

# Echocardiographic reference ranges for normal non-invasive myocardial work indices: results from the EACVI NORRE study

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## Aims

To obtain the normal ranges for 2D echocardiographic (2DE) indices of myocardial work (MW) from a large group of healthy volunteers over a wide range of ages and gender.

## Methods and results

A total of 226 (85 men, mean age: 45 ± 13 years) healthy subjects were enrolled at 22 collaborating institutions of the Normal Reference Ranges for Echocardiography (NORRE) study. Global work index (GWI), global constructive work (GCW), global work waste (GWW), and global work efficiency (GWE) were estimated from left ventricle (LV) pressure–strain loops. Peak LV systolic pressure was non-invasively derived from brachial artery cuff pressure. The lowest values of MW indices in men and women were 1270 mmHg% and 1310 mmHg% for GWI, 1650 mmHg% and 1544 mmHg% for GCW, and 90% and 91% for GWE, respectively. The highest value for GWW

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was 238 mmHg% in men and 239 mmHg% in women. Men had significant lower values of GWE and higher values of GWW. GWI and GCW significantly increased with age in women.

## Conclusion

The NORRE study provides useful 2DE reference ranges for novel indices of non-invasive MW.

## Keywords

adult echocardiography • 2D echocardiography • myocardial work • reference values

## Introduction

Myocardial strain analysis has emerged in the last decade as a reliable tool for studying myocardial mechanics, adding information on cardiac performance when compared with traditional parameters of left ventricle (LV) systolic function, such as ejection fraction (EF).<sup>1–4</sup> However, their relative load dependency makes the myocardial deformation indices unable to account for changes in pre- and afterload. Myocardial work (MW) is emerging as an alternative tool for studying LV myocardial systolic function, because it incorporates both deformation and load into its analysis. In this context, MW could be considered as an advancement of myocardial strain, allowing to investigate LV performance also in cases of changes in afterload that could lead to misleading conclusions if relying only on strain analysis. Conditions of increased afterload can in fact negatively impact on myocardial strain even if MW is normal.

MW assessment was initially calculated using invasive pressure measurements, which limited its widespread use in clinical practice.<sup>5,6</sup> Recently, Russell *et al.*<sup>7</sup> demonstrated that pressure–strain loops (PSLs) could estimate LV performance in a non-invasive manner, deriving LV pressure (LVP) curves from non-invasively acquired brachial artery cuff pressure. To date, the technique has been applied in

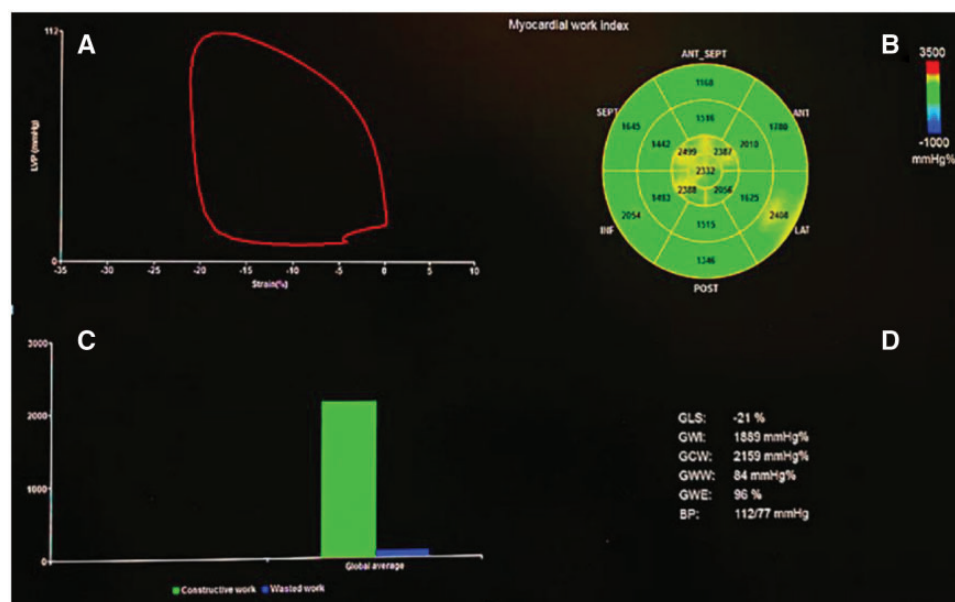
myocardial ischaemia and in identification of cardiac resynchronization therapy (CRT)-responders with good results.<sup>8–11</sup>

