation	FS	CM, STS	PUH, GG	TT, VC	MW, FAE
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	FS (all sections)	CM (all sections, except the first draft)	STS, PUH (all sections, except the first draft)		

Explanations (if applicable):

Publication (complete reference): **Sahiti F,** Morbach C, Cejka V, Albert J, Eichner FA, Gelbrich G, Heuschmann PU*, Störk S*. Left Ventricular Remodeling and Myocardial Work: Results From the Population-Based STAAB Cohort Study. Front Cardiovasc Med. 2021 Jun 11;8:669335. doi: 10.3389/fcvm.2021.669335. PMID: 34179134; PMCID: PMC8232934.
*equally contributed

Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	FS	CM, STS	PUH, GG		
Data Collection	FS	CM, STS	PUH, GG	VC, JA, FAE	
Data Analysis and Interpretation	FS	CM, STS	PUH, GG	VC, JA, FAE	
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	FS (all sections)	CM (all sections, except the first draft)	STS, PUH (all sections, except the first draft)		

Explanations (if applicable):

Publication (complete reference): **Sahiti F**, Morbach C, Henneges C, Stefenelli U, Scholz N, Cejka V, Albert J, Heuschmann PU, Ertl G, Frantz S, Angermann CE, Störk S. Dynamics of Left Ventricular Myocardial Work in Patients Hospitalized for Acute Heart Failure. J Card Fail. 2021 Dec;27(12):1393-1403. doi: 10.1016/j.cardfail.2021.07.004. Epub 2021 Jul 29. PMID: 34332057.					
Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	FS	CM, STS			
Data Collection	FS	CM, STS	CEA, GE, SF	NSCH, JA, VC	PUH, CH, US
Data Analysis and Interpretation	FS	CM, STS	CEA, CH, GE	SF, NSCH, JA	VC, PUH, US
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	FS (all sections)	CM (all sections, except the first draft)	STS (all sections, except the first draft)		

Explanations (if applicable):

Publication (complete reference): Morbach C, **Sahiti F**, Tiffe T, Cejka V, Eichner FA, Gelbrich G, Heuschmann PU*, Störk S*; STAAB consortium. Myocardial work - correlation patterns and reference values from the population-based STAAB cohort study. PLoS One. 2020 Oct 8;15(10):e0239684. doi: 10.1371/journal.pone.0239684. PMID: 33031416; PMCID: PMC7544116. *equally contributed					
Participated in	**Author Initials,** Responsibility decreasing from left to right				
Study Design Methods Development	CM	FS	STS	PUH, GG	
Data Collection	CM	FS,STS	PUH, GG	TT, VC, FAE	
Data Analysis and Interpretation	CM	FS, STS	PUH, GG	TT, VC, FAE	
Manuscript Writing Writing of Introduction Writing of Materials & Methods Writing of Discussion Writing of First Draft	CM (all sections)	FS (all sections, except the first draft)	STS, PUH (all sections, except the first draft)		

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Primary Supervisor´s Name	Date	Place	Signature

10.2.2 Statement of author contributions to figures and tables in the manuscripts

Publication (complete reference): **Sahiti F**, Morbach C, Cejka V, Tiffe T, Wagner M, Eichner FA, Gelbrich G, Heuschmann PU*, Störk S*. Impact of cardiovascular risk factors on myocardial work-insights from the STAAB cohort study. J Hum Hypertens. 2021 Mar 2. doi: 10.1038/s41371-021-00509-4. Epub ahead of print. PMID: 33654241.
*equally contributed

Figure	**Author Initials,** Responsibility decreasing from left to right				
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Supplemental Table 2	FS	CM	STS	GG	PUH

Explanations (if applicable):

Publication (complete reference): **Sahiti F**, Morbach C, Cejka V, Albert J, Eichner FA, Gelbrich G, Heuschmann PU*, Störk S*. Left Ventricular Remodeling and Myocardial Work: Results From the Population-Based STAAB Cohort Study. Front Cardiovasc Med. 2021 Jun 11;8:669335. doi: 10.3389/fcvm.2021.669335. PMID: 34179134; PMCID: PMC8232934.
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Figure	**Author Initials,** Responsibility decreasing from left to right				
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Explanations (if applicable):

Publication (complete reference): **Sahiti F**, Morbach C, Henneges C, Stefenelli U, Scholz N, Cejka V, Albert J, Heuschmann PU, Ertl G, Frantz S, Angermann CE, Störk S. Dynamics of Left Ventricular Myocardial Work in Patients Hospitalized for Acute Heart Failure. J Card Fail. 2021 Dec;27(12):1393-1403. doi: 10.1016/j.cardfail.2021.07.004. Epub 2021 Jul 29. PMID: 34332057.

