INTERNATIONAL DOCTORAL PROGRAM IN CARDIOVASCULAR
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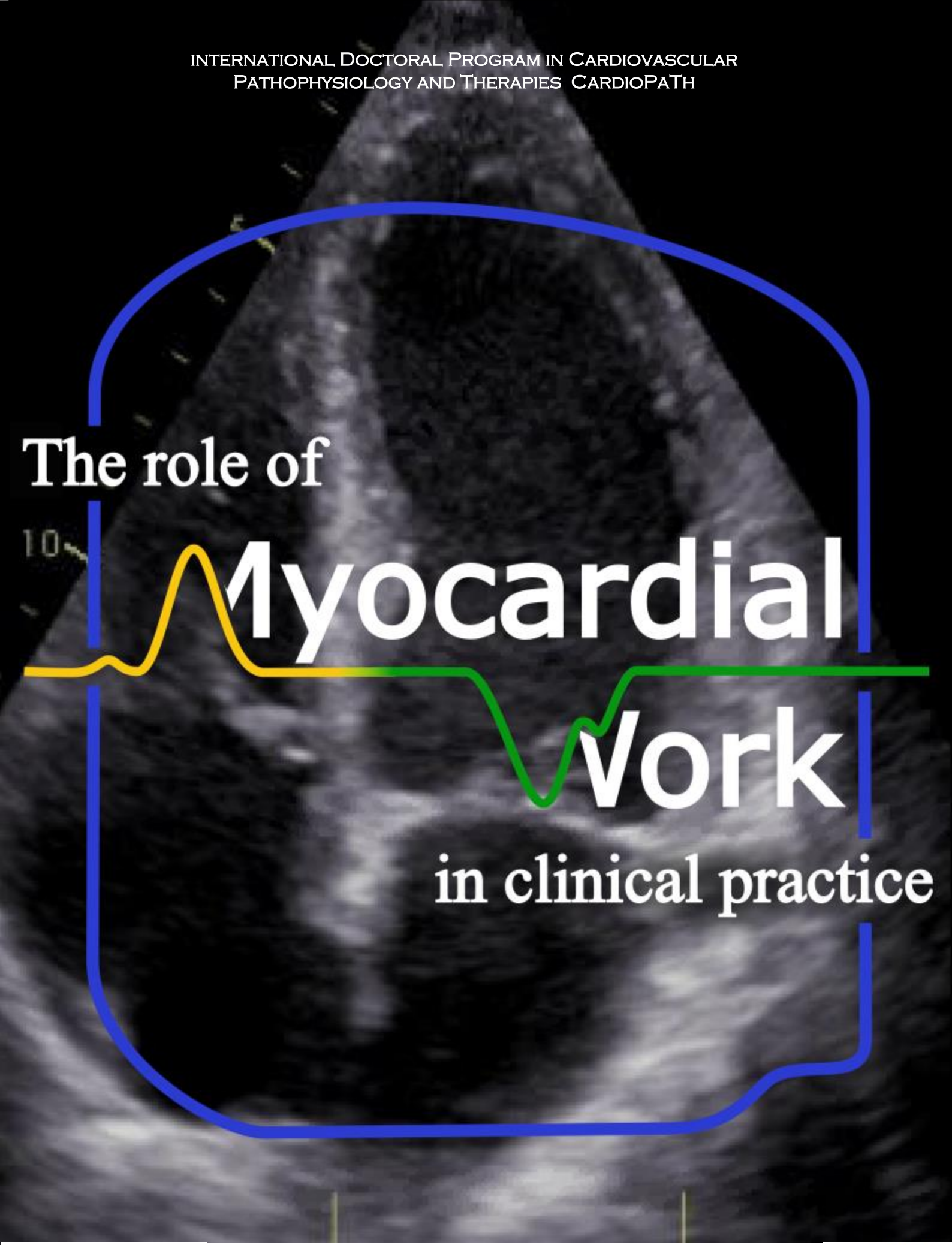

The role of Myocardial Work in clinical practice

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The role of
Myocardial Work
in clinical practice

MYOCARDIAL WORK ASSESSMENT FOR EARLY DETECTION OF SUBCLINICAL HEART FAILURE ACROSS VARIOUS CARDIAC PATHOLOGIES AND ITS PROGNOSTIC SIGNIFICANCE IN LONG-TERM FOLLOW-UP

PhD Thesis

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En la línea del horizonte, hijos míos, parecen unirse el cielo y la tierra. Pero no, donde de verdad se juntan es en ***VUESTROS CORAZONES****, cuando vivís santamente la vida ordinaria.*

San Josemaría Escrivá

Heaven and earth seem to merge, my sons and daughters, on the horizon. But where they really meet is in ***YOUR HEARTS****, when you sanctify your everyday lives.*

Sint Josemaría Escrivá

CONTENT

LIST OF ABBREVIATIONS

AR	aortic valve regurgitation
ARNI	angiotensin receptor-neprilysin inhibitor
AS	aortic valve stenosis
ATTR	cardiac transthyretin amyloidosis
AUC	area under the curve
AV	aortic valve
AVA	aortic valve area
BP	blood pressure
BSA	body surface area
CA	cardiac amyloidosis
CAD	coronary artery disease
CO	cardiac output
CRT	cardiac resynchronization therapy
CTRCD	cancer therapy-related cardiac dysfunction
CV	cardiovascular
CW	constructive work
DBP	diastolic blood pressure
D-TGA	dextro- transposition of the great arteries
ECG	electrocardiogram
EDA	end diastolic area
EDV	end diastolic volume
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESA	end systolic area
ESC	European Society of Cardiology
ESV	end systolic volume
FAC	fractional area change
GCW	global constructive work
GLS	global longitudinal strain
GWE	global work efficiency
GWI	global work index
GWW	global wasted work
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	heart rate
HTN	hypertension
ICC	intraclass correlation coefficient
IVC	isovolumic contraction
IVR	isovolumic relaxation
LAS	left atrial strain
LAVI	left atrial volume index
LBBB	left bundle branch block
LV	left ventricle
LVAD	left ventricle assistance device
LVEF	left ventricular ejection fraction

LVOT	left ventricular outflow track
LVP	left ventricular pressure
LW	lateral wall
MACE	major adverse cardiovascular events
MCW	myocardial constructive work
MR	mitral regurgitation
MVC	mitral valve closure
MVO	mitral valve opening
MW	myocardial work
MWE	myocardial work efficiency
MWI	myocardial work index
MWW	myocardial wasted work
NAC	National Amyloidosis Centre
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PSL	pressure-strain loop
ROC	receiver operating characteristic
ROI	region of interest
RV	right ventricle
SAVR	surgical aortic valve replacement
SBP	systolic blood pressure
SD	standard deviation
sPAP	systolic pulmonary pressure
sRV	subaortic right ventricle
SS	septal segments
sST2	soluble suppression of tumorigenicity 2
STE	speckle tracking echocardiography
SV	stroke volume
TAPSE	tricuspid annular plane systolic excursion
TAVR	transcatheter aortic valve replacement
TR	tricuspid regurgitation
Trop HS	high-sensitivity troponin
TTE	transthoracic echocardiography
WW	wasted work

Aims

This PhD thesis aims to investigate the potential role of myocardial work analysis in detecting subclinical heart failure as well as its prognostic value across various cardiac pathologies. Myocardial work is a sophisticated echocardiographic tool derived from pressure-strain loop analysis that allows a comprehensive assessment of cardiac performance. Its calculation relies on the acquisition of high-quality echocardiographic images for strain analysis and the integration of valve event timing and intraventricular pressure. In non-invasive myocardial work, the intraventricular pressure curve is estimated using the cuff measurement of the arterial blood pressure. The exceptional added value of myocardial work analysis consists of the combination of multiple complementary parameters, namely, myocardial work index, myocardial work efficiency, constructive work, and wasted work. The assessment of all parameters together allows a better understanding of the (patho-)physiology behind each cardiac condition and an enhanced evaluation of the cardiac function.

To date, myocardial work has not been implemented in the daily clinical practice as its clinical benefit has not been demonstrated yet by large randomized controlled clinical trials. By contrast, highly promising results from smaller studies have been published in the last years, and there is increasing interest for this method as a pivotal research topic in non-invasive cardiac imaging. Nevertheless, a considerable lack of data and knowledge still prevents us from guiding clinical decisions based on myocardial work analysis. Additionally, its methodology requires a notable level of expertise from the sonographer as well as adequate software support.

Learning to interpret myocardial work values and values' changes in each cardiac condition is crucial for its implementation in daily practice. Therefore, this PhD thesis pursues to highlight the usefulness of myocardial work analysis in different clinical scenarios and to propose practical ways to implement this novel technique to guide clinical decisions and patient's management.

This PhD thesis consists of 5 chapters. The first chapter provides an overview of the state-of-the-art on myocardial work. Next to its principle, methodology and pitfalls, the chapter includes relevant studies and publications on the use of myocardial work in different cardiac pathologies previous to this work. The consecutive chapters focus each on a different cardiac condition and investigate the potential role of myocardial work analysis in that specific pathology: cardio-oncology (chapter 2), aortic valve stenosis (chapter 3), congenital heart disease (chapter 4) and cardiac amyloidosis (chapter 5). The chapters are followed by the discussion, conclusion and future perspectives. Additionally, the appendix includes smaller analysis from which the results seamless align with the findings and conclusions of the different chapters.

At last, the reader can find the author's curriculum vitae and list of publications endorsed. This PhD thesis ends by acknowledging the contribution of many people whose dedication and support made this work possible.

Chapter 1

Myocardial Work State-of-the-Art

NON-INVASIVE ASSESSMENT OF LEFT VENTRICULAR FUNCTION

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The assessment of myocardial work (MW) using noninvasive pressure-strain loop analysis is a novel echocardiographic method that provides a more precise assessment of cardiac performance by considering the left ventricular loading condition. By integrating various MW components such as index, efficiency, and constructive and wasted work, an extensive analysis of left ventricular mechanics and energetics can be achieved. This approach offers a more comprehensive assessment of global cardiac function and performance, surpassing conventional surrogate indices. In this review, we aim to summarize the existing knowledge on MW and its distinctive characteristics in various cardiac pathologies.

Left Ventricular Ejection Fraction (LVEF) is a widely used echocardiographic parameter for evaluating cardiac function. Its simplicity and good correlation with clinical outcomes has made it a convenient tool in daily clinical practice.[1] However, LVEF has inherent limitations, including low sensitivity and load-dependency which compromise its reliability and usefulness as a comprehensive assessment of cardiac function.[2]

Over the past few decades, myocardial strain analysis using speckle tracking has emerged as a more sensitive and reproducible parameter for assessing regional myocardial function and the speed of contraction.[3] In addition 2 dimensional (2D) Global Longitudinal Strain (GLS) has been shown to detect early deterioration in myocardial function that may not be evident based on changes in LVEF alone. Therefore, the evaluation of GLS plays an important role in cardiac surveillance, allowing for the detection of hidden subclinical alterations in myocardial function.[4–6] Although GLS exhibits lower load-dependency compared to LVEF, it is still vulnerable to changes in load. The significant impact of load on GLS may result in misinterpretations, thereby limiting its use and value in the clinical setting.[7]

Pressure-strain loop (PSL) analysis is an innovative echocardiographic method used to quantify myocardial work (MW). This approach, initially introduced by Russell et al[8] involves the combination of information derived from speckle tracking strain imaging and a non-invasive estimate of the left ventricular pressure (LVP). By incorporating the left ventricular loading condition, PSL analysis offers a superior approach for assessing myocardial performance. It facilitates the quantification of both the global and regional contractile capacity of the myocardium providing insights into its energetics and O2 consumption. This in-depth evaluation enables the detection of subclinical myocardial dysfunction.[9,10]

The objective of this review is to provide a comprehensive overview of the MW methodology, including reference values, interpretation, and potential pitfalls. Additionally, we explore its clinical use in various cardiac pathologies.

Background, Methodology, and Reference Values

The left ventricle (LV) loading state is dynamic and influenced by changes in pre- and afterload. The conventional LV pressure-volume loop (PVL) provides a visual representation of this intricate, illustrating the physiological adaptation of the heart to maintain stroke volume (SV) at different loading conditions (***Figure 1***). Additionally, the PVL area is proportional to the myocardial oxygen consumption.[11,12]

The concept of MW is not new, as it was first introduced by an experimental study from Suga et al[11] in 1979. In their study, they validated the concept by directly measuring PVL during cardiac catheterization. They demonstrated that myocardial work is influenced by the temporal relationship between intracardiac pressure and myocardial contraction. Additionally, they

established a correlation between the area of the invasively derived PVL and myocardial oxygen consumption. Such invasive MW assessment is accurate and reliable, yet demanding and not feasible to acquire on a routine basis.[13,14]

Regarding practical clinical implementation, Russel et al[8] introduced a novel non-invasive method for quantifying LV MW. Their approach involved combining information derived from LVP curves with strain measurements (***Figure 2***). They achieved this by associating peripheral systolic blood pressure (SBP) with cardiac event times including isovolumic contraction (IVC), systolic ejection, and isovolumic relaxation (IVR), which were determined using echocardiographic valvular opening and closure events. In situations where the visualization of the opening and closing times of the aortic and mitral valves is challenging, such as in the presence of valve calcification or a prosthetic valve, Doppler traces can be employed to determine valve timing events. In addition, global and regional longitudinal strain curves were obtained using speckle tracking echocardiography (STE) from the 2-, 3- and 4-chamber apical views. By integrating these strain with the pressure curves, a non-invasive LV PSL could be generated, enabling the quantification of MW. This non-invasive MW assessment was validated by comparing it with invasive LV PSL as well as by correlating it with oxygen consumption and regional myocardial glucose uptake and metabolism obtained through positron emission tomography. Compared to parameters as GLS and LVEF which are influenced by afterload, MW takes into account the loading conditions during myocardial deformation. This characteristic enhances its accuracy, making it a theoretically appealing approach for comprehensive assessment of myocardial function.

MW is characterized by four distinct components that contribute to the understanding of LV mechanics; the global work index (GWI), the global wasted work (GWW), the global constructive work (GCW), and the global work efficiency (GWE) which represents the proportion of constructive to the total work. Each of these components provides different information about LV mechanics (***Table 1***).

First, GWI quantifies the indexed total work performed by the LV throughout the entire mechanical systole including IVC and IVR. It is visually represented by the area enclosed by the PSL and corresponds to the translation of myocardial energy into mechanical energy between mitral valve closure (MVC) and opening (MVO). Positive work results from shortening of the myocardium while negative work results from the lengthening of the myocardium.

On the one hand, GCW represents the positive work performed by shortening during IVC and systole as well as the negative work during isovolumic relaxation (IVR) that results from lengthening of the myocardium. GCW quantifies the energy consumed by the myocardium that effectively contributes to cardiac output (CO) by facilitating LV ejection.

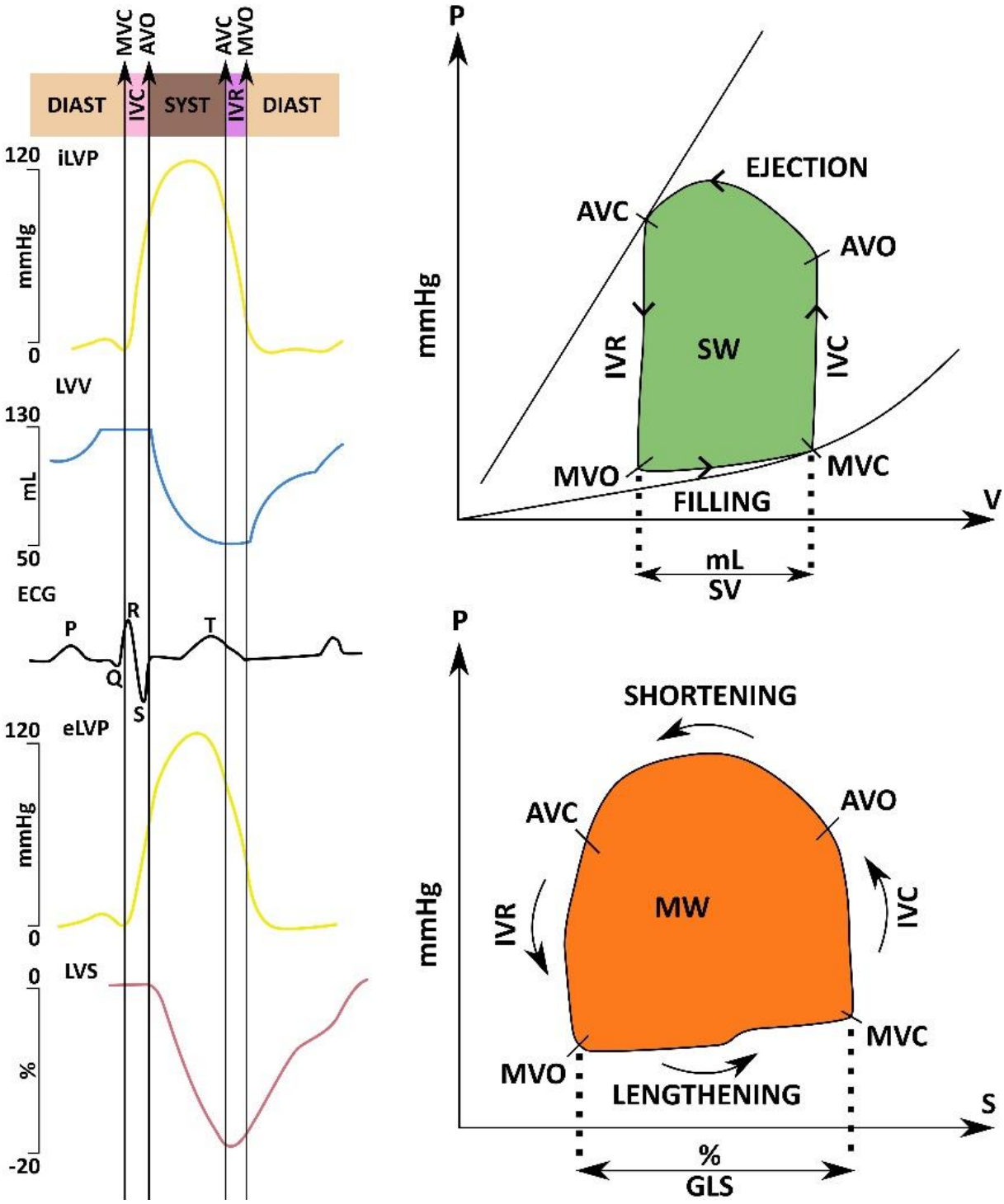


Figure 1: Visual presentation illustrating the relationship between the pressure-volume loop and pressure-strain loop. *AVC, aortic valve closure; AVO, aortic valve opening; DIAST, diastole; eLVP, estimated left ventricular pressure; GLS, global longitudinal strain; iLVP, invasive left ventricular pressure; IVC, isovolumic contraction; IVR, isovolumic relaxation; LVS, left ventricular strain; LVV, left ventricle volume; MVC, mitral valve closure; MVO, mitral valve opening; MW, myocardial work; P, pressure; SV, stroke volume; SW, stroke work; SYST, systole; V, volume*

On the one hand, GCW represents the positive work performed by shortening during IVC and systole as well as the negative work during isovolumic relaxation (IVR) that results from lengthening of the myocardium. GCW quantifies the energy consumed by the myocardium that effectively contributes to cardiac output (CO) by facilitating LV ejection.

On the other hand, GWW represents the LV work that does not contribute to LV ejection. It includes negative work during IVC and systole where the myocardium undergoes lengthening as well as positive work during IVR when the myocardium undergoes shortening. GWW quantifies the energy consumed by the myocardium that is wasted and does not contribute to CO.

Lastly, GWE is the ratio between constructive work and total (constructive and wasted) work. It reflects the net percentage of MW performed that is actually translated into CO. The formula for GWE is GCW divided by the sum of GCW and GWW [GCW/(GCW+GWW)].

Table 1: Definition of the different MW components Parameter

Parameter		Definition
Global Work Index	GWI	Indexed total work performed by the LV throughout the entire mechanical systole including IVC and IVR. It is visually represented by the PSL area and corresponds to the myocardial energy translated into mechanical energy between MVC and MVO.
Global Work Efficiency	GWE	Ratio between constructive work and total (constructive and wasted) work. It reflects the net percentage of MW performed that is actually translated into CO [GCW/(GCW+GWW)].
Global Constructive Work	GCW	LV work that contributes to LV ejection and is performed by shortening (positive work) during IVC and systole or by lengthening (negative work) in IVR. It quantifies the energy consumed by the myocardium that effectively contributes to CO.
Global Wasted Work	GWW	LV work that does not contribute to LV ejection and is the work performed by lengthening (negative work) during IVC and systole or by shortening (positive work) in IVR. It quantifies the energy consumed by the myocardium that is wasted and does not contribute to CO

The European Association of Cardiovascular Imaging Normal Reference Ranges for Echocardiography (EACVI-NORRE) multicenter study (European Association of Cardiovascular Imaging Normal Reference Ranges for Echocardiography)[15], the German general population study: Characteristics and Course of Heart Failure STAges A/B and Determinants of Progression, known as the STAAB cohort[16], a preliminary study from the Hospital of Rennes[17] and an analysis from Copenhagen City Heart Study (CCHS)[18] all have sought to establish normal values for MW components as shown in ***Table 2*** and ***Table 3***. In the four studies calculation was performed using software provided by General Electric (GE). In a meta-analysis of normal ranges of non-invasive MW indices[19], the three first studies were included presenting the highest weight in the random-effect model. The last one was not included due to later publication.

Interpretation and pitfalls

The strength of PSL lies in its ability to integrate various MW components for evaluation LV mechanics. Rather than relying on a single variable, the interpretation of all MW variables provides a more thorough understanding of how the LV adapts to specific clinical loading conditions. This approach allows for a more nuanced assessment, where values above or below the normal range are equally abnormal and may indicate different pathophysiological conditions. For instance, in high afterload conditions GWI will increase indicating a harder working myocardium that is striving to maintain CO against elevated resistance. However, a high/normal GWI can be associated with a low GWE which can result from either an increase in GWW or a decrease in GCW. An elevated GWW may be related to rhythm disorders, dyssynchrony or impaired relaxation with either a prolonged IVC or IVR. Otherwise, a decrease in GCW primarily reflects (ir)reversible myocardial tissue damage such as oedema or fibrosis[20]. Furthermore, El Mahdiui et al[21] demonstrated that the MW efficiency is not influenced solely by the presence of CV risk factors in the absence of structural heart disease. By considering the combined interpretation of MW variables, PSL provides valuable insights into LV function and helps discern different pathophysiological mechanisms underlying abnormal findings.

Table 2: Summary of the main studies providing reference values for MW in healthy individuals Study. *Data are presented as mean ± SD or median (CI)/[interquartile range]*

Study	Population	male:female	Age (years)
EACVI-NORRE	226 healthy individuals 22 centers	85:141 38:62 %	45 ± 13
STAAB	779 healthy individuals 1 center	319:460 41:59 %	49 ± 10
RENNES	115 healthy individuals 1 center	77:38 67:33 %	36 [18-69]
CCHS	1827 healthy individuals 1 center	713:1114 39:61 %	45 [32-57]

MW analysis is subject to certain assumptions, which can introduce inherent errors. Firstly, it assumes that the LV wall thickness is equal across all myocardial segments. However, regional hypertrophy can impact strain and consequently affect MW as well.[22] Secondly it is assumed that LV pressure is uniformly distributed throughout the entire LV wall which may not always be the case. For example in conditions like left bundle branch block (LBBB), the activation of the LV free wall is delayed compared to the septal wall. This delayed contraction under higher afterload leads to additional MW.[23]

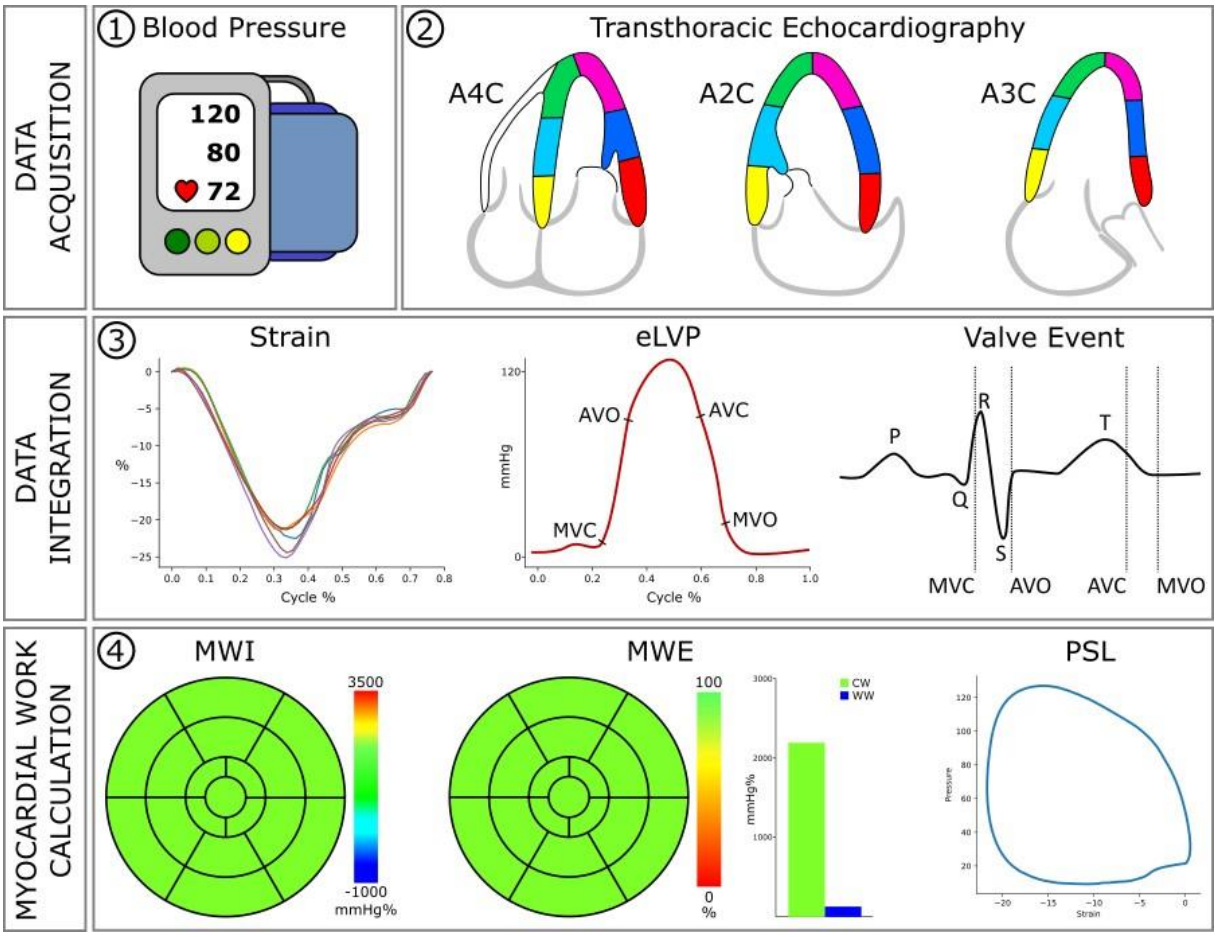


Figure 2: Protocol sequence demonstrating the data acquisition and integration of measurements for accurate assessment of MW. *1. Measure cuff blood pressure during the echocardiographic examination, while ensuring that the patient is in the same position as during image acquisition. This step is crucial because the SBP measured will be used as an estimate for peak LVP in the calculation of MWI. 2. Acquire the three standard transthoracic apical views with the patient in the left lateral decubitus position, using a frame rate of 60 to 80 frames per second to achieve optimal image quality and minimize heart rate variability between the images. 3. Perform GLS analysis, ensuring successful tracking of all segments, and generate a strain bull's-eye plot. Use the apical three-chamber view to visually assess the timing of valve events such as aortic and mitral valve opening and closure. In cases where visualizing valve timing events is challenging, Doppler traces can be utilized to determine the timing. Input the previously measured blood pressure. 4. Calculate the components of MW after aligning the electrical and mechanical phases appropriately. Visualize regional and global MWI and MWE in bull's-eye plots. Compute the PSL to further analyze the myocardial function. A4C, apical 4-chamber view; A3C, apical 3-chamber view; A2C, apical 2-chamber view; AVC, aortic valve closure; AVO, aortic valve opening; BP, blood pressure; GLS, global longitudinal strain; LVP, left ventricular pressure; MVC, mitral valve closure; MVO, mitral valve opening; MW, myocardial work; MWE, myocardial work efficiency; MWI, myocardial work index; PSL, pressure-strain loop; SBP, systolic blood pressure.*

Thirdly, the geometry of the LV in accordance with Laplace's law, plays a crucial role. A more spherical and dilated LV will exhibit a lower MW index (MWI) for a similar GLS when compared to a smaller, less dilated LV.[24] Fourthly, the MW analysis only utilizes longitudinal strain, neglecting the work related to radial and circumferential shortening and lengthening, which also contribute to LV contractility.

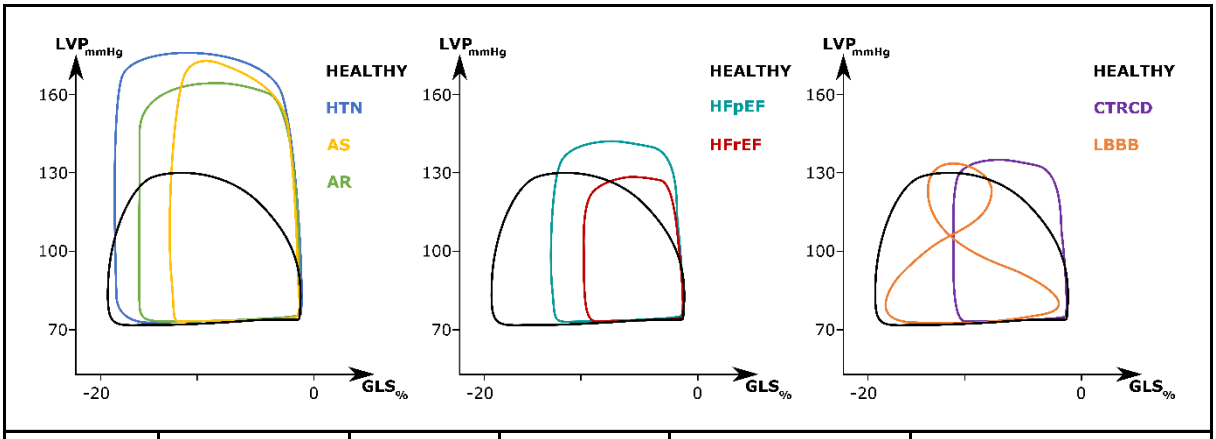
Finally, peak systolic LVP is assumed to be equal to arterial SBP but this assumption holds true only in the absence of aortic valve stenosis (AS). Notwithstanding all these

shortcomings, the significant advantage of MW analysis is its reliability and accuracy in daily clinical practice.[10,25,26] While it is important to recognize these shortcomings, MW analysis still provides valuable insights into LV function and may serve as a useful tool in routine clinical assessment.

Table 3: Comprehensive overview of MW reference values stratified by age and gender.

			GWI *mmHg%*	**GCW** *mmHg%*	**GWW** *mmHg%*	**GWE** *%*
EACVI-NORRE STUDY	*20-40*	*male*	1758 ± 270	2186 ± 240	99 (68-144.5)	95 (93-97)
		female	1800 ± 251	2109 ± 289	90 (48-145)	95 (94-97)
	40-60	*male*	1900 ± 317	2267 ± 327	89 (58-122.5)	96 (95-97)
		female	2027 ± 341	2329 ± 365	76 (51-118)	96 (95-97)
mean ± sd, median (CI)	*>60*	*male*	1866 ± 286	2226 ± 328	85 (49-129)	96 (94-97)
		female	2002 ± 270	2338 ± 386	90 (48-145)	95 (94-97)
STAAB STUDY	*<45*	*male*	2141 (2099-2183)	2366 (2330-2402)	73 (70-76)	96 (96-96)
		female	2206 (2168-2245)			
	>45	*male*	2187 (2149-2224)	2457 (2428-2486)	na	na
mean (CI)		*female*	2252 (2220-2284)			
HOSPITAL of RENNES	*≤25*	*all*	1915 ± 233	2212 ± 222	97 (65–145)	95 (93–97)
		male	1912 ± 217	2231 ± 217	93 (64–115)	95 (95–97)
		female	1923 ± 276	2172 ± 238	114 (69–154)	95 (93–96)
	25-35	*all*	1935 ± 220	2203 ± 220	84 (58–116)	96 (94–97)
		male	1927 ± 255	2179 ± 200	72 (52–120)	96 (94–97)
		female	1954 ± 109	2260 ± 267	93 (62–112)	95 (94–96)
	35-45	*all*	1939 ± 289	2242 ± 250	100 (55–134)	96 (94–97)
		male	1832 ± 252	2184 ± 250	111 (63–149)	94 (93–97)
		female	2190 ± 206	2376 ± 207	71 (50–96)	97 (96–98)
	≥45	*all*	1911 ± 251	2240 ± 230	82 (67–107)	96 (95-97)
mean ± sd, median (IQR, 5° and 95° percentile)		*male*	1824 ± 196	2174 ± 145	81 (69–94)	96 (95-96)
		female	2058 ± 275	2350 ± 306	92 (59–132)	96 (94-97)
CCSH	*32-57*	*all*	2118 ± 277	2262 ± 283	64 (47–89)	97 (96–98)
		male	2062 ± 269	2229 ± 275	60 (42–84)	97 (96–98)
mean ± sd, median (IQR)		*female*	2155 ± 275	2283 ± 286	68 (49–93)	97 (96–98)

CI: confidence interval, IQR: inter-quartile range, GCW: global constructive work, GWE: global work efficiency, GWI: global work index, GWW: global wasted work.



Cardiac condition	**Peak LVP** *afterload*	**LVEDV** *preload*	**Peak GLS** *myoc. shortening*	**MWI** *myoc. energetics*	**Reference**
Healthy	± 120mmHg	± 120mL	± -20%	± 1800mmHg%	EACVI-NORRE study
HTN	↑	≈	≈/↓	↑	Chan et al. 2019 Li et al. 2021 Sahiti et al. 2021
AS	↑	↓/≈	↓	↑	Fortuni et al. 2020 Jain et al 2021 De Rosa et al. 2022
AR	↑	↑	≈/↓	↑	Meucci et al. 2022 Jain et al. 2022
HFpEF	↑	↓	↓	≈/↓	Tomoaia et al. 2020 D'Andrea et al 2021 Lin et al. 2022
HFrEF	≈	↑	↓	↓	Chan et al. 2019 Hedwig et al. 2021 Wang et al. 2021
LBBB	↓/↑	≈	↓	GWW↑ ; GWE ↓	Russel et al. 2013 Aalen et al. 2019 Calle et al. 2021
CTRCD	≈/↑	≈	↓	↓	Guan et al. 2021 Zhan et al. 2022 Calvillo-Argüelles et al. 2022

Figure 3, CENTRAL ILLUSTRATION: Characteristic PSL patterns in different cardiac pathologies demonstrating the impact of changes in pre- and afterload on myocardial performance. It is important to note that the presented PSL values for AS and AR are based on reported changes in GLS and LVP compared with normal conditions. However, it should be emphasized that the available studies do not directly compare PLS values between AS and AR patients and control individuals. In case of complete LBBB, the presence of an 8-shaped PSL corresponds to the expected peak systolic longitudinal strain at the septal wall, rather than globally. This characteristic feature of MW in complete LBBB is highly indicative of the performance of the septal wall. *AR; aortic valve regurgitation, AS ; aortic valve stenosis, CTRCD; cancer therapeutics-related cardiac dysfunction, GLS; global longitudinal strain, GWE; global work efficiency, GWW; global wasted work, HFpEF; heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, HTN; hypertension, LBBB; left bundle branch block, LVEDV; left ventricle end diastolic volume, LVP; left ventricular pressure, MR; mitral valve regurgitation, MWI; myocardial work index, myoc.; myocardial.*

MYOCARDIAL WORK AND AFTERLOAD

In cardiac conditions characterized by increased afterload LV remodeling is a common phenomenon. Elevated pressure forces the myocardium to compensate for the higher afterload, resulting in progressive thickening of the LV wall. The contractile function may remain preserved, but over time its deterioration becomes evident through a decline in GLS. The adaptive changes in LV remodeling can be reversible and GLS may normalize when the pressure-overload that triggered the remodeling process subsides, a phenomenon referred to as reverse remodeling. However, in cases of long-standing pressure-overload, adverse LV remodeling can occur, characterized by the development of myocardial fibrosis and irreversible tissue damage. It is important to monitor GLS as a sensitive indicator of LV function, as it can provide insights into the extent of LV remodeling and the potential reversibility of these changes.

Hypertensive heart disease

Arterial hypertension (HTN) leads to an elevation in afterload, triggering compensatory mechanisms to preserve CO. Initially, MW gradually increases without significant alterations in LVEF and GLS. However as the heart is less capable of adapting to the heightened afterload and increasing wall stress myocardial strain begins to drop. ***Figure 3*** presents the clinical characteristics and the expected pattern of PSL for HTN patients.

The severity of hypertension is closely related to the elevated GWI and is also associated with peak oxygen uptake.[27–29] It is worth noting that changes in MW components are not only correlated with systolic blood pressure but also with mean blood pressure (BP) and diastolic blood pressure (DBP).[30] Specifically, an elevated DBP has been linked to reduced GWE primarily due to an imbalanced increase in GWW relative to GCW, with GWW showing a relatively greater rise.[31]

The impact of disturbances in LV relaxation and stretching, which arise from myocardial stiffness and interstitial fibrosis, on MW remains unclear. Tadic et al[29] reported no changes in GWE and GWW whereas Li et al[30] found a decreased in GWE accompanied by an increase in GWW. Similar changes in GWW, GCW and GWE were observed in a sub-analysis from the STAAB[32] population indicating that elevated wall stress and ventricular-arterial coupling ratio contribute to a decrease in contraction efficiency in hypertensive patients.