The NORRE (Normal Reference Ranges for Echocardiography) study is the first European, large, prospective, multicentre study performed in 22 laboratories accredited by the European Association of Cardiovascular Imaging (EACVI) and in one American laboratory, which has provided reference values for all 2D echocardiographic (2DE) measurements of all cardiac chambers,<sup>12</sup> Doppler parameters,<sup>13</sup> aortic dimensions,<sup>14</sup> 3D echocardiographic measurements of the LV volumes and strain,<sup>15</sup> 2DE measurement of LV strains and twist,<sup>16</sup> and 2D and 3D measurement of left atrial function.<sup>17</sup> The present study aimed (i) to establish normal reference limits for MW indices in healthy adults and (ii) to examine the influence of age and gender on normal reference ranges.

## Methods

### Patient population

A total of 734 healthy European subjects constituted the final NORRE study population. The local ethics committees approved the study protocol. Only patients whose echocardiographic exams were acquired using



**Figure 1** Measurement of myocardial work parameters by 2D echocardiography. (A) LV pressure–strain loop; (B) bull's eye of GWI; (C) bar graph representing GCW and GWW; and (D) results from myocardial work analysis. GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global work waste; LV, left ventricle.

**Table 1** Characteristics of the population

Parameters	Total (n = 226)	Male (n = 85)	Female (n = 141)	P-value
Age (years)	45 ± 13	45 ± 14	44 ± 13	0.6
Height (cm)	170 ± 10	178 ± 8	164 ± 7	<0.001
Weight (kg)	68 ± 12	78 ± 9	62 ± 9	<0.001
Body surface area (m <sup>2</sup> )	1.8 ± 0.2	1.9 ± 0.1	1.7 ± 0.1	<0.001
Body mass index (kg/m <sup>2</sup> )	23 ± 3	24 ± 2	23 ± 3	<0.001
Systolic blood pressure (mmHg)	116 ± 12	122 ± 9	113 ± 12	<0.001
Diastolic blood pressure (mmHg)	73 ± 8	75 ± 8	72 ± 9	0.01
Glucose (mg/dL)	91 ± 11	94 ± 7	89 ± 12	0.001
Cholesterol (mg/dL)	182 ± 31	187 ± 29	180 ± 32	0.019

**Table 2** 2DE parameters of myocardial work

	Total, mean ± SD or median (IQR)	Total, 95% CI or limits of normality ± SE <sup>a,b</sup>	Male, mean ± SD or median (IQR)	Male, 95% CI or limits of normality ± SE <sup>a,b</sup>	Female, mean ± SD or median (IQR)	Female, 95% CI or limits of normality ± SE <sup>a,b</sup>	P-value*
GWl (mmHg%)	1896 ± 308	1292–2505	1849 ± 295	1270–2428	1924 ± 313	1310–2538	0.07
GCW (mmHg%)	2232 ± 331	1582–2881	2228 ± 295	1650–2807	2234 ± 352	1543–2924	0.9
GWW (mmHg%)	78.5 (53–122.2)	226 ± 28 <sup>a</sup>	94 (61.5–130.5)	238 ± 33 <sup>a</sup>	74 (49.5–111)	239 ± 39 <sup>a</sup>	0.013
GWE (mmHg%)	96 (94–97)	91 ± 0.8 <sup>b</sup>	95 (94–97)	90 ± 1.6 <sup>b</sup>	96 (94–97)	91 ± 1 <sup>b</sup>	0.026

CI, confidence interval; GCW, global constructive work; GWE, global work efficiency; GWl, global work index; GWW, global work waste; IQR, interquartile range; SD, standard deviation; SE, standard error.

<sup>a</sup>Highest expected value.

<sup>b</sup>Lowest expected value.

\*P-value differences between genders.

