

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).¹⁻⁴ 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.^{5,6} Recently, Russell *et al.*⁷ 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.^{8–11}

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,¹² Doppler parameters,¹³ aortic dimensions,¹⁴ 3D echocardiographic measurements of the LV volumes and strain,¹⁵ 2DE measurement of LV strains and twist,¹⁶ and 2D and 3D measurement of left atrial function.¹⁷ 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

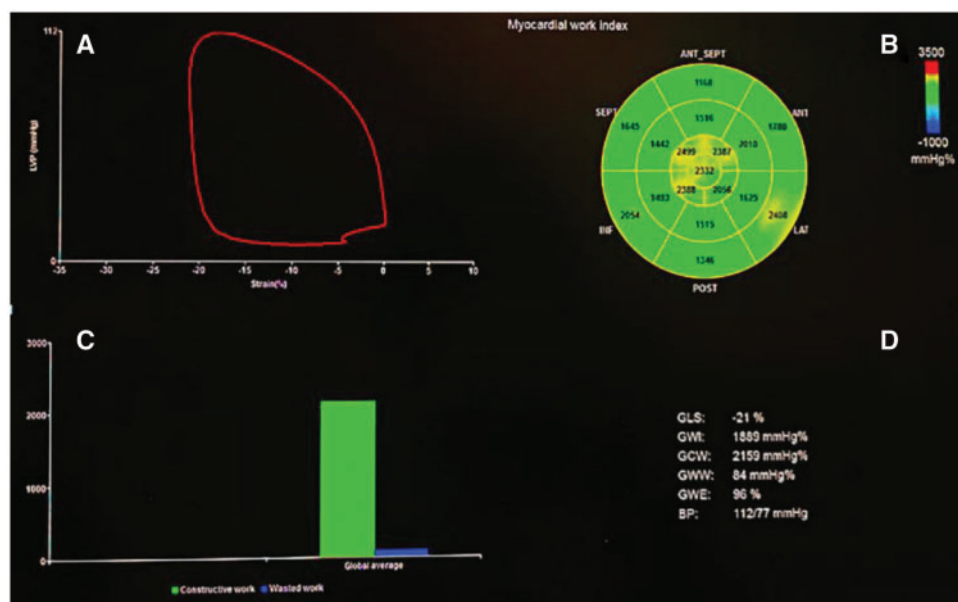


Figure 1 Measurement of myocardial work parameters by 2D echocardiography. (A) LV pressure–strain loop; (B) bull’s eye of GWI; (C) bar graph representing GCW and GWW; and (D) results from myocardial work analysis. GCW, global constructive work; GWE, global work efficiency; GWI, global work index; GWW, 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 ²)	1.8 ± 0.2	1.9 ± 0.1	1.7 ± 0.1	<0.001
Body mass index (kg/m ²)	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 ^{a,b}	Male, mean ± SD or median (IQR)	Male, 95% CI or limits of normality ± SE ^{a,b}	Female, mean ± SD or median (IQR)	Female, 95% CI or limits of normality ± SE ^{a,b}	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 ^a	94 (61.5–130.5)	238 ± 33 ^a	74 (49.5–111)	239 ± 39 ^a	0.013
GWE (mmHg%)	96 (94–97)	91 ± 0.8 ^b	95 (94–97)	90 ± 1.6 ^b	96 (94–97)	91 ± 1 ^b	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.
^aHighest expected value.
^bLowest 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.^{18,19} 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.⁷ Global Longitudinal Strain (GLS) was obtained as previously reported.¹⁶ 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



To date, MW has been investigated in the field of CRT, showing promising results as a reliable predictor of response to CRT.^{9–11} Preliminary interesting results have also been found in coronary artery disease. Boe *et al.*⁸ 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.*²⁵ reported the results of MW indices in

three cardiovascular conditions, e.g. hypertension, ischaemic, and not-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 not-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 role in the serial assessment of patients with or at risk of developing cardiovascular disease as in those with hypertension or cancer.²⁶ In particular, GWI and GCW could find more applications as indices of myocardial performance, being an expression of positive LV work. They provide complementary