In patients with hypertensive disease, MW analysis provides insights not only into global myocardial performance but also into regional performance. The characteristic apex-to-base strain gradient observed in HTN, is reflected by higher MWI in the apical segments compensating for the impaired contraction observed in the basal segments.[33]

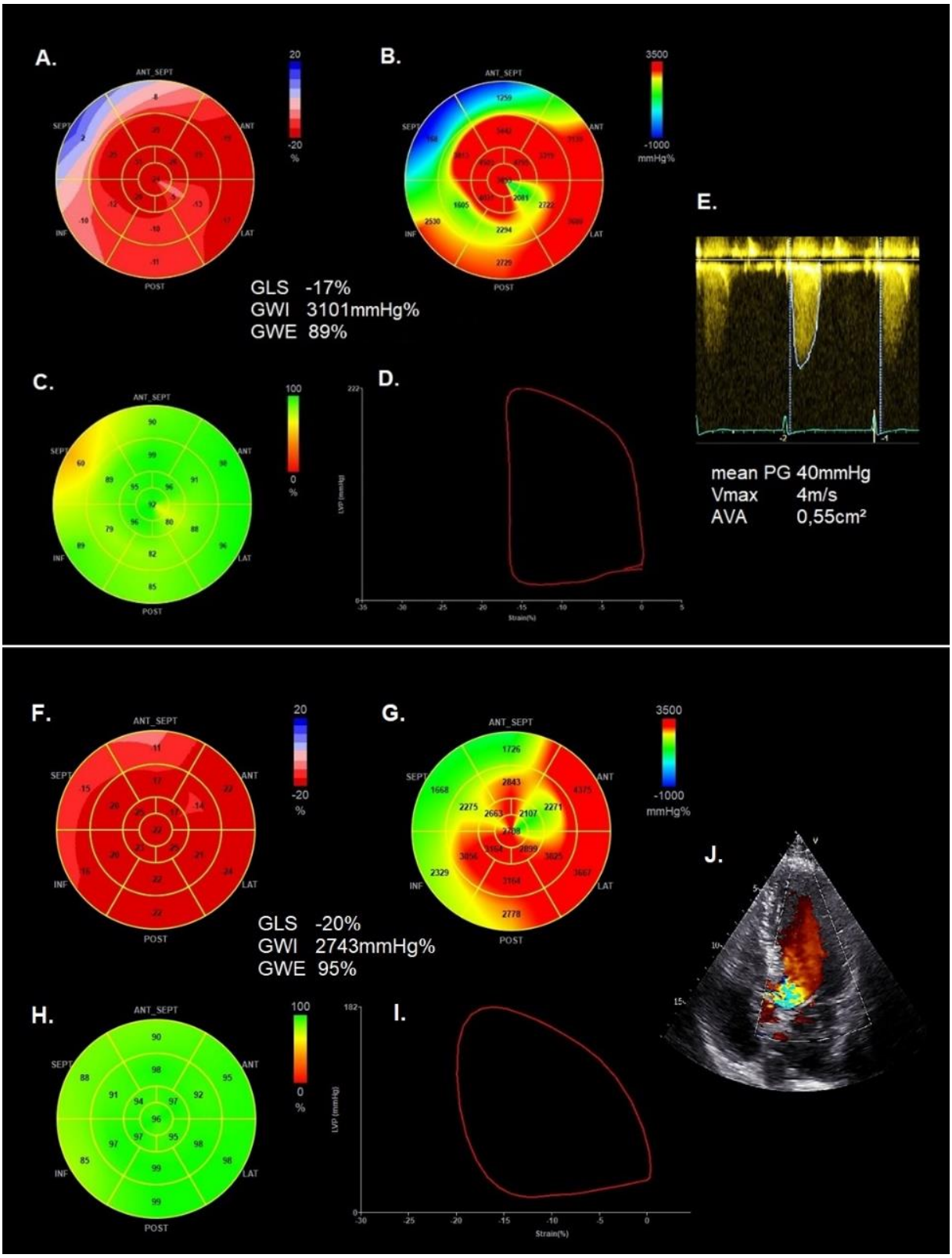


Figure 4: Longitudinal strain (A, F), myocardial work index (B, G), myocardial work efficiency (C, H) bull's eye and PSL (D, I) in a patient with pressure overload due to severe AS (A-E) and in a patient with volume overload due to severe AR (F-J). *AR, aortic valve regurgitation; AS, aortic valve stenosis; AVA, aortic valve area; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; PG, pressure gradient; V, velocity.*

Aortic Valve Stenosis

In AS patients, estimating LVP solely using brachial artery BP is limited due to the presence of valve obstruction which creates a higher peak intraventricular pressure compared to the peripheral SBP. To address this limitation Fortuni et al[34] introduced a method in which they combined the mean gradient over the aortic valve measured by echocardiography with arterial SBP, creating a new parameter for the non-invasive estimation of the LVP in AS patients. By using this corrected LVP, the GWI is significantly higher compared to using SBP alone as a surrogate for LVP, highlighting the direct impact of the elevated afterload in AS on LV performance.[35] Interestingly GWI and GLS tend to vary over time in AS patients. Initially, when the AS is compensated and LV contractile function is preserved, both GWI and GCW increase while absolute GLS may appear incorrectly low due to its dependency on afterload. However, in decompensated AS when LV contractile function becomes impaired, GWI and GCW decrease and the patient develops hear failure symptoms irrespective of the underlying GLS.[34] Even in asymptomatic AS patients, lower GWI values serve as a marker of decompensation and have been associated with increased mortality.[36,37] ***Figure 3*** shows the generally expected PSL-pattern for AS patients and ***Figure 4*** shows an illustrative example of MW in a patient with pressure overload due to severe AS.

Following transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) the immediate reduction in afterload does not only lead to the restoration of abnormal GLS to some extent but also results in a decrease in the elevated GWI and increase GCW, indicating a potential recovery of myocardial contractile function. However, it should be noted that this improvement may not necessarily be accompanied by changes in GWW and GWE after TAVR/SAVR.[35,38]

Aortic Valve Regurgitation

Aortic valve regurgitation (AR) is characterized by an increase in both pre- and afterload. Initially, the regurgitant volume flows back into the LV during diastole, reducing forward CO and increasing LV end-diastolic volume (EDV). The elevated preload triggers LV adaptation according to the Frank-Starling law, leading to an increase in SV and compensating for the volume-overload (***Figure 3***). However, sustained high SV eventually leads to increased afterload. Over time, the combination of volume and pressure overload causes myocardial fibrosis which impairs the recovery of the LV function. Furthermore, poor survival after SAVR is associated with impaired pre-interventional LV function.[39] ***Figure 4*** illustrates an example of MW in a patient with volume overload due to severe AR.

To date, only one study reported MW values in patients with moderate or severe chronic AR and preserved LVEF. Prior to surgical valve repair, both GWI and GCW were elevated in

relation to the severity of AR. Following valve repair, GWI, GCW and GWE decreased while GWW remained unchanged. Interestingly, in 28% of patients GWI remained abnormal suggesting reduced LV reverse remodeling in the presence of irreversible myocardial damage.[40,41]

MYOCARDIAL WORK IN HEART FAILURE

The 2021 European Society of Cardiology (ESC) guidelines provide a definition of heart failure (HF) as a clinical syndrome characterized by specific symptoms and signs accompanied by elevated cardiac pressures due to functional or structural abnormalities, resulting in inadequate cardiac performance.[42] HF is categorized based on LVEF into three subtypes: HF with reduced ejection fraction (HFrEF, LVEF≤40%), HF with mildly reduced ejection fraction (HFmrEF, LVEF 41-49%) and HF with preserved ejection fraction (HFpEF, LVEF≥50%). While HFmrEF is a relatively new entity, this review will primarily focus on HFrEF and HFpEF.

HFrEF

In HFrEF the rise in intracardiac filling pressures initially occurs due to contractile dysfunction and, in advanced stages, it is exacerbated by diastolic and RV dysfunction. As a response to volume overload and myocyte loss, HFrEF hearts undergo eccentric remodeling, resulting in a large LV cavity with a thin myocardial wall (***Figure 3***). The myocardial dysfunction is evident through a significant reduction in GLS, GWI and GWE.[27] An illustrative example of MW in a patient with HFrEF is presented in ***Figure 5***.

GWI, along with GLS and LVEF, serves as a predictor of all-cause mortality and HF hospitalization.[43] It correlates with peak oxygen consumption and NT-proBNP levels particularly in patients with ischemic dilated cardiomyopathy and amyloidosis.[44–46] Using a cut-off value of 455 mmHg% for GWI (AUC: 0.80; P<0.0001; sensitivity 77.4%; specificity 71.6%) and 530 mmHg% for GCW (AUC: 0.80; P<0.001; sensitivity 74.2%; specificity 78.4%) the accuracy of predicting all-cause mortality, need for heart transplantation or LVAD implant in end stage HFrEF is high.[45]

Secondary mitral regurgitation (MR) is common in dilated failing hearts and significantly impacts the patient's prognosis.[47] MW analysis in these patients demonstrates the tight relationship between the degree of MR and LV performance. As secondary MR worsens, GWI and GCW decrease, while GWW is lower in patients with severe MR compared to those with mild or moderate MR.[48] The LV may struggle to generate sufficient work to pump blood into a higher-pressure chamber (the aorta) while it empties into a low-pressure chamber (the left atrium), providing some relative benefit to myocardial energetics.[49,50] Nonetheless, lower GWI, GCW and GWW are associated with a higher risk of all-cause mortality, indicating the greater

impact of the loss of contractile function on the survival of this patients. These findings align with the results of Tunyan et al[51], who identified GCW as the best predictor of worsening clinical outcomes in primary MR.

The impact of HF therapy on MW has been the subject of recent investigation. Bouali et al[52] conducted a study that revealed a significant increase in GWE and GCW following the initiation of sacubitril/valsartan treatment. Interestingly they observed earlier improvement in GCW at 6 months compared to GWE which showed improvement only at 12 months. These findings were further supported by Gonçalves et al[53] who also noted a decrease in GWW, although the decrease was not significant. The beneficial effects of an Angiotensin Receptor-Neprilysin Inhibitor (ARNI) may contribute to these observed changes. It is believed that the anti-fibrotic properties of ARNI play a role in reducing myocardial stiffness improving myocardial perfusion and metabolism. As a result, there may be enhanced myocyte shortening during systole leading to improved myocardial performance characterized by higher GCW and GWE.

HFpEF

HFpEF encompasses a diverse range of phenotypes, making it a highly heterogeneous disease. It is characterized by elevated ventricular filling pressures caused by impaired relaxation, increased myocardial stiffness and diminished restoring forces. The HFpEF heart, due to its high myocardial stiffness, exhibits reduced compliance and becomes more vulnerable to changes in volume. This is particularly evident during exercise, when HFpEF patients with normal resting values experience an abnormal rise in filling pressures, thereby unmasking the underlying disease.[54] ***Figure 3*** illustrates the clinical characteristics and generally expected PSL-pattern for HFpEF patients while ***Figure 5*** presents an illustrative example of MW in a patient with HFpEF.

Although further extensive clinical trials are necessary before MW can be fully implemented as a diagnostic tool for HFpEF[55], preliminary findings from small-scale studies evaluating its role in HFpEF are pro-impairment and a correlation with LV filling pressures and diastolic function parameters is observed.[56] In patients with a new diagnosis of HFpEF, the GWW demonstrates the highest diagnostic performance for predicting the first hospitalization.[57] Moreover, compared to age- and sex-matched controls, individuals with HFpEF exhibit lower resting GWE values and higher resting GWW values. Those with reduced GWE display lower exercise capacity, increased pulmonary congestion and attenuated LV contractile reserve during exercise.[58]

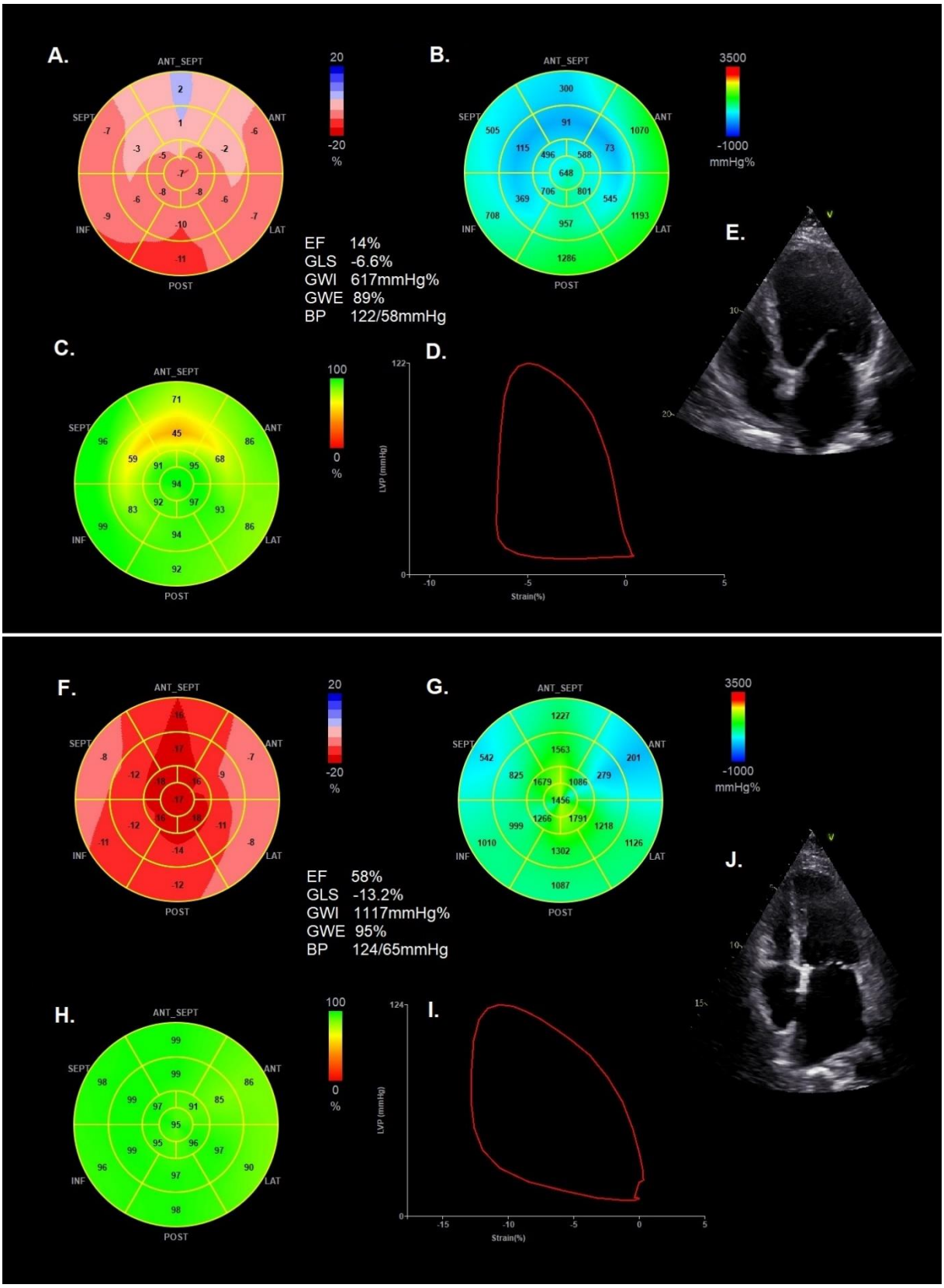


Figure 5: Longitudinal strain, (A, F), myocardial work index (B, G), myocardial work efficiency (C, H) bull's eye and PSL (D, I) in 2 HF patients with reduced ejection fraction (A-E) and preserved ejection fraction (F-J). *BP, blood pressure; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index.*

LV hypertrophy and concentric remodeling are commonly features in HFpEF. However unlike the hypertrophy observed in athletes, HFpEF-related hypertrophy is characterized by an imbalanced ratio between the number of myocytes and the extent of collagen deposition. This leads to increased LV stiffness and, in HFpEF, GCW and GWE correlate with the relative wall thickness (RWT) in HFpEF.[59] HFpEF patients with more extensive hypertrophy (RWT>0.42) exhibit lower GWE values compared to healthy individuals, while GCW was similar between both groups.

These findings contradict a previous study[60] that reported lower GCW in hypertrophic hearts. Through multivariate analysis, GCW emerged as the sole predictor of LV fibrosis with a cut-off value of 1623 mmHg%; demonstrating 82% sensitivity and 67% specificity.

To date, only one study has analyzed the impact of medication on MW in HFpEF. In a sub-analysis of the SpironolacTone in myocaRdial dysfUnCTion with redUced exeRcisE capacity (STRUCTURE) trial[61] which performed exercise echocardiograms at baseline and at 6 months in patients receiving either spironolactone or placebo, those treated with spironolactone showed a significant improvement in exercise capacity along with higher exertional increases in GCW at follow-up. This suggests that GCW might serve as a valuable measure of LV contractile response to exertion and could outperform GLS in evaluating exercise capacity.

MYOCARDIAL WORK IN DYSSYNCHRONY

Left Bundle Branch Block

Approximately 20-30% of congestive HF patients have LBBB, which is associated with increased mortality.[62] In the presence of uncoordinated LV contractions the myocardial segments in the septal and lateral wall experience differential shortening (positive work) and lengthening (negative work) at various time points and against different afterload levels. The septal segments (SS) contract early in systole at low intraventricular pressure generating minimal positive work while the lateral wall (LW) segments contract late in systole at maximal intraventricular pressure, producing a considerably greater amount of positive work than the SS. Additionally, as the LW shortens, the SS elongates, absorbing the positive work generated by the LW as negative work.[63] This results in a characteristic PSL pattern of the SS, resembling the shape off an eight (***Figure 3***). Notably, the net work performed by SS during systole is negative, indicating that septal contraction does not contribute to ventricular ejection.[23,64] The compensation for this counterwork is achieved by the extra work performed by the LW to maintain CO. It is important to mention that different degrees of LBBB can occur, resulting in varying degrees of septal rebound stretch and lateral pre-stretch.[65] Therefore not all patients

will exhibit a clearly defined 8-shaped PSL for the SS, but the typical regional strain features can still be recognized in the regional PSL. In asymptomatic LBBB patients at rest, the balance of workload is compromised during exercise when heart rate and filling pressures increase, exacerbating dyssynchrony and leading to inefficient LV performance and limited exercise capacity.[63]

The lower workload in the SS leads to reduced metabolic activity and thinning of the myocardium, while the elevated workload in the LW results in higher metabolic demand and myocardium thickening. Delhaas et al[66] conducted a study examining the relationship between regional myocardial work, blood flow and oxygen uptake revealing significantly lower total mechanical work, myocardial blood flow and oxygen uptake in earlier activated regions compared to those activated late.

Cardiac Resynchronization Therapy

While dyssynchrony in patients with LBBB leads to adverse remodeling and asymmetric LV hypertrophy, the implantation of a Cardiac Resynchronization Therapy (CRT) device induces reverse remodeling.[10,64,67] Cvijic et al[68] observed three interesting changes after CRT: 1- the difference between SS and LW disappeared due to septal thickening and lateral thinning, 2- there was no difference in time to onset shortening between SS and LW after CRT implantation, 3- a more uniform distribution of myocardial work was observed. Subsequently, Duchenne et al[69] found that the acute redistribution of work across the septal and lateral walls was the strongest determinant of reverse remodeling.

MW can also be utilized to predict the response to CRT which is associated to the extent of energy loss as measured by the workload difference between SS and LW.[70,71] Prior to CRT, responders exhibit higher levels of GWW compared to non-responders. After implantation a decrease in GWW is observed only in those who positively respond to the therapy. Additionally, the uncoordinated contraction of the LV due to the LBBB activation results in diverse values of regional wasted work (WW), making septal WW a better predictor than GWW for CRT response. Moreover when septal WW is combined with the wall motion score index (WMSI), a marker of dyssynchrony, its predictive value for CRT response can be further enhanced.[64] Furthermore, GCW before CRT corresponds to residual myocardial metabolic activity and contractile reserve, and correlates with LV remodeling after CRT.[72]

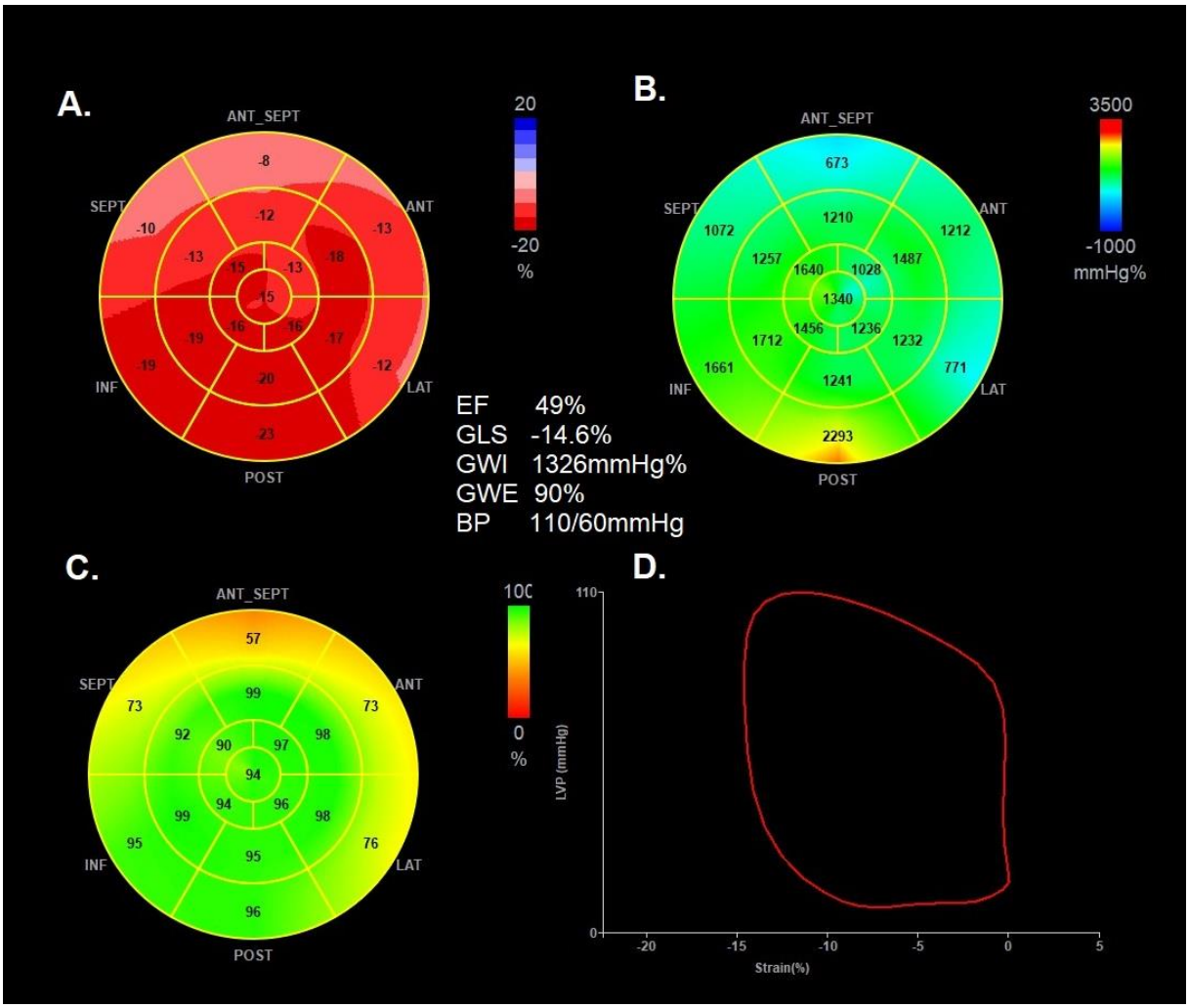


Figure 6: Longitudinal strain (A), myocardial work index (B), myocardial work efficiency (C) bull's eye and PSL (D) in a patient with cancer treatment–related cardiac dysfunction after anthracycline therapy. *BP, blood pressure; EF, ejection fraction; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index.*

MYOCARDIAL WORK IN CARDIO-ONCOLOGY

The diagnosis and classification of Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD) is based on symptoms combined with LVEF, GLS and cardiac biomarkers. Despite the availability of data on MW in patients receiving anthracyclines and targeted therapies, its role in predicting CTRCD has not been included in the recent guidelines[73], leading to ongoing debate. ***Figure 3*** illustrates the expected PSL-pattern for patients with CTRCD, while ***Figure 6*** provides an illustrative example of MW in a patient with moderate CTRCD following anthracyclines therapy.

In a large retrospective study that examined LVEF, GLS and MW parameters before, during and after anthracycline chemotherapy, Zhan et al[74] demonstrated the superiority of MW over GLS in early CTRCD detection. Specifically, hematological malignancies, were associated with lower GWI and GWE as well as higher GCW and GWW in comparison to other malignancies. A 15% decline in GWW and GWI preceded CTRCD defined by GLS, and the

changes in GWI and GCW were directly proportional to the cumulative dose of anthracyclines administered.

Guan et al[75] also reported a decrease in GWI and GWE, following chemotherapy. However, in contrast to Zahn et al[74], they found that the sensitivity of GWI and GWE in predicting CTRCD was lower compared to GLS. Specifically, they concluded that GLS is superior to GWI in predicting CTRCD, particularly in patients with minimal BP variability. The impact of BP variation on LV function and MW during chemotherapy was further explored in a case-control study by Kosmala et al[76]. They found that individuals with a BP change greater than 20 mmHg had increased GCW and GWI with normal or impaired GLS. This observation can be attributed to the influence of afterload on LV performance and the absence of direct myocardial dysfunction. Furthermore, a decline in GWI and GCW in CTRCD patients with a BP change exceeding 20 mmHg suggested limited contractile reserve in response to afterload elevation.

Finally, the incremental value of GWI and GCW in combination with clinical characteristics and GLS was shown by Calvillo-Argüelles et al[77]. Their findings indicated that changes in afterload may be less relevant for prognosis when there is a significant change in GLS. Interestingly, they identified a specific patient phenotype of patient characterized by higher GWW and lower GWE at baseline, which rendered them more susceptible to the development of CTRCD. However, in a more recent study[78] it was revealed that GWI, GWE and GCW at baseline, rather than GWW, were able to predict the occurrence of moderated CTRCD.

OTHER RESEARCH DIRECTIONS

Coronary Artery Disease

While coronary artery disease (CAD) may not directly affect the loading conditions of the LV, the impaired oxygen metabolism in ischemic myocardium can have an impact on the myocardial work. Following revascularization, there is often a significant improvement in GWI, GCW and GWE during the initial months which may be attributed to myocardial stunning.[79] Of note, GWI and GCW are significantly depressed in CAD patients with normal LV function and wall motion abnormalities.[80] However, the presence of both volume and pressure overload makes it challenging to determine whether ischemia is the primary driver for the observed changes in MW.[81] To address this issue, the assessment of regional instead of global MW may be helpful for diagnosing ischemia. Guo et al[79] demonstrated that regional MWI and CW were significantly lower in ischemic LV segments perfused by vessels with a fractional flow reserve (FFR) ≤ 0.75. By using a cut-off value of <1623.7 mmHg% for MWI and <1962.4 mmHg% for

CW it is possible to distinguish between ischemic and non-ischemic segments. As expected, regional MWI and CW improved after percutaneous coronary intervention. Moreover, Boe et al[82] provided evidence supporting the superior effectiveness of regional MWI in detecting acute coronary occlusion in patients with non-ST segment elevation acute coronary syndrome. They also proposed the use of regional MWI as a means of identifying patients who require prompt invasive treatment. ***Figure 7*** shows an illustrative example of MW in a patient with subacute occlusion of the left artery descending.

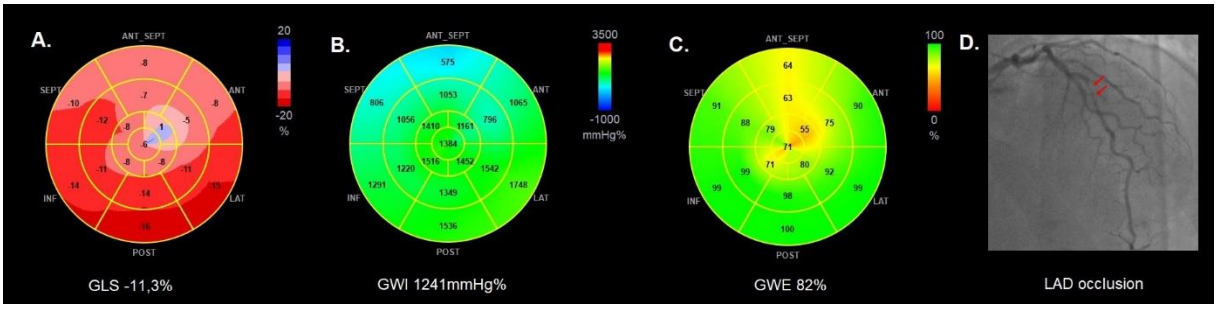


Figure 7: Longitudinal strain (A), myocardial work index (B) and myocardial work efficiency (C) bull's eye in a patient with CAD and subacute occlusion of the left artery descending (D). *CAD, coronary artery disease; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index, LAD, left artery descending.*

Cardiac Amyloidosis

Patients with cardiac amyloidosis (CA) exhibit a distinct pattern of regional differences in LV deformation known as apical sparing, characterized by more severe impairment of strain in the basal and mid-segments compared to the apical segments. The apical-to-basal strain gradient is also associated with regional variations in MW specifically depressed GWI and GWE in the basal segments. An illustrative example of MW in a patient with CA is depicted in ***Figure 8***. Studies[83,84] have shown that the high apical-to-basal segmental work ratio serves as a reliable predictor for major adverse cardiovascular events (MACE) and all-cause mortality in patients with CA. Stasen et al[85] demonstrated the superiority of GWC compared to GLS to discriminate CA from hypertrophic cardiomyopathy. Additionally, GWI and GWE at rest have been found to be correlated with levels of NT-proBNP.[46]

Right Ventricle

The concept of right ventricular MW remains uncertain and requires further investigation for its clinical implementation.[86] While Butcher et al[87] showed its prognostic value in patients with pulmonary hypertension, additional research is necessary to validate and understand its implications before it can be widely used in clinical practice.

CONCLUSION

The evaluation of global and regional MW assessment through non-invasive PSL analysis offers a reliable method for a comprehensive assessment of LV performance. This approach holds particular significance in cardiac conditions characterized by abnormal afterload and dyssynchrony. Furthermore, the integrated interpretation of MW's various components provides valuable insights into underlying pathophysiological mechanisms. While the potential of MW is promising and has garnered increasing interest, larger studies are necessary to further investigate its role and application in routine clinical practice.

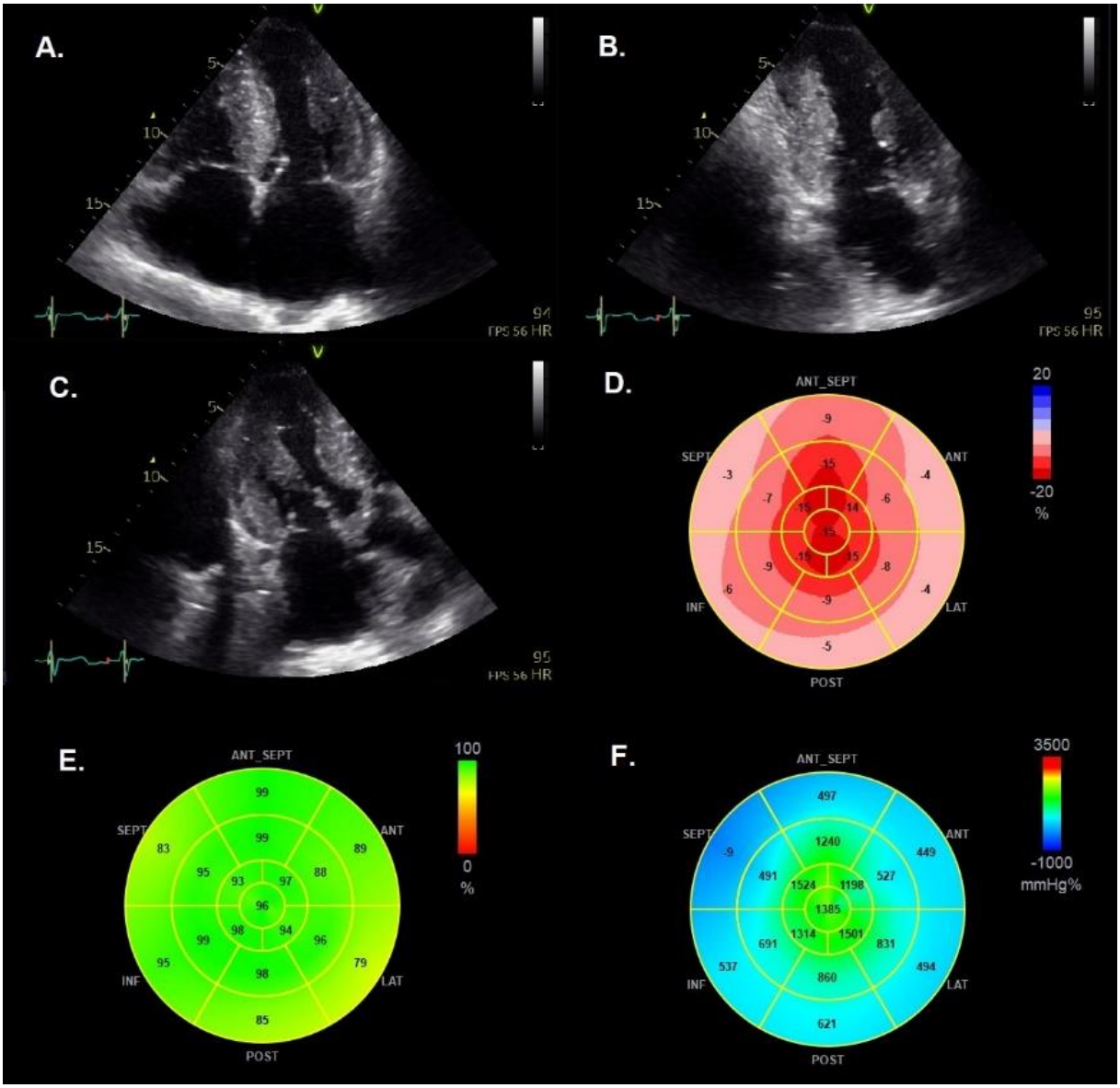


Figure 8: Typical LV wall thickening (A-C) and apical sparing pattern in the longitudinal strain (D) myocardial work efficiency (E) and myocardial work index (F) bull's eye in a patient with CA.

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Chapter 2

Myocardial Work in Cardio-Oncology

Serial Non-Invasive Myocardial Work Measurements for Patient Risk Stratification and Early Detection of Cancer Therapeutics-Related Cardiac Dysfunction in Breast Cancer Patients: A Single-Centre Observational Study

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Serial transthoracic echocardiographic (TTE) assessment of LVEF and GLS are the gold standard in screening Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD). Non-invasive left ventricle (LV) pressure-strain loop (PSL) emerged as a novel method to quantify Myocardial Work (MW).

This study aims to describe the temporal changes and longitudinal trajectories of MW indices during cardiotoxic treatment. We included 50 breast cancer patients with normal LV function referred for anthracycline therapy w/wo Trastuzumab. Medical therapy, clinical and echocardiographic data were recorded before and 3, 6, 12 months after initiation of the chemotherapy. MW indices were calculated through PSL analysis. According to ESC guidelines, mild and moderated CTRCD was detected in 10 and 9 patients respectively (20% CTRCDmild, 18% CTRCDmod) while 31 patients remained free of CTRCD (62% CTRCDneg). Prior to chemotherapy MWI, MWE and CW were significantly lower in CTRCDmod than in CTRCDneg and CTRCDmild. Overt cardiac dysfunction in CTRCDmod at 6 months was accompanied by significant worse values in MWI, MWE and WW compared to CTRCDneg and CTRCDmild.

MW features like low baseline CW, especially when associated with a rise in WW at follow-up, may identify patients at risk for CTRCD. Additional studies are needed to explore the role of MW in CRTCD.

INTRODUCTION

Cardiotoxicity is a growing concern in patients referred for chemo-therapy and anti-cancer drugs. This is in part related to the significantly prolonged survival of cancer patients in general but also because of the growth of the therapeutic armamentarium with the emergence of novel targeted cancer therapies. Several types of chemotherapeutics are related to cardiac dysfunction[1,2] which poses a management dilemma in balancing between a potentially life-saving anti-cancer treatment and the risk of Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD).[3,4] In the new ESC guidelines on cardio-oncology the main cardiovascular (CV) risk factors are used to assess the risk for and monitor patients with CTRCD. Unfortunately, specific measurable CTRCD predictors are still lacking.[5,6]

Echocardiography is the method of choice for cardiac function surveillance[6,7] due to its widespread use, accessibility and scientific foundation. In the same ESC guidelines symptomatic heart failure (HF) is differentiated from asymptomatic HF in CTRCD. The severity of CTRCD in asymptomatic patients is determined by the decrease of left ventricular ejection fraction (LVEF) in combination with relative changes in global longitudinal strain (GLS) and levels of serum cardiac biomarkers.[6,8,9]

Nonetheless, all these indices have limitations and lack specificity in the surveillance throughout cancer treatment as it was proven in prospective follow-up studies.[10,11] Of note, GLS which can detect early changes in left ventricle (LV) function and is recommended in the cardio-oncology guidelines, is influenced by blood pressure (BP) changes.[9] This afterload dependency will impact its accuracy even in the absence of any change in myocardial function. Non-invasive Myocardial Work (MW) indices derived from LV pressure-strain loops (PSL) can overcome this load dependent limitation by incorporating estimated LV pressure in their equation.[12] This novel approach characterizes better LV function and allows to prognosticate adverse outcomes within various cardiac conditions.[13-15] In addition, the assessment of iso-volumetric contraction and relaxation as well as the ejection phase by MW indices, grants a more granular evaluation of the myocardial function.[16,17] Unfortunately, data validating MW in patients receiving chemotherapeutics are still scarce.[18-21]

Therefore, this observational longitudinal follow-up study was set up to investigate the temporal changes and longitudinal trajectories of MW indices during cancer treatment and assess the potential role of serial MW analysis in patient risk stratification and early detection of CTRCD.