GE echocardiographic ultrasound equipment ( $n = 378$ ), which is the only one, that to date provides software for calculating MW, were included in the present study. After the exclusion of patients who had incompatible image formats and/or poor-image quality and/or no blood pressure measurements available at the time of echocardiographic examination, the final study population consisted of 226 (31%) normal subjects.

## Echocardiographic examination

A comprehensive echocardiographic examination was performed using state-of-the-art echocardiographic ultrasound system (GE Vivid E9; Vingmed Ultrasound, Horten, Norway) following recommended protocols approved by the EACVI.<sup>18,19</sup> All echocardiographic images were recorded in a digital raw-data format and centralized for further analysis, after anonymization, at the EACVI Central Core Laboratory at the University of Liege, Belgium.

## 2D MW analysis

Quantification of MW was performed using commercially available software package (Echopac V.202, GE). It was measured from PSLs areas, which were constructed from non-invasive LVP curves combined with strain acquired with speckle tracking echocardiography (STE), as proposed by Russell *et al.*<sup>7</sup> Global Longitudinal Strain (GLS) was obtained as previously reported.<sup>16</sup> After calculating GLS, inserting values of brachial blood pressure and indicating the time of valvular events by echocardiography, the software derived non-invasive PSLs. Strain and pressure data

were synchronized by aligning the valvular event times, which were set by pulse-wave Doppler recordings at mitral valve and aortic valve level and then confirmed by 2DE evaluation of the apical long-axis view. The area of the loop served as an index of regional and global MW (Figure 1A). Work was evaluated from mitral valve closure to mitral valve opening. A bull's eye with the segmental and global work index (GWl) values was also provided (Figure 1B). Moreover, additional indices of MW were obtained as follows (Figure 1C and D): global constructive work (GCW, work performed during shortening in systole adding negative work during lengthening in isovolumetric relaxation); global wasted work (GWW, negative work performed during lengthening in systole adding work performed during shortening in isovolumetric relaxation); and global work efficiency (GWE, constructive work divided by the sum of constructive and wasted work).

## Statistical analysis

Normality of the distribution of continuous variables was tested by the Kolmogorov–Smirnov test. All data were expressed as mean ± standard deviation (SD) or median (interquartile range) as appropriate. The 95% confidence interval was calculated as ±1.96 SDs from the mean. The lowest (2.5th percentile) and highest (97.5th percentile) expected values for GWW and GWE were estimated in 1000 bootstrap samples to generate sampling distribution. Differences between groups were analysed for statistical significance with the unpaired *t*-test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed continuous variables. Comparison of continuous variables

**Table 3** 2DE parameters of myocardial work and blood pressure values according to gender and age

	Age 20–40 years (n = 95)		Age 40–60 years (n = 97)		Age ≥60 years (n = 34)		P-value		Male		Female	
	Male, mean ± SD or median (IQR)	Female, mean ± SD or median (IQR)	Male, mean ± SD or median (IQR)	Female, mean ± SD or median (IQR)	Male, mean ± SD or median (IQR)	Female, mean ± SD or median (IQR)	Male	Female	R	P-value	R	P-value
SBP (mmHg)	120 ± 10	108 ± 10*	124 ± 8	115 ± 13*	121 ± 7	122 ± 12	0.1	<0.001	0.12	0.3	0.4	<0.001
DBP (mmHg)	73 ± 9	69 ± 8*	76 ± 6	74 ± 9	74 ± 8	76 ± 8	0.1	0.002	0.12	0.2	0.3	0.001
GWl (mmHg%)	1758 ± 270	1800 ± 251	1900 ± 317	2027 ± 341	1866 ± 286	2002 ± 270	0.2	<0.001	0.16	0.1	0.25	0.002
GCW (mmHg%)	2186 ± 240	2109 ± 289	2267 ± 327	2329 ± 365	2226 ± 328	2338 ± 386	0.5	0.001	0.09	0.3	0.22	0.007
GWW (mmHg%)	99 (68–144.5)	90 (48–145)*	89 (58–122.5)	76 (51–118)	85 (49–129)	90 (48–145)	0.5	0.6	-0.13	0.2	0.06	0.4
GWE (mmHg%)	95 (93–97)	95 (94–97)*	96 (95–97)	96 (95–97)	96 (94–97)	95 (94–97)	0.6	0.8	0.12	0.2	-0.03	0.7

CI, confidence interval; DBP, diastolic blood pressure; GCW, global constructive work; GWE, global work efficiency; GWl, global work index; GWW, global work waste; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation.