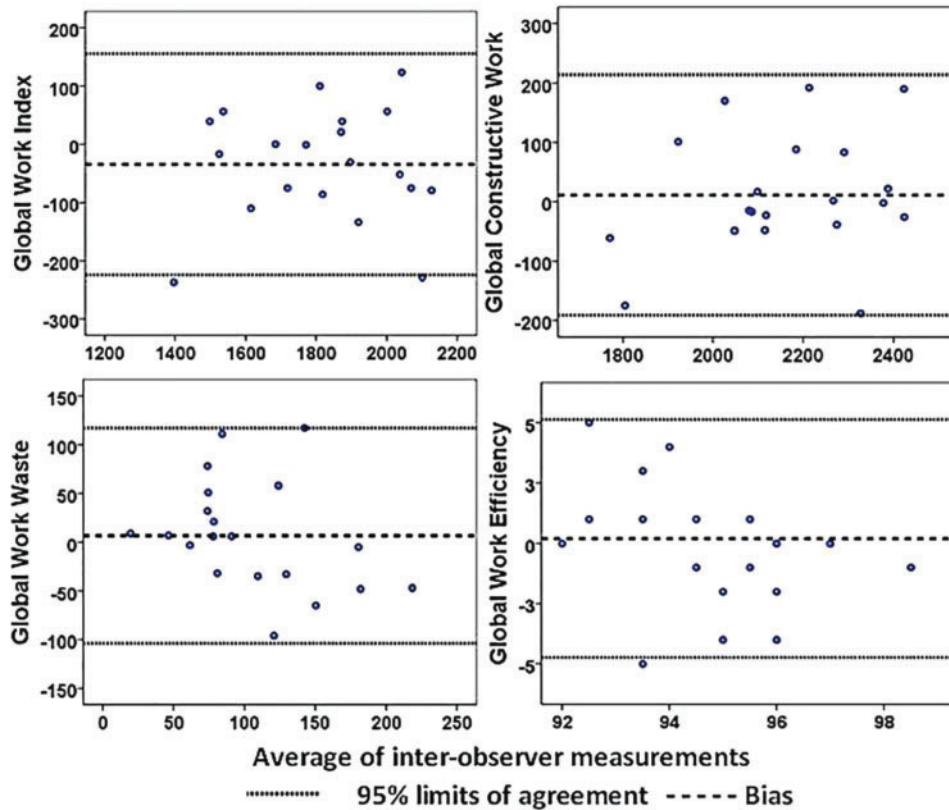


Figure 4 The Bland–Altman analysis for assessing inter-observer variability of global work index, global constructive work, global work waste, and global work efficiency. Dotted lines represent bias and 95% limits of agreement for measurements performed in 20 patients.

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 β -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 ²)	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 ²)	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 ²)	-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 ²)	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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IMAGE FOCUS

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Cardiac tamponade from a fractured inferior vena cava filter

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A 79-year-old female patient was admitted with chest pain and shortness of breath. Nineteen years earlier, the patient had history of pulmonary embolus with implantation of inferior vena cava (IVC) filter. Initial work up included echocardiography which showed large pericardial effusion with signs of cardiac tamponade (Panel A). Pericardiocentesis was performed with drainage of 550 cc bloody pericardial effusion.

Several hours later, she complained of abdominal pain which prompted an abdominal X-ray and computed tomography (CT) scan.

The imaging showed a fractured IVC filter strut with migration through the right ventricle (RV) into the pericardial space (Panel B) and to the hepatic vein (Panel C). Repeat echocardiogram showed re-accumulation of circumferential pericardial effusion. Cardiothoracic surgery performed a midline sternotomy with evacuation of haemopericardium. A 5 mm sized ecchymotic lesion was noted on the epicardial right ventricular free wall with a strut fragment perforating the right ventricular wall into the pericardial space (Panel D). A metallic strut measuring approximately 3 cm (Panel E) was then retrieved by accessing the intraventricular right ventricular cavity via the right atrial appendage, the ventricular defect was repaired with bovine patch. The patient later underwent laparotomy for retrieval of the IVC filter and hepatic vein fractured strut.

IVC filter placement is considered by many physicians as an effective treatment for recurrent pulmonary embolisms. This case showed that IVC filters may be a source of dramatic and dangerous multiorgan injury which can develop many years after its insertion.

(Panel A) Diastolic collapse of RV free wall with large pericardial effusion. (Panel B) Red arrow, opaque foreign object noted on non-contrast CT scan sagittal view protruding through RV and pericardium. (Panel C) Yellow arrow, opaque foreign object noted on non-contrast CT scan sagittal view in the right hepatic vein. (Panel D) Black arrow, midline sternotomy view of the RV free wall with ecchymosis. (Panel E) IVC filter strut retrieved from RV free wall.