Figure	**Author Initials,** Responsibility decreasing from left to right				
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Supplemental Table 4	FS	CM	STS	CH	
Supplemental Table 5	FS	CM	STS	CH	

Explanations (if applicable):

Publication (complete reference): Morbach C, **Sahiti F**, Tiffe T, Cejka V, Eichner FA, Gelbrich G, Heuschmann PU*, Störk S*; STAAB consortium. Myocardial work - correlation patterns and reference values from the population-based STAAB cohort study. PLoS One. 2020 Oct 8;15(10):e0239684. doi: 10.1371/journal.pone.0239684. PMID: 33031416; PMCID: PMC7544116.
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Figure	**Author Initials,** Responsibility decreasing from left to right				
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Explanations (if applicable):

I also confirm my primary supervisor's acceptance.

Doctoral Researcher's Name Date Place Signature

10.3 Acknowledgments

The current research was carried out at the Comprehensive Heart Failure Center, University Hospital Würzburg, from March 2018 to February 2021.

“Shoku i mirë me shok shumë” (“A good friend has a lot of friends”) is an Albanian saying I carry close to my heart and which has blessed me during the past few years of my PhD journey. My accomplishments are the fruit of a mutual endeavor because all my mentors, family, friends, and colleagues have contributed to what I have achieved with their support, inspiration, and motivation. They have been there for me throughout the whole process.

First of all, I would like to thank the Interdisciplinary Center for Clinical Research (IZKF) for the financial support and the opportunity to become part of the MD/PhD program at the Clinical Sciences Section, Graduate School of Life Sciences, Julius-Maximilians-University of Würzburg, and University Hospital Würzburg.

Next, I would like to thank my supervisor, Professor Stefan Störk — a great person and a truly inspiring mentor- for giving me the opportunity to be part of his working group, his endless support, and his supervision. My PhD journey started with an email I sent to Prof. Störk on August 29^{th,} 2016. I consider myself a lucky man since I received a positive response from him. Then, after being selected as a fellow for the MD/PhD program a year later, the time came for me to move to a foreign country that would soon become my second home. And I, personally and professionally, owe my supervisor a lot for his trust, support, help, advice, and the journey we have shared so far.

I am also grateful to the thesis committee members: Professor Peter Heuschmann for the opportunity to be part of this program and the support I received throughout it, Professor Wolfgang Bauer for his collaboration and input, Professor Michaela Kuhn and her Physiology team led earlier by Dr. Katarina Spiranec for their hospitality and a great preparatory and instructive phase at the beginning of the PhD program.

My mentor, PD Dr. Caroline Morbach, holds a special and valuable place in this journey. She is the person who introduced me to the world of echocardiography and was with me during every step of my scientific development so far. I am grateful for your instructions and endless support. Thank you, Caro!

I would also like to extend my sincere thanks to the staff of the Comprehensive Heart Failure Center Würzburg. During the past three and a half years, the friendly and amazing people of CHFC have made me feel at home. I want to thank, in particular, the Echo Technicians: Martina Bauer, Jasmin Simon, and Frances Knobeloch, the wonderful STAAB study team led by Sabine Cäsar and Melanie Roos for their cooperation and positivity at work.

Special thanks go to my amazing friends/colleagues and inspiring doctors/scientists Felipe Montellano, Vladimir Cejka, Judith Albert, Martin Christa, Vasco Sequeira, and Fabian Kerwagen for the thought-provoking discussions and their contributions to my scientific work.

Last but not least, I would like to thank my parents, Zija and Sabrije, as well as my brother Arben and sisters Arbana and Florina for their love and constant support, their understanding and patience. Although they live thousands of kilometers away, thanks to present-day modern technology, they were with me every day and provided emotional support and unlimited love and hope, which gave me strength and kept me going on my PhD journey.

11 Affidavit

I hereby confirm that my thesis entitled **"Myocardial Work - Application and Clinical Characterization of a New Echocardiographic Tool"** is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process, neither identical nor similar form.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation "**Myocardial Work – Anwendung und klinische Charakterisierung einer neuen Echokardiographie-basierten Methode"** eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

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