\*P-value < 0.05 vs. male.

according to age groups was done with the one-way analysis of variance test. When a significant difference was found, the *post hoc* testing with Bonferroni comparisons to identify specific group differences was used. Correlation between continuous variables was performed using Pearson's or Spearman's correlation coefficient. Multivariable linear regression analyses were performed to examine the independent correlates between MW indices and baseline parameters. Intra-observer and inter-observer variability was assessed in 20 randomly selected subjects using the Bland–Altman analyses.  $P < 0.05$  was considered as statistically significant. All statistical analyses were carried out using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

## Results

### Demographic data

Table 1 summarizes the demographic data of the NORRE population analysed in the present study. A total of 85 men (mean age  $45 \pm 14$  years) and 141 women (mean age  $44 \pm 13$  years) were included. 2DE MW indices obtained from the study population are displayed in Table 2. The lowest expected values of MW indices were 1270 mmHg% in men and 1310 mmHg% in women for GWl, 1650 mmHg% and 1544 mmHg% for GCW, and 90% and 91% for GWE, respectively. The highest expected value for GWW was 238 mmHg% in men and 239 mmHg% in women. GWW was higher in men than in women, while the opposite occurred for GWE.

### Age and MW indices relationship

Relationships between age and MW indices are shown in Table 3 and Figure 2. GWl and GCW increased with age in women ( $R^2 = 0.06$ ,  $P = 0.002$  and  $R^2 = 0.04$ ,  $P = 0.007$ , respectively) along with systolic and diastolic blood pressure ( $R^2 = 0.16$ ,  $P < 0.001$  and  $R^2 = 0.09$ ,  $P = 0.001$ , respectively). In the subgroup 20–40 years, GWW was higher in men than in women and the opposite occurred for GWE ( $P = 0.01$  and  $P = 0.04$ , respectively), while no other gender differences were found in the different age subgroups.

### Repeatability and reproducibility

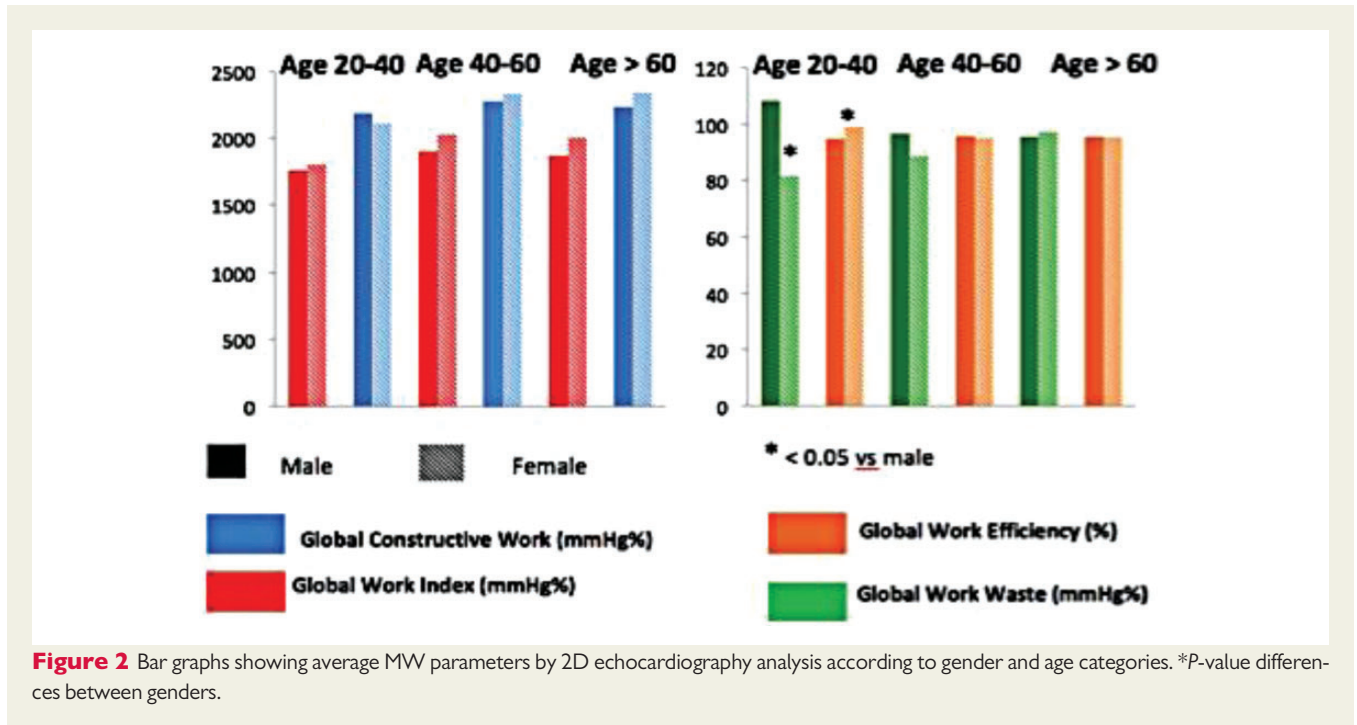
Intra-observer and inter-observer variability for MW indices are summarized in Table 4. Intra-observer and inter-observer analyses showed good repeatability and reproducibility in MW indices (Table 4, Figures 3 and 4).