MATERIALS AND METHODS

Study Population

In a prospective cohort we recruited 50 breast cancer patients receiving sequential therapy with anthracyclines w/wo Trastuzumab between April 2016 and September 2020 . All patients followed a similar anthracycline and taxane treatment regimen consisting of a combination of 4 cycles of Epirubicin and Cyclophosphamide every 2 or 3 weeks followed by 12 weekly doses of Paclitaxel. In addition, 33 HER2+ breast cancer patients received Trastuzumab every three weeks with the first dose being administered jointly with the first dose of Paclitaxel. Patients with a history of coronary artery disease, valvular stenosis or regurgitation of more than moderate severity, persistent atrial fibrillation, episodes of heart failure (≥ NYHA 2) before chemotherapy or depressed LV function (LVEF<50% and GLS>-18%) at baseline were excluded.[5] Patient's medical history and CV risk factors were collected at inclusion. Medical therapy, clinical parameters and echocardiographic data were recorded before onset of the chemotherapy (baseline) and during follow-up (at 3, 6, 12 months).

CTRCD definition

CTRCD was defined using LVEF and GLS according to the recent ESC guidelines. Patients were categorized as having no CTRCD (CTRCDneg) with a LVEF≥50% at follow-up and no relative decline in GLS>15% from baseline, mild CTRCD (CTRCDmild) with a LVEF≥50% and a relative decline in GLS>15% from baseline, moderate CTRCD (CTRCDmod) with a LVEF<50% together with a relative decline in GLS>15% from baseline and severe CTRCD with a LVEF<40%.[6] As none of the patients met the threshold for severe CTRCD, only patients with no, mild and moderate CTRCD were included in the analysis. Patients were grouped for analysis regardless the time of CTRCD onset.

Transthoracic Echocardiography

All patients underwent serial standard greyscale and Doppler transthoracic echocardiograms at baseline and at 3, 6, 12 months using GE Vivid 7 and 9 ultrasound systems (General Electric Vingmed Ultrasound, Horten, Norway) equipped with a 5-MHz multifrequency transducer. Dedicated apical 2- and 4-chamber images were obtained for measurement of bi-plane LVEF (Simpson method). For measurements of GLS, optimized 2-, 3- and 4-chamber apical view images of the LV were obtained for 3 cardiac cycles at high frame rates (55–75 frame per second) and were stored digitally for off-line analysis using dedicated software (EchoPac, GE Vingmed Ultra-sound, Horten, Norway).

Speckle Tracking Imaging

Semi-automated 2D speckle tracking was applied to the three apical views to assess 2D-GLS and to obtain the LV strain bull-eye with the segmental strain values. Myocardium contour and region of interest (ROI) width were manually adjusted if necessary by the operator according to patient anatomy. The timing of aortic and mitral valve events was visually determined at the apical 3-chamber view. After measuring the peak negative value on the strain curve, GLS was calculated as the average from all LV segments interrogated.[9,22]

MW assessment

MW analysis was performed off-line and was not intended to guide patients' therapy during follow-up. During post-processing strain, non-invasive BP, measured at the brachial artery at the time of the examination, and valve events were integrated with an automated dedicated software tool. This software package constructs a non-invasive LV pressure curve, adjusted according to the duration of isovolumic and ejection phases defined by valvular timing events.[23] Strain and pressure data were synchronized using the onset of R-wave on the ECG. MWI, MWE, global CW and global WW were recorded. MWI, derived from the area of the LV PSL, reflects the total work calculated from mitral valve closure to mitral valve opening, CW is the work performed by the LV contributing to LV ejection during systole, WW is the work performed by the LV that does not contribute to LV ejection. MWE is defined by CW divided by the sum of CW and WW. Global values were obtained as average from all myocardial segments.[12]

Reproducibility

The intra- and interobserver variability for GLS and MW are reported in ***Table S1***. Briefly, ten patients were randomly selected, and repeated measures were performed by two independent observers (expert echocardiographers) blinded to the patient's clinical data and each other's results. Intra-observer variability was performed by the sonographer on off-line data at different points in time. Interobserver variability was performed by repeating measurements from the same images by the 2 sonographers. Intra- and interobserver variability were calculated by intraclass correlation coefficient (ICC) and the standard error of measurements.

Statistics

Descriptive data are reported as mean ± SD for normally distributed continuous variables. Normality testing was performed by graphical analysis with histograms and QQ-plots. Differences between groups were compared using One way ANOVA test for continuous variables and Pearson's χ^2 test for categorical variables. Additionally, CTRCDneg and

CTRCDmild were grouped together for comparison with CTRCDmod using an independent 2-tailed T test. The predictive value for moderate CTRCD of MW and GLS indices was analyzed using a random effects logistic regression model with random slope. For a clinical meaningful interpretation of the fixed effects of the regression model we rescaled the predictor variables with 10^{-3} for MWI and CW and with 10^{-1} for MWE. Odds ratios and 95% CI were reported. For all tests, a p-value below 0.05 was considered statistically significant. All statistics analysis were performed using SPSS for Windows Version 25 (SPSS, IBM headquarters, Armonk, New York, US).

RESULTS

Baseline patients' characteristics

Between April 2016 and September 2020, 50 breast cancer patients (mean age 56 ± 12 years) were included in the study and were followed for at least 1 year after the start of their chemotherapy. During follow-up moderated CTRCD was detected in 9 patients (18% CTRCDmod), occurring at 6 and 12 months in 5 and 4 patients respectively, mild CTRCD was observed in 10 pts patients (20% CTRCDmild) occurring at 3, 6 and 12 months in 3, 4 and 3 patients respectively and 31 patients remained free of CTRCD (62%, CTRCDneg). None of the patients developed severe CTRCD at follow-up. Baseline patients' characteristics are summarized in ***Table 1***. No significant differences in CV risk factors, therapy or clinical parameters were noted between the different groups.

Temporal changes in LV systolic function in patients with/without cardiotoxicity

Echocardiographic data are presented in ***Table 2***. Before the onset of cancer therapy, all patients presented with normal LV systolic and diastolic function. Interestingly, although baseline GLS was within normal limits in the three cohorts, those in the CTRCDmod group presented with an already significantly lower GLS at baseline compared to the CTRCDneg and CTRCDmild group.

In the CTRCDneg and CTRCDmild groups, the LVEF remained un-changed at follow-up whereas in the CTRCDmod group, LVEF at 6 months was significantly lower compared to CTRCDneg and CTRCDmild patients. At 12 months, LV dysfunction persisted in the CTRCDmod group (***Table 2***, ***Figure 1***).

By definition GLS remained unchanged at follow-up in CTRCDneg patients whereas it significantly worsened in CTRCDmild and CTRCDmod (***Table 2***). In this last group the GLS at 6 and 12 months was significantly impaired compared to the other groups. Interestingly, the deterioration of GLS in the CTRCDmild group was accompanied by a significantly higher afterload at 12 months compared to the other groups (***Table 3***).

Table 1: Baseline patients' characteristics and medical therapy.

	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	p-value	TOTAL
N *(%)*	31 (62)	10 (20)	9 (18)	-	50
Age, yo *(mean ± SD)*	56 ± 13	53 ± 11	59 ± 12	0.49	56 ± 12
Cardiovascular risk factors					
Diabetes mellitus, *n (%)*	2 (6,5)	0	0	0.53	2 (4)
Arterial hypertension, *n (%)*	6 (19,4)	2 (20)	1 (11,1)	0.84	9 (18)
Hyperlipidemia, *n (%)*	5 (16,1)	1 (10)	0	0.41	6 (12)
Obesity, *n (%)*	5 (16,1)	0	1 (11,1)	0.41	6 (12)
Smoking, *n (%)*	3 (9,7)	1 (10)	0	0.58	4 (8)
Alcohol, *n (%)*	0	0	0	0.87	0
Family history of CVD, *n (%)*	2 (6,5)	1 (10)	1 (11,1)	0.34	4 (8)
Medication					
Beta blocker, *n (%)*	3 (9,7)	1 (10)	1 (11,1)	0.99	5 (10)
ACE-I or ARB, *n (%)*	3 (9,7)	0	0	0.38	3 (6)
Cardiotoxic drugs					
Trastuzumab, *n (%)*	18 (58,1)	8 (80)	7 (77,8)	0.34	33 (66)
Epirubicin, *cd mg (mean ± SD)*	574 ± 108	622 ± 94	598 ± 61	0.39	588 ± 99
Clinical parameters					
BMI *(mean ± SD)*	24,9 ± 4,1	25,9 ± 4,1	23,6 ± 2,2	0.50	25,0 ± 4
HR, *bpm (mean ± SD)*	75 ± 10	73 ± 9	73 ± 11	0.86	74 ± 10
QTc *(mean ± SD)*	422 ± 21	444 ± 34	435 ± 34	0.17	429 ± 27
QRS width, *ms (mean ± SD)*	82 ± 18	89 ± 5	89 ± 6	0.47	87 ± 7

ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, cd: cumulative dose, HR: heart rate, CTRCD: cancer treatment-related cardiac dysfunction, mod: moderate, neg: negative.

Temporal changes and longitudinal trajectories of MW in patients with/without cardiotoxicity

Temporal changes in MW indices are summarized in ***Table 3*** together with BP values as estimation of afterload variation. Longitudinal trajectories of MW are graphically presented in ***Figure 1*** together with the concurrent progression of LVEF and GLS. Baseline MWI, MWE and CW were significantly lower in the CTRCDmod group compared to the CTRCDneg and CTRCDmild groups. However, baseline WW was similar in all groups. For all MW indices, the CTRCDmod group showed persistent worse values during follow-up.

Despite equivalent values between the different cohorts at 3 months, MW indices remarkably deteriorated at 6 months and were significantly worse in the CTRCDmod group compared to the CTRCDmild and CTRCDneg groups. For MWI, WW and MWE this intergroup difference remained significant at 12 months.

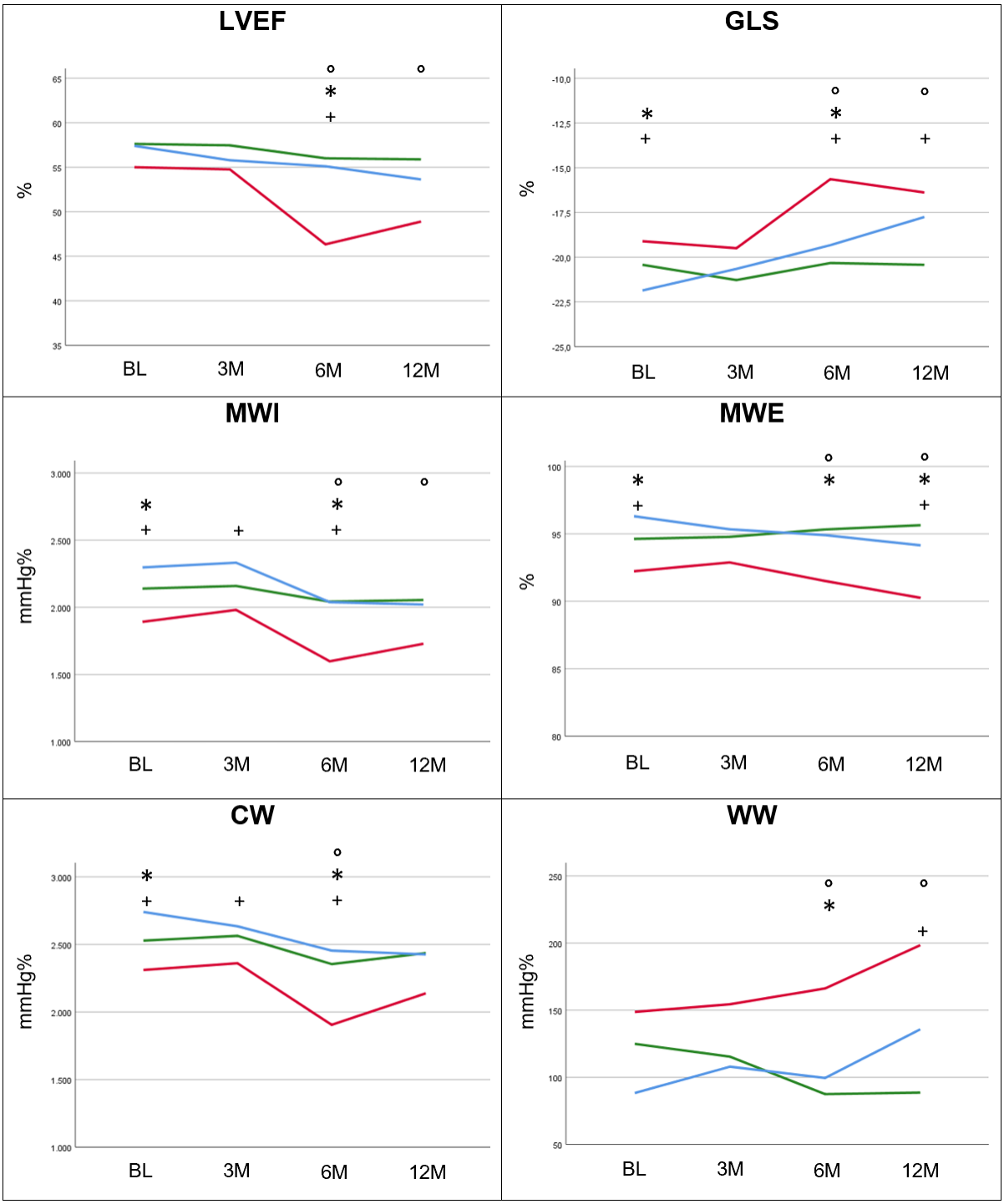

Figure 1. Main Figure. Temporal changes and trajectories of LVEF, GLS and MW indices in CTRCDneg (green), CTRCDmild (blue) and CTRCDmod (red) group. *°CTRCDmod vs CTRCDneg; *CTRCDmod vs CTRCDmild; +CTRCDmod vs CTRCDneg+mild; p≤0.05.*

The trajectories of MWI, MWE, CW and WW were significantly different between patients with and without CTRCD as well as between those with mild and moderate CTRCD (***Figure 1***). This is visually expressed in the differences in PSL-area at 12 months follow-up (***Figure 2***) between the three groups. Whereas CTRCDneg and CTRCDmild had similar MWI values and PSL-area at 12 months, the narrower and more elongated PSL in CTRCDmild suggests a physiological decrease in GLS due to increased afterload but without myocardial impairment. In contrast, the lower MWI value in CTRCDmod is consistent with the smaller PSL-area. Finally, an illustrative example of the different temporal changes in MWI in an individual patient, represented by the PSL-area, is shown in ***Figure 3***.

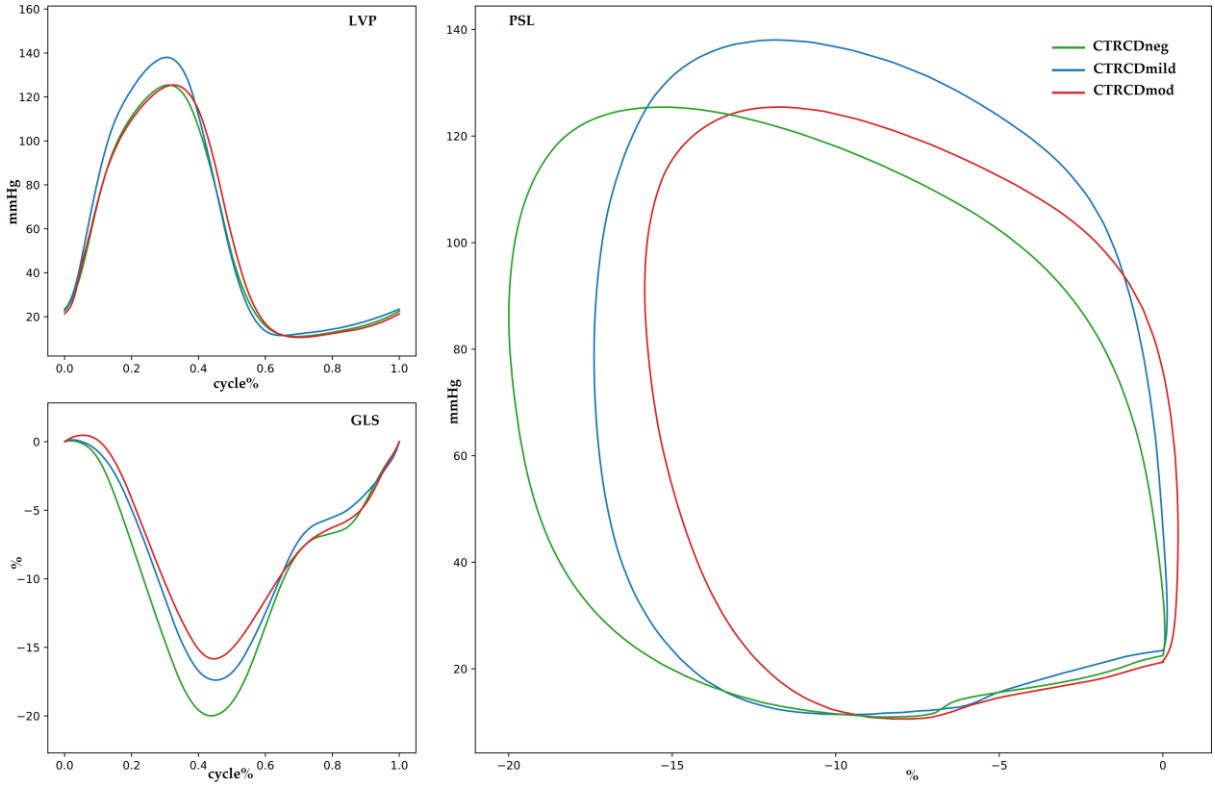

Figure 2. PSL-analysis for CTRCDneg, CTRCDmild and CTRCDmod at 12M follow-up.

Table 2: Echocardiographic data for CTRCDneg, CTRCDmild and CTRCDmod at baseline (BL) and follow-up (3M, 6M, 12M). **vs CTRCDmod, °vs CTRCDneg, +vs CTRCDneg+mild, p≤0.05*

		BL			3M			6M			12M		
		$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$
LV dimensions	**LVEDD** *(mean ± SD, mm)*	46 ± 4	46 ± 4	47 ± 4	44 ± 6	47 ± 5	45 ± 6	44 ± 5	44 ± 6	46 ± 7	45 ± 4	45 ± 4	46 ± 12
	LVESD *(mean ± SD, mm)*	30 ± 4	29 ± 6	32 ± 4	29 ± 6	33 ± 5	30 ± 6	30 ± 4	31 ± 6	33 ± 10	31 ± 7	32 ± 4	36 ± 11
	LVEDV *(mean ± SD, mm)*	91 ± 21	101 ± 21	95 ± 21	80 ± 31	104 ± 25°	80 ± 33	88 ± 20	93 ± 29	99 ± 29	84 ± 18	99 ± 16	92 ± 39
	LVESV *(mean ± SD, mm)*	34 ± 10	34 ± 11	34 ± 10	34 ± 16	43 ± 16	36 ± 14	36 ± 10*	39 ± 16	48 ± 22°	37 ± 10*	44 ± 10	52 ± 32°
	LV mass *(mean ± SD, g)*	129 ± 32	140 ± 24	131 ± 33	144 ± 50	146 ± 57	131 ± 39	133 ± 51	148 ± 37	137 ± 27	133 ± 38	135 ± 24	150 ± 70
	LV mass index *(mean ± SD, g/m²)*	75 ± 18	78 ± 12	72 ± 16	80 ± 22	77 ± 13	69 ± 7	73 ± 19	76 ± 20	78 ± 16	73 ± 15	75 ± 14	69 ± 31
LV-SF	**LVEF** *(mean ± SD, %)*	57,6 ± 4,3	57,4 ± 3,6	55 ± 4,5	57,5 ± 5,4	55,8 ± 4,4	54,8 ± 8,7	56,0 ± 4,6*	55,1 ± 4,5*	46,3 ± 4,5^{+}	55,9 ± 4,7*	53,6 ± 3,0	48,9 ± 10,1
	GLS *(mean ± SD, %)*	-20,4 ± 2,5	-21,9 ± 1,6*	-19,1 ± 1,7^{+}	-21,3 ± 2,6	-20,7 ± 3,6	-19,5 ± 3,1	-20,3 ± 2,0*	-19,3 ± 2,3*	-15,6 ± 3,2^{+}	-20,4 ± 2,9*	-17,8 ± 2,5	-16,4 ± 4,4^{+}
LV-DF	**E peak** *(mean ± SD, m/s)*	0,64 ± 0,17	0,68 ± 0,11	0,67 ± 0,18	0,66 ± 0,16	0,70 ± 0,16	0,68 ± 0,12	0,63 ± 0,17	0,71 ± 0,21	0,57 ± 0,15	0,65 ± 0,14	0,72 ± 0,15	0,69 ± 0,17
	A peak *(mean ± SD, m/s)*	0,72 ± 0,17	0,67 ± 0,17	0,78 ± 0,26	0,71 ± 0,18	0,70 ± 0,12	0,80 ± 0,21	0,68 ± 0,15	0,70 ± 0,14	0,71 ± 0,16	0,67 ± 0,18	0,74 ± 0,07	0,80 ± 0,22
	E/A ratio *(mean ± SD)*	0,95 ± 0,35	1,06 ± 0,25	0,93 ± 0,31	0,98 ± 0,37	1,02 ± 0,28	0,92 ± 0,33	0,97 ± 0,30	1,05 ± 0,31	0,81 ± 0,19	1,03 ± 0,36	0,99 ± 0,24	0,93 ± 0,31
	e' sept *(mean ± SD, m/s)*	0,07 ± 0,03	0,07 ± 0,02	0,9 ± 0,04	0,07 ± 0,02	0,10 ± 0,02°	0,08 ± 0,03	0,07 ± 0,02	0,08 ± 0,03	0,08 ± 0,03	0,08 ± 0,03	0,18 ± 0,25	0,08 ± 0,02
	e' lat *(mean ± SD, m/s)*	0,10 ± 0,04	0,10 ± 0,03	0,11 ± 0,06	0,09 ± 0,0,03	0,12 ± 0,04	0,10 ± 0,04	0,09 ± 0,02	0,11 ± 0,02	0,11 ± 0,04	0,11 ± 0,04	0,12 ± 0,03	0,11 ± 0,02
	E/e' *(mean ± SD)*	8,1 ± 2,8	7,9 ± 2,5	9,6 ± 1,2	8,0 ± 2,2	7,5 ± 2,1	8,5 ± 2,1	7,5 ± 1,9	7,0 ± 1,8	7,0 ± 3,5	7,5 ± 2,2	7,6 ± 1,7	7,4 ± 2,3
RV & LA	**LAVI** *(mean ± SD, ml/m^2)*	25 ± 7	21 ± 6	25 ± 15	25 ± 8	35 ± 4*°	20 ± 4	27 ± 9	29 ± 5	23 ± 7	30 ± 11	24 ± 3*	40 ± 10
	TAPSE *(mean ± SD, mm)*	22 ± 4	23 ± 4	23 ± 4	23 ± 3	23 ± 3	21 ± 2	22 ± 4	23 ± 4	22 ± 4	23 ± 4	22 ± 3	21 ± 4

(legenda Table 2) BL: baseline, DF: diastolic function, GLS: global longitudinal strain, LA: left atrium, LAVI: left atrial volume index, LV: left ventricle, LVEDD: left ventricular end diastolic diameter, LVEDV: left ventricular end diastolic volume, LVEF: left ventricle ejection fraction, LVESD: left ventricular end systolic diameter, LVESV: left ventricular end systolic volume, mod: moderate, neg: negative, RV: right ventricle, SF: systolic function, TAPSE: tricuspid annular plane systolic excursion, 3M: three months follow-up, 6M: six months follow-up, 12M: twelve months follow-up.

Predictive value of MW indices and GLS for CTRCD

The random effect logistic regression model demonstrated that MWI, MWE and CW were significant univariate predictors for moderate CTRCD. By contrast, GLS and WW were unable to predict moderate CTRCD. The odds ratio and confidence interval for fixed effects are summarized in ***Table 4***.

DISCUSSION

Our observational single center study demonstrates that in a population of breast cancer women undergoing treatment with anthracyclines the assessment of non-invasive MW by LV PSL analysis helps to estimate patient's risk and detect CTRCD. We demonstrated that patients with previous normal GLS but lower CW were at higher risk for developing CTRCD. In addition to lower baseline CW, patients with moderate CTRCD were characterized by a significant higher WW at follow-up. We conclude that MW assessment may be an additional confirmatory marker for patient risk stratification and detection of subsequent CTRCD. Therefore, further prospective studies addressing its use in breast cancer patients are warranted.

Surveillance and precision in CTRCD diagnosis

As cardiotoxicity may become one of the main determinants of poor quality of life and mortality in oncologic patients, the early detection of myocardial tissue damage related to cancer therapy remains of utmost importance. Currently, cardiac surveillance is guided by serial 2D echocardiographic evaluation of LVEF which is affected by several limitations including load dependency, its substantial variability and the need of geometric assumptions for its calculation. As an alternative, 2D-GLS has shown optimal feasibility and reproducibility and its relative change precedes LVEF reduction during chemotherapy.[24] However also this technique is hampered by limitations such as the inter-vendor variability, technical requirements intrinsic to the strain technology and its load dependency.[25] In our study all patients started anti-cancer therapy with intravenous anthracyclines administration every 3 weeks and completed this part of the treatment after 3 months. As anthracyclines provoke a cumulative dose-dependent cardiotoxic damage with irreversible cellular necrosis (Type 1 CTRCD), changes in LVEF and GLS are usually not detected before 3 months follow-up.[19]

Table 3: Myocardial Work indices and blood pressure (afterload) for CTRCDneg, CTRCDmild and CTRCDmod at baseline (BL) and follow-up (3M, 6M, 12M) **vs CTRCDmod, °vs CTRCDneg, +vs CTRCDneg+mild, p≤0.05*

	BL			3M			6M			12M		
	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$	$CTRCD_{neg}$	$CTRCD_{mild}$	$CTRCD_{mod}$
MWI *(mean ± SD, mmHg%)*	2139 ± 364	2297 ± 338*	1892 ± 215^{+}	2159 ± 437	2332 ± 652	1981 ± 162^{+}	2042 ± 380*	2038 ± 386*	1598 ± 347^{+}	2054 ± 267*	2021 ± 407	1728 ± 578
CW *(mean ± SD, mmHg%)*	2527 ± 391	2740 ± 383*	2310 ± 265^{+}	2563 ± 498	2633 ± 608	2360 ± 170^{+}	2354 ± 392*	2453 ± 317*	1905 ± 447^{+}	2436 ± 310	2426 ± 459	2138 ± 670
WW *(mean ± SD, mmHg%)*	125 ± 90	88 ± 50	149 ± 86	115 ± 88	108 ± 47	154 ± 79	87 ± 31*	100 ± 32*	166 ± 153	89 ± 48*	136 ± 90	198 ± 103^{+}
MWE *(mean ± SD, %)*	95 ± 4	96 ± 2*	92 ± 5^{+}	95 ± 3	95 ± 2	93 ± 4	95 ± 2*	95 ± 1*	92 ± 6	96 ± 2*	94 ± 3*	90 ± 5^{+}
SBP *(mean ± SD, mmHg)*	131 ± 15	134 ± 12	130 ± 12	125 ± 16	135 ± 18	131 ± 14	128 ± 14	132 ± 17	128 ± 9	128 ± 10	143 ± 21*°	126 ± 12
DBP *(mean ± SD, mmHg)*	78 ± 10	85 ± 12°	80 ± 11	72 ± 10	85 ± 12°	75 ± 18	76 ± 8	76 ± 11	76 ± 9	73 ± 8	86 ± 12*°	70 ± 6

BL: baseline, DF: diastolic function, GLS: global longitudinal strain, LA: left atrium, LAVI: left atrial volume index, LV: left ventricle, LVEDD: left ventricular end diastolic diameter, LVEDV: left ventricular end diastolic volume, LVEF: left ventricle ejection fraction, LVESD: left ventricular end systolic diameter, LVESV: left ventricular end systolic volume, mod: moderate, neg: negative, RV: right ventricle, SF: systolic function, TAPSE: tricuspid annular plane systolic excursion, 3M: three months follow-up, 6M: six months follow-up, 12M: twelve months follow-up.

This is in line with our results where the LV systolic function in the CTRCDmild and CTRCDmod groups was normal at 3 months and an evident deterioration was detected at 6 months follow-up in the CTRCDmod group when both LVEF and GLS were impaired compared to CTRCDneg and CTRCDmild. This relatively late detection of LV dysfunction may slow down the timely initiation of cardio-protective treatment and indicates the need for earlier detection of subtle changes in LV function to surveil hemodynamic deterioration.

The role of MW in CTRCD

To overcome the load dependency limitation of GLS, Russel et al[26] developed a non-invasive method for MW assessment which implements the patient's loading condition at the time of examination and offers a more complete picture of the LV function by quantifying both constructive as well as wasted work. Although MW indices, particularly MWI and CW, have diagnostic and prognostic value in a variety of cardiovascular conditions,[13-15] its role in patients receiving chemotherapy is limited.

In our results, baseline quantification of MW indices allowed to identify patients at higher risk of developing CTRCD. Interestingly, those with moderate CTRCD differentiated from the other groups by a lower MWE and CW at baseline. Moreover, we demonstrated that MWI, MWE and CW (and not WW and GLS) were able to predict moderate CTRCD. This in line with previous observations that showed a lower MWE at baseline in patients who developed CTRCD during follow-up.[27] As MWE is related to variations in both CW and WW with CW reflecting the myocardial work that contributes to cardiac output and WW the work that does not contribute to it, changes in each of these parameters could account for this observation. In contrast to the work of Calvillo-Argüelles et al[27] we demonstrated that not a higher WW but rather lower CW was responsible for the depressed MWE at baseline in patients with moderated CTRCD during follow-up. This may suggest there exists a distinct phenotype with a higher susceptibility for developing CTRCD, characterized by an inherent less efficient LV performance due to lower contractile capacity. Therefore MW features like low baseline CW, especially when associated with a rise in WW during follow-up, may identify patients at risk for CTRCD.

Limitations

The study presents some limitations. First, MW assessment is a relatively new and unexplored method especially in cancer patients where clear and robust reference values are still lacking. The adoption of MW assessment in routine practice requires the commitment of echocardiography laboratories and professionals' training. As experience is important for precision in strain measurements, sites adopting this approach should promote minimal annual volumes to maintain competency. Second, this advanced and sophisticated analysis requires

high quality images that are not easy to acquire in the daily practice. This study was also limited by its small sample size and single-center design which hampers statistical analysis to explore the role of MW indices in the multivariate context. Certainly, larger scale studies are needed for further validation of these results and to establish the clinical utility of MW in cancer patient surveillance.

In contrast with previous studies,[28-30] we did not collect data on the effect of cardioprotective treatment as our analysis was observational and not intended to guide medical therapy. Additionally, we categorized patients according to the first ESC guidelines on cardio-oncology which were published only after patients' data were collected. Finally, the addition of cardiac biomarkers to the analysis would definitely have enriched our results and longer follow-up would be of interest to explore the long-lasting cardiac effects of chemotherapy.

Table 4: Univariate random effect logistic regression model for Myocardial Work indices and GLS.

	Odds ratio	95% CI	p value
MWI x10^{-3}	0,89	0,82-0,96	0,01
MWE x10^{-1}	0,98	0,96-0,99	0,04
CW x10^{-3}	0,91	0,85-0,98	0,01
WW x10^{-2}	1	0,99-1,00	0,06
GLS	1	0,99-1,01	0,43

CW: constructive work, GLS: global longitudinal strain, MWE: myocardial work efficiency, MWI: myocardial work index, WW: wasted work.

CONCLUSIONS

In women with breast cancer receiving treatment with anthracycline w/wo Trastuzumab, lower CW at baseline as well as higher WW during follow-up identifies a subgroup of patients at risk for developing CTRCD irrespectively of LVEF and GLS. Our findings point out the usefulness of non-invasive MW assessment as a sophisticated tool for risk stratification previous to cancer treatment as well as clinical surveillance of cardiac function during follow-up. These promising results warrant additional studies to explore the role of MW for prediction and early detection of CRTCD. Similar to strain-guided initiation of cardioprotective therapy in patients at risk for CTRCD, studies exploring the role of a MW-guided approach in this patient population are needed.

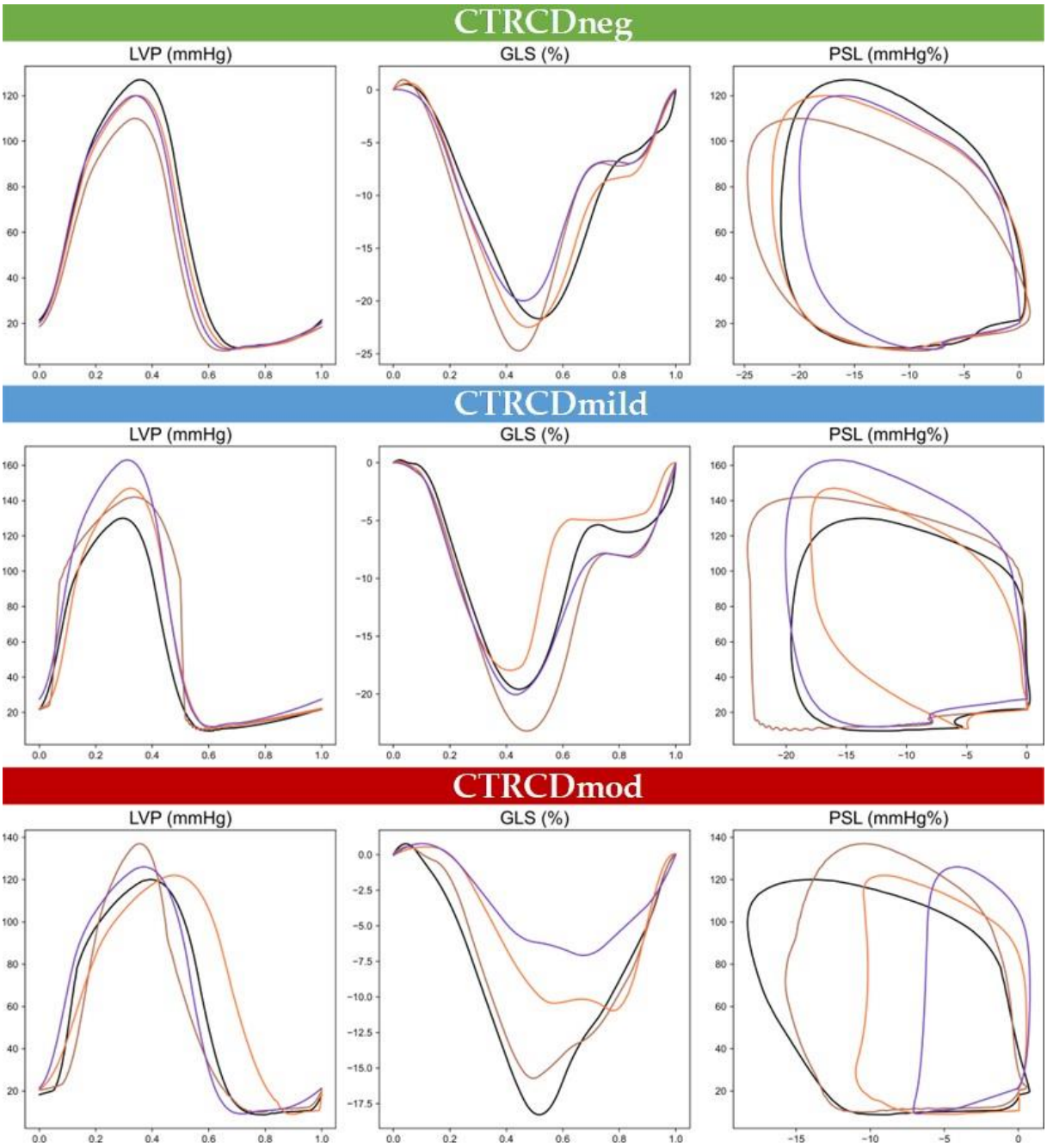

Figure 3. An illustrative example of temporal changes in LVP, GLS and MWI, graphically represented by the PSL-area, in 3 different patients without and with mild or moderate CTRCD. *Black: BL, brown:3M, orange:6M, purple:12M.*

Table S1. Intra- and Inter-observer variability.