### MW indices and baseline parameters relationship

Multivariable analysis for MW indices showed that GWl and GCW increased with systolic blood pressure ( $\beta$ -coefficient = 0.67,  $P < 0.001$  and  $\beta$ -coefficient = 0.61,  $P < 0.001$ , respectively, Table 5). There was a significant increase in GWl and GCW according to age in univariable analysis but no association was observed after adjustment for confounders. Higher values of GWE in women than in men were observed only by univariable analysis (Table 5).

## Discussion

The present prospective, EACVI, multicentre study provides contemporary normal reference values for 2DE measurements of non-invasive MW indices in a large cohort of healthy volunteers over a



**Table 4** Repeatability and reproducibility of 2D echocardiographic data

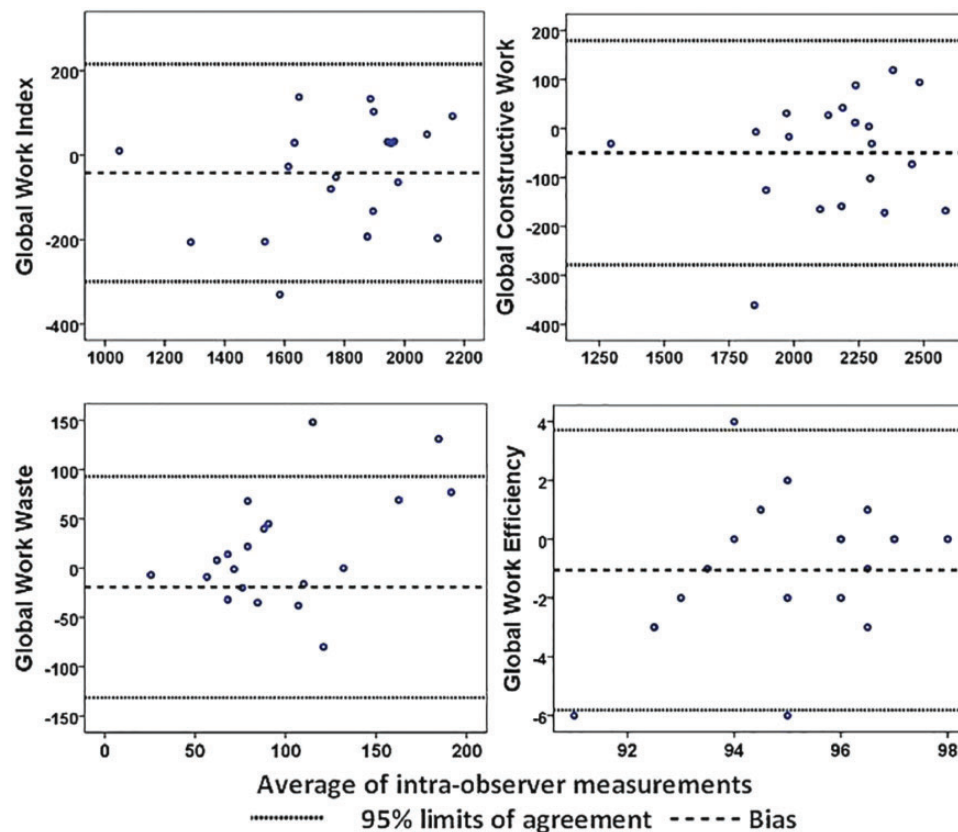
Variables	Mean $\pm$ SD	Mean $\pm$ SD	Bias	P-value	95% LOA
Intraobserver					
GWI (mmHg%)	1760 $\pm$ 301	1802 $\pm$ 269	-42.1	0.1	215 to -299.3
GCW (mmHg%)	2128 $\pm$ 305	2178 $\pm$ 288	-49.7	0.07	179.2 to -278.7
GWW (mmHg%)	108 $\pm$ 62	89 $\pm$ 38	19.2	0.1	92.9 to -131.3
GWE (%)	94.4 $\pm$ 2.5	95.5 $\pm$ 1.7	-1	0.06	3.7 to -5.8
Interobserver					
GWI (mmHg%)	1798 $\pm$ 225	1833 $\pm$ 223	-34.6	0.1	155.3 to -224.5
GCW (mmHg%)	2167 $\pm$ 209	2156 $\pm$ 187	11.1	0.6	213.5 to -191.3
GWW (mmHg%)	109 $\pm$ 48	103 $\pm$ 65	6.6	0.6	116.8 to -103.6
GWE (%)	95 $\pm$ 1.7	95 $\pm$ 2.4	-0.2	0.7	5.1 to -4.7

GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, global work waste; IQR, interquartile range; LOA, lower limits of agreement; SD, standard deviation.