	Intra-observer variability			Inter-observer variability		
	ICC (95% CI)	*Bias*	*Limits of agreement*	*ICC (95% CI)*	*Bias*	*Limits of agreement*
LVEF, %	0.616 (-0.144-0.871)	2.07 ± 5.6	-8.9 to 13.0	0.598 (0.068-0.859)	-4.1 ± 6.2	-16.3 to 8.1
GLS, %	0.898 (0.700-0.965)	0.80 ± 1.8	-2.8 to 4.4	0.861 (0.600-0.953)	-0.6 ± 2.1	-4.7 to 3.5
MWI, mmHg%	0.932 (0.782-0.978)	-101.0 ± 198.9	-490.9 to 288.8	0.869 (0.601-0.956)	2.8 ± 267.4	-521.4 to 527.07
MWE, %	0.921 (0.758-0.974)	-1.07 ± 2.2	-5.5 to 3.4	0.886 (0.441-0.967)	1.8 ± 2.2	-2.4 to 6.1
CW, mmHg%	0.925 (0.735-0.976)	-150.0 ± 249.9	-639.9 to 339.9	0.925 (0.778-0.975)	23.1 ± 229.6	-427.1 to 473.3
WW, mmHg%	0.952 (0.862-0.984)	14.2 ± 43.6	-71.2 to 99.7	0.815 (0.298-0.943)	-60.5 ± 78.6	-214.6 to 93.5

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Chapter 3

Myocardial Work in Aortic Valve Stenosis

Myocardial work predicts outcome in asymptomatic aortic stenosis: sub analysis of randomized AVATAR trial

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Two randomized clinical trials, AVATAR (Aortic Valve ReplAcemenT versus Conservative Treatment in Asymptomatic SeveRe Aortic Stenosis) and RECOVERY (Randomized Comparison of Early Surgery Versus COnventional Treatment in VERY Severe Aortic Stenosis), have reported improved clinical outcomes in asymptomatic patients with severe aortic stenosis (AS) undergoing early aortic valve replacement (AVR) as compared to those under conservative management.[1,2] This suggests that currently recommended triggers of aortic valve intervention such as the onset of AS-related symptoms or decrease in left ventricular ejection fraction (LVEF) might be insensitive in decision making by reflecting already adverse myocardial adaptation to sustained pressure overload. Recently, left ventricular (LV) myocardial work (MW) has been validated as an echocardiographic index of LV systolic performance incorporating afterload.[3] Thus, assessment of MW may be useful in this setting because AS is associated with interindividual and longitudinal variations in LV afterload imposed by stenotic aortic valve and peripheral circulation. Therefore, we investigated the association between global work index (GWI) and outcomes in asymptomatic patients with severe AS who were randomized to early AVR vs conservative treatment.

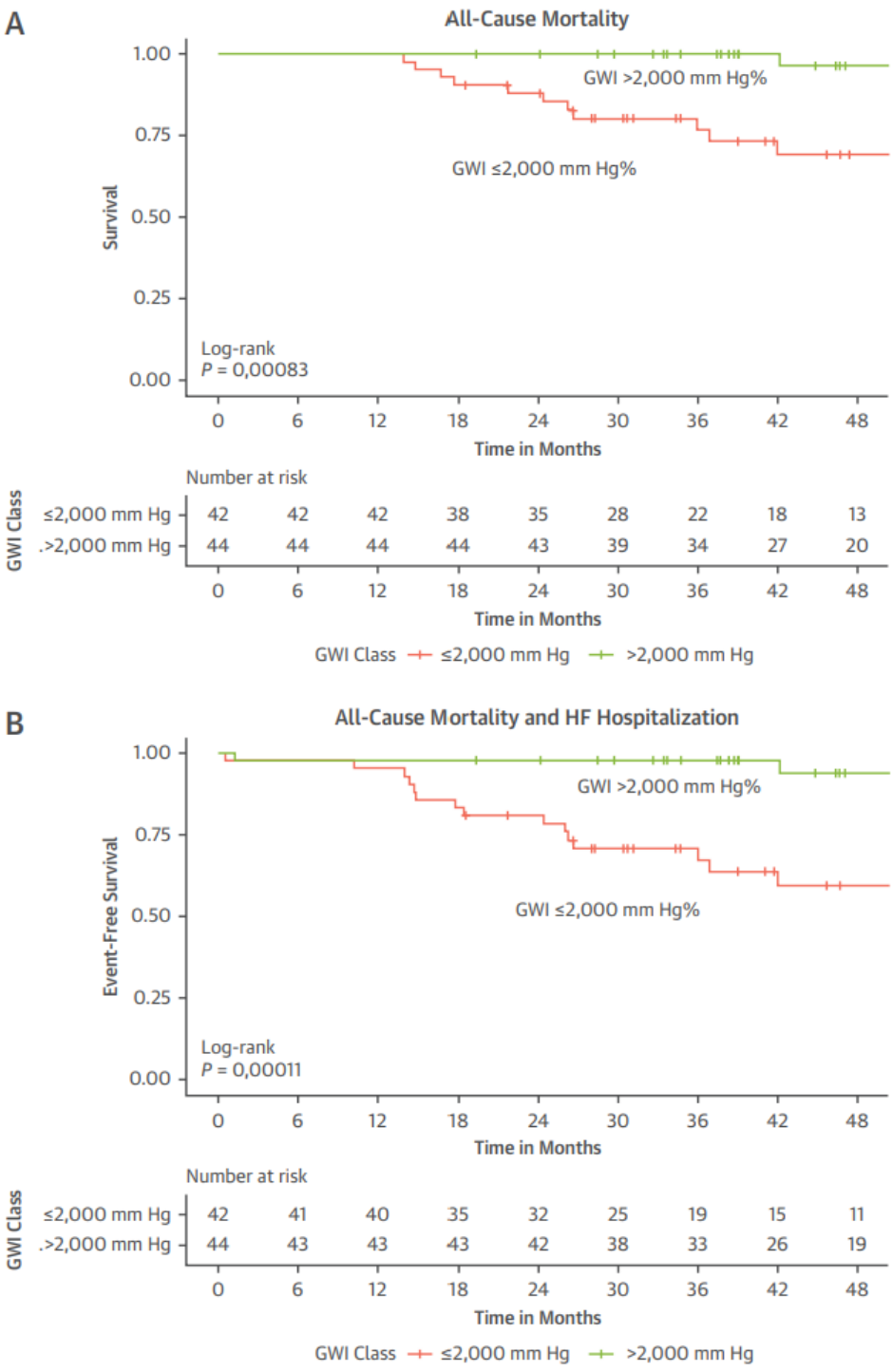
This analysis included all eligible patients (n=86; age 67±11 years; 43% female) with asymptomatic severe AS (mean transaortic pressure gradient [P mean]: >40 mm Hg; aortic valve area: <1cm²), preserved LVEF (>50%), and available echocardiographic images for MW analysis. The study protocol was approved by the ethics committees of all institutions. All patients signed informed consent.

All baseline echocardiographic images were recorded using a Vivid E9, 95, or S70 machine (GE Healthcare Horten) and analyzed off-line using dedicated software (EchoPAC, version 202). MW was assessed as described previously from global longitudinal strain (GLS) and a noninvasively estimated LV pressure curve, calculated by entering the sum of a subject's brachial cuff systolic blood pressure and mean pressure gradient across the aortic valve into the measurement tool.[3-5] This method has been validated in patients with AS.[4,5] GWI was calculated as the average of segmental values. During a median follow-up of 1305 (IQR: 931-1655) days, a total of 12 (14%) patients died, and an additional 8 (9%) subjects were admitted for heart failure (HF) decompensation. When spline curve and time-dependent receiver-operating characteristic analysis was used, patients with a GWI of ≤2000 mm Hg% vs >2000 mm Hg% showed increased risk for all-cause mortality (26% vs 2%; log-rank P < 0.001) or its composite with HF hospitalization (42% vs 5%; log rank P < 0.001) (***Figure 1***). In a multivariable Cox regression analysis, only GLS and GWI emerged as independent predictors of all-cause mortality (HR: 0.81 [95% CI: 0.66-0.99]; P=0.045 and HR: 0.50 [95% CI: 0.32-0.78]; P < 0.001, respectively) or its composite with HF hospitalization (HR: 0.79 [95% CI: 0.66-0.94]; P=0.008 and HR: 0.63 [95% CI: 0.52- 0.76]; P < 0.001, respectively). GWI also remained

an independent predictor for both endpoints in the subgroup analysis of patients who underwent AVR (HR: 0.90 [95% CI: 0.82-0.99]; P=0.036 and HR: 0.56 [95% CI: 0.61-0.86]; P=0.001, respectively) or who were managed conservatively (HR: 0.42 [95% CI: 0.21- 0.87]; P=0.02 and HR: 0.28 [95% CI: 0.11-0.71]; P=0.008, respectively). In a time-dependent receiver-operating characteristic analysis, GWI showed a significantly larger area under the curve than GLS both for all-cause mortality (0.87 vs 0.70; P=0.034) and its composite with HF hospitalization (0.89 vs 0.77; P=0.039). These results seem to support higher predictive accuracy of GWI compared with the GLS. In matched healthy individuals (n=20), the normal value of GWI was 1.965±288 mm Hg%.

To conclude, in asymptomatic patients with severe AS and preserved LVEF, a supranormal GWI is associated with better clinical outcomes, whereas normal or impaired values appear to identify patients with an unfavorable course. The present study adds to the evidence that GWI, as an afterload-adjusted parameter of LV systolic performance, may be more useful than load dependent indices (ie, ejection fraction or GLS) in the conditions characterized by variable afterload between visits or individuals with AS. Nevertheless, the results of this study must be interpreted with caution because of the small sample size (55% of the original AVATAR population) and small number of events during follow-up. However, the baseline characteristics of patients included in the subanalysis were similar to the whole AVATAR population. Therefore, this limitation may not hamper the interpretability of results.

FIGURE 1 **Kaplan-Meier Curves for Left Ventricular GWI Using Cutoff Values (≤2,000 mm Hg% vs >2,000 mm Hg%)**



(A) All-cause mortality. **(B)** Composite of all-cause mortality and HF hospitalization. GWI = global work index; HF = heart failure.

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Myocardial work and risk stratification in patients with severe aortic valve stenosis referred for transcatheter aortic valve replacement

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Transcatheter aortic valve replacement (TAVR) has shown clear survival benefits in severe aortic valve stenosis (AS). However, patients unable to recover left ventricle function remain at risk with poor long-term survival. This single-center prospective study aims to analyze the supplementary benefits of myocardial work (MW) assessment for baseline risk stratification in patients with severe AS referred for TAVR.

A total of 110 patients with severe AS referred for TAVR were included in the study. Baseline ECG data, transthoracic echocardiographic (TTE) images and blood samples were obtained. The TTE examination was repeated one day and one month after valve replacement. The primary outcome of the study was a composite endpoint consisting of all-cause mortality and HF hospitalization. During a mean follow-up period of 521±343 days, 29 patients (26.4 %) reached the composite endpoint. Baseline troponins, NT-proBNP, sST2, GWI and GCW showed statistically significant differences between groups. Patients with a baseline GWI<2323 mmHg% (sensitivity 0.63 and specificity 0.76) had significantly worse outcome following TAVR. A basic predictive model included QRS-length, TAPSE, LAVI and E/e'. The addition of biomarkers did not yield any further advantages whereas incorporating the GWI cut-off value of 2323 mmHg% significantly enhanced the predictive value. Although there were no significant changes in LVEF and GLS, all patients exhibited a significant reduction in GWI and GCW immediately after TAVR.

Our findings provide evidence for the enhanced usefulness of MW analysis in the initial risk stratification of patients with severe AS referred for TAVR. Specifically, a baseline GWI<2323 mmHg% demonstrates an independent predictor associated with increased incidence of all-cause mortality and HF hospitalization following TAVR.

INTRODUCTION

Aortic valve stenosis (AS) is the most common valve disease observed among the elderly population in Europe[1,2]. Transcatheter aortic valve replacement (TAVR) has shown significant survival benefits and is recommended for older patients who are at high risk or unsuitable for surgery[3,4]. However, the longstanding high pressure in the left ventricle (LV) can lead to irreversible myocardial damage. As a result, patients may not recover normal LV function after the intervention leading to a worsened prognosis and decreased survival rates. Consequently, there is an urgent need for a meticulous patient risk stratification system to guide disease management.

In 2017, Généreux et al.[5] developed a classification system consisting of five stages to categorize severe AS based on the extent of associated extra-valvular cardiac damage or dysfunction. Each stage is associated with an increased risk of mortality within 1 year, ranging from 4% in stage 0 to 25% in stage 4. More recently, the role of myocardial work (MW) has also been validated in AS patients[6,7]. This advanced echocardiographic tool analyzes the LV myocardial performance by incorporating afterload through pressure-strain loops[8,9]. Given the abrupt drop in afterload experienced by patients with severe AS after TAVR, MW analysis has emerged as a promising area of research in this patient population. Previous studies have demonstrated that MW parameters are not only independently associated with heart failure (HF) symptoms[10] but also with post-TAVR outcomes[11,12.] However it is important to note that MW assessment was not included in the Généreux et al. classification of AS, which consist of five stages : Stage 0 – No extra-aortic valve damage; Stage 1 – LV damage as defined by the presence of LV hypertrophy (LV mass index ≥95 g/m² for women, ≥115 g/m² for men), elevated LV filling pressures (E/e'≥14) or LV systolic dysfunction (LVEF ≤50%); Stage 2 – Left atrial or mitral valve damage/dysfunction as defined by the presence of enlarged left atrium (volume index ≥34 mL/m²), the presence of atrial fibrillation, or the presence of at least moderate mitral regurgitation; Stage 3 – Pulmonary artery vasculature or tricuspid valve damage/dysfunction as defined by the presence of systolic pulmonary hypertension (systolic pulmonary arterial pressure ≥60 mmHg or the presence of at least moderate tricuspid regurgitation; Stage 4 – Right ventricle damage as defined by the presence of at least moderate dysfunction (either tricuspid annulus systolic velocity S'≤9.5 cm/s, tricuspid annular plane systolic excursion ≤17 mm or stroke volume index ≤30ml/m²).

This single-center prospective study was designed to assess the prognostic significance of baseline characteristics in severe AS patients referred for TAVR. In particular, we focused on evaluating the additional value of MW parameters in risk stratification of these

patients at baseline. Furthermore, we investigated the longitudinal changes in LV function and performance immediately following TAVR and during long term follow-up.

METHODS

Patient selection and data collection

Between July 2020 and October 2023, all patients with symptomatic or asymptomatic severe AS referred for TAVR at Onze Lieve Vrouw Hospital in Aalst (Belgium) were screened for inclusion. Exclusion criteria comprehended patients who had previously undergone aortic valve replacement, had a mitral valve prosthesis, cardiac amyloidosis, moderate or severe mitral valve stenosis or pacemaker dependency. Patients who did not give consent or had inadequate echocardiographic image quality were also excluded. This study was conducted in accordance with the Declaration of Helsinki (1975) and was approved by the local Ethics Committee of the OLV Hospital Aalst. Informed consent was obtained from all subjects involved.

Data regarding signs and symptoms of HF, medical treatment, comorbidities, and cardiovascular risk factors were extracted from the patients' clinical records. Each patient underwent an electrocardiogram (ECG), blood pressure (BP) measurement and transthoracic echocardiographic (TTE) imaging and blood collection at the time of inclusion, one day before the intervention (baseline). The TTE examination was then repeated one day (post-TAVR) and one month (follow-up) after valve replacement. All patients were followed for a minimum of three months after TAVR.

Blood samples were analyzed to determine the plasma level of selected cardiac biomarkers including high-sensitivity troponin (Trop HS)[13], N-terminal pro-B-type natriuretic peptide (NT-proBNP)[14], and soluble suppression of tumorigenicity 2 (sST2)[15].

Echocardiographic data acquisition and measurements

A comprehensive TTE was performed using a Vivid S70 ultrasound system which was equipped with M4S transducers (GE Vingmed Ultrasound, Horten, Norway). Two-dimensional (2D), color, pulsed and continuous wave Doppler images were obtained from parasternal and apical views adhering to current recommendations. The TTE examinations were performed with patients in the left lateral decubitus position at rest[16]. The peak aortic jet velocity and the LV outflow tract (LVOT) velocity-time integral were estimated using the continuous and pulsed wave Doppler recordings from the apical 5-chamber view. The velocity-time integral measured on the pulsed-wave Doppler recordings of the LVOT was used to calculate the stroke volume

index (SVi). The aortic valve area (AVA) was calculated using the continuity equation, which involved the velocity time integrals of the LVOT and aortic valve (AV), and was then indexed for body surface area (BSA). The mean and peak transvalvular pressure gradients were calculated using the Bernoulli equation[17]. In the parasternal long-axis view, the end-diastolic and end-systolic volume were measured, and the LV mass was calculated and indexed for BSA. The LV ejection fraction (LVEF), the LA volume and LA volume index (LAVI) were calculated using the Simpson's biplane method in the 2- and 4-apical views and indexed for BSA. In the apical 4-chamber view, pulsed wave Doppler at the mitral valve was used to assess LV diastolic function and filling pressures, while tissue Doppler was used at the mitral annulus. The Proximal Iso-velocity Surface Area method was employed to evaluate mitral valve regurgitation. The right ventricular pressure was calculated based on the peak velocity of the tricuspid regurgitant jet. Consequently the systolic arterial pulmonary pressure (sPAP) was estimated by adding the right atrial pressure determined by the inspiratory collapse of the inferior vena cava[18]. The right ventricular function was evaluated by measuring tricuspid annular plane systolic excursion (TAPSE) using M-mode in the apical 4-chamber view 19. Myocardial Work calculation.

The optimized 2-, 3- and 4-chamber apical view images of the LV were digitally stored in cine-loop format at high frame rates (55–75 frame per second) for subsequent offline calculation of MW parameters using dedicated software (EchoPac, GE Vingmed Ultrasound, Horten, Norway). Semi-automated 2D speckle tracking was employed to analyze the three apical views to evaluate the global longitudinal strain (GLS) and obtain the LV bull's-eye with the segmental strain values. If necessary, the myocardium contour and region of interest width were manually adjusted by the operator according to the patient anatomy. LV systolic pressure was estimated using echocardiography by adding the mean aortic transvalvular gradient to the aortic systolic pressure obtained from cuff measurement at the time of examination[10]. The timing of aortic and mitral valve events was visually determined from the apical 3-chamber view. To construct non-invasive pressure-strain loops of the LV, strain values, echocardiography-derived LV systolic pressure and valve events were integrated. The global work index (GWI), efficiency (GWE) as well as global constructive (GCW) and wasted work (GWW) were computed using previously described methods[20].

Statistical analysis

The primary outcome of the study was a composite endpoint of all-cause mortality and HF related hospitalization. Baseline characteristics were compared between groups (Group A: patients who did not meet the study composite endpoint, Group B: patients who reached the study composite endpoint) using independent t-test for continuous variables. The Chi-square

test was performed to analyze association of the categorical variables with the study composite endpoint. The prognostic value of these characteristics was assessed through univariate and multivariate Cox analysis. Additionally, the Receiver Operating Characteristic (ROC) method was employed to analyze MW parameters with the calculation of the Area Under the Curve (AUC) to determine the optimal cut-off value that maximizes sensitivity and specificity. Patients were subsequently categorized according to this threshold and the survival rates were calculated using the Kaplan-Meier method with the long rank (mantel-cox) test for intergroup difference. Significant longitudinal changes in LVEF, GLS and MW parameters were analyzed using paired samples T test.

Continuous data were presented as mean ± SD while categorical data were presented as frequencies and percentages (n, %). SPSS software version 23.0 (IBM, Armonk, New York) was used for statistical analyses. A two-sided p value <0.05 was considered statistically significant.

The intra- and interobserver variability analysis was performed for LVEF, GLS and MW parameters. Briefly, ten patients were randomly selected for each analysis. Intra-observer variability was performed by the sonographer repeating measurements on off-line data with a time interval of at least three months. Interobserver variability was performed by repeating measurements from the same images by 2 independent expert sonographers blinded to the patient's clinical data and each other's results. Intra- and interobserver variability were calculated by intraclass correlation coefficient (ICC) and the standard error of measurements.

RESULTS

Baseline characteristics and outcome

A total of 110 patients diagnosed with severe AS who were referred for TAVR were enrolled in the study. The baseline characteristics of the patients are displayed in ***Supplemental Table 1***. Over a mean follow-up period of 521 ± 343 days after procedure, the combined endpoint was reached by a total of 29 patients (26.4%): 22 patients died (20%), whereas 12 patients were hospitalized due to HF (11%).

Patients in Group B, who died or were hospitalized for HF, displayed a relatively higher prevalence of AS stage 3 or 4, NYHA class 3, atrial fibrillation, and severe dyspnea compared to patients in group A, who did not meet the endpoint. Additionally, this group exhibited a higher prevalence of smoking history, severe tricuspid or mitral valve regurgitation and diuretic intake. Baseline QRS duration, Trop HS, NT-proBNP, sST2, GWI, GCW, TAPSE, E/A, LA volume, LAVI, septal e' and E/e', mean E/e' and sPAP all showed statistically significant differences

between the two groups. Furthermore, all these parameters, apart from sST2 and sPAP, appeared to be associated with outcome based on the univariate Cox analysis (***Table 1***).

Baseline Myocardial Work parameters as predictors of outcome

Among the MW parameters, only baseline GWI and GCW were found to be significantly different between patients groups A and B. In the ROC curve analysis both variables had an AUC of 0.657 (***Figure 1A***). A baseline GWI of 2323mmHg% was established as the cut-off for categorizing patients with a sensitivity of 0.63 and specificity of 0.76. Survival analysis demonstrated a significant association between a lower, GWI<2323mmHg% and worse outcome following TAVR (***Figure 1B***).

Based on the variables from the AS staging system developed by Généreux et al[5], a prognostic model was constructed to incorporate cardiac biomarkers and MW parameters for predicting outcomes following TAVR. The specific outcomes considered in the model were all-cause death or HF hospitalization. The baseline variables included were QRS length, TAPSE, LAVI, and mean E/e' (***Table 2***). The addition of NT-proBNP, Trop HS or sST2 to the initial model did not yield any discernible advantages. However, the model showed significant improvement when incorporating the baseline GWI cut-off value of 2323mmHg%.

Table 1: Clinical parameters, ECG values, serum biomarkers' levels and TTE measurements in patients with negative vs positive endpoint. Univariate cox analysis of variables showing significant intergroup difference at baseline. *Group A: patients who did not meet the study composite endpoint, Group B: patients who reached the study composite endpoint*

	ALL (110)	**Group A (81)**	**Group B (29)**		**Univariate Cox Analysis**	
	Mean ± SD	*Mean* ± SD	*Mean* ± SD	*p value*	χ^2	*p value*
General Characteristics						
Age *years*	83 ± 6	83 ± 6	82 ± 6	0.36		
BSA *m²*	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	0.81		
SBP *mmHg*	143 ± 25	146 ± 25	136 ± 23	0.06		
DBP *mmHg*	83 ± 89	85 ± 103	76 ± 11	0.42		
PR *ms*	176 ± 38	174 ± 36	184 ± 44	0.33		
QTc *ms*	426 ± 29	423 ± 27	433 ± 34	0.12		
QRS *ms*	106 ± 41	100 ± 23	123 ± 69	**0.01**	8.16	<0.01
QRS>120ms *n(%)*	19 (17.3)	14 (17.3)	5 (17.2)	0.99		
Afib *n(%)*	10 (9.3)	6 (7.5)	4 (14.3)	0.31		
Cardiac Biomarkers						
Trop HS *ng/l*	36.4 ± 38.7	31.5 ± 37.2	49.8 ± 40.3	**0.04**	4.78	0.03
NT-proBNP *ng/l*	2460 ± 3875	1924 ± 3006	3931 ± 5418	**0.02**	4.58	0.03
sST2 *ng/l*	30.7 ± 14.5	28.3 ± 12.0	36.7 ± 18.4	**0.03**	3.76	0.05
Echocardiographic Parameters						
LV EDV *ml*	93 ± 42	90 ± 37	101 ± 55	0.27		
LV ESV *ml*	43 ± 30	40 ± 27	51 ± 38	0.16		
LV mass *mg*	215 ± 61	210 ± 56	231 ± 70	0.12		
LVEF *%*	51 ± 10	51 ± 10	49 ± 11	0.33		
E max *m/s*	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	0.19		
A max *m/s*	1.0 ± 0.4	1.0 ± 0.3	0.9 ± 0.4	0.34		
E/A	1.1 ± 0.9	1.0 ± 0.7	1.5 ± 1.4	**0.02**	7.24	<0.01
E/e' mean	17.2 ± 7.6	16.2 ± 7.0	20.3 ± 8.5	**0.02**	5.03	0.03
LA vol *ml*	78 ± 29	73 ± 24	91 ± 36	**<0.01**	10.9	<0.01
LAVI *ml/m²*	45 ±17	43 ± 14	52 ± 20	**0.03**	7.42	<0.01
TAPSE *mm*	22 ± 5	23 ± 5	20 ± 6	**0.03**	5.37	0.02
TR Vmax *m/s*	2.8 ± 0.9	2.7 ± 0.9	2.9 ± 0.7	0.23		
TR Pmax *mmHg*	32 ± 16	30 ± 15	37 ± 18	0.07		
sPAP *mmHg*	38 ± 16	35 ± 15	44 ± 18	0.04	3.47	0.06
Aortic Valve Parameters						
LVOT *mm*	19 ± 5	20 ± 5	19 ± 4	0.53		
AVA *cm²*	0.6 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.85		
AV Vmax *m/s*	4.3 ± 0.6	4.4 ± 0.6	4.3 ± 0.7	0.45		
AV Pmean *mmHg*	50 ± 15	51 ± 16	47 ± 15	0.36		
AV Pmax *mmHg*	77 ± 22	77 ± 22	74 ± 23	0.51		
SVi *ml/m²*	49 ± 17	50 ± 17	46 ± 17	0.35		
Advanced Echocardiographic parameters						
GLS *%*	-15.7 ± 5.8	-16.2 ± 6.2	-14.2 ± 4.4	0.07		
GWI *mmHg%*	2381 ± 785	2485 ± 775	2091 ± 750	**0.02**	4.78	0.03
GCW *mmHg%*	2940 ± 942	3061 ± 928	2604 ± 913	**0.03**	4.78	0.03
GWW *mmHg%*	239 ± 191	236 ± 206	247 ± 145	0.77		
GWE *%*	91 ± 6	91 ± 6	89 ± 6	0.08		

(Legend Table 1) A: late diastolic peak velocity, Afib: atrial fibrillation, AV: aortic valve, AVA: aortic valve area, BSA: body surface area, DBP: diastolic blood pressure, e': early diastolic tissue velocity, E: early diastolic peak velocity, EDV: end diastolic volume, ESV: end systolic volume, GCW: global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, LA vol: left atrium volume, LAVI: left atrium volume index, LV: left ventricle, LVEF: left ventricle ejection fraction, LVOT: left ventricle outflow track, NT-proBNP: N-terminal pro-B-type natriuretic peptide, Pmax: peak gradient, Pmean: mean velocity, SBP: systolic blood pressure, SD: standard deviation, sPAP: peak systolic pulmonary artery pressure, sST2: soluble suppression of tumorigenicity 2, SVi: stroke volume index, TAPSE: tricuspid annular plane systolic excursion, TR: tricuspid valve regurgitation, Trop HS: high sensitive troponins, Vmax: peak velocity.

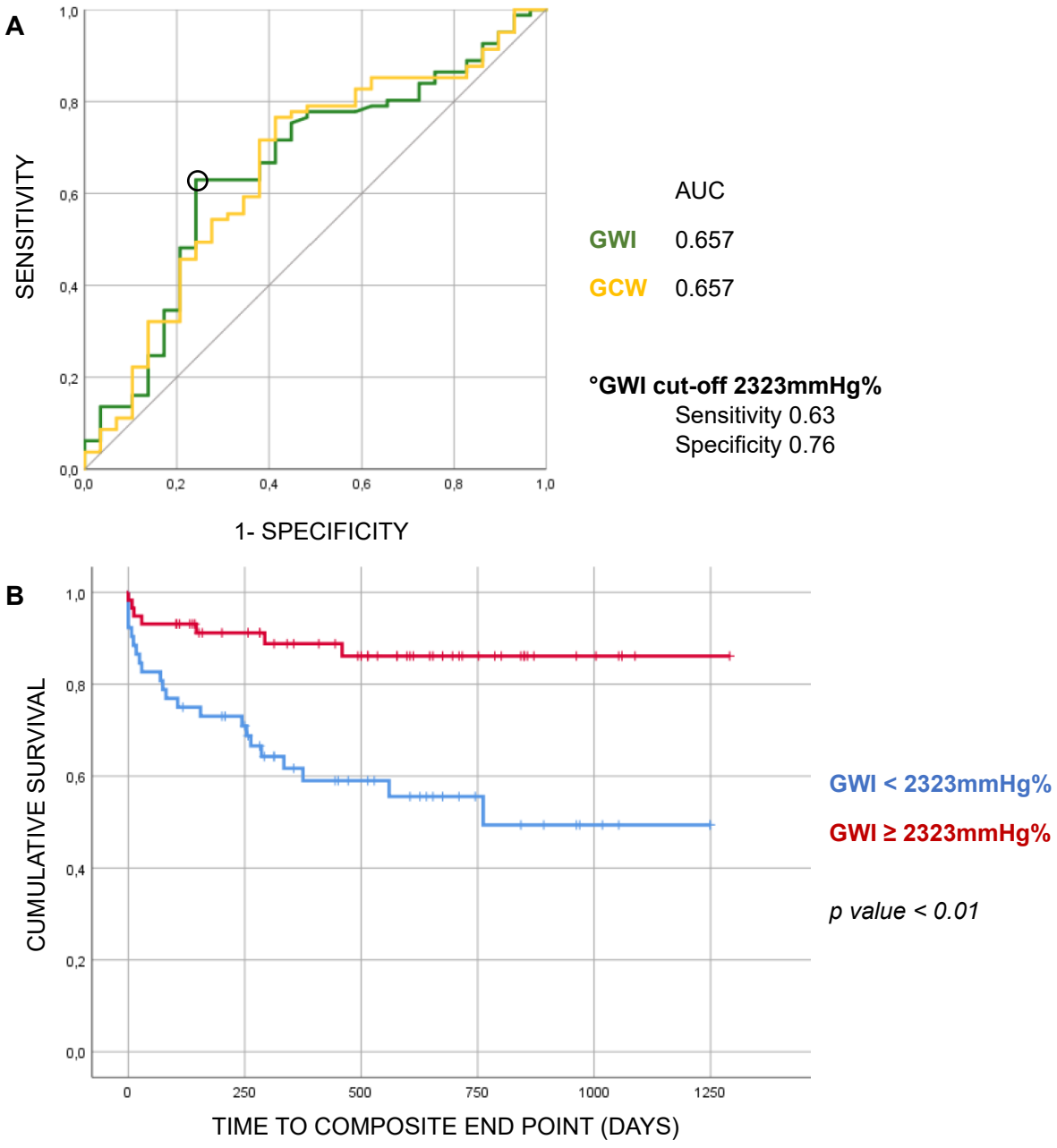


Figure 1: ROC curve analysis (A) of GWI (green) and GCW (yellow). Kaplan-Meier plot (B) for survival rates analysis in patients with baseline GWI ≥ 2323mmHg% (red) vs baseline GWI < 2323mmHg% (blue). GWI: global work index, GCW: global constructive work.

Table 2: Multivariate Cox analysis of selected variables to build a predictive model for all-cause death and HF hospitalization after TAVR including MW assessment.

Basic model			**Basic model + NT-proBNP**			**Basic model + NT-proBNP + GWI<2323mmHg%**		
	X²	***p***		***X²***	***p***		***X²***	***p***
Model score	22.3	<0.01	***Model score***	22.5	<0.01	***Model score***	39.9	<0.01
Variables	***HR***		***Variables***	***HR***		***Variables***	***HR***	
QRS	1.01	0.06	QRS	1.01	0.06	QRS	1.01	0.03
TAPSE	0.94	0.08	TAPSE	0.93	0.08	TAPSE	0.98	0.42
LAVI	1.02	0.08	LAVI	1.02	0.08	LAVI	1.04	0.07
E/e' mean	1.08	<0.01	E/e' mean	1.09	<0.01	E/e' mean	1.08	0.04
			NT-proBNP	1.00	0.59	NT-proBNP	1.00	0.44
						GWI<2323mmHg%	0.18	0.01
			vs basic model		0.58	***vs basic model***		0.02
						vs previous model		<0.01

GWI: global work index, HR: hazard ratio, LAVI: left atrium volume index, NT-proBNP: N-terminal pro-B-type natriuretic peptide, TAPSE: tricuspid annular plane systolic excursion.

Longitudinal changes in Myocardial Work parameters

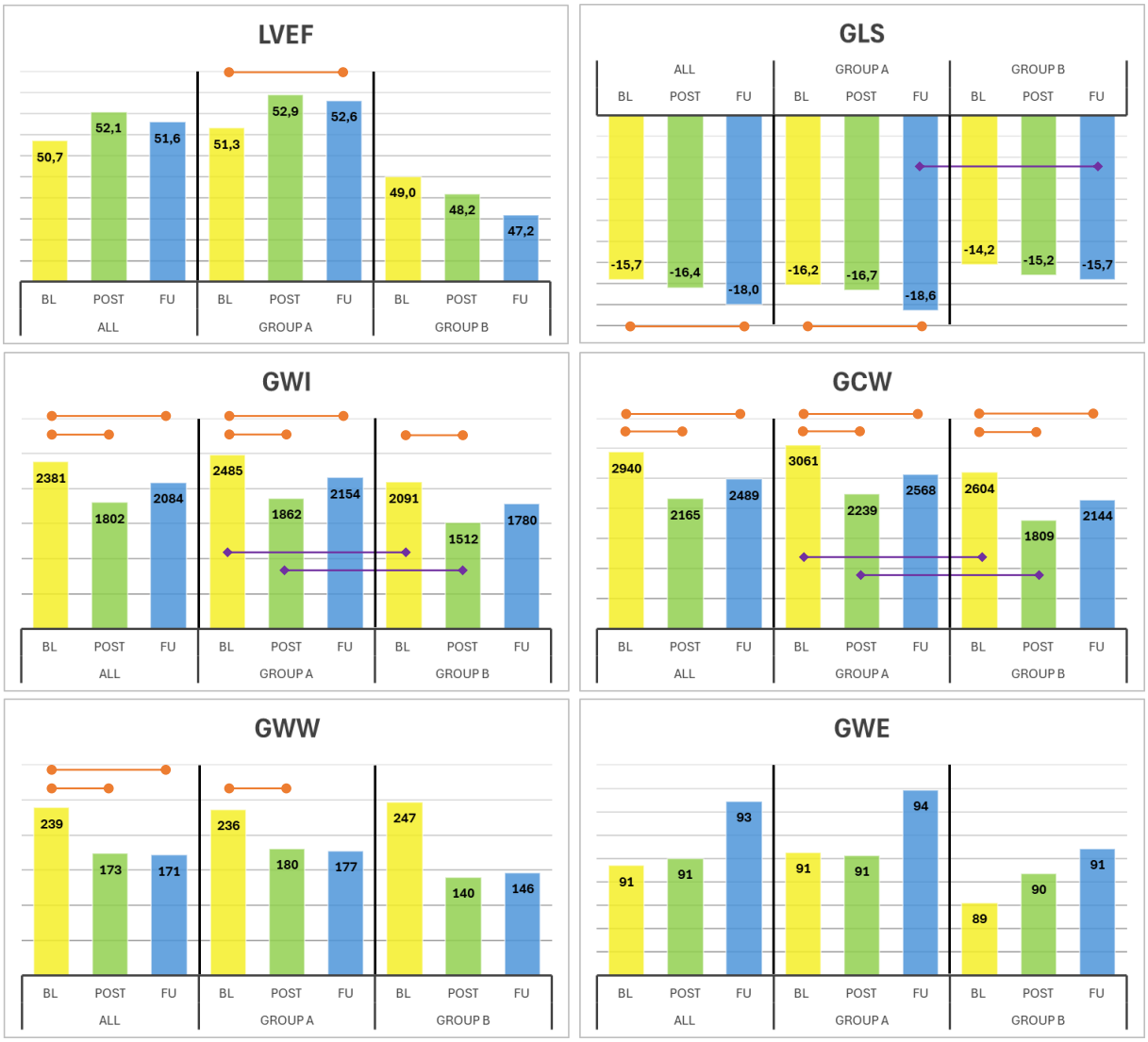
Serial MW measurements were compared at three time points: baseline, one day after intervention and at one month follow-up in each group (***Supplemental Table 2***). Furthermore, patients from group A and B, with negative or positive composite endpoint respectively, were compared to each other (***Supplemental Table 3***).

Whereas patients in group A demonstrated a considerable improvement in LVEF and GLS, patients in group B did not exhibit such improvement at one month follow-up.

Although both groups showed a significant decline in GWI and GCW immediately after TAVR, only patients in group A demonstrated significant change in GWI at follow-up when compared to baseline (***Figure 2***). Both GWI and GCW were significantly lower at baseline and one day after intervention in group B with respect to group A. However, the differences between both groups were not statistically significant at one month follow-up.

GWW demonstrated an initial decline following the intervention in all patients, only statistically significant in group A, however no further reduction was observed in the long-term follow-up. Furthermore, a gradual enhancement in GWE was observed across all patients although this improvement did not reach statistical significance.

Finally, the intra- and interobserver variability for LVEF, GLS and MW parameters are reported in ***Supplemental Table 4***.



Significant difference between groups at a specific time point (bl/post/fu), p<0.01

Significant change over time inside a specific group (better/worse outcome), p<0.01

Figure 2: Measurements of LVEF, GLS and MW parameters in the whole study population (ALL) and per study group (NEG: negative endpoint, POS: positive endpoint) at baseline. (BL, yellow), one day (POST, green) and one month (FU, blue) after TAVR. (Group A: patients who did not meet the study composite endpoint, Group B: patients who reached the study composite endpoint)

DISCUSSION

The main findings of this study can be summarized as follows. Firstly, baseline MW parameters, specifically GWI and GCW demonstrate a significant correlation with TAVR outcome. Secondly, a GWI below 2323mmHg% at the baseline may serve as a valuable tool for identifying patients at higher risk and can provide additional predictive value for TAVR outcomes. Lastly, when compared to measures such as LVEF and GLS, MW analysis proves to be more sensitive for assessing longitudinal changes in cardiac function in patients with severe AS undergoing TAVR.