wide range of ages. 2DE analysis was performed using an EchoPAC workstation, which is the only system that currently provides software to calculate MW. The MW, derived from LVP/volume or pressure/length loops, has been investigated for almost 40 years,<sup>20-23</sup> and has been recently shown to also provide similar physiological information to pressure/strain loops.<sup>6,7,24</sup> Russell et al.,<sup>7,11</sup> more recently, introduced a method for calculating non-invasive MW, by STE and estimation of LVP from brachial artery cuff pressure. Moreover, these authors recently demonstrated a strong correlation of LV-PSLs area with regional glucose metabolism, assessed by fluorine 18-fluorodeoxyglucose-positron emission tomography.

The present NORRE sub-study is the first one, to date, to provide reference ranges for 2DE non-invasive MW in a multicentre study

design. In our population of healthy individuals, univariable analysis denoted age-related changes in GWI and GCW. However, when analysing for gender-groups, both the previous indices increased with age in women, while no differences were found in men. This finding can be easily explained when considering the significant increase of both systolic and diastolic blood pressure, even if still in the normal range, according to age in women while no significant differences were found in men. Both GWI and GCW were in fact strongly correlated to blood pressure, as previously demonstrated. The increase in systolic blood pressure translates into an increase in afterload, which probably shifts LV work to a higher level of energy. Moreover, multivariable analysis revealed significant correlation only with systolic blood pressure for both GWI and GCW, with no gender and