Previous studies have suggested that the LVEF is not sensitive enough to detect early left ventricular dysfunction in patients with severe AS[21,22]. More recent studies have shown that even asymptomatic patients with subtle impairment in left ventricle function may benefit from early aortic valve replacement[23]. Our study also highlights that there is no difference in baseline LVEF between patients with favorable or unfavorable outcome after TAVR, indicating that ventricles with "low-normal" LV function face a significant afterload challenge, which could be linked to a poorer prognosis. These ventricles may be more prone to decompensation with sudden changes in afterload compared to other ventricles. These findings support the idea that the concept of a "normal LVEF" in severe AS is not valid, and emphasize the need for new parameters to effectively characterize the extent of (subclinical) left ventricular dysfunction.

It is noteworthy that the variables we found to be lower at baseline in patients with unfavorable outcome, strongly coincide with the variables included in the AS staging proposed by Généreux et al[5]. This correlation is not surprising as a higher AS stage has shown to be associated with worse outcome. Additionally, we have observed significantly higher serum levels of Trop HS and NT-proBNP along with significantly lower values of GWI and GCW among patients with a less favorable outcome (group B). These findings provide evidence that, despite the similarities in standard measurements of LV systolic function, such as GLS and EF, in both cohorts, MW analysis reveals subtle differences in LV performance otherwise unnoticed. The lower GWI and GCW baseline values indicate increased myocardial stress and impaired myocardial performance in patients with poorer outcome following TAVR. These parameters, unlike other echocardiographic measurements of LV function such as GLS or EF, are able to detect these subtle abnormalities in contractile function.

Of note patients in group B displayed a substantially longer QRS duration, which was associated with outcome, and a higher incidence of atrial fibrillation. Both characteristics could potentially impact the parameters of MW analysis[24]. However, we did not observe any significant association between QRS duration or atrial fibrillation and MW parameters. This

may be attributed to the limited number of patients exhibiting these abnormalities. Consequently, further research is required to establish a potential impact of atrial fibrillation and QRS prolongation on MW analysis in AS patients.

As GWI corresponds to the translation of myocardial energy into mechanical energy, depressed values reflect impaired LV contractile function and thus compromised cardiac performance.[20] Different cut-off values for GWI have been proposed for diagnosing or predicting outcomes in multiple pathologies. In the study conducted by Wang et al[25], a GWI value below 750 mmHg% was found to be significantly associated with an increased risk of all-cause mortality and HF hospitalization in patients with reduced ejection fraction. In cardio-oncology, lower GWI at baseline was related to a higher risk for developing cancer treatment related cardiac dysfunction, irrespectively of LVEF and GLS baseline values[26]. Additionally, Guo et al[27] reported that a regional MW index below 1623.7mmHg% could serve as a differentiating factor between ischemic and non-ischemic segments in individuals with coronary artery disease.

Although the prognostic value of MW parameters in AS patients undergoing TAVR has been studied previously[12,] baseline cut-off values for risk stratification are still lacking in clinical practice. Our results suggest that a GWI <2323mmHg% at baseline might be useful in identifying patients at high risk after TAVR intervention. The abnormally increased LV pressure in AS patients is an important variable in MW calculation and probably the reason for this remarkable high GWI threshold as it is combined with a whether or not decreased strain.

In the longitudinal analysis of LV function, the observed decrease in GCW along with an increase in GLS after TAVR aligns with the results reported by Jain et al[6]. However, our study, which includes a third evaluation at one month follow-up, reveals that GLS experiences a gradual recovery instead of an immediate one after TAVR whereas GCW increases after the initial decline following the intervention. The longitudinal evolution in GCW can be explained by the subsequent changes in its components. Initially, the valve replacement results in a dramatic decrease in afterload which causes a substantial reduction in GCW. Consequently, the normal LV loading condition is restored directly while the recovery of LV myocardial contractility takes longer. Subsequently, there is a gradual increase in GLS without any significant change in afterload resulting in a corresponding rise in GCW. Interestingly, all patients showed similar longitudinal changes in LV function. However, only the changes observed in patients with favorable outcome (group A) were statistically significant. This suggests that patients who are unable to sufficiently recover LV function after TAVR have a poorer prognosis and lower chances of survival in the long term. Importantly, GWI and GCW,

but not LVEF and GLS, were significantly worse at baseline and could help in the earlier detection of the patients at risk as suggested by De Rosa et al[11].

In conclusion, our results provide evidence for enhanced use of MW analysis in the initial risk stratification of patients with severe AS who are referred for TAVR. We observed that a baseline GWI<2323mmHg% is correlated with increased rates of all-cause mortality and HF hospitalization following TAVR intervention. Moreover, longitudinal MW analysis facilitates the identification of patients who truly benefit from TAVR and further research is warranted to evaluate the impact of TAVR on LV performance through serial MW assessment.

LIMITATIONS

This study has several limitations that should be acknowledged. Firstly, MW assessment is an advanced and sophisticated technique that relies heavily on the acquisition of high-quality echocardiographic images. However, obtaining such images in daily clinical practice can be challenging. Secondly, the longitudinal analysis of the study was hampered by the loss of follow-up of patients referred from other hospitals. This limitation prevented the researchers from obtaining a complete picture of the long-term outcomes. Finally, MW is a relatively new method and there is still a lack of clear and robust reference values, specifically for patients with severe AS. This lack of standardized reference values limits the ability to interpret MW measurements in the context of severe AS. Lastly, this study was limited by its small sample size and single-center design. These factors may introduce bias and limit the generalizability of the findings. Therefore, large scale studies are warranted to validate these results and establish a more comprehensive understanding of the application of MW in severe AS as well as its prognostic value after TAVR.

SUPPLEMENTAL MATERIAL

Supplemental Table 1: *Baseline Patients' Characteristics, Therapy, Comorbidities and Symptoms in Patients with Negative (Group A) vs Positive (Group B) Composite Endpoint.*

		ALL (110)	Group A (81)	Group B (29)	Chi-square test
		N (%)	*N (%)*	*N (%)*	*p value*
ENDPOINTS	*all-cause death*	22 (20.0)			
	HF hospitalization	12 (10.9)			
	composite endpoint	29 (26.4)			
AS stage (Généreux et al.)	*0*	7 (6.4)	7 (8.6)	0 (0.0)	
	1	26 (23.6)	21 (25.9)	5 (17.2)	
	2	65 (59.1)	48 (59.3)	17 (58.6)	**0.04**
	3	10 (9.1)	4 (4.9)	6 (20.7)	
	4	2 (1.8)	1 (1.2)	1 (3.4)	
AS hemodynamic	*low flow – low gradient*	5 (5)	2 (3)	3 (11)	0.08
NYHA class	*I*	45 (44.1)	37 (49.3)	8 (29.6)	
	II	41 (40.2)	32 (42.7)	9 (33.3)	**0.02**
	III	16 (15.7)	6 (8.0)	10 (37.0)	
ECG rhythm	*sinus rhythm*	93 (86.1)	73 (91.0)	20 (71.4)	
	atrial fibrillation	10 (9.3)	6 (7.5)	4 (14.3)	**0.03**
	other rhythm	5 (4.6)	1 (1.3)	4 (14.3)	
Sex	*female*	59 (53.6)	46 (56.8)	13 (44.8)	0.27
	male	51 (46.4)	35 (43.0)	16 (55.2)	
Comorbidities	*diabetes*	33 (30.6)	27 (33.8)	6 (21.4)	0.22
	hypertension	67 (61.5)	51 (63.7)	16 (55.2)	0.42
	peripheral venous disease	11 (10.1)	9 (11.3)	2 (6.9)	0.51
	hyperlipidemia	17 (15.6)	14 (17.5)	3 (10.3)	0.36
	cholesterolemia	49 (45.0)	35 (43.8)	14 (48.3)	0.68
	obesitas	20 (18.3)	14 (17.5)	6 (20.7)	0.71
	current/history smoke	16 (14.7)	8 (10.0)	8 (27.6)	**0.02**
	family history of CVD	11 (10.1)	8 (10.0)	3 (10.3)	0.96
Medical Therapy	*diuretics*	48 (44.0)	30 (37.5)	18 (62.1)	**0.02**
	ACE inhibitor	28 (25.7)	18 (22.5)	10 (34.5)	0.21
	MRA	20 (18.7)	19 (24.1)	1 (3.6)	**0.02**
	beta-blocker	57 (52.3)	43 (53.8)	14 (48.3)	0.61
	amiodarone	9 (8.3)	3 (3.8)	6 (20.7)	**<0.01**
	nitrates	5 (4.6)	3 (3.8)	2 (6.9)	0.49
	anti-coagulation	74 (67.9)	53 (66.3)	21 (72.4)	0.54
	anti-arrhythmic	2 (1.8)	1 (1.3)	1 (3.4)	0.45
	calcium antagonist	30 (27.5)	24 (30.0)	6 (20.7)	0.34
HF symptoms	*dyspnea*	50 (50.0)	30 (41.2)	20 (74.1)	**<0.01**
	orthopnea	5 (5.0)	4 (5.5)	1 (3.7)	0.72
	peripheral oedema	8 (8.0)	4 (5.5)	4 (14.8)	0.13
	palpitations	8 (8.0)	8 (11.0)	0 (0.0)	**0.07**
	syncope	9 (9.0)	6 (8.2)	3 (11.1)	0.65
	respiratory crackles	4 (4.0)	3 (4.1)	1 (3.7)	0.93
Concomitant valvular disease	*TR ≥ moderate*	17 (16.3)	5 (6.7)	12 (41.2)	**<0.01**
	MR ≥ moderate	24 (24.2)	11 (14.9)	14 (48.2)	**<0.01**

ACE: aldosterone converting enzyme, AS: aortic valve stenosis, CVD: cardiovascular disease, ECG: electrocardiogram, HF: heart failure, MR: mitral valve regurgitation, MRA: mineraloid receptor antagonist, NYHA: New York Heart Association, TR: tricuspid valve regurgitation.

Supplemental Table 2: *Longitudinal changes in LVEF, GLS and MW parameters one day (POST-TAVR) and one month (FOLLOW-UP) after TAVR compared to baseline per study group. (Group A: patients who did not meet the study composite endpoint, Group B: patients who reached the study composite endpoint)*

All patients											
	BASELINE		**POST-TAVR**				**BASELINE**		**FOLLOW-UP**		
N=64	*Mean*	*SD*	*Mean*	*SD*	*p value*	N=64	*Mean*	*SD*	*Mean*	*SD*	*p value*
LVEF	50.7	10.4	52.1	9.3	0.17	**LVEF**	49.8	10.1	51.6	8.6	0.09
GLS	-15.8	6.6	-16.4	6.1	0.53	**GLS**	-15.5	6.5	-18.0	3.9	0.00
GWI	2454	766	1802	593	<0.01	**GWI**	2365	767	2084	634	0.00
GCW	2982	885	2165	591	<0.01	**GCW**	2958	926	2489	702	<0.01
GWW	220	135	173	134	0.01	**GWW**	246	219	171	119	0.02
GWE	91	5	91	6	0.59	**GWE**	91	6	93	12	0.11
Group A											
	BASELINE		**POST-TAVR**				**BASELINE**		**FOLLOW-UP**		
N=53	*Mean*	*SD*	*Mean*	*SD*	*p value*	N=52	*Mean*	*SD*	*Mean*	*SD*	*p value*
LVEF	51.5	10.3	52.9	9.4	0.21	**LVEF**	50.2	10.1	52.6	8.4	0.05
GLS	-16.1	7.0	-16.7	6.5	0.61	**GLS**	-15.7	6.9	-18.6	3.6	0.00
GWI	2542	769	1862	601	<0.01	**GWI**	2432	765	2154	603	0.01
GCW	3095	875	2239	572	<0.01	**GCW**	3034	905	2568	651	<0.01
GWW	226	136	180	143	0.03	**GWW**	243	228	177	127	0.07
GWE	92	5	91	7	0.63	**GWE**	91	6	94	13	0.16
Group B											
	BASELINE		**POST-TAVR**				**BASELINE**		**FOLLOW-UP**		
N=11	*Mean*	*SD*	*Mean*	*SD*	*p value*	N=12	*Mean*	*SD*	*Mean*	*SD*	*p value*
LVEF	47.1	10.4	48.2	7.8	0.61	**LVEF**	48.5	10.6	47.2	8.7	0.28
GLS	-14.4	4.1	-15.2	4.3	0.60	**GLS**	-14.9	4.9	-15.7	4.3	0.42
GWI	2031	618	1512	476	0.02	**GWI**	2078	739	1780	700	0.14
GCW	2440	748	1809	577	0.03	**GCW**	2631	987	2144	839	0.04
GWW	191	129	140	80	0.28	**GWW**	260	181	146	77	0.06
GWE	91	5	90	5	0.81	**GWE**	90	6	91	6	0.26

GCW: global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, LVEF: left ventricle ejection fraction, SD: standard deviation, TAVR: transcatheter aortic valve replacement.

Supplemental Table 3: *Difference in LVEF, GLS and MW parameters between study groups one day (POST-TAVR) and one month (FOLLOW-UP) after TAVR. (Group A: patients who did not meet the study composite endpoint, Group B: patients who reached the study composite endpoint)*

POST-TAVR					
	Group A (N=53)		**Group B (N=11)**		
	Mean	*SD*	*Mean*	*SD*	*p value*
LVEF	53	9.4	48	7.8	0.10
GLS	-16.7	6.5	-15.2	4.3	0.37
GWI	1862	601	1512	476	0.05
GCW	2239	572	1809	577	0.04
GWW	180	143	139	80	0.20
GWE	91	6.6	90	4.5	0.64
FOLLOW-UP					
	Group A (N=52)		**Group B (N=12)**		
	Mean	*SD*	*Mean*	*SD*	*p value*
LVEF	53	8.3	47	8.7	0.07
GLS	-18.6	3.6	-15.7	4.3	0.05
GWI	2154	603	1780	700	0.11
GCW	2568	651	2144	839	0.12
GWW	177	127	146	77	0.42
GWE	94	13.4	91	6.5	0.35

GCW: global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, LVEF: left ventricle ejection fraction, SD: standard deviation, TAVR: transcatheter aortic valve replacement.

Supplemental Table 4: *Intra- and inter-observer variability*

	Intra-observer variability			**Inter-observer variability**		
	ICC *(95% CI)*	***Bias***	***Limits of agreement***	***ICC*** *(95% CI)*	***Bias***	***Limits of agreement***
LVEF, %	**0.88** (0.67-0.96)	0.82 ± 5.47	-9.89 to 11.54	**0.89** (0.72-0.96)	-1.05 ± 3.98	-8.85 to 6.75
GLS, %	**0.78** (0.40-0.92)	-0.65 ± 3.07	-6.66 to 5.36	**0.94** (0.85-0.98)	-0.99 ± 2.14	-3.19 to 5.17
GWI, mmHg%	**0.95** (0.85-0.98)	102 ± 292	-471 to 674	**0.95** (0.88-0.98)	-184 ± 337	-844 to 477
GCW, mmHg%	**0.98** (0.94-0.99)	-18 ± 267	-505 to 540	**0.96** (0.91-0.99)	-191 ± 339	-856 to 474
GWW, mmHg%	**0.97** (0.91-0.99)	9.00 ± 40.19	-69.8 to 87.8	**0.96** (0.91-0.99)	8.65 ± 40.48	-70.7 to 88.0
GWE, %	**0.90** (0.72-0.96)	-0.71 ± 1.72	-4.08 to 2.67	**0.95** (0.86-0.98)	-1.40 ± 1.90	-5.13 to 2.33

GLS, global longitudinal strain; GWI, global work index; LVEF, left ventricular ejection fraction; GWE, global work efficiency; GWW, global wasted work; GCW, global constructive work.

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Chapter 4

Myocardial Work in Congenital Heart Disease

Assessing Systemic Right Ventricular Function Through Myocardial Work Analysis

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The Mustard and Senning operations for dextro-transposition of the great arteries (D-TGA) establish a biventricular physiology with a subaortic right ventricle (sRV). While prolonged QRS has been associated with worse prognosis in these patients, current echocardiographic tools fall short in adequately assessing the (mal)performance and function decline of the sRV during follow-up. The present study is the first to characterize Myocardial Work (MW) indices of the sRV in D-TGA patients after Mustard/Senning repair.

All adult D-TGA patients at follow-up in the University Hospital of Leuven between 2018-2022 were screened for inclusion. We retrospectively collected the most recent electrocardiogram parameters, 2D echocardiographic images and serum biomarkers' values. Offline calculations of MW indices were performed. We established correlations between all variables and categorized patients into QRS<120ms and QRS≥120ms for further analysis. A total of 51 D-TGA patients were included (13 Mustard, 33 male, 39±6 years). QRS duration increased with age and was correlated with sRV dimensions and serum levels of troponins ($R=0.42$, $p<0.01$) and NT-proBNP ($R=0.31$, $p=0.03$). However, no significant correlation was found between QRS duration and intraventricular dyssynchrony or conventional functional echocardiographic parameters. QRS prolongation was associated with a deterioration in septal, but not lateral, MW parameters. Patients with QRS≥120ms had significantly larger ventricles and higher levels of troponins and NT-proBNP.

QRS prolongation after Mustard/Senning repair is linked to ventricular dilatation and worse performance, particularly affecting the septal wall. Global and regional MW analysis may be useful to assess the subclinical deterioration of sRV function.

INTRODUCTION

Transposition of the great arteries (TGA) accounts for approximately 6% of all congenital heart diseases with a male to female sex ratio that varies between 1.5:1 and 3.2:1.[1,2] TGA is often an isolated finding, however, approximately 30-50% of patients also present with associated congenital heart defects.[3] In cases of dextro-TGA (D-TGA) the combination of atrioventricular concordance with ventriculoarterial discordance results in 2 parallel and unconnected blood circuits necessitating early surgical intervention. The Mustard and Senning operations are two types of atrial switch repair that aim to correct blood flow at the atrial level establishing a biventricular physiology in which a subaortic right ventricle (sRV) supports the systemic circulation. Although the arterial switch operation replaced this approach in the 90s, there are still adult patients who underwent Mustard or Senning procedures requiring ongoing cardiac surveillance.[4] Long-term complications including baffle leaks, arrhythmias, QRS prolongation, tricuspid regurgitation (TR) or heart failure are frequently encountered following atrial switch repair.[5,6] In patients with a sRV, chronic pressure overload leads to right ventricle (RV) dilatation and hypertrophy while progressive tricuspid valve regurgitation causes chronic volume overload. Unfortunately, the absence of reference values and adequate diagnostic tools to assess sRV function, makes it difficult to determine the moment when this progressive physiological remodeling transitions into ventricular dysfunction.[7,8,9] Transthoracic echocardiography (TTE) is the primary diagnostic method for evaluating sRV function.[10] However, there is currently no straight evidence indicating which echocardiographic parameter has the highest reliability and greatest prognostic value. Tissue Doppler imaging with global longitudinal strain (GLS) analysis, is a highly advanced and promising tool for analyzing myocardial function.[11] Yet it remains a load-dependent parameter that proves challenging to interpret in a sRV exposed to chronic pressure and volume overload.

Non-invasive Myocardial Work (MW) indices derived from left ventricle (LV) pressure–strain loops (PSL) can overcome the limitation associated with load-dependency by incorporating estimated LV pressure into their calculation.[12,13] Additionally, different MW parameters provide complementary information that can contribute to a more comprehensive analysis of ventricular function and physiology. The global work index (GWI) is derived from the area of the sRV PSL and reflects the total work calculated from tricuspid valve closure to tricuspid valve opening. On the other hand, the global constructive work (GCW) represents the work performed by the sRV contributing to ventricular ejection during systole. Conversely, the global wasted work (GWW) is the work performed by the sRV that does not contribute to ventricular ejection. As such, the global work efficiency (GWE) is defined as the ratio of GCW divided by the sum of GCW and GWW. Initially, this principle was applied to the RV by Butcher et al.[14] in a cohort of patients with pulmonary hypertension. More recently, the relationship

between RV PSL-derived MW and contractility has been shown in patients with pulmonary hypertension and validated with invasive pressure-volume analysis.[15]

The present explorative study seeks to describe MW indices of the sRV in a cohort of adult D-TGA patients with the aim of gaining a deeper understanding of its evolution following Mustard/Senning repair. Additionally, we pursue to identify sensitive echocardiographic determinants that can assess sRV function over the long-term follow up of these patients.

METHODS

Patient population

All D-TGA patients who had undergone atrial switch repair at follow-up in the University Hospital of Leuven between 2018 and 2022 were retrospectively screened (***Figure 1***).Patients with double switch, a redo Mustard/Senning operation or a combination of Senning and Rastelli, Eisenmenger syndrome, a mechanical tricuspid valve or mechanical ventricular support were excluded. Furthermore, we excluded patients who either lacked echocardiographic images or had images of suboptimal quality and those with missing clinical parameters for MW calculation at the time of examination. In order to assure the highest-level accuracy in the calculation of MW parameters, only patients with BP measurements taken on the same day as the TTE were included in the analysis. In cases where multiple measurements were available on the same day, we calculated the average in order to avoid relying on isolated high or low values. This study was approved by the local Ethics Committee of the University Hospital of Leuven (s66145).

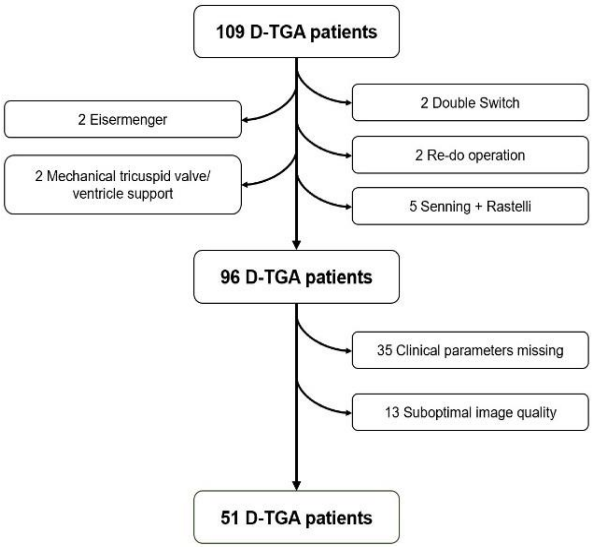

Figure 1: Flow chart of the patients' *screening for inclusion in the study.*

Data collection

All data were collected retrospectively from the latest available clinical reports. Parameters to evaluate cardiac electrical activity were obtained from the last available electrocardiogram and included heart rate (HR), PR interval, QRS duration and QTc interval. For the assessment of sRV function we analyzed the most recent 2D echocardiographic images including M-mode, Doppler and tissue Doppler acquisitions. These images were analyzed offline for calculation of both morphological and functional characteristics. The following dimensional variables were measured in a 4-chamber view: end systolic area (ESA),

end diastolic area (EDA), end systolic volume (ESV), end diastolic volume (EDV) and stroke volume (SV). In addition to dimensional measurements, we assessed various functional variables for the sRV, including tricuspid annular plane systolic excursion (TAPSE), annular s' and fraction area change (FAC) as well as ejection fraction (EF) using the Simpson's method and GLS. Furthermore, we evaluated mechanical dyssynchrony by utilizing the regional strain curves to compute the time-to-peak difference between the septal and lateral walls.[16] Finally we recorded the most recent serum levels of troponins and NT-proBNP.

Myocardial Work calculation

The software originally developed for the assessment of LV MW by 2D speckle tracking echocardiography was applied to the sRV for calculation of the MW indices following the methodology of Butcher et al.[17] and Russel et al.[13] A RV-focused apical four-chamber view was used to obtain sRV GLS. In contrast with Butcher et al., the RV pressure was not measured using invasive right heart catheterization. Like Russel et al. did for the LV, we estimated the sRV intraventricular pressure by associating the peripheral arterial blood pressure (BP) with cardiac event times derived from tricuspid and aortic valve opening and closure. RV strain, non-invasive BP, measured at the brachial artery and valve events were integrated for MW calculation.[18] The global MW values were obtained as average from all myocardial segments from the apical four-chamber view (***Figure 2***). Additionally, regional MW values for the lateral and septal wall separately were recorded.

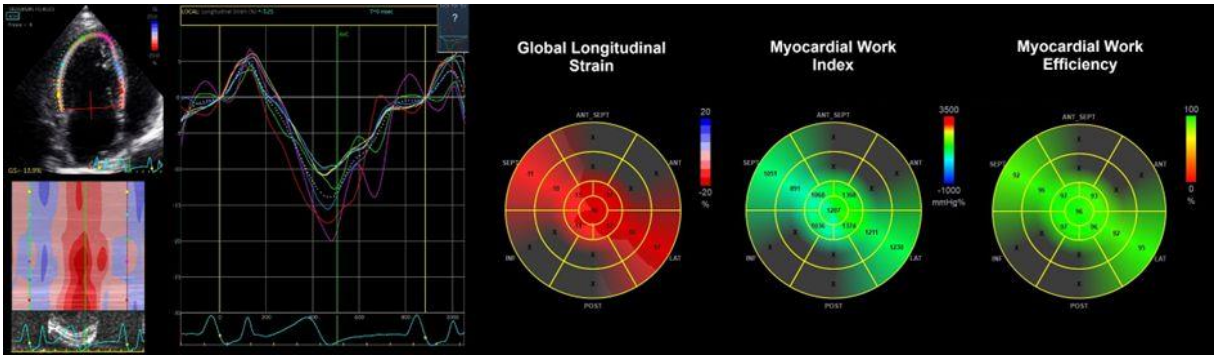

Figure 2: Illustrative example of Myocardial Work calculation in a sRV. A RV-focused apical four-chamber view was used to obtain the sRV regional strain curves and calculate the global average. We estimated the sRV intraventricular pressure curve by associating the brachial arterial blood pressure with cardiac valve events. MW was automatically calculated by the software which integrates the sRV strain and non-invasive estimated intraventricular pressure. The regional MW values were presented in a color-coded bull's eye and the global MW values were obtained as average from all myocardial segments from the apical four-chamber view.

Statistical analysis

Descriptive data are reported as the mean ± sd for normally distributed continuous variables and as median [IQR] for continuous variables without normal distribution. Normality testing was performed by graphical analysis with histograms and QQ-plots. Pearson R correlation value between all continue variables was obtained. Based on previous studies

reporting the association between QRS prolongation and sudden cardiac death in Mustard/Senning patients[19,20] QRS duration was used to categorize patients in two groups; QRS<120ms and QRS≥120ms. Intergroup differences were determined using the T-test and Mann-Whitney U-test for continue variables with or without normal distribution respectively. The Chi-square test was performed to analyze intergroup differences for the categorical variables. To identify clinically relevant differences between the study groups, the logarithmic transformation was applied to NT-proBNP and MW parameters. This was necessary as these variables exhibited either an exponential distribution or extensive range of values with a difference of more than 1000 units between the lowest and highest value. For all tests, a p-value below 0.05 was considered statistically significant. All statistics analysis were performed using SPSS for Windows Version 25 (SPSS, IBM headquarters, Armonk, NY, USA).

RESULTS

Study population

In our final analysis a total of 51 patients (33 male, 39 ± 6 years) were included in the final analysis. Patients' baseline characteristics are summarized in ***Table 1***. Troponin and NT-proBNP were missing in 4 patients. Additionally, only troponin was missing in 3 patients. Only 5 patients had a pacemaker and none of them was pacing-dependent. Additionally, during the most recent pacemaker interrogation before inclusion the percentage pacing was 0%. Atrial fibrillation was present in 2 patients. For the myocardial work analysis in these patients, images of the three apical views with similar HR were selected. While TR more than moderate was found to be present in 62% of the patients, we did not find a significant difference in the prevalence of TR in patients with QRS<120ms vs those with QRS≥120ms. Moreover, there is currently a lack of available data on the potential effect of TR on the myocardial work analysis of the right ventricle.

Correlations

The positive correlation between QRS duration and age advocates for an increase in electromechanical dissociation in parallel with age. Additionally, QRS duration correlated with several sRV morphological features such as the EDA, ESA, ESV, EDV as well as with the serum levels of troponins and NT-proBNP (***Table 2***). However, we did not find any significant correlation between QRS duration and parameters related to intraventricular mechanical dyssynchrony or sRV function such as TAPSE, annular s', EF and GLS. Still, a weak correlation was found between QRS duration and FAC. Interestingly, we discovered a significant correlation between the global MW parameters and the QRS duration with the exception of GCW. When looking at regional MW analysis, we found that all septal MW parameters, correlated with the QRS duration (***Figure 3***) whereas this correlation was not observed for the lateral MW parameters.

Normal vs prolonged QRS duration

Patients with a prolonged QRS had significantly larger sRV compared to patients with a normal QRS duration while no notable differences between the two groups were observed regarding mechanical dyssynchrony parameters (***Table 3***). Despite the substantially higher serum levels of troponins and NT-proBNP in the QRS≥120ms group, no intergroup difference was found in terms of LV functional parameters (EF and GLS). Interestingly, when evaluating global and regional MW parameters significant intergroup differences were observed for MW index, MW efficiency, CW and WW, particularly in the septal region (***Figure 4, Table 3***) Additionally, the mean septal PSL, which is used to determine septal MW parameters, showed a reduce surface area in patients with a QRS duration ≥120ms compared to patients with normal QRS duration (***Figure 5***).

Table 1: Patient's baseline characteristics for the whole study population and for each group separately.

	TOTAL	QRS<120ms	QRS≥120ms	p-value
N (male %)	51 (65)	33 (55)	18 (83)	0.04
Age, mean±sd	39 ± 6	38 ± 6	41 ± 6	0.18
Mustard, n(%)	13 (25)	5 (15)	8 (44)	0.02
Senning, n(%)	38 (75)	28 (85)	10 (56)	0.02
Diabetes mellitus, n(%)	0	0	0	-
Arterial hypertension, n(%)	1 (2)	1 (3)	0	0.46
Dyslipidemia, n(%)	1 (2)	0	1 (6)	0.17
Obesity, n(%)	4 (8)	3 (9)	1 (6)	0.65
Palpitations, n(%)	15 (29)	7 (21)	8 (44)	0.08
Sinus rhythm, n(%)	40 (78)	27 (82)	13 (72)	0.43
Atrial fibrillation, n(%)	2 (4)	1 (3)	1 (6)	0.67
Right bundle branch block, n(%)	11 (22)	2 (6)	9 (50)	<0.01
Grade tricuspid valve regurgitation ≥ moderate, n(%)	31 (62)	21 (63)	10 (56)	0.57
Atrio-ventricular block, n(%)	3 (6)	0	3 (17)	0.02
NYHA class 1	41 (80)	29 (88)	12 (67)	0.07
NYHA class 2	10 (20)	4 (12)	6 (33)	0.07
Beta-blocker, n(%)	18 (35)	11 (33)	5 (28)	0.69
RAAS inhibitor, n(%)	19 (37)	11 (33)	8 (44)	0.43
Diuretics, n(%)	8 (16)	4 (12)	4 (22)	0.34
Anticoagulants, n(%)	13 (25)	4 (12)	9 (50)	<0.01
Statins, n(%)	2 (4)	1 (3)	1 (6)	0.66

NYHA: New York Heart Association, RAAS: renin-angiotensin-aldosterone system

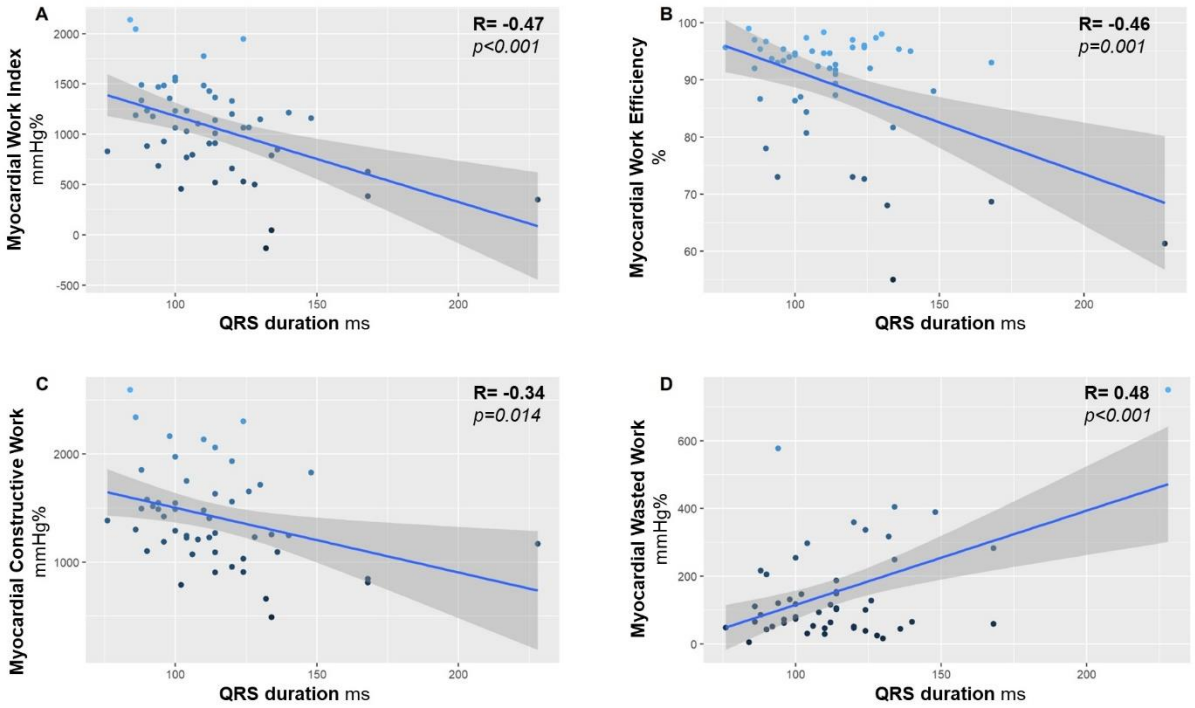

Figure 3: Correlation between QRS duration and the different septal MW parameters.

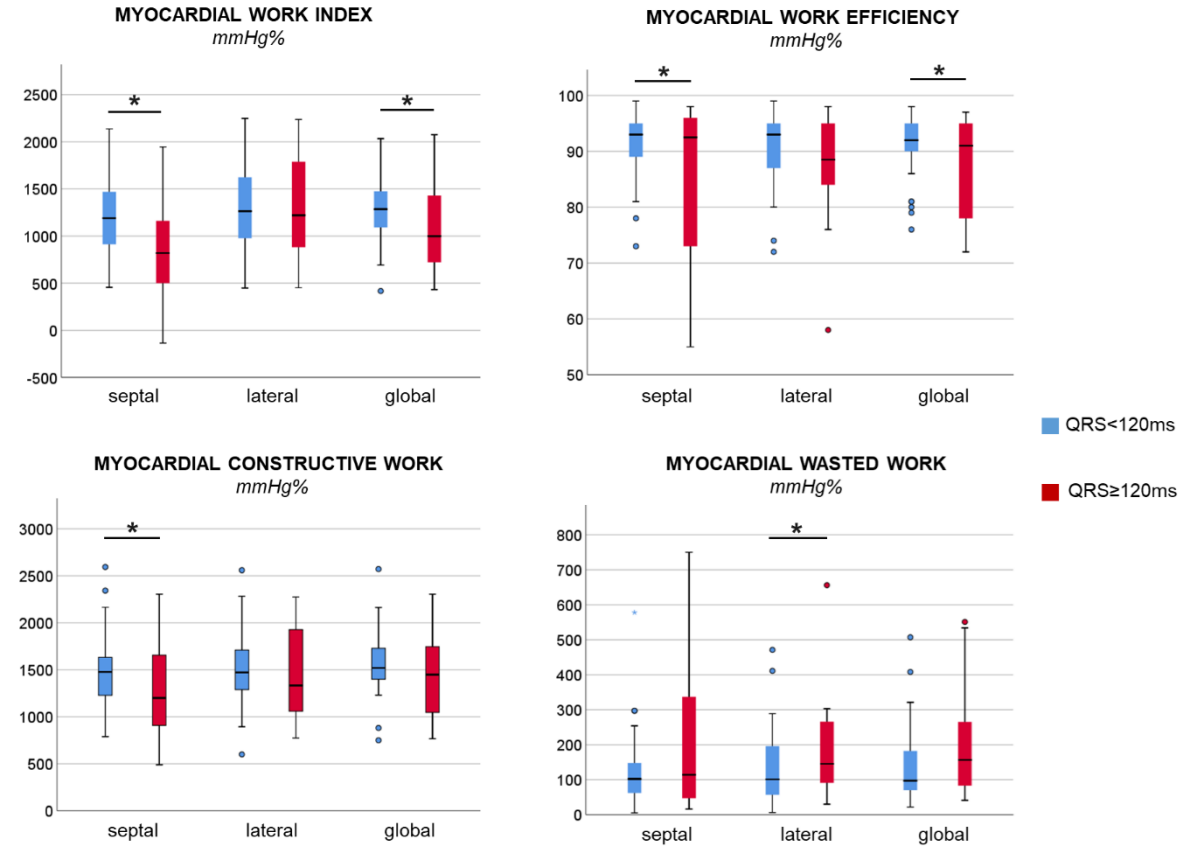

Figure 4: Regional and global Myocardial Work parameters according to QRS duration. (logarithmic scale, *p≤0.05)

Table 2: Pearson R correlation coefficient with QRS duration.

	QRS duration	p-value
VENTRICLE DIMENSIONS (sRV)		
End systolic area	*0,449*	*0,001*
End diastolic area	*0,405*	*0,003*
End systolic volume	*0,428*	*0,002*
End diastolic volume	*0,416*	*0,002*
BIOMARKERS		
TnT	*0,421*	*0,004*
NT-proBNP	*0,314*	*0,032*
VENTRICLE FUNCTION (sRV)		
TAPSE	-0,088	0,541
Annular s'	-0,276	0,093
FAC	*-0,314*	*0,025*
EF (a4C)	-0,184	0,197
GLS (a4c)	0,137	0,337
INTRAVENTRICULAR DYSYNCHRONY (sRV)		
Time-to-peak lateral	*0,331*	*0,017*
Peak strain lateral	-0,064	0,656
Time-to-peak septal	0,150	0,293
Peak strain septal	*0,301*	*0,032*
Dyssynchrony lateral-septal	-0,146	0,306
GLOBAL MYOCARDIAL WORK		
Global Work Index	*-0,297*	*0,035*
Global Work Efficiency	*-0,393*	*0,004*
Global Constructive Work	-0,255	0,071
Global Wasted Work	*0,393*	*0,004*
LATERAL MYOCARDIAL WORK		
Myocardial Work Index	0,094	0,511
Myocardial Work Efficiency	-0,089	0,535
Constructive Work	0,033	0,816
Wasted Work	0,099	0,488

Table 2 (Continuation)

	QRS duration	p-value
SEPTAL MYOCARDIAL WORK		
Myocardial Work Index	*-0,474*	*<0,001*
Myocardial Work Efficiency	*-0,462*	*0,001*
Constructive Work	*-0,343*	*0,014*
Wasted Work	*0,481*	*<0,001*

a4C: apical 4-chamber view, EF: ejection fraction, FAC: fractional area change, GLS: global longitudinal strain, NT-proBNP : N-terminal pro-brain natriuretic peptide, sRV: subaortic right ventricle, TAPSE : tricuspid annular plane systolic excursion, TnT: Troponins T

Intra- and interobserver variability were calculated using intraclass coefficient (ICC) and the standard error of measurements (***Table 4***). While a slightly higher intra- and interobserver variability was observed for GWE and GWW compared to GWI and GCW, the interclass correlation coefficient (ICC) was excellent (>0.9) for intra-observer variability in all MW parameters. By contrast, for the interobserver variability, ICC was good (>0.8) for GWE and GWW and excellent for GWI and GCW.

DISCUSSION

To the best of our knowledge, this study sets the first attempt to describe global and regional MW parameters in D-TGA patients who have undergone Mustard/Senning repair and have a sRV. The main results of our analysis can be summarized as follows: 1- There is an age-related increase in QRS duration in D-TGA patients which is associated with a dilatation of the sRV but not with a more pronounced mechanical dyssynchrony. 2- D-TGA patients with prolonged QRS and overloaded sRV exhibit higher levels of cardiac biomarkers. 3- MW parameters, as opposed to conventional echocardiographic parameters for assessment of RV or LV function, are closely linked to QRS duration. 4- Patients with prolonged QRS duration show more pronounced impairment in septal MW parameters whereas lateral MW parameters remain relatively unaffected. These findings shed new light on the relationship between QRS duration, sRV function, and MW parameters in D-TGA patients following Mustard/Senning repair.

Assessment of the sRV function by Myocardial Work

Prolonged QRS duration is a well-known documented phenomenon following Mustard/Senning repair and has been associated with the deterioration of the sRV function.[19, 21] Also QRS fragmentation has been shown to have an impact on the post-surgical survival as demonstrated by Helsen et al[22] However, our analysis could not prove a significant correlation between conventional echocardiographic parameters and QRS duration. It is worth noting that

the anatomical and physiological differences between the ventricles pose a challenge for using conventional echocardiographic parameters designed for assessing normal RV and LV function to properly evaluate the sRV function.[23, 24] By contrast, our study manifests the potential advantages of employing global and regional MW analysis for this purpose, as it incorporates the peripheral arterial BP into the assessment of sRV function. Notably, three MW parameters -GWI, GWE and GWW- progressively worsen with QRS prolongation.

Even though the calculation of MW may be primarily influenced by fiber shortening rather than by afterload, the use of MW parameters and components offer a more comprehensive assessment of the sRV performance compared to GLS and TAPSE. To date, PSL-derived MW analysis has been investigated in various pathologies like pulmonary hypertension[25], atrial septum defect[26] and advanced heart failure.[27] However, clear reference values are still lacking due to the limited data available. Additionally, while normal MW values have been determined for the LV, these values cannot be directly applied to sRV. Therefore, further research is warranted to understand the clinical significance of different MW values in sRV.

Of note, while lateral MW did not show a correlation with QRS duration, the septal MW parameters, particularly wasted work (WW), displayed the highest correlation. This finding suggests that sRV dysfunction and eventual failure may originate at the septum and might be related to the subpulmonary LV function (***Figure 5***).[28, 29] The pressure and volume overload experienced by the sRV will cause preferentially the free wall to stretch leading to an increase in size of the RV chamber and bowing of the septum toward the left side. Ultimately this process can lead to septal hypokinesia and dysfunction.[30] Although a considerable number of patients presented with at least moderated TR, its potential impact on MW parameters of the sRV, remains uncertain and warrants further investigation.

The prevalence of atrial fibrillation could make the MW analysis complicate and less reliable. However, Liu and colleagues[31] demonstrated that the calculation of MW parameters is feasible in various types of atrial fibrillation. Additionally, the proportion of patients with atrial fibrillation in our study population was very limited. It should be noted that the cardiac index measured in our study population falls below the normal range. This might be related to several factors. On the one hand, our calculation of the ventricular volume relays on one single 2D-image and the complex geometry of the sRV makes it challenging to acquire high quality images for accurate measurements. On the other hand, this may also indicate impaired contractility of the sRV ultimately leading in the long term to a depressed cardiac performance.

Table 3: Hemodynamic, anatomical and functional characteristics of the whole study population and per group.

	ALL	QRS<120	QRS≥120	p-value
	mean ± sd / median [IQR]			
GENERAL				
Age, years	39 ± 6	38 ± 6	41 ± 6	0,184
Systolic blood pressure, mmHg	125 ± 16	128 ± 17	121 ± 13	0,148
Diastolic blood pressure, mmHg	76 ± 13	79 ± 13	70 ± 11	*0,014*
Body Surface Area, m²	1,9 ± 0,2	1,9 ± 0,2	1,8 ± 0,2	0,518
ECG PARAMETERS				
Heart rate, bpm	68 ± 13	69 ± 15	66 ± 9	0,480
PR interval, ms	166 ± 33	154 ± 25	191 ± 36	*0,003*
QRS duration, ms	114 ± 26	100 ± 10	139 ± 26	*<0,001*
QTc interval, ms	433 ± 34	422 ± 28	453 ± 37	*0,004*
VENTRICLE DIMENSIONS (sRV)				
End systolic area, cm²	23 ± 7	20 ± 5	28 ± 8	*<0,001*
End diastolic area, cm²	32 ± 7	29 ± 5	36 ± 7	*0,002*
End systolic volume, ml	68 ± 31	57 ± 19	88 ± 39	*<0,001*
End diastolic volume, ml	109 ± 38	95 ± 29	135 ± 39	*0,001*
Stroke volume, ml	41 ± 17	38 ± 18	47 ± 14	*0,046*
BIOMARKERS				
TnT, ng/l	6 [4, 8]	6 [4, 8]	9 [5, 23]	*0,030*
NT-proBNP, ng/l	258 [164, 432]	247 [144, 346]	308 [174, 977]	*0,045**
INTRA-VENTRICLE DYSYNCHRONY				
Time-to-peak lateral, s	0,41 ± 0,06	0,40 ± 0,05	0,42 ± 0,07	0,325
Peak strain lateral, %	-13,95 ± 4,58	-13,85 ± 4,29	-14,14 ± 5,21	0,845
Time-to-peak septal, s	0,37 ± 0,06	0,36 ± 0,04	0,37 ± 0,09	0,807
Peak strain septal, %	-12,61 ± 4,14	-13,28 ± 3,59	-11,40 ± 4,86	0,161
Dyssynchrony lateral-septal, s	-0,04 ± 0,07	-0,04 ± 0,05	-0,06 ± 0,09	0,114
VENTRICLE FUNCTION (sRV)				
TAPSE, mm	13 ± 3	13 ± 4	12 ± 3	0,143
Annular s'	6 ± 2	6 ± 2	5 ± 2	0,072
FAC, %	28 ± 11	30 ± 12	24 ± 8	*0,016*
EF (a4C), %	39 ± 12	40 ± 12	37 ± 12	0,467
GLS (a4C), %	-13 ± 4	-13 ± 3	-12 ± 5	0,381

Table 3 (Continuation)

	ALL	QRS<120	QRS≥120	p-value
	mean ± sd / median [IQR]			
GLOBAL MYOCARDIAL WORK				
Global Work Index, mmHg%	1200 ± 385	1268 ± 327	1073 ± 455	*0,043°*
Global Work Efficiency, %	92 [84, 95]	92 [89, 96]	91 [78, 95]	*0,031°*
Global Constructive Work, mmHg%	1515 ± 378	1572 ± 349	1409 ± 416	0,103°
Global Wasted Work, mmHg%	109 [70, 206]	97 [69, 187]	157 [79, 272]	0,166°
LATERAL MYOCARDIAL WORK				
Myocardial Work Index, mmHg%	1313 ± 428	1300 ± 378	1336 ± 519	0,935°
Myocardial Work Efficiency, %	92 [86, 95]	93 [86, 96]	89 [84, 95]	0,184°
Constructive Work, mmHg%	1489 ± 415	1494 ± 382	1480 ± 481	0,741°
Wasted Work, mmHg%	120 [69, 199]	101 [57, 197]	146 [89, 271]	*0,040°*
SEPTAL MYOCARDIAL WORK				
Myocardial Work Index, mmHg%	1065 ± 466	1199 ± 388	819 ± 506	*0,007°*
Myocardial Work Efficiency, %	93 [87, 95]	93 [88, 95]	93 [72, 96]	*0,014°*
Constructive Work, mmHg%	1421 ± 450	1508 ± 412	1261 ± 482	*0,049°*
Wasted Work, mmHg%	102 [52, 216]	102 [57, 151]	114 [47, 343]	0,374°

a4C: apical 4-chamber view, ECG: electrocardiogram, EF: ejection fraction, FAC: fractional area change, GLS: global longitudinal strain, NT-proBNP: N-terminal pro-brain natriuretic peptide, sRV: subaortic right ventricle, TAPSE : tricuspid annular plane systolic excursion, TnT: Troponins T. °logarithmic scale.

The impact of QRS prolongation on sRV function

While mechanical dyssynchrony did not directly correlate with QRS prolongation, the regional MW analysis has unveiled discrepancy in the performance between the septal and lateral wall in patients with QRS≥120ms compared to those with normal QRS duration. Patients with QRS≥120ms were characterized by lower septal CW, MW index and MW efficiency. This finding contrasts with the previous correlation analysis which primarily linked septal WW to QRS duration.

In accordance with our results, Pluymen et al[21] reported the association of sRV size with NT-proBNP levels and QRS duration following Mustard/Senning repair. Also Roos-Hesselink and colleagues[32] confirmed a significant increase in QRS duration over long-term follow-up accompanying deterioration in sRV function as measured by echocardiography. QRS prolongation, ventricular dilatation and cardiac dysfunction represent gradual processes, stemming from the chronic pressure and volume overload on the sRV in D-TGA patients. Consequently, establishing normal cut-off values for these parameters proves challenging.

Therefore, in further research, a serial assessment approach may offer a more comprehensive evaluation of sRV (mal)performance and function decline over time. Based on our results, MW analysis emerges as a potentially valuable tool for this purpose.

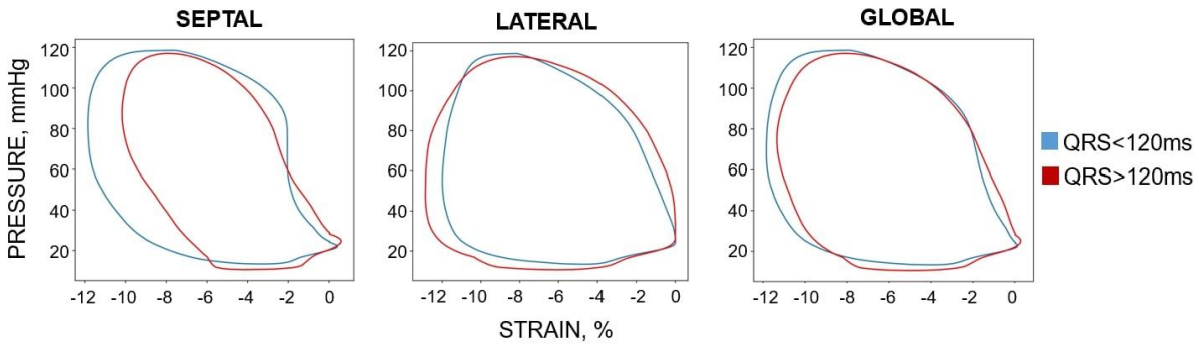

Figure 5: Global and regional pressure-strain loops van de sRV according to QRS duration.

Limitations

This study does have certain limitations. First, it focuses on a distinctive aging patient population with post-surgical sRV and unique characteristics resulting from Mustard/Senning procedures. Consequently, this study is limited by a relatively small sample size and a single-center design which hampers statistical analysis. Therefore, possible accidental findings need to be confirmed in larger studies. Second, MW assessment is a relatively and underexplored method that has not been extensively applied to the RV. Additionally, whereas cardiac magnetic resonance is considered the gold standard to measure RV volumes our analysis is based on TTE images, as it is a more accessible technique in the daily practice. Lastly, the advanced nature of this analysis demands high quality images which may not be readily obtainable in routine clinical practice. Given the retrospective nature of the study, the inclusion of patients was limited by the availability of suitable data. Also, potential differences between the Mustard and Senning procedure may affect outcomes among populations with different proportions.

CONCLUSION

Our study is the first to describe MW values in the sRV of D-TGA patients after Mustard/Senning repair. We have observed a post-surgical prolongation of QRS duration which aligns with a ventricular dilatation and more impaired cardiac performance. In the context of chronic pressure and volume overload, it appears that the underperformance of the sRV after Mustard/Senning repair may originate at the septal wall. Global and regional MW analysis, particularly septal MW values, emerges as a promising tool to assess subclinical sRV dysfunction. Instead of targeting direct clinical implications, our study aims to opens new perspectives for cardiac assessment in patients with a sRV. Certainly, follow-up studies are warranted to determine its prognostic value and delineate its clinical implications.

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Chapter 5

Myocardial Work in Amyloidosis

Myocardial work assessment to improve baseline risk stratification in patients with transthyretin amyloidosis

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Cardiac transthyretin amyloidosis (ATTR) is an often underdiagnosed and potentially fatal disorder associated with poor survival. The National Amyloidosis Centre (NAC) staging system, based on NT-proBNP level and eGFR value, discriminates patients according to survival rates. However, NAC stage II involves a heterogenous group of patients with variable prognosis. This retrospective single-center study was set up to explore the potential role of myocardial work (MW) analysis to enhance risk stratification of ATTR patients prior to therapy.

In total, 37 patients diagnosed with ATTR between March 2021 and August 2023 were included. Baseline NT-proBNP and eGFR values were collected and LVEF, GLS and MW parameters were obtained from stored echocardiographic images. Patients were categorized per NAC stage (16 NAC I, 13 NAC II and 8 NAC III). Whereas the survival rate in NAC II and NAC III was significantly worse than in NAC I (p=0.031 and p=0.045 respectively), no significant difference was found between NAC II and III. In the ROC analysis, GCW proved to be the best survival predictor (AUC: 0.7) with optimal cut-off value 1294 mmHg%. Patients from NAC stage II were re-stratified according to GCW cut-off into HIGH RISK together with patients from NAC III or LOW RISK together with patients from NAC I. Patients in the HIGH RISK group exhibited a significantly worse prognosis with only 40% survival at 2 years follow-up.

Our results demonstrate the advantages of incorporating MW analysis, particularly the use of a GCW cut-off, in the baseline risk stratification of ATTR patients.

INTRODUCTION

Cardiac transthyretin amyloidosis (ATTR) is a fatal disorder characterized by the progressive deposition of misfolded transthyretin amyloid fibrils in the myocardium resulting in biventricular hypertrophy and subsequent impairment of systolic and diastolic function.[1] This disease manifests in two distinct forms, hereditary and wild-type with the latter being more prevalent among elderly males. The prognosis when untreated is poor, with median survival estimates ranging from 2 to 6 years following diagnosis.[2] To date, no curative treatment exists for the wild-type of ATTR. However, the treatment with Tafamidis has shown to slow disease progression by stabilizing transthyretin with an acceptable safety profile.[3,4]

Despite the increasing awareness of the disease, which has certainly improved the diagnosis rates, the early detection of ATTR remains challenging due to its heterogenic presentation.[5] As determining the stage of the disease at the time of diagnosis plays a critical role in prognosis and patient risk stratification, Gillmore and colleagues[6] developed a prognostic staging system called the National Amyloidosis Centre (NAC) stages, applicable to both, the wild-type and the hereditary form of ATTR. This system relies in the assessment of cardiac biomarkers' levels, particularly N-terminal pro B-type natriuretic peptide (NT-proBNP), and renal function, as reflected by the estimated glomerular filtration rate (eGFR). Stage I is defined as NT-proBNP<3000 ng/L and eGFR>45ml/min, stage III is defined as NT-proBNP>3000 ng/L and eGFR<45ml/min, and the remaining patients are classified as stage II. This staging system proves to be effective in differentiating between patients with different survival rates.[7] NAC stage I, II and III are associated with an estimated survival of 62, 47, 24 months respectively.

However, it should be noted that stage II represents a rather heterogenic group of patients with either predominantly cardiac or renal dysfunction. Therefore, additional characterization of patients in this subgroup may be beneficial.

In the surveillance of patients with ATTR, echocardiography plays a crucial role in evaluating the progression of the disease by characterizing the functional and morphological impact of amyloid depositions in the myocardium. Recent studies demonstrated that 40% of patients had impaired ventricular function at the time of ATTR diagnosis.[8] However, standard echocardiographic parameters alone are insufficient for determining the prognosis accurately at the time of diagnosis. As the left ventricular ejection fraction (LVEF) is significantly impaired mainly in advanced stages of the disease, this parameter lacks the necessary sensitivity in the early stages.[9] Additionally, the strain pattern referred to as 'apical sparing' characterized by reduced strain values in the basal segments and preserved strain values in the apical region, is not specific to ATTR and may only be modestly present.[2,10]

Non-invasive myocardial work (MW) has emerged as a potential alternative method for assessing LV function through echocardiography by incorporating both myocardial deformation and afterload in its analysis.[11] Several recent studies have investigated the diagnostic and predictive value of MW indices in different pathological conditions[12,13,14], however, the potential role of MW analysis in risk stratification of ATTR patients has not yet been explored.

This retrospective single-center study was set up to examine whether MW analysis can be utilized to enhance risk stratification and prognosis estimation of ATTR patients prior to therapy.

METHODS

Patient screening and data collection

All patients, diagnosed with ATTR and referred for Tafamidis treatment between March 2021 and August 2023 were retrospectively screened for inclusion. Patients lacking laboratory data or echocardiographic images prior to therapy or with images of suboptimal quality were excluded as well as patients who were missing blood pressure measurements for MW calculation at the time of examination (***Figure 1***). Clinical data, patients' risk factors, comorbidities and medical therapy were collected at the time of inclusion. Baseline serum levels of creatinine, troponins and NT-proBNP as well as baseline eGFR values were collected and the NAC stage was calculated for each patient.[6] The extent of cardiac amyloid deposition was estimated using Technetium scintigraphy and graded with Perugini.[15] Echocardiographic measurements for LV structure and function were obtained from two-dimensional (2D) images, color Doppler, pulsed-wave and continuous-wave Doppler images of parasternal and apical views, adhering to current echocardiographic guidelines.[16]

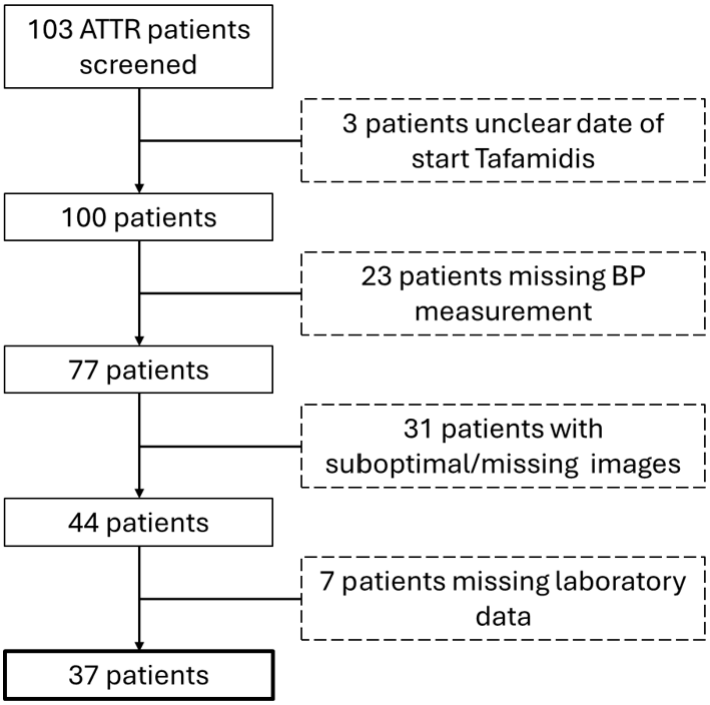

Figure 1: Flow chart of the patients' *screening for inclusion.*

Myocardial Work calculation

The 2-, 3- and 4-chamber apical view images of the LV, digitally stored in cine-loop format at high frame rates (55–75 frames per second) were used for offline calculation of LVEF, global longitudinal strain (GLS) and MW parameters using dedicated software (EchoPac, GE Vingmed Ultrasound, Horten, Norway). In the 2- and 4-apical views, LVEF was calculated using the Simpson's biplane method of discs. Semi-automated 2D speckle tracking was employed to analyze the three apical views to obtain the LV bull's-eye with the segmental strain values and calculate GLS. If necessary, the myocardium contour and the width of the region of interest were manually adjusted by the operator based on the patient's anatomy. Simultaneous measurement of aortic systolic pressure obtained from a cuff measurement was used as surrogate for LV peak systolic pressure. For the MW analysis, blood pressure measurements were input into the program following the strain analysis derived from the three apical views. The timing of aortic and mitral valve events was visually determined on the apical 3-chamber view. Ultimately, the LV strain values, estimated LV systolic pressure and valve events were integrated through a specialized software tool to construct non-invasive pressure-strain loops of the LV. The software computed global work index (GWI) and efficiency (GWE) as well as global constructive (GCW) and wasted work (GWW) using previously described methods.[17]

Ten patients were randomly selected for intra- and inter-observer variability analysis of de MW parameters. Intra-observer variability was performed by the sonographer repeating measurements on off-line data with a time interval of at least three months. Interobserver variability was performed by repeating measurements from the same images by 2 independent expert sonographers blinded to the patient's clinical data and each other's results. Intra- and interobserver variability were calculated by intraclass correlation coefficient (ICC) and the standard error of measurements. The results of the intra- and inter-observer variability are presented in ***Supplemental Table 1***.

Statistical analysis

Categorical data are presented as n (%). Descriptive data are reported as the mean ± SD for normally distributed continuous variables. Normality testing was performed by graphical analysis with histograms and QQ-plots. Differences between NAC stages were analyzed using the one-way ANOVA test for continuous variables and the Chi-square test for categorical variables. The Receiver Operating Characteristic (ROC) method was applied to assess the survival predictive value of MW parameters and determine the optimal cut-off with the highest sensitivity and specificity. Patients from NAC stage II were reclassified according to GCW value either to HIGH RISK (GCW<1294mmHg%) together with NAC stage III patients or to LOW RISK (GCW≥1294mmHg%) together with patients from NAC stage I. Survival rates were

calculated by the Kaplan-Meier method using the long rank (mantel-cox) test for intergroup difference. For all tests, a p-value below 0.05 was considered statistically significant. All statistical analysis were performed using SPSS for Windows Version 25 (SPSS, IBM headquarters, Armonk, NY, USA).

RESULTS

A total of 37 patients were included in the analysis before starting Tafamidis treatment for ATTR. Among them, sixteen patients were classified in NAC stage I, 13 in NAC stage II, 8 in NAC stage III. ***Table 1*** displays the baseline characteristics of the patients according to their NAC stage. Throughout a mean follow-up of 572 [321, 752] days, eight patients died, and seven patients were hospitalized at least once with symptomatic heart failure.

Table 1: Patients' baseline characteristics, laboratory and echocardiographic data per NAC stage.

	All patients (37)	**NAC stage I (16)**	**NAC stage II (13)**	**NAC stage III (8)**	**p-value #**
Male	33 (89)	14 (87)	11 (85)	8 (100)	0.522
Dead	8 (22)	1 (6)	4 (31)	3 (38)	0.131
Perugini 1	2 (5)	1 (6)	0	1 (13)	0.175
Perugini 2	24 (65)	12 (75)	10 (77)	2 (25)	
Perugini 3	10 (27)	3 (20)	3 (23)	4 (50)	
NYHA class 1	25 (68)	11 (69)	10 (76)	4 (50)	0.262
NYHA class ≥2	11 (30)	4 (25)	3 (23)	4 (50)	
Comorbidities					
Myocardial infarction	3 (7)	1 (6)	0	2 (25)	0.117
Cardiac device	7 (16)	0	3 (23)	4 (50)	0.012
Arterial hypertension	22 (50)	7 (44)	6 (46)	5 (63)	0.670
Atrial fibrillation	22 (50)	6 (38)	6 (46)	6 (75)	0.217
Coronary artery disease	15 (34)	4 (25)	5 (39)	5 (63)	0.203
Diabetes	11 (25)	5 (31)	2 (15)	1 (13)	0.457
Medical therapy					
ACEi/ARB/ARNI	21 (48)	9 (56)	7 (54)	2 (25)	0.316
BB	25 (58)	7 (44)	8 (62)	5 (63)	0.405
MRA	26 (59)	10 (63)	8 (62)	7 (88)	0.396
SGLT2i	7 (16)	4 (25)	0	2 (25)	0.144
Clinical data					
Age (years)	81 ± 7	*78 ± 8**	*81 ± 5*	*86 ± 5*	*0.030*
BSA (m²)	1.89 ± 0.16	1.93 ± 0.17	1.94 ±0.12	1.82 ± 0.17	0.210
SBP (mmHg)	125 ± 18	131 ± 18	120 ± 18	121 ± 20	0.623
DBP (mmHg)	72 ± 9	74 ± 7	72 ± 12	70 ± 7	0.724
Laboratory data					
Creatinine (mg/dL)	1.28 ± 0.63	*1.01± 0.21**	*1.29 ± 0.36**	*2.05 ± 1.04*	*<0.001*
Troponin (ng/L)	67.6 ± 51.1	*46.9 ± 39.6**	*68.0 ± 29.1*	*102.2 ± 78.2*	*0.054*
NT-proBNP (ng/L)	401± 3506	*1278 ± 980**	*5380± 3330°*	*7251 ± 3100*	*<0.001*
eGFR (mL/min/1.73m²)	58 ± 19	*70 ± 13**	*53 ± 15*°*	*34 ± 10*	*<0.001*

Table 1 (continuation)

Echocardiographic data					
LVEDD (mm)	46 ± 6	47 ± 6	45 ± 8	47 ± 7	0.724
LVESD (mm)	35 ± 7	35 ± 8	34 ± 5	38 ± 10	0.420
IVS (mm)	14 ± 4	15 ± 3	14 ± 3	14 ± 2	0.816
PW (mm)	14 ± 4	15 ± 4	15 ± 3	14 ± 4	0.927
LV mass (g)	268 ± 70	313 ± 80	259 ± 66	263 ± 29	0.106
LV mass index (g/m²)	141 ± 36	161 ± 39	134 ± 39	145 ± 18	0.180
E peak velocity (m/s)	79 ± 24	79 ± 22	69 ± 32	88 ± 16	0.271
e' lateral (m/s)	6.8 ± 2.3	6.6 ± 2.6	6.3 ± 1.9	7.8 ± 2.0	0.459
e' septal (m/s)	4.7 ± 1.8	4.4 ± 1.4	5.0 ± 2.1	4.6 ± 2.9	0.727
E/e' lateral	12 ± 5	13 ± 4	12 ± 8	12 ± 4	0.838
E/e' septal	20 ± 11	20 ± 6	18 ± 15	25 ± 14	0.436
E/e' average	15 ± 7	16 ± 5	15 ± 11	15 ± 5	0.876
TAPSE (mm)	18 ± 5	*20 ± 4**	*18 ± 4**	*14 ± 4*	*0.005*
Left Ventricular Function					
LVEF (%)	45 ± 10	47 ± 10	43 ± 11	40 ± 9	0.282
GLS** (%)	13.3 ± 4.3	14.2 ± 4.1	12.5 ± 5.0	10.9 ± 2.7	0.200
GWI (mmHg%)	1281 ± 527	1404 ± 563	1081 ± 410	1021 ± 411	0.110
GCW (mmHg%)	1498 ± 569	*1657± 617**	*1297 ± 406*	*1149 ± 459*	*0.057*
GWW (mmHg%)	79 ± 49	87 ± 57	82 ± 58	69 ± 36	0.742
GWE (%)	94 ± 4	93 ± 5	93 ± 5	94 ± 2	0.945

*Categorical variables are presented as n (%) and continuous variables as mean ± sd. # intergroup difference with all groups together (Oneway ANOVA test) *p<0.05 vs NAC stage III (T-test), °p<0.05 vs NAC stage I (T-test), **absolute value. ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor/neprilysin inhibitor, BB: beta blocker, MRA: mineralocorticoid receptor antagonist, BSA: body surface area, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GCW global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, IVS: inter-ventricular septum, LV: left ventricle, LVEDD: left ventricle end diastolic diameter, LVEF: left ventricle ejection fraction, LVESD: left ventricle end systolic diameter, NAC: National Amyloidosis Centre, NT-proBNP: N-terminal pro b-type natriuretic peptide, NYHA: New York Heart Association, PW: posterior wall, SBP: systolic blood pressure, SGLT2i: sodium-glucose co-transporter-2 inhibitors TAPSE: tricuspid annulus plane systolic excursion.*

Patients in NAC stage III were older and had significantly higher levels of serum troponins and creatinine along with worse right ventricle function compared to NAC stage I and II patients (***Table 1***). Higher NAC stage was associated with worse LVEF, GLS, GWI and GCW although the differences between stages did not reach statistical significance. The only parameter that showed a significant difference between NAC stage III and NAC stage I was GCW. Additionally, GCW exhibited a negative correlation with NT-proBNP level (R=-0.477, $p<0.05$) and a positive correlation with eGFR (R= 0.405, $p<0.05$). Therefore, among all MW parameters, GCW emerged as the most appropriate for patient risk stratification. Furthermore, in the ROC analysis, we determined the optimal GCW cut-off value for predicting survival according to the Youden index (area under the curve = 0.7). A GCW of 1294mmHg%, corresponded to the highest specificity (0.63) and sensitivity (0.58) values.

Reclassification rate

Based on the GCW cut-off value of 1294mmHg%, the patients were recategorized into two risk levels: the HIGH RISK group included all patients from NAC stage III, regardless their GCW value, and patients from NAC stage II with GCW value below 1294mmHg%, the LOW RISK group included all patients from NAC stage I, regardless their GCW value, and patients from NAC stage II with GCW value above or equal to 1294mmHg%.

For each NAC cohort, the proportion of patients assigned to each risk level according to GCW value is shown in ***Figure 2***. In details, 8 patients (62%) from NAC stage II were classified in the HIGH RISK and 5 patients (38%) in the LOW RISK cohort. Further, 6 patients (38%) from NAC stage I were categorized as LOW RISK even though presenting GCW<1294mmHg% whereas 3 patients (38%) from NAC stage III were classified as HIGH RISK despite having GCW>1294mmHg%.

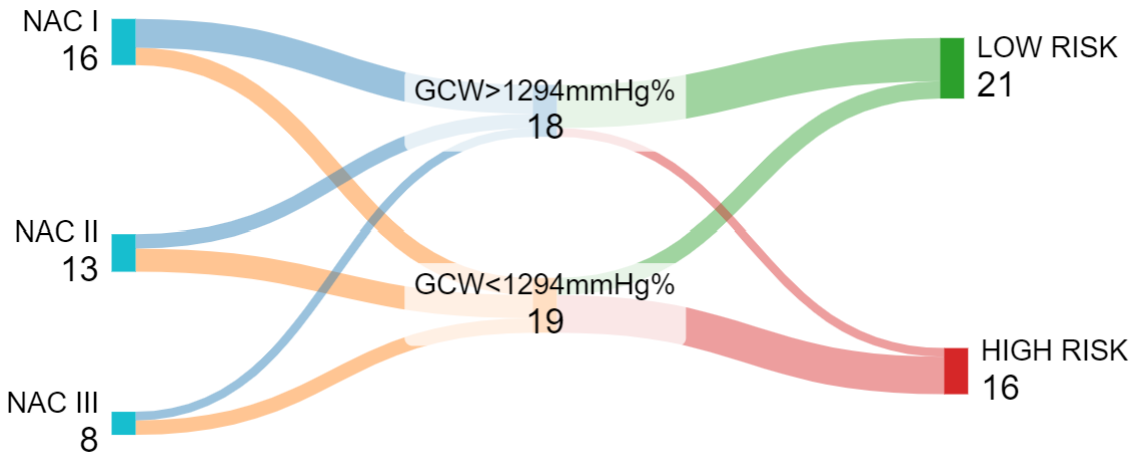

Figure 2: Sankey diagram for patient risk re-stratification by combining NAC stage and MW analysis.

The adoption of the GCW value on top of the NAC criteria drives a novel system for patient risk stratification based on three cut-offs: eGFR < 45ml/min, NT-proBNP > 3000ng/L and GCW < 1294mmHg%. ATTR patients with two or more positive criteria are labelled as HIGH RISK while patients with one or zero positive criteria are categorized as LOW RISK (***Figure 3A***).

HIGH RISK vs LOW RISK

After reclassification, patients labelled as HIGH RISK exhibited not only worse values for creatinine, troponins, NT-proBNP and eGFR, but they also demonstrated more pronounced right and left ventricular dysfunction compared to LOW RISK patients. This was evident from significantly lower values of TAPSE, LVEF, GLS (absolute value), GWI and GCW (***Table 2***).

Nevertheless, when comparing patients from NAC stage II reclassified as HIGH RISK to those reclassified as LOW RISK no significant difference was found in age, comorbidities, biomarkers of echocardiographic parameters (***Table 3***).

Table 2: Clinical, laboratory and echocardiographic data in HIGH RISK patients vs LOW RISK patients.

	LOW RISK mean ± sd	**HIGH RISK** mean ± sd	**p-value**
Clinical data			
Age (years)	80 ± 7	83 ± 6	0.143
BSA (m²)	1.93 ± 0.16	1.88 ± 1.5	0.261
SBP (mmHg)	*130 ± 18*	*117 ± 17*	*0.029*
DBP (mmHg)	74 ± 9	70 ± 8	0.260
Laboratory data			
Creatinine (mg/dL)	*1.1 ± 0.2*	*1.7 ± 0.9*	*0.012*
Troponin (ng/L)	*49.0 ± 36.1*	*90.7 ± 59.6*	*0.019*
NT-proBNP (ng/L)	*2166 ± 2730*	*6432 ± 2924*	*<0.001*
eGFR (mL/min/1.73m²)	*66 ± 15*	*43 ± 16*	*<0.001*
Echocardiographic data			
LVEDD (mm)	47 ± 7	46 ± 8	0.802
LVESD (mm)	35 ± 7	36 ± 8	0.570
IVS (mm)	14 ± 3	14 ± 2	0.667
PW (mm)	14 ± 3	15 ± 4	0.515
LV mass (g)	284 ± 83	276 ± 51	0.747
LV mass index (g/m²)	146 ± 42	148 ± 31	0.873
E peak velocity (m/s)	76 ± 22	80 ± 29	0.682
e' lateral (m/s)	6.7 ± 2.4	6.7 ± 2.3	0.969
e' septal (m/s)	5.0 ± 1.7	4.2 ± 2.3	0.271
E/e' lateral	12 ± 4	13 ± 7	0.677
E/e' septal	18 ± 7	24 ± 15	0.135
E/e' average	15 ± 5	17 ± 10	0.443
TAPSE (mm)	*20 ± 4*	*15 ± 5*	*0.003*
Left Ventricular Function			
LVEF (%)	*47 ± 10*	*40 ± 9*	*0.043*
GLS (absolute value, %)	*14,6 ± 4.5*	*10,6 ± 2.8*	*0.002*
GWI (mmHg%)	*1419 ± 508*	*931 ± 340*	*0.002*
GCW (mmHg%)	*1673 ± 546*	*1089 ± 346*	*0.001*
GWW (mmHg%)	88 ± 54	72 ± 51	0.388
GWE (%)	94 ± 5	93 ± 5	0.828

BSA: body surface area, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GCW global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, IVS: inter-ventricular septum, LV: left ventricle, LVEDD: left ventricle end diastolic diameter, LVEF: left ventricle ejection fraction, LVESD: left ventricle end systolic diameter, NT-proBNP: N-terminal pro b-type natriuretic peptide, PW: posterior wall, SBP: systolic blood pressure, TAPSE: tricuspid annulus plane systolic excursion.