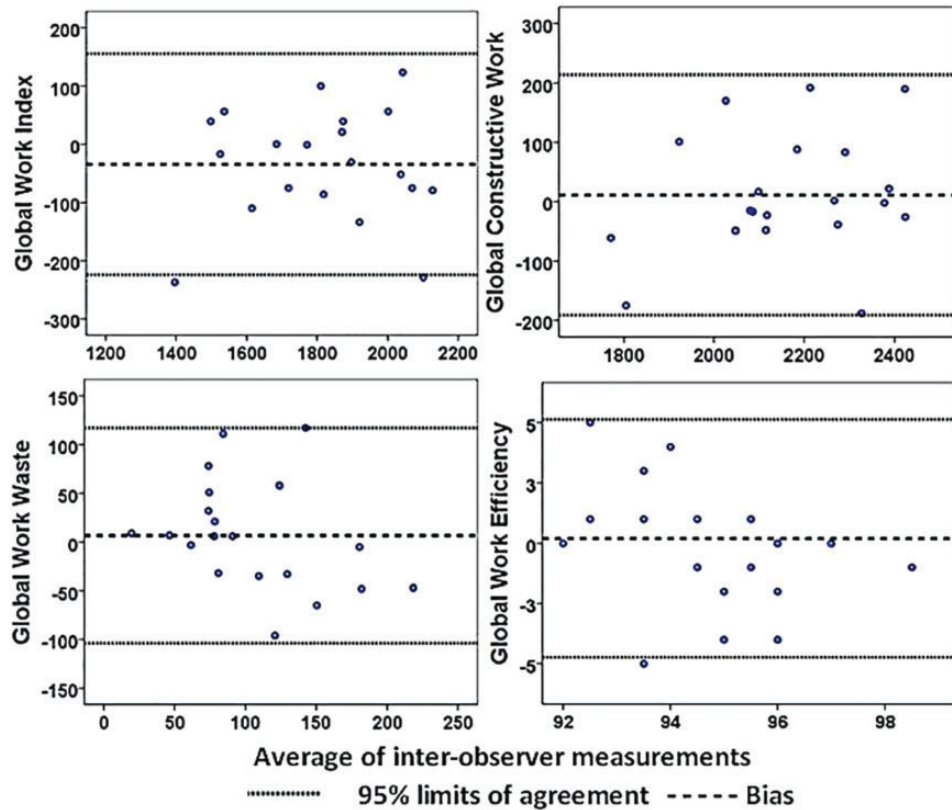
**Figure 3** The Bland–Altman analysis for assessing intra-observer variability of global work index, global constructive work, global work waste, and global work efficiency. Dotted lines represent bias and 95% limits of agreement for measurements performed in 20 patients.

age-related changes. Univariable analysis for GWW and GWE showed lower and higher values in women than in men, respectively, with no significant differences according to age. Specifically, when age and gender are considered, GWW and GWE were only different in the subgroup of 20–40 years olds. Again, this is highly related to the effect of blood pressure, which was higher in male, accounting for higher values of GWW. In the same sub-group, no differences were observed for GCW between men and women, while GWE was lower in men, as expected if considering that GWE is indirectly derived from the ratio of constructive and wasted MW. These results were, however, not confirmed in multivariable analysis.

Our data, thus, provide evidence of the absence of a strong dependence of MW on age and gender, while they highlight the association between GWI and GCW with systolic blood pressure. Moreover, MW takes into account deformation as well as afterload, potentially being superior to strain in assessing cardiac performance. As previously demonstrated, an increase in afterload may lead to reduction in systolic strain in the presence of preserved or even increased MW.<sup>8</sup>

To date, MW has been investigated in the field of CRT, showing promising results as a reliable predictor of response to CRT.<sup>9–11</sup> Preliminary interesting results have also been found in coronary artery disease. Boe et al.<sup>8</sup> showed increased sensitivity and specificity in identifying acute coronary occlusion in patients with non-ST-segment

elevation myocardial infarction using regional cardiac work index, compared with all other echocardiographic parameters, including strain imaging. More recently, Chan et al.<sup>25</sup> reported the results of MW indices in three cardiovascular conditions, e.g. hypertension, ischaemic, and non-ischaemic dilated cardiomyopathy. Particularly, as in our study, they confirmed the high impact of blood pressure on MW indices by showing a significant increase in GWI in hypertensive patients when compared with controls, despite a normal global longitudinal strain. So, likely, in conditions of high arterial pressure, the LV works at higher energy level to compensate the increased afterload, as reflected by the higher GWI. Moreover, in the population of ischaemic and non-ischaemic dilated cardiomyopathy, they found a significant increase in GWW, with an impairment of myocardial performance, as expressed by reduced values of both GWI and GWE, along with global longitudinal strain. The prognostic significance of wasted work in dyssynchronous ventricles was described in previous studies, while the potential role of GWI and GWE in dilated cardiomyopathies with overt LV systolic dysfunction probably needs to be further investigated. However, it can be postulated that they could offer interesting results and additional information about cardiac performances at a very early stage of the disease, when LV is only mildly dilated and an overt systolic dysfunction is not observed, as well as in every condition of heart failure with preserved left ventricular EF. Therefore, in clinical practice, MW could play a promising