Prognostic value

The Kaplan-Meier curve analysis confirmed that patients within the NAC stage II and III cohort exhibited markedly lower survival rates compared to those within NAC stage I, however, no statistical difference was found between NAC stage II and III (***Figure 3B***). By contrast, patients categorized as HIGH RISK had significantly worse survival rates when compared to LOW RISK patients (p=0.039), with only 40% survival at 2 years follow-up despite medical therapy (**Figure 3C**).

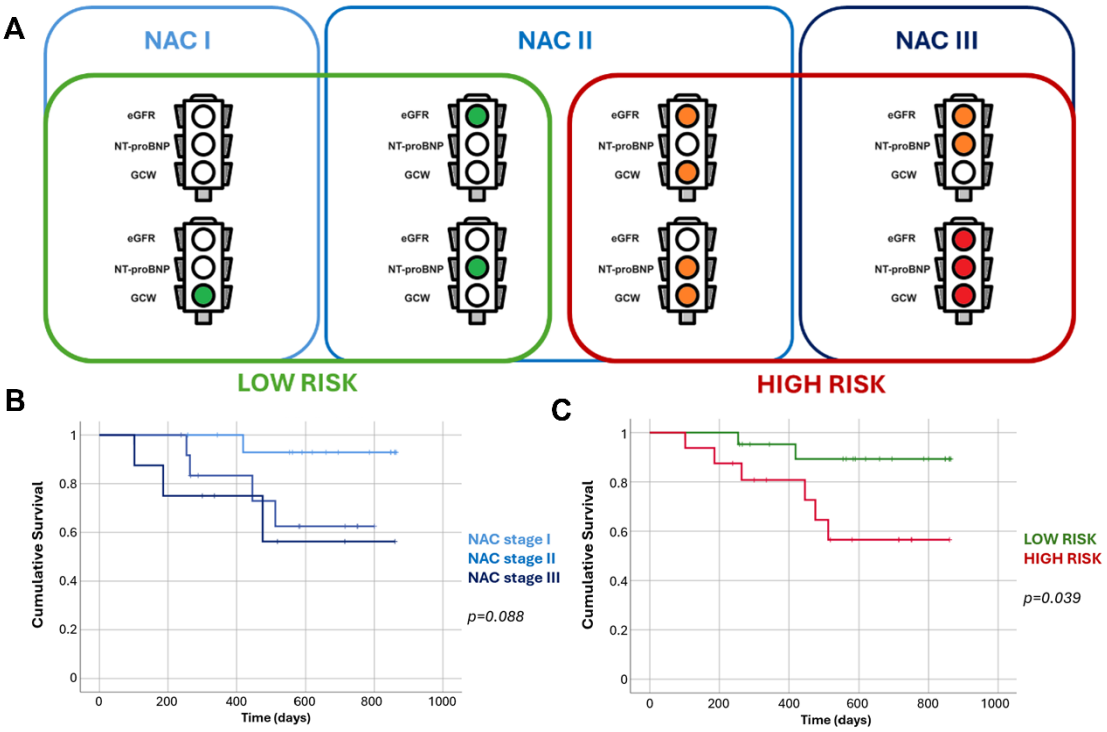

Figure 3: Patient risk assessment combining NAC criteria and MW parameters (cut-offs: eGFR < 45ml/min, NT-proBNP > 3000ng/L and GCW < 1294mmHg%) **A.** Patients with ≤1 criteria are classified as LOW RISK and patients with ≥2 criteria are classified as HIGH RISK. **B.** Survival analysis per NAC stage. **C.** Survival analysis after re-stratification in HIGH RISK and LOW RISK.

Table 3: Reclassified patients from NAC II, LOW RISK (5 patients) vs HIGH RISK (8 patients)

	LOW RISK mean ± sd	**HIGH RISK mean ± sd**	**p-value**
Clinical data			
Age (years)	*84 ± 5*	*80 ± 5*	0.19
BSA (m²)	*2.0 ± 0.1*	*1.9 ± 0.1*	0.66
SBP (mmHg)	*130 ± 21*	*114 ± 14*	0.18
DBP (mmHg)	*73 ± 15*	*71 ± 10*	0.71
Laboratory data			
Creatinine (mg/dL)	1.3 ± 0.3	1.3 ± 0.4	0.77
Troponin (ng/L)	55 ± 28	77 ± 28	0.19
NT-proBNP (ng/L)	5008 ± 4519	5612 ± 2679	0.79
eGFR (mL/min/1.73m²)	53 ± 17	53 ± 14	0.97
Echocardiographic data			
TAPSE (mm)	19 ± 2	17 ± 4	0.26
LVEF (%)	47 ± 10	40 ± 11	0.27
GLS (absolute value, %)	16 ± 6	10 ± 3	0.09
GWI (mmHg%)	1466 ± 310	841 ± 247	*0.01*
GCW (mmHg%)	1725 ± 237	1029 ± 192	*<0.01*
GWW (mmHg%)	92 ± 51	76 ± 65	0.64
GWE (%)	94 ± 3	93 ± 6	0.46
Patient Characteristics			
Male (%)	80	88	0.72
Dead (%)	20	38	0.51
Perugini 2 (%)	80	75	0.84
Perugini 3 (%)	20	25	0.84
Comorbidities			
Cardiac device (%)	0	38	0.12
Arterial hypertension (%)	80	25	0.05
Atrial fibrillation (%)	40	50	0.73
Coronary artery disease (%)	20	50	0.28
Diabetes (%)	40	0	0.05
Medical Therapy			
ACEi/ARB/ARNI (%)	40	63	0.43
BB (%)	40	75	0.21
MRA (%)	40	75	0.21

ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor/neprilysin inhibitor, BB: beta blocker, MRA: mineralocorticoid receptor antagonist, BSA: body surface area, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, GCW global constructive work, GLS: global longitudinal strain, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, LVEF: left ventricle ejection fraction, NT-proBNP: N-terminal pro b-type natriuretic peptide, SBP: systolic blood pressure, TAPSE: tricuspid annulus plane systolic excursion.

DISCUSSION

In this study, we investigated the added value of MW analysis in combination with the NAC staging system to risk-stratify patients with ATTR, treated by Tafamidis at the time of diagnosis. The three main findings are: i) Among all MW parameters, GCW demonstrated the best predictive value (AUC 0.7) for the survival of patients with ATTR. ii) The NAC stage II cohort consisted of a diverse group of patients with varying levels of risk where the GCW threshold of 1294mmHg% (specificity 0.63, sensitivity 0.58) permitted to distinguish patients at high risk from those at low risk. iii) The prognostic value of the NAC staging system in estimating outcome of patients with ATTR could be enhanced by incorporating MW assessment, particularly the GCW value. In brief, the results of our study underline the benefit of combining cardiac imaging and laboratory data for a more accurate the risk assessment in patients with ATTR.

ATTR staging: a laboratory data based approach

The NAC staging system presents a simple but powerful method to risk-stratify ATTR patients based on cardiac and renal function as reflected by the NT-proBNP value and the eGFR value.[6] In contrast to previous studies we observed no significant difference in mortality between NAC II and NAC III patients. However, significantly better survival rates were noted in NAC I compared to both NAC II and NAC III, when analyzed separately. These findings indicate, on the one hand, the high sensitivity of the NAC staging system for discriminating patients who are free of risk in the short term while on the other hand highlighting its poor specificity in determining which patients are at the highest risk. Consequently, the incorporation of cardiac imaging parameters may be beneficial in enhancing patient risk stratification based on NAC stages. Furthermore, while patients in NAC stage I and III are associated with a more favorable and a clearly adverse prognosis, respectively, NAC stage II encompasses a rather heterogeneous group of patients exhibiting varying levels of risk. As previously mentioned, all patients with abnormal values for either NT-proBNP or eGFR are classified as NAC stage II. However, apart from cardiac and renal function, other factors such as race, body mass index or the patient's filling state, can significantly influence these parameters, thereby complicating accurate risk estimation. Moreover, the diverse clinical presentation of ATTR and its individual-specific disease progression necessitate the integration of various diagnostic tools into a more comprehensive clinical evaluation.

Myocardial work for patient risk stratification in ATTR

Modern echocardiographic techniques allow for the advanced analysis of myocardial function and morphology. Consequently, advanced echocardiography may prove valuable in

evaluating the impact of transthyretin myocardial deposition on the cardiac function and patient survival.

Previous research has already suggested the integration of MW assessment into the clinical evaluation and management of ATTR patients. Roger-Rollé and colleagues[18] demonstrated the correlation between MW indices and well-known prognostic markers. However, in contrast to our study, they exclusively investigated GWI and GWE omitting left GCW and GWW from their analysis. They advocated incorporating MW analysis in the severity assessment of the disease to improve the selection of candidates for therapeutic intervention. Furthermore, Stassen et al[19] reported the independent diagnostic value of GCW for detecting cardiac amyloidosis, in addition to standard echocardiographic measurements and Ladefoged et al[20] identified GWI as an independent predictor of survival in patients with wild-type ATTR. The latter finding contrasts with the results of our study which identified GCW as the most effective MW parameter for predicting survival in ATTR patients. While further research is still needed to determine the MW parameter with the highest clinical impact, our results align with previous studies underscoring the benefits of MW analysis in the clinical assessment of ATTR patients.

ATTR risk stratification: imaging and laboratory data combined approach

The unspecific risk profile of patients in NAC stage II and the prognostic value of MW indices in ATTR[21], point out the potential complementary role of advanced echocardiography in addition to laboratory data to improve risk assessment in patients with ATTR. Our findings suggest particularly the addition of the GCW cutoff to the well-known NAC criteria. Before cardiac dysfunction becomes evident by a drop in LVEF or the manifestation of heart failure signs and symptoms, impaired GCW may indicate the presence of subclinical myocardial dysfunction. This impairment is characterized by decreased contractile performance and is associated with worse prognosis.[12,22] It is noteworthy that although GCW was identified as the most significant predictor of survival in the ROC analysis, an AUC of 0.7 reflects a moderate level of predictive power. Furthermore, the GCW threshold of 1294mmHg% was associated with moderate sensitivity and specificity, including both false positive and false negative errors. Nevertheless, our findings suggest that, while patients in NAC stage I or III do not necessitate additional MW assessment, patients in NAC stage II, may still benefit from this approach (***Figure 3***).

Clinical implications

The integration of advanced echocardiography and biomarkers profile, allows for a more accurate estimation of patient's prognosis. While suggesting potential benefits, our data lack robust evidence to support the integration of MW assessment in the routine evaluation of

ATTR. Nevertheless, these preliminary findings indicate that the integration of MW assessment along with NT-proBNP and eGFR in the diagnostic work-up could potentially enhance the prognosis estimation, particularly in patients with NAC stage II.

Limitations

This study has some limitations to be acknowledged. Firstly, MW assessment is still a new echocardiographic tool to be underexplored in the context of ATTR. Moreover, this relatively novel approach necessitates the availability of high-quality images which may not always be easily attainable in the routine clinical setting. For optimal image acquisition and analysis, comprehensive operator training is crucial and the lack of knowledge and experience may negatively impact the reproducibility of the measurements. In our study, we chose highly qualified echocardiographers to improve the reproducibility of our results. However, given that all images were acquired and analyzed with GE support, our findings should be interpreted with an awareness of potential vendor dependency. Secondly, the retrospective nature of the study and its single-center design imposed limitations on patient inclusion and availability of data. Therefore, at this stage, our results should be regarded as hypothesis-generating and further studies are warranted to explore the potential role of MW in prognostication of patients with ATTR.

CONCLUSION

In conclusion, incorporating MW analysis, particularly GCW, into the baseline evaluation of ATTR patients may potentially improve risk stratification, allowing for more personalized therapeutic decisions. A GCW cut-off might be useful to discriminate patients in NAC stage II who are at higher risk due to impaired myocardial performance. Apart from medical therapy, these patients may benefit from further study to evaluate whether more intensive monitoring is warranted.

Supplemental Table 1: Intra- and inter-observer variability

	Intra-observer variability			**Inter**-observer variability		
	ICC (95% CI)	Bias	Limits of agreement	**ICC** (95% CI)	Bias	Limits of agreement
GWI, mmHg%	**0.977** (0.777-0.998)	-32.0 ± 97.5	-223 to 159	**0.999** (0.99-1.00)	-38.4 ± 37.9	-35.8 to 112.6
GCW, mmHg%	**0.942** (0.439-0.994)	-59.4 ± 151.8	-236 to 355	**0.997** (0.97-1.00)	-29.6 ± 74.4	-116.2 to 175.4
GWW, mmHg%	**0.852** (-0.426-0.985)	2.4 ± 9.0	- 15 to 20	**0.934** (0.37-0.99)	2.2 ± 11.9	-21.2 to 25.6
GWE, %	**0.800** (-0.921-0.979)	0 ± 0.7	-1.39 to 1.39	**0.995** (0.95-0.99)	-0.4 ± 0.5	-1.5 to 0.7

GCW: global constructive work, GWE: global work efficiency, GWI: global work index, GWW: global wasted work, ICC: interclass correlation coefficient.

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Discussion

The advantages and new possibilities associated with myocardial work analysis are set to significantly impact clinical practice. Numerous clinical studies have demonstrated the usefulness of this echocardiographic tool beyond certain challenges, thereby, encouraging its implementation to guide medical care and strategies. However, multicenter randomized controlled trials are still warranted to substantiate the evidence of these findings. Compared to other surrogates for left ventricular function such as ejection fraction or global longitudinal strain, myocardial work analysis more effectively incorporates the cardiac loading condition. The set of myocardial work indices may therefore facilitate a more accurate and comprehensive assessment of left ventricular mechanics and energetics, thereby enhancing the understanding of physiological changes and adaptive mechanisms that maintain cardiac performance in various cardiac conditions. Interestingly, the most relevant myocardial work parameters vary depending on specific cardiac conditions, with each parameter showing unique adaptations to acute or chronic changes. This PhD thesis aims to advance knowledge on this novel echocardiographic tool and provide supplementary evidence regarding the additional value of myocardial work analysis to support its implementation in clinical practice. The *Central Illustration* of **Chapter 1** presents different cardiac conditions with the expected changes in the shape of the pressure-strain loop and myocardial work parameters, consistent with findings and observations from previous studies. Furthermore, this research focusses on pathologies characterized by both progressive and abrupt changes in the loading condition like severe aortic valve stenosis treated with transcatheter aortic valve replacement, as well as conditions where clinical data on myocardial work analysis are relatively scare, including cardio-oncology, the systemic right ventricle in congenital heart disease and amyloidosis.

In the field of cardiovascular research, there is notable and growing interest in the recently emerged subdiscipline of cardio-oncology. In recent decades, an increasing number of studies has been published and the first European Society of Cardiology (ESC) Guidelines on cardio-oncology came out in 2022. However, given that myocardial work analysis is a relatively novel methodology and that the existing data are limited, its specific role in the field of cardio-oncology and its impact in the clinical management of cancer patients remain to be elucidated. In **Chapter 2** we explored the temporal changes and longitudinal trajectories of myocardial work parameters before, during and after treatment with anthracyclines. We also examined the potential value of baseline myocardial work indices in predicting cancer treatment-related cardiac dysfunction (CTRCD) as defined in the recent ESC Guidelines. Interestingly, different degrees of CTRCD are associated with varying trajectories and all myocardial work parameters demonstrated significance at different follow-up time points. Specifically, baseline myocardial work index, efficiency and constructive work were depressed in patients who subsequently developed moderate CTRCD during follow-up and emerged as

independent predictors of moderate CTRCD. This finding suggests the existence of a distinct phenotype associated with an increased susceptibility to develop CTRCD, marked by an inherent reduced left ventricular efficiency resulting from diminished contractile capacity. Consequently, the integration of myocardial work analysis into the individual risk assessment prior to anthracycline therapy may enhance the identification of patients at elevated risk for developing subsequent CTRCD. Inversely, the wasted work progressively increased during the first year following the initiation of therapy in patients exhibiting moderated CTRCD. This observation might potentially be related to minor changes in the QRS duration or subtle uncoordinated contractions resulting from cardiotoxic treatment in the absence of overt arrhythmia or dyssynchrony. Regardless the underlying trigger behind the gradual increase in wasted work, serial myocardial work assessments during and after anthracyclines therapy could assist physicians in diagnosing CTRCD in ambiguous cases. This is particularly relevant when patients show a clear tendency toward increased wasted work during follow-up, well in advance of detectable changes in left ventricular ejection fraction and global longitudinal strain. Based on these findings, further prospective multicenter studies are warranted to evaluate serial myocardial work measurements as a novel strategy for the detection and management of patients with CTRCD.

The atrio-ventricular coupling plays an crucial role in global cardiac performance as subtle changes in atrial function can significantly impact ventricular performance. Therefore, integrating left ventricular contractile capacity and left atrial function facilitates a more comprehensive evaluation of global cardiac performance. Consequently, we performed a subanalysis to investigate the incremental value of left atrial strain in conjunction with myocardial work to predict CTRCD in breast cancer patients treated with anthracycline therapy (**Appendix A**). Our results indicated that the predictive power of myocardial work could be significantly enhanced by incorporating measurements of the left atrial function. Specifically the combination of the myocardial work index and left atrial reservoir strain measured prior to the initiation of chemotherapy demonstrated the highest predictive capability. The atrial reservoir strain corresponds to the process of atrial relaxation and filling that occurs during ventricular systole. It is quantitively defined as the sum of atrial conduit and contractile strain, which correspond to the early (passive filling) and late (active filling) phases of ventricular diastole, respectively. Impaired left atrial reservoir strain reflects abnormal atrial relaxation which may subsequently result in diminished ventricular filling during diastole. The integration of the myocardial work index, as a surrogate for the ventricular contractile capacity, and left atrial reservoir strain, as a surrogate for ventricular diastolic filling, may be instrumental in enhancing baseline cardiovascular toxicity risk assessments in cancer patients prior to anthracycline therapy.

Myocardial work analysis, as an afterload-adjusted parameter of left ventricular systolic performance, may yield more valuable insights than load dependent indices, such as ejection fraction or strain, in cardiac conditions characterized by variability in afterload between visits. This is particularly relevant for individuals experiencing a progressive increase in afterload, such as arterial hypertension and aortic valve stenosis. In these instances, myocardial work parameters change as the disease advances, providing important insights into the potential benefits of intervention. Consequently, we dedicated **Chapter 3** to the role of myocardial work analysis in managing patients with severe aortic valve stenosis. We primarily investigated the predictive power of baseline myocardial work parameters for outcome and survival after valve replacement. In our subanalysis of the randomized AVATAR study, a baseline global work index below 2000mmHg% was associated with poor survival after aortic valve replacement in asymptomatic patients with severe aortic valve stenosis and preserved ejection fraction. This highlights the superiority of myocardial work analysis to unmask subclinical cardiac dysfunction before evident symptoms of heart failure appear. Consequently, the incorporation of myocardial work analysis into the routine assessment of patients with progressive aortic valve stenosis was further corroborated by our second study, which investigated the potential value of myocardial work analysis in enhancing patient risk stratification prior to transcatheter aortic valve replacement (TAVR). Both baseline global work index and constructive work were found to correlate with outcome and a baseline global work index below 2323mmHg% was associated with a higher rate of heart failure hospitalization and increased mortality. Furthermore, using the 2323mmHg% cut-off value for the global work index in conjunction with the parameters suggested by Généreux et al. to risk stratify patients based on extra-valvular damage or dysfunction was effective in identifying high-risk patients before intervention. Numerous studies have shown the prognostic value of myocardial work indices and their relationship with outcome after aortic valve replacement. However, the optimal cut-off for monitoring patients with asymptomatic severe aortic valve stenosis before referring for intervention remains undetermined.

Additionally, we studied the evolution of myocardial work parameters before and after TAVR to delineate the different trajectories in patients with favorable versus unfavorable outcome. All patients showed a significant decrease in myocardial work index and constructive work, attributes to the acute drop in afterload, whereas only patients with favorable outcome also demonstrated a significant decrease in wasted work. Similar myocardial work trajectories were observed in multiple additional subanalysis which revealed that an insufficient decrease in myocardial work indices was linked to long-term left ventricular dysfunction and worse prognosis (**Appendix C, D, E**). This may be due to extra-valvular myocardial damage caused by prolonged elevated afterload, which hinders left ventricular function recovery and limits the

benefits of valve implantation. Patients who are unable to adequately recover left ventricular function after TAVR, as measured by myocardial work analysis, exhibit a poorer prognosis and diminished chances of long-term survival.

In complex congenital cardiac diseases, where reliable assessment of the global cardiac performance is highly challenging, regional myocardial work analysis might be of interest to better understand the physiological adaptations of ventricular function, mechanics and energetics under exceptional conditions. Therefore, **Chapter 4** presents our findings from an investigation into the myocardial work indices of the subaortic right ventricle (sRV) in a cohort of patients with dextro-transposition of the great arteries. This study aims to enhance our understanding of the evolution of sRV function following Mustard/Senning repair. After surgery an increase in QRS duration was associated with ventricular dilatation and elevated levels of cardiac biomarkers. Of note, patients with longer QRS duration exhibited poorer global values of myocardial work index, efficiency and constructive work. Interestingly, the analysis of regional myocardial work revealed significant impairment in septal myocardial work parameters while lateral parameters remained relatively stable. Additionally, while lateral myocardial work showed no correlation with QRS duration, septal myocardial work parameters, especially wasted work, demonstrated a highly significant correlation. In comparison to the normal right and left ventricle, the sRV exhibits significantly lower global constructive work and higher wasted work (**Appendix F**). While ventricular enlargement due to increased afterload may primarily contribute to the decline in contractility, QRS prolongation may be associated with energy waste resulting in less effective contractions. In the context of chronic pressure and volume overload, the underperformance of the sRV after Mustard/Senning repair may be attributed to dysfunction in the septal wall. Global and regional myocardial work analysis, particularly septal myocardial work values, emerge as a promising tool to assess subclinical sRV dysfunction in this patient population.

A promising area for research is the combination of advance echocardiographic imaging and biomarkers for both diagnostic and prognostic porpoises. This multimodality approach ensures higher accuracy and reliability by integrating different measuring methods and sources of information. However, literature is notably scare in this aspect. Therefore, we explored the potential value of integrating myocardial work parameters with serum cardiac biomarkers levels in two cardiac pathologies: aortic valve stenosis and cardiac amyloidosis. In patients with severe aortic valve stenosis, baseline troponin levels were identified as the biomarker with the highest predictive value for early mortality after TAVR. Additionally troponin levels demonstrated a significant correlation with all myocardial work parameters except for wasted work (**Appendix B**). By integrating troponin level and the wasted work value prior to intervention, it may be possible to more effectively identify patients at high risk for early

mortality after TAVR. It is important to note that this analysis was conducted on a small scale, where patients were risk-stratified based on the median values of troponins and wasted work within the study population. Therefore, to establish reliable and robust cut-off values for clinical use, larger studies are necessary. Nonetheless, our findings present new and promising perspectives to enhance the surveillance of patients with aortic valve stenosis undergoing TAVR. Additionally, they support the integration of cardiac imaging and biomarkers to improve patient management.

Similarly, in patients with cardiac amyloidosis, integrating cardiac imaging with laboratory data proves to be beneficial. In **Chapter 5** we present a retrospective single-center study designed to investigate prognostication of patients with cardiac transthyretin amyloidosis prior to initiation of therapy. Currently, risk stratification for patients with amyloidosis follows the three stages determined by National Amyloidosis Centre (NAC) based on established cut-offs for NT-proBNP levels and eGRF value. Our results demonstrated that incorporating myocardial work analysis alongside with NT-proBNP and eGFR in the diagnostic work-up can improve prognosis estimation, particularly for patients in NAC stage II. Specifically, we propose adding a third cut-off (global constructive work of 1294mmHg%) to better categorize patients in NAC-stage II. This integration of myocardial work into the risk stratification system is schematically represented in *Figure 3* of the same chapter. Diagnosis of cardiac amyloidosis poses a complex challenge and the timing of the diagnosis significantly influences treatment effectiveness and disease progression. By enhancing risk stratification and prognosis estimation, myocardial work analysis could positively impact the clinical management of patients with cardiac amyloidosis.

In summary, myocardial work analysis represents a promising echocardiographic tool for the advanced and comprehensive assessment of ventricular function across various cardiac conditions. The integration of its components along with the evaluation of both global and regional values facilitates a deeper understanding of the physiological adaptations of the heart in response to diverse and dynamic loading conditions, thereby ensuring adequate cardiac performance. Its incorporation into the clinical practice can provide valuable support for physicians in clinical decision-making and optimize patient management.

Conclusion and future perspectives

The scientific knowledge regarding myocardial work analysis and its potential clinical applications has advanced significantly in recent years. This PhD thesis aims to contribute to the global advancements made worldwide in this fascinating research area within cardiology. While stunning and promising results have already been achieved, yet several research questions remain open and unresolved, necessitating further investigation.

Currently, there exist several unexplored knowledge gaps in the domain of myocardial work such as the potential benefit of a myocardial work-guided cardioprotection strategy in cardio-oncology as well as the effects of cardioprotective medications on myocardial work indices. Similarly, in the context of cardiac amyloidosis, the impact of Tafamidis treatment on myocardial work values remains undetermined at present as does the association of changes in these parameters with patient's prognosis and survival.

Moreover, the promising results from previous studies that advocate the use of myocardial work to guide patient management in clinical practice require validation through multicenter randomized controlled trials. For instance, specific myocardial work cut-off values need to be established to guide optimal intervention timing in asymptomatic patients with valvular diseases as well as reliable myocardial work reference values for the right ventricle.

Furthermore, advancements in technology are essential to equip new machines with the advanced software that enables rapid and efficient calculation of myocardial work during a routine clinical evaluation. This step is decisive in order to measure the real impact and benefits of myocardial work analysis in the clinical practice enhancing medical care and patient management.

In summary, the integration of myocardial work into the daily practice undoubtedly presents significant advantages and benefits. Once sufficient evidence has been established and the echocardiographic tool is deemed ready for clinical application, myocardial work has the potential to revolutionize the assessment of ventricular function through non-invasive cardiovascular imaging, across various pathologies.

Appendix

A. Baseline Myocardial Work And Left Atrial Strain As Predictors For Cardiovascular Toxicity In Cancer Patients Referred For Anthracycline Therapy

Abstract presented in Cardio-Oncology Summit 2022

INTRODUCTION: Since the risk for cancer therapy-related cardiac dysfunction (CTRCD) depends in part on the patient's baseline risk, the new ESC guidelines on cardio-oncology offer a comprehensive cardiovascular (CV) toxicity risk assessment for patient's risk stratification before the initiation of therapy. Unfortunately, myocardial work (MW) and left atrium stain (LAS), while being sophisticated echocardiographic tools, are not included. In this study we analyzed the potential value of baseline MW and LAS parameters to predict anthracycline related CTRCD.

METHODS: A total of 50 consecutive breast cancer patients (56 ± 12 years, all female) treated with anthracyclines therapy were included. Two patients were diabetic, 9 had arterial hypertension, 6 were obese and 6 had hyperlipidemia (***Table 1***) . After 1 year follow-up, mild and moderated CTRCD was diagnosed in 10 and 9 patients respectively, according to ESC guidelines definitions, while 31 patients remained free of CTRCD (20%CTRCDmild, 18%CTRCDmod, 62%CTRCDneg). Baseline MW and LAS parameters were obtained offline.

RESULTS: No significant differences in CV risk factors or baseline clinical parameters were noted between the different groups. Prior to chemotherapy MW index (MWI), MW efficiency (MWE) and constructive work (CW) were significantly lower in CTRCDmod compared to the combined CTRCDneg and CTRCDmild groups (***Figure 1***). Additionally, reservoir LAS (rLAS) but not conduit or contractile LAS (cdLAS, ctLAS) was significantly worse in CTRCDmod group compared to the other groups. A significant correlation was found for rLAS with MWE (R=0.49, p=0.001) and CW (R=0.33, p=0.036) but not with MWI. In the ROC curve analysis MWI and rLAS showed the best predictive value for moderate CTRCD with AUC of 0.79 and 0.72 respectively. Finally, the combination of MWI and rLAS significantly improved the predictive value of each parameter alone (AUC 0.84, ***Figure 2***).

CONCLUSION: Our data demonstrate that patients with anthracycline-related moderate CTRCD have lower baseline MWI and rLAS compared to mild and non-CTRCD patients and that both parameters can be used as predictors for CTRCD. Since the simultaneous

assessment of the left ventricle contractile capacity and the left atrial function allows better evaluation of the baseline cardiac performance and shows superior performance in predicting CTRCD, the integration of MW and LAS information could be valuable for the baseline CV toxicity risk assessment in cancer patients.

Table 1: Patients' characteristics

	TOTAL	CTRCDneg	CTRCDmild	CTRCDmod
N *(%)*	50	31 (62)	10 (20)	9 (18)
Age, yo *(mean ± SD)*	56 ± 12	56 ± 13	53 ± 11	59 ± 12
BMI *(mean ± SD)*	25,0 ± 4	24,9 ± 4,1	25,9 ± 4,1	23,6 ± 2,2
Diabetes mellitus, *n (%)*	2 (6,5)	2 (6,5)	0	0
Arterial hypertension, *n (%)*	9 (18)	6 (19,4)	2 (20)	1 (11,1)
Hyperlipidemia, *n (%)*	6 (12)	5 (16,1)	1 (10)	0
Obesity, *n (%)*	6 (12)	3 (9,7)	0	1 (11,1)
Smoking, *n (%)*	4 (8)	5 (16,1)	1 (10)	0
Family history of CVD, *n (%)*	4 (8)	2 (6,5)	1 (10)	1 (11,1)
Beta blocker, *n (%)*	5 (10)	3 (9,7)	1 (10)	1 (11,1)
ACE-I or ARB, *n (%)*	3 (6)	3 (9,7)	0	0

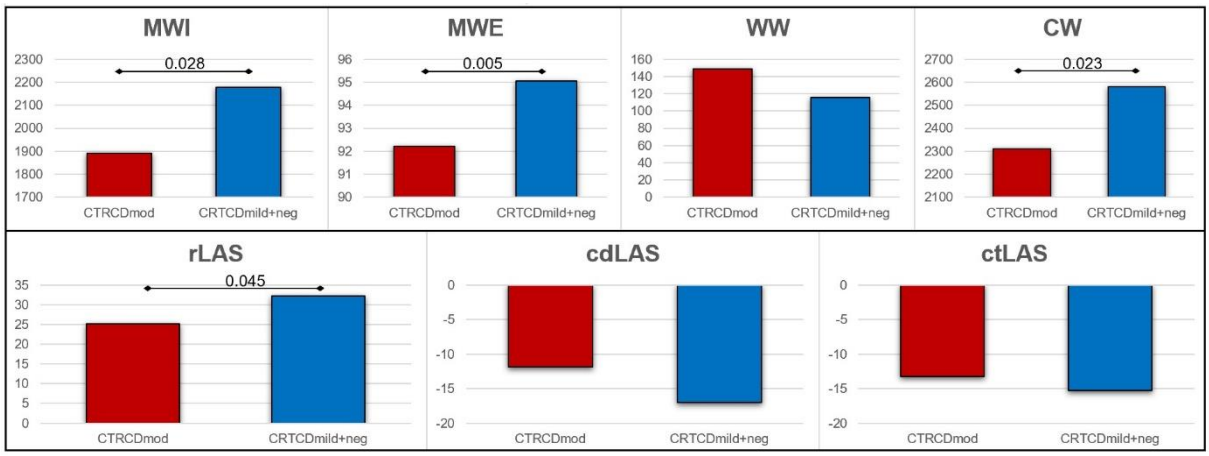

Figure 1: Baseline myocardial work and left atrial strain parameters in patients with moderate CTRCD vs patients with mild or non CTRCD.

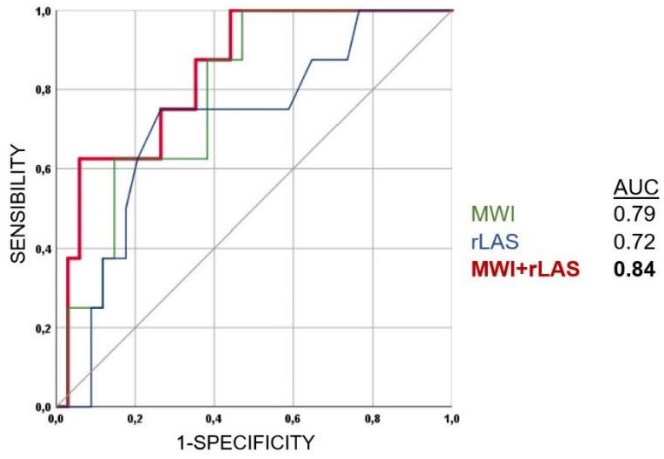

Figure 2: ROC analysis to predict moderate CTRCD.

B. Prognostic value of baseline wasted myocardial work and serum troponins in severe AS patients referred for TAVR

Abstract presented in Heart Failure congress 2023

INTRODUCTION: In patients with severe AS, the persistent high LV pressures will induce significant, often irreversible, myocardial damage and result in clinical overt heart failure. Therefore, timely intervention is of utmost importance to prevent cardiac dysfunction and improve patients' prognosis. Recently, biomarkers as well as myocardial work (MW) parameters have been associated with prognosis in patients with AS undergoing transcatheter aortic valve replacement (TAVR).

PURPOSE: This study was set up to assess the prognostic value of pre-interventional levels of serum cardiac biomarkers in combination with MW and identify patients at risk for early mortality after TAVR.

METHODS: Between June 2020 and October 2022, serum samples and echocardiographic derived MW parameters were prospectively obtained from patients with severe AS referred for TAVR. Patients with more than moderate MS/MR, history of TEER or mitral/aortic valve prothesis were excluded. Before TAVR Troponins HS (TROP), NT-proBNP and sST2 plasma levels were obtained and MW parameters were calculated using brachial arterial pressure and mean aortic valve gradient to estimate the LV pressure. ROC curves were constructed to assess the predictive value of each variable and Kaplan-Meier survival curves were created for groups of patients with high vs low biomarkers' levels and high vs low MW values. The log-rank test was used to evaluate the overall difference between the curves.

RESULTS: From the 119 AS patients screened, 82 patients were included in the final analysis (37male, age 83±6y, BSA 1.3±0.2, EF 52±10%, GLS -16±5%, AVA 0.6±0.3cm2, AVAi 0.4±0.2cm2/L, MPG 50±18mmHg). During a mean follow-up of 310±222 days, 15 patients (18%) died. Baseline characteristic were similar between survivors and non-survivors. Of note no significant difference in troponin, sST2, NT-proBNP as well as MW parameters was observed between survivors and non-survivors. ROC curve analysis demonstrated the highest predictive value of TROP for post-TAVR mortality (AUC 0.73). As WW was the only MW parameter not correlated to TROP (R=-0.15, p=0.18, ***Table 1***) patients were further categorized following TROP and WW median values (TROP 22.5ng/L, WW 218.5mmHg%) into: $TROP_{low}$-WW_{low} (15 patients, 18%), $TROP_{high}$-WW_{low} (25 patients, 31%), $TROP_{low}$-WW_{high} (27 patients, 33%), $TROP_{high}$-WW_{high} (15 patients, 18%). Patients with $TROP_{high}$-WW_{high} showed significantly

higher post-TAVR mortality compared to the other groups (intergroup difference, p=0.008) with less than 50% survival at 1 year follow-up (***Table 2***, ***Figure 1***).

CONCLUSION: Patients with both elevated TROP and WW above the median prior to TAVR have a significant poor survival after TAVR. These findings demonstrate the potential utility of combining biomarkers and imaging parameters to aid in risk stratification of patients with AS. Larger studies are warranted for further evaluation of these observations.

Table 1: Baseline characteristics, biomarkers and echocardiographic values.

BASELINE CHARACTERISTICS		PARAMETERS	MEAN ± SD	AUC	CORR. with TROP	P-value
N (male)	82 (37)	TROP (ng/L)	38 ± 38	0.73	1	
Time FU (days)	310 ± 222	NTproBNP (ng/L)	2867 ± 4346	0.72	0.595	<0.01
Dead (%)	15 (18)	sST2 (ng/L)	31 ± 15	0.64	-0.031	0.81
Age (years)	83 ± 6	EF (%)	52 ± 10	0.62	-0.349	<0.01
BSA	1.3 ± 0.2	GLS (%)	-16 ± 5	0.65	-0.476	<0.01
AVA (cm²)	0.6 ± 0.3	MWI (mmHg%)	2270 ± 873	0.59	-0.361	<0.01
AVAi (cm²/L)	0.4 ± 0.2	MWE (%)	89 ± 6	0.60	-0.254	0.02
MPG (mmHg)	50 ± 18	CW (mmHg%)	2916 ± 987	0.55	-0.428	<0.01
Vmax (m/s)	4.4 ± 0.8	WW (mmHg%)	281 ± 214	0.61	-0.148	0.18

Table 2: Characteristics, biomarkers and echocardiographic values per study group

	TROPhigh-WWhigh	TROPhigh-WWlow	TROPlow-WWhigh	TROPlow-WWlow
N (%)	15 (18)	25 (31)	27 (33)	15 (18)
Time FU (days)	240 ± 225	314 ± 196	293 ± 226	403 ± 242
Dead (%)	7 (47)	4 (16)	3 (11)	1 (7)
NTproBNP (ng/L)	3043 ± 4000	4515 ± 5540	2003 ± 3656	1836 ± 3360
sST2 (ng/L)	35 ± 23	35 ± 13	29 ± 12	25 ± 7
EF (%)	49 ± 12	48 ± 11	55 ± 9	55 ± 8
GLS (%)	-14 ± 4	-14 ± 5	-17 ± 4	-18 ± 3
MWI (mmHg%)	1904 ± 659	1919 ± 836	2504 ± 869	2803 ± 772
MWE (%)	83±6	90 ± 5	88 ± 5	94 ± 3
CW (mmHg%)	2669 ± 801	2367 ± 907	3299 ± 914	3390 ± 956

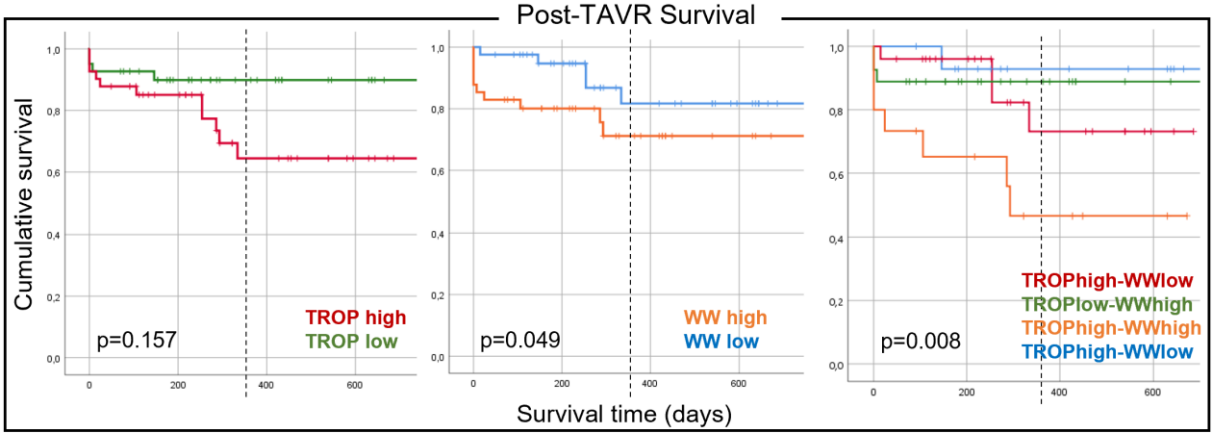

Figure 1: Post-TAVR survival per study group.