**Figure 4** The Bland–Altman analysis for assessing inter-observer variability of global work index, global constructive work, global work waste, and global work efficiency. Dotted lines represent bias and 95% limits of agreement for measurements performed in 20 patients.

role in the serial assessment of patients with or at risk of developing cardiovascular disease as in those with hypertension or cancer.<sup>26</sup> In particular, GWI and GCW could find more applications as indices of myocardial performance, being an expression of positive LV work. They provide complementary information to the one offered by EF and global longitudinal strain. Moreover, the assessment of GCW could play an important role in identifying responders to CRT, as an index of contractile reserve, fundamental for the success of the electrical therapy. On the contrary, but for the same purpose, GWW, which is an index of energy loss, as result of dyssynchronous and remodelled LV, could be an additional tool to identify possible responders to CRT. MW indices could also be helpful to examine the impact of treatment on LV function. Of note, our data showed a good reproducibility for the assessment of MW, reinforcing the possibility of a promising application of this new advanced echocardiographic parameter in clinical practice.

## Limitations

This study presents several limitations. Only one-third of the patients included in the NORRE database were analysable by the current available software. Also, whether the NORRE study results can be extrapolated to non-Caucasian European individuals is still unknown.

## Conclusion

The EACVI NORRE study provides applicable 2DE reference ranges for MW indices. Multivariable analysis did not show that age and gender were independently associated with MW indices.

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**Conflict of interest:** C.O. is Senior Research Associate at the National Funds for Scientific Research (F.R.S.-FNRS, Belgium). All remaining authors have declared no conflicts of interest.

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**Table 5** Univariable and multivariable analysis for 2DE MW parameters

Variables	Univariable analysis Coefficient	P-value	Multivariable analysis $\beta$ -coefficient	P-value
Global work index (mmHg%)				
Age (years)	0.20	0.002		
Male gender (=1)	-0.11	0.07		
Body mass index (kg/m <sup>2</sup> )	0.12	0.05		
Systolic blood pressure (mmHg)	0.57	<0.001	0.67	<0.001
Diastolic blood pressure (mmHg)	0.37	<0.001		
Glycaemia (g/dL)	0.17	0.01		
Cholesterol (g/dL)	0.13	0.05		
Global constructive work (mmHg%)				
Age (years)	0.19	0.009		
Male gender (=1)	-0.008	0.9		
Body mass index (kg/m <sup>2</sup> )	0.12	0.05		
Systolic blood pressure (mmHg)	0.63	<0.001	0.61	<0.001
Diastolic blood pressure (mmHg)	0.41	<0.001		
Glycaemia (g/dL)	0.25	<0.001		
Cholesterol (g/dL)	0.15	0.02		
Global work waste (mmHg%)				
Age (years)	-0.006	0.9		
Male gender (=1)	0.13	0.05		
Body mass index (kg/m <sup>2</sup> )	-0.56	0.4		
Systolic blood pressure (mmHg)	0.11	0.07		
Diastolic blood pressure (mmHg)	0.05	0.4		
Glycaemia (g/dL)	0.04	0.5		
Cholesterol (g/dL)	0.03	0.6		
Global work efficiency (%)				
Age (years)	0.01	0.7		
Male gender (=1)	-0.14	0.03		
Body mass index (kg/m <sup>2</sup> )	0.04	0.5		
Systolic blood pressure (mmHg)	0.01	0.8		
Diastolic blood pressure (mmHg)	0.02	0.7		
Glycaemia (g/dL)	0.02	0.7		
Cholesterol (g/dL)	-0.02	0.7		

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