C. Myocardial work for serial assessment of LV function in severe AS patients undergoing TAVR

Abstract presented in Heart Failure congress 2023

INTRODUCTION: Left ventricle (LV) function recovery after transcatheter aortic valve replacement (TAVR) is related to prognosis in patients with severe aortic stenosis (AS). Load-dependent ejection fraction (EF) and strain (GLS) are inaccurate parameters for cardiac evaluation in these patients considering the abrupt drop in afterload after TAVR. In contrast, Myocardial Work (MW) incorporates the LV loading condition and might therefore be a superior method for cardiac surveillance in severe AS patients undergoing TAVR.

PURPOSE: To compare the additional information derived from MW to standard contractile indices like GLS and EF in a cohort of patients with severe AS before and after TAVR.

METHODS: All AS patients undergoing TAVR between July 2020 and September 2022 were screened. Patients with more than moderate MS/MR or mitral/aortic valve protheses as well as those with suboptimal image quality or missing blood pressure (BP) measurements were excluded. Patients underwent comprehensive transthoracic echocardiography with myocardial deformation analysis before and 1 month after TAVR. MW parameters were calculated using brachial arterial pressure and mean aortic valve gradient to estimate the LV pressure.

RESULTS: A total of 57 patients were included (23male, age 83±5y, BSA 1.3±0.2, AVA 0.6±0.2cm2, AVAi 0.3±0.1cm2/L, MPG 52±16mmHg) of which 28 presented with symptoms and 30 with history of hypertension (***Table 1***). During a follow-up of 41±25 days, 12 patients underwent pacemaker implantation and 9 patients died. No difference in baseline EF, GLS or MW parameters was observed between symptomatic vs asymptomatic neither between hypertensive vs non-hypertensive patients (***Table 2***). After TAVR, EF remained unchanged and afterload decreased ensuing in a significant improvement in GLS (-15.2±4.8 vs -17.3±4.5%, $p<0.01$). The opposite rise in GLS and decrease in afterload (LVPs) induced a down- and leftward shift of the individual LV pressure-strain loop with no change in MW index (MWI). However, following TAVR MW efficiency improved significantly from 88±7 to 93±15% (MWE, $p<0.05$) due to a relatively higher change in wasted work (WW: 297±230 vs 184±122mmHg%, $p<0.01$) vs constructive work (CW: 2869±984 vs 2544±824mmHg%, $p<0.01$) (***Figure 1***).

CONCLUSION: MW analysis is a potential new technique that allows better understanding on the impact of TAVR upon LV remodeling and contractile performance in AS patients. Following TAVR there is a proportionally bigger decrease in wasted vs constructive work so that MW

efficiency improves. We speculate that the decrease in wasted work may reflect the decreased wall stress in the myocardium against a lower afterload following the procedure.

Table 1: Patients' characteristics

Patients' characteristics	
N (male:female)	57 (23:34)
Age, mean±sd (yo)	83 ± 5
AVA (cm²)	0.6 ± 0.2
AVA index (cm²/L)	0.3 ± 0.1
MPG (mmHg)	52 ± 16
Dyspnea, n (%)	28 (49)
Hypertension, n (%)	30 (53)
Time follow-up, mean±sd (days)	41 ± 25
Post-TAVR pacemaker, n(%)	12 (21)
Post-TAVR death, n(%)	9 (16)

Table 2: Echocardiographic parameters for assessment of the left ventricular function

	pre-TAVR	post-TAVR	P value
EF (%)	51 ± 11	51 ± 10	0.68
GLS (%)	-15 ± 5	-17 ± 5	<0.01
MWI (mmHg%)	2245 ± 828	2137 ± 748	0.46
CW (mmHg%)	2869 ± 984	2544 ± 824	<0.01
WW (mmHg%)	297 ± 230	184 ± 122	<0.01
MWE (mmHg%)	88 ± 7	93 ± 15	0.04
LVP systolic (mmHg)	195 ± 35	156 ± 24	<0.01
AP diastolic (mmHg)	74 ± 14	73 ± 9	0.72

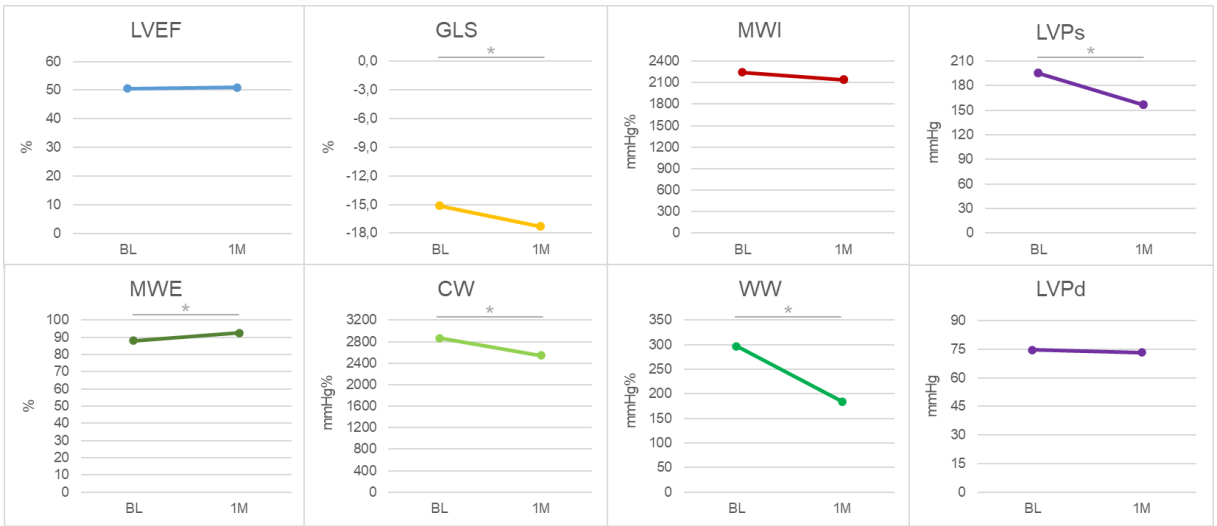

Figure 1: Changes in LVEF, GLS, MW parameters and LV pressure from baseline to 1 month follow-up after TAVR.

D. Myocardial work predicts left ventricular dysfunction following transcatheter aortic valve replacement in patients with aortic valve stenosis

Abstract presented in Heart Failure congress 2024

BACKGROUND: Transcatheter aortic valve replacement (TAVR) is the preferred treatment for high-risk patients with severe aortic stenosis (AS) who are not eligible for surgery. However, despite its clinical benefits, some patients still experience significant myocardial dysfunction after the procedure. Myocardial Work (MW) integrates afterload and shortening to evaluate myocardial performance and may therefore be a valuable tool in patients undergoing TAVR.

PURPOSE: This study aims to assess changes in myocardial function in severe AS patients referred for TAVR, using MW assessment before and after the procedure.

METHODS: All patients who underwent TAVR for severe AS between July 2020 and July 2023 were included in the study. Patients with an unstable heart rate, poor image quality, or missing blood pressure measurements were excluded. A comprehensive transthoracic echocardiography with myocardial deformation analysis was performed one day before the procedure and one month after. MW parameters were calculated offline using brachial arterial pressure and mean aortic valve gradient to estimate left ventricular pressure. At the one-month follow-up patients were classified as having myocardial dysfunction (global longitudinal strain, GLS≥-16%) or not (GLS<-16%). Additionally, baseline MW parameters were analyzed for their predictive value.

RESULTS: A total of 81 patients were included (39 males, average age 81±14 years, AVA 0.7±0.3 cm², AVAi 0.4±0.2 cm²/dL, MPG 47±16 mmHg). During a mean follow-up of 455±276 days, 19 patients required pacemaker implantation and 8 patients died. After TAVR, there was a general improvement in cardiac function, as evidenced by significant changes in ejection fraction (EF), GLS, global work index (GWI), constructive work (CW), and wasted work (WW). However, 28 patients still had significant myocardial dysfunction (GLS ≥ -16%) at one-month follow-up with poor long-term survival (***Figure 1***). At baseline, these patients (GROUP A) had significantly ($p<0.01$) worse EF (41±12% vs 52±8%), GLS (-11.4±4.4% vs -17.3±3.6%), GWI (1543±755mmHg% vs 2514±623mmHg%), CW (1990±912mmHg% vs 3139±767mmHg%), and global work efficiency (GWE, 86±8% vs 92±4 %) compared to the rest (GROUP B). While EF, GLS, GWI, CW, and WW significantly improved in GROUP B, no significant changes were observed after TAVR in GROUP A, except for CW. Interestingly, baseline GWI and CW showed the best predictive value for myocardial dysfunction post-TAVR with a cut-off GWI of 2059mmHg% (sensitivity 0.85 and specificity 0.83, ***Figure 2***).

CONCLUSION: Patients with persistent myocardial dysfunction one month after TAVR have a poor long-term survival. These patients already had impaired cardiac function at baseline which did not improve after the procedure. Interestingly, baseline GWI could be useful in identifying patients at-risk.

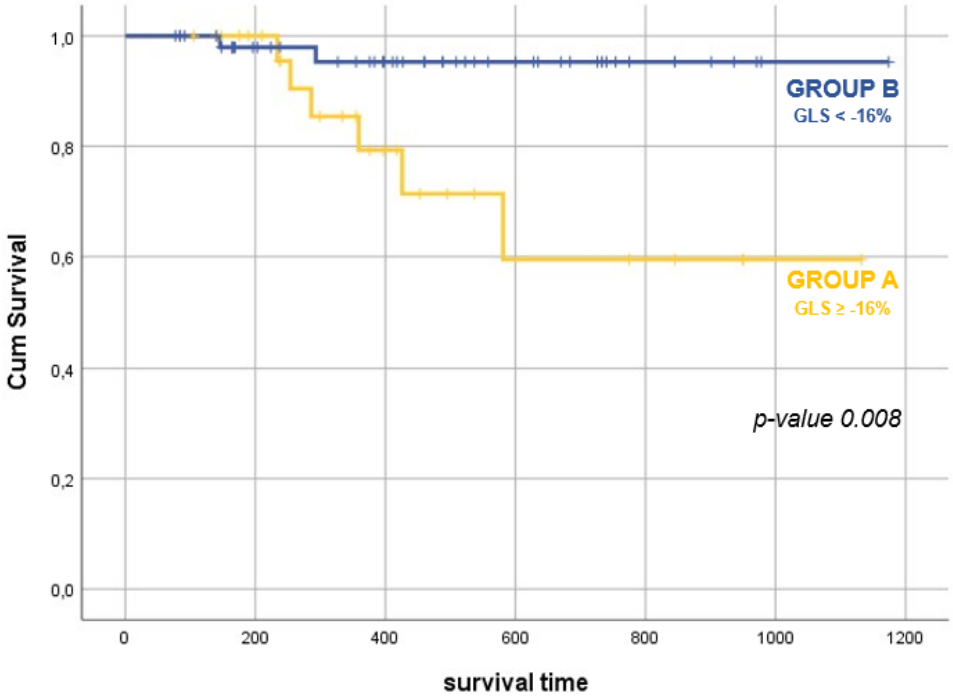

Figure 1: Survival in patients with myocardial dysfunction (GROUP A, GLS≥-16%) and without (GROUP B, GLS<-16%).

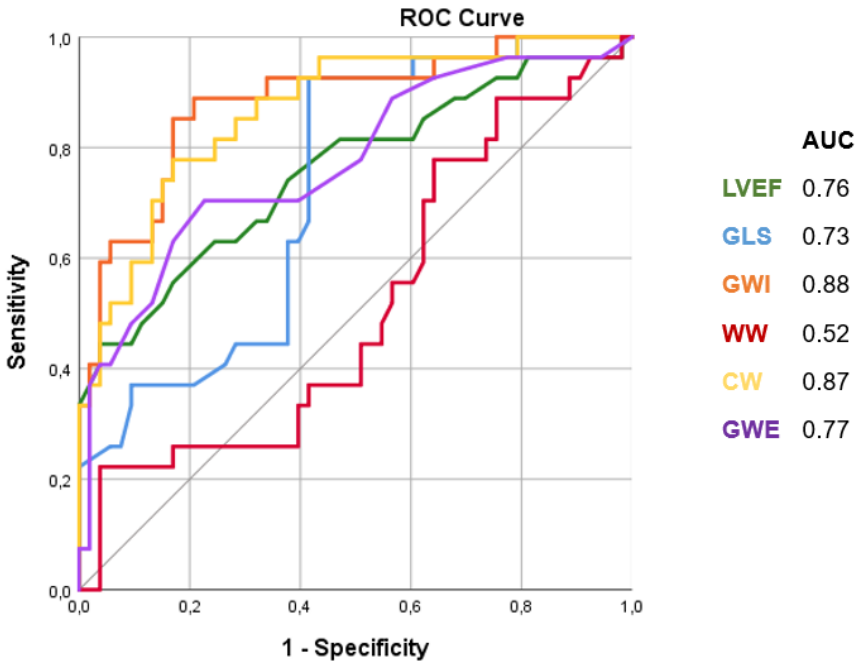

Figure 2: ROC analysis of baseline LV function parameters to predict myocardial dysfunction (GLS≥-16%) after TAVR.

E. Myocardial work assessment for immediate changes in left ventricular function and survival analysis after transcatheter aortic valve replacement

Abstract presented in Heart Failure congress 2024

BACKGROUND: In patients with severe aortic stenosis (AS), longstanding high pressure in the left ventricle (LV) can cause cardiac dysfunction. Transcatheter aortic valve replacement (TAVR) relives the LV from elevated afterload with subsequent effect on the myocardial performance. When assessing cardiac function in AS pts referred for TAVR, it may be more beneficial to use myocardial work (MW) which integrates LV pressure and myocardial shortening rather than relying solely on load-dependent parameters like ejection fraction (EF) and global longitudinal strain (GLS) .

PURPOSE: This study aims to assess the immediate changes in LV function after TAVR based on MW analysis and its relationship with patient's long-term survival.

METHODS: All patients with severe AS who underwent TAVR between July 2020 and July 2023 were screened. Patients with more than moderate mitral valve stenosis/regurgitation or mitral/aortic valve protheses as well as those with suboptimal image quality or missing blood pressure measurements were excluded. Patients underwent comprehensive transthoracic echocardiography with myocardial deformation analysis the day before and after TAVR. MW parameters were calculated using brachial arterial pressure and mean aortic valve gradient to estimate the LV pressure. A ROC curve analysis was performed to assess the predictive value of the change in MW parameters pre- and post-TAVR. For the survival analysis, patients were categorized as having significant immediate improvement or not using as cut-off the median value of the change in MW parameters.

RESULTS: A total of 67 patients were included (***Table 1).*** During a follow-up of 548±264 days, 8 patients died. While not significant change was observed in EF and GLS, the immediate effect of TAVR on myocardial function was reflected by the significant decrease in global work index (GWI, 2273±795 vs 1694±601mmHg%), constructive work (CW, 2789±923 vs 2073±608mmHg%) and wasted work (WW, 237±159 vs 193±171mmHg%). Global work efficiency remained stable as the CW and WW decreased proportionally (***Table 2***). In the ROC curve analysis, the changes in GWI (ΔGWI), CW (ΔCW), and WW (ΔWW) had respective AUC values of 0.64, 0.67, and 0.67. The cut-off values for ΔGWI, ΔCW, and ΔWW were determined to be 377mmHg%, 572mmHg%, and 25mmHg%, respectively. Survival analysis only showed a significant difference in survival between patients when using the cut-off value for ΔGWI (***Figure 1***). Furthermore, at the 1-month follow-up, patients with an immediate ΔGWI ≥ -

377mmHg%, above median, had significantly worse EF (53±8% vs 47±11%) and GLS (-18.7±2.9% vs -14.9±4.9%) compared to patients with ΔGWI < -377mmHg% whereas no difference was seen post-TAVR.

CONCLUSION: TAVR causes immediate changes in myocardial performance which can be assessed by MW analysis. Patients who experience an insufficient decrease in GWI shortly after TAVR are at higher risk of developing LV dysfunction during follow-up and have a poorer long-term survival outcome.

Table 1: Patients' characteristics

PATIENTS' CHARACTERISTICS		
Age	*(years, mean ± sd)*	78 ± 18
Sex	*(males, %)*	33 (49)
AVA	*(cm², mean ± sd)*	0.66 ± 0.24
AVAi	*(cm²/dL, mean ± sd)*	0.38 ± 0.11
MPG	*(mmHg, mean ± sd)*	48 ± 15
Dead	*(n, %)*	8 (12)
PM need	*(n, %)*	19 (28)
Dyspnea	*(n, %)*	33(49)
Diabetes	*(n, %)*	26 (39)
HTN	*(n, %)*	45 (67)

Table 2: Echocardiographic parameters before and after TAVR.

		pre-TAVR	post-TAVR	*p value*
LVEF	*(%, mean ± sd)*	49.5 ± 11.0	50.8 ± 10.2	ns
GLS	*(%, mean ± sd)*	-15.7 ± 4.9	-16.2 ± 5.0	ns
GWI	*(mmHg%, mean ± sd)*	2273 ± 795	1694 ± 601	<0.01
GCW	*(mmHg%, mean ± sd)*	2789 ± 923	2073 ± 608	<0.01
GWW	*(mmHg%, mean ± sd)*	237 ± 159	193 ± 171	0.02
GWE	*(%, mean ± sd)*	90 ± 6	90 ± 7	ns
SBP	*(mmHg, mean ± sd)*	140 ± 25	134 ± 18	ns
DBP	*(mmHg, mean ± sd)*	87 ±	64 ± 11	ns

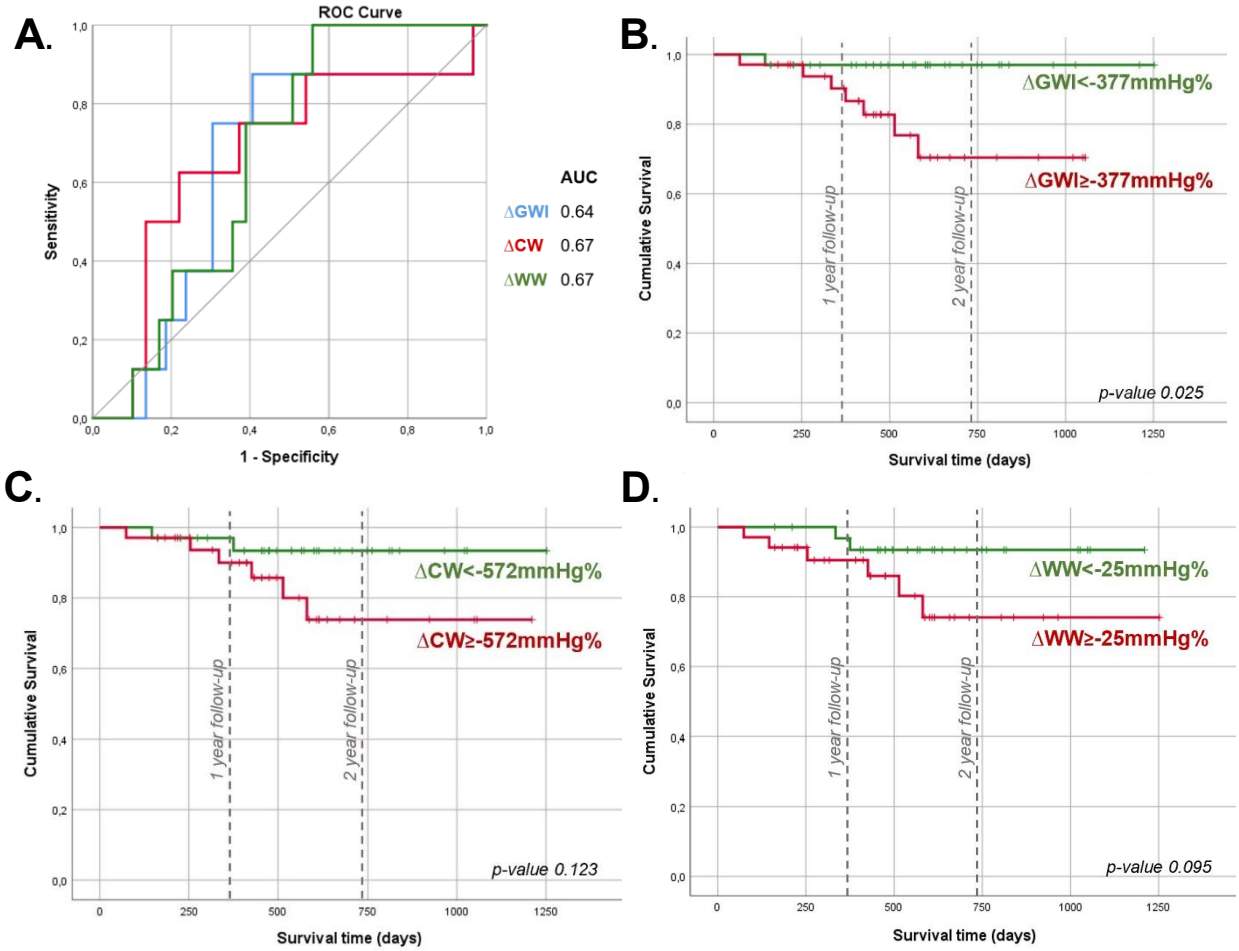

Figure 1: ROC analysis of the change in myocardial work parameters and survival analysis according to best cut-off values. A- ROC analysis of ΔGWI, ΔCW and ΔWW. B- Survival analysis of patients categorized based on ΔGWI value. C- Survival analysis of patients categorized based on ΔCW value. D- Survival analysis of patients categorized based on ΔWW value.

F. Novel insights in systemic right ventricle function after Mustard/Senning repair: myocardial work analysis

Abstract presented in ACHD congress 2023

BACKGROUND: The Mustard/Senning repair for transposition of the great arteries (d-TGA) results in a systemic right ventricle (sRV). Due to anatomical and functional discrepancy, standard imaging modalities might be confusing to detect heart failure. Also, to differentiate physiologic adaptation to increased afterload from pathologic remodeling of the sRV remains challenging. Myocardial Work (MW) incorporates both ventricular load and longitudinal deformation for a more accurate evaluation of the sRV performance. However, data are still scare.

METHODS: All d-TGA patients with Mustard/Senning repair at follow-up between 2019-2022 were screened. Exclusion criteria were ventricular septal defect, Eisenmenger syndrome, ventricular assist device, tricuspid valve prothesis and suboptimal transthoracic echocardiographic (TEE) image quality. MW parameters were calculated from TTE-images using brachial arterial pressure to estimate the sRV pressure. Results from the NORRE study and Butcher et al were used as normal reference value for LV and RV respectively.[1,2]

RESULTS: From 100d-TGA patients screened, 55 were included (36male, 40±6.4year, 15 Mustard). Thirty-four had right bundle branch block and 4 had a pacemaker. Although asymptomatic, the sRV function was lower when compared to the reference values of the RV and LV (***Table 1***). Global work index and constructive work (CW) were higher than normal RV but lower than normal LV reference values. Further, elevated wasted work (WW) was documented (***Figure 1***). Of note, the sRV dimensions were negatively correlated with CW while abnormal electrocardiographic parameters (QRS duration, QTc time) were positively correlated with WW (correlation coefficients 0.35 and 0.38 respectively, $p<0.01$ for both, ***Figure 2***).

CONCLUSIONS: MW analysis offers new insights in the physiological adaptation of the sRV after Mustard/Senning repair. The ventricular enlargement due to increased afterload might be the main cause for contractility loss while the QRS prolongation might be related to energy waste and as a consequence less efficient contractions. Further analysis is warranted to determine the usefulness of MW for the clinical follow-up.

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[2] S. C. Butcher, F. Fortuni, J. M. Montero, N. A. Marsan, V. Delgado, and J. J. Bax, “Right ventricular myocardial work : new method for non-invasive assessment of right ventricular function in HFrEF,” *ESC Congr. 2020*, no. September, p. 1017, 2020.

Table 1: Patients’ clinical and echocardiographic data with reference value for normal right and left ventricular function.

Electrocardiogram	**sRV**	**ref.**		
HR (bpm)	69 ± 14	60-90		NL
PR (ms)	166 ± 33	120- 200		NL
QRS (ms)	115 ± 26	80-100		OR
QTc (ms)	437 ± 38	<420		OR
Ventricle morphology	**sRV**	**ref. RV**	**ref. LV**	**p-value**
ESa (cm²)	23 ± 7	11 ± 3	-	<0.01
EDa (cm²)	31 ± 6	19 ± 5	-	<0.01
ESv (ml)	67 ± 30	-	34 ± 12	<0.01
EDv (ml)	108 ± 38	-	94 ± 27	<0.01
Ventricular function	**sRV**	**ref. RV**	**ref. LV**	
TAPSE (mm)	13 ± 4	22 ± 6	-	<0.01
annular s' (cm/s)	6 ± 2	12 ± 3	-	<0.01
FAC (%)	28 ± 11	45 ± 9	-	<0.01
EF (%)	39 ± 12	-	63 ± 6	<0.01
GLS (%)	-13 ± 4	-	-23 ± 3	<0.01
Ventricular load				
SBP (mmHg)	126 ± 16	-	116 ± 12	<0.01
DBP (mmHg)	75 ± 13	-	73 ± 8	0.183

DBP: diastolic blood pressure, EDa: end-diastolic area, EDv: end-diastolic volume, EF: ejection fraction, ESa: end-systolic area, ESv: end-systolic volume, FAC: fractional area change, GLS: global longitudinal strain, HR: heart rate, LV: left ventricle, RV: right ventricle, SBP: systolic blood pressure, sRV: systolic right ventricle, TAPSE: tricuspid annulus plane systolic excursion.

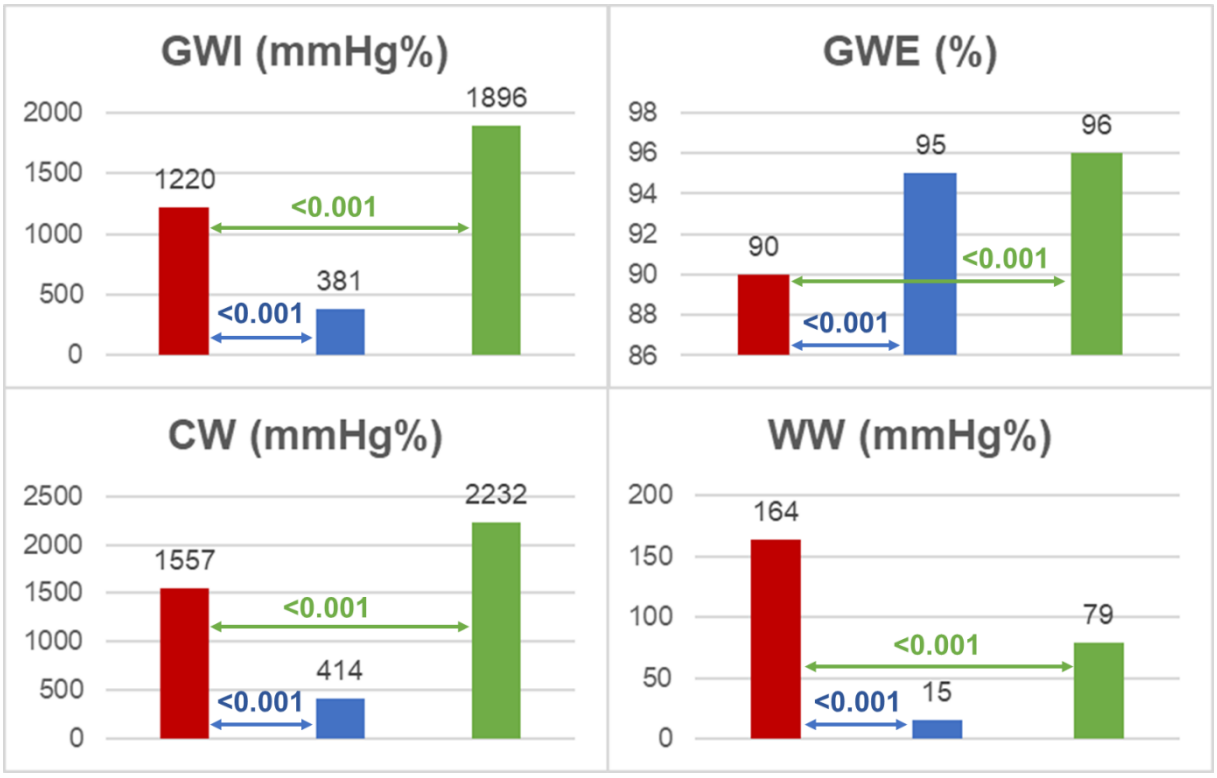

Figure 1: Myocardial work parameters in systemic RV vs normal RV and LV reference values. CW: constructive work, GWE: global work efficiency, GWI: global work index, WW: wasted work.

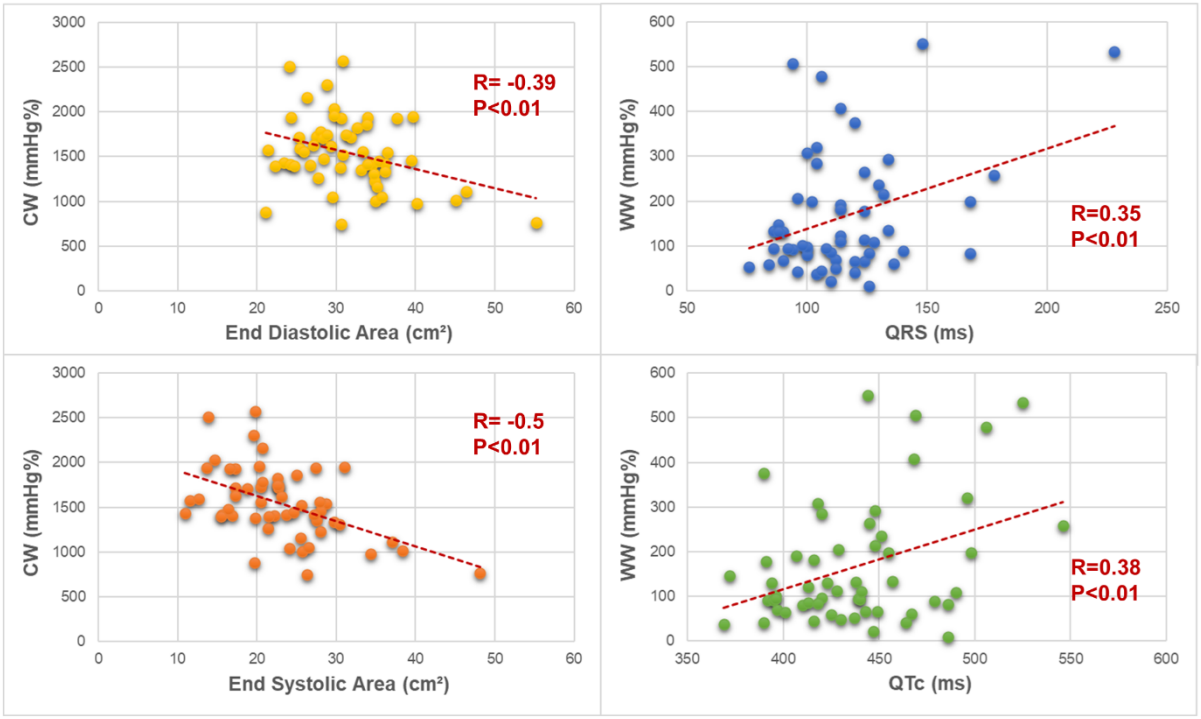

Figure 2: Correlations of the myocardial work parameters with the ventricular dimensions and QRS duration in sRV. CW: constructive work, GWE: global work efficiency, GWI: global work index, WW: wasted work.

Curriculum Vitae

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Non-invasive cardiac imaging, research design, data collection and analysis, results evaluation in several research fields: Cardio-Oncology, Aortic Valve Stenosis, Heart Failure and Adult Congenital Cardiology.

DATABASE MANAGER

- EUROMACS: follow-up LVAD patients *OLVZ AALST since 2019*
- EUROTRANSPLANT: follow-up HTX patients *OLVZ AALST since 2019*
- STARS II study & CORRELATE study *UZ LEUVEN* 2019

LEADERSHIP AND PROJECTS

START DYSPNEA CLINIC OLV AALST *since 2023*

I have actively collaborated in the start of the dyspnea clinic, specifically, in the incorporation of non-invasive imaging. My current work in the clinic involves:

- Multi-disciplinary communication inside the whole team
- Imaging acquisition and analysis
- Support in the results interpretation and discussion
- Database management and analysis

START CARDIO-ONCO CLINIC OLV AALST *since 2022*

I have actively collaborated in the start of the cardio-oncology clinic, specifically, by elaborating a care pathway, based on the ECS guidelines, for implementation in the daily practice.

My current work in the clinic involves:

- Coordination of multi-disciplinary collaboration between oncology, hematology and cardiology.
- Patient's baseline evaluation, risk stratification and follow-up
- Imaging acquisition and analysis
- Database management and publication of study results

ADULT CONGENITAL HEART DISEASE CLINIC OLV AALST *since 2019*

I collaborate in the clinic through specialized non-invasive imaging acquisition (transthoracic echocardiography), image analysis and result reporting.

EDUCATION

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HFA SILVER MEMBERSHIP active
COUNCIL OF CARDIO-ONCOLOGY active
WG ON ADULT CONGENITAL HEART DISEASE active
ESC PROFESSIONAL MEMBER until 2023
EACVI REGULAR MEMBERSHIP active

DIPLOMAS	**ICH GOOD CLINICAL PRACTICE E6**	*TGHN 2022*
	REANIMATION PRACTICE	*UZ LEUVEN 2018*
CONGRESS & SYMPOSIA	**CARDIOTOX 2024** Clinical cases presentation 'MW in cardio-oncology'	*MADRID 2024*
	2024 CARDIO ONCOLOGY SYMPOSIUM	*OTHO STATE 2024*
	HEART FAILURE CONGRESS Fire Abstracts presenter (2)	*LISBON 2024*
	STRESS ECHOCARDIOGRAPHY	*HASSELT 2024*
	HEART FAILURE SYMPOSIUM: ADVANCED HEART FAILURE PATIENT'S THERAPIES	*OORDEGEM 2024*
	GLOBAL CARDIO-ONCOLOGY SUMMIT e-Poster presenter	MADRID *2023*
	HEART FAILURE CONGRESS Moderated Posters (2) and Clinical case	*PRAGE 2023*
	EURO ACHD CONGRESS e-Poster presenter	*PARIS 2023*
	BELGIAN HF NURSES SYMPOSIUM Presenter	*AFFLIGEM 2022*
	ESC CONGRESS Moderated Posters (2)	*BARCELONA 2022*
	HEART FAILURE CONGRESS e-Poster presenter	*MADRID 2022*
	MYOCARDIAL FUNCTION IMAGING	*LEUVEN 2022*
	EACVI BEST OF IMAGING	*ONLINE 2021*
	ATHLEET HEART – BWGNICI	*BRUSSELS 2021*
	ESC CONGRESS – THE DIGITAL EXPERIENCE e-Poster presenter	*ONLINE 2021*
	EACVI – BEST OF IMAGING e-Poster presenter	*ONLINE 2020*
	ESC DIGITAL HEALTH WEEK poster	*ONLINE 2020*
	EUROECHO poster presenter	VIENNA 2019
RESEARCH AREAS OF INTERESS	**HEART FAILURE** **CARDIO-ONCOLOGY** **AORTIC VALVE STENOSIS AND TRANSCATHETER AORTIC VALVE REPLACEMENT** **CONGENITAL CARDIOLOGY** **CPET ECHOCARDIOGRAPHY** **CARDIAC IMAGING AND BIOMARKERS**	
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INFORMATICS	KWS, Microsoft Office, **Echopac, Tomtec, SPSS**	

List of publications

First Author

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