ESC European Society of Cardiology

European Heart Journal - Imaging Methods and Practice (2024) **2**, qyae091
https://doi.org/10.1093/ehjimp/qyae091

ORIGINAL ARTICLE

Reference values of strain-derived myocardial work indices in heart transplant patients

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Received 8 April 2024; accepted after revision 23 August 2024; online publish-ahead-of-print 30 August 2024

Abstract

Aims

Myocardial work (MW) is a relatively novel non-invasive echocardiographic method with increasing fields of application. Normal reference ranges of MW indices in patients who have undergone a heart transplant (HTx) have not been determined yet. The aim of this study was to obtain the reference ranges for 2D echocardiographic indices of MW for adult HTx patients and to compare them with the results of the European Association of Cardiovascular Imaging (EACVI) Normal Reference Ranges for Echocardiography (NORRE) study.

Methods and results

All consecutive HTx patients admitted at our institution (University Hospital of Siena, Italy) between September 2019 and May 2022 who underwent endomyocardial biopsy (EMB) were considered. Patients with a history of rejection, a history of coronary artery vasculopathy, either acute cellular rejection or acute antibody-mediated rejection at EMB, and donor-specific antibodies were excluded. MW retrospectively performed for the included patients was retrieved, and the results were compared with those from the EACVI NORRE study. Out of 176 HTx patients who underwent EMB, 94 patients were excluded. The study population consisted of 82 HTx patients [68.3% male, median age 53 (46–62) years]. The median duration from HTx was 5 (2–22) months. The main MW indices such as global work efficiency (GWE, 84 ± 8%), global work index (GWI, 1447 ± 409 mmHg%), global constructive work (GCW, 2067 ± 423 mmHg%), and global wasted work [GWW, 310 (217–499) mmHg%] did not differ according to gender. Each of these indices significantly differed from those reported in the EACVI NORRE study (*P*-value <0.001), with lower GWI, GCW, and GWE and higher GWW values in the HTx population.

Conclusion

This study provides reference ranges for MW indices in an adult HTx population free from transplant-related complications which proved to be different from those previously reported in healthy volunteers.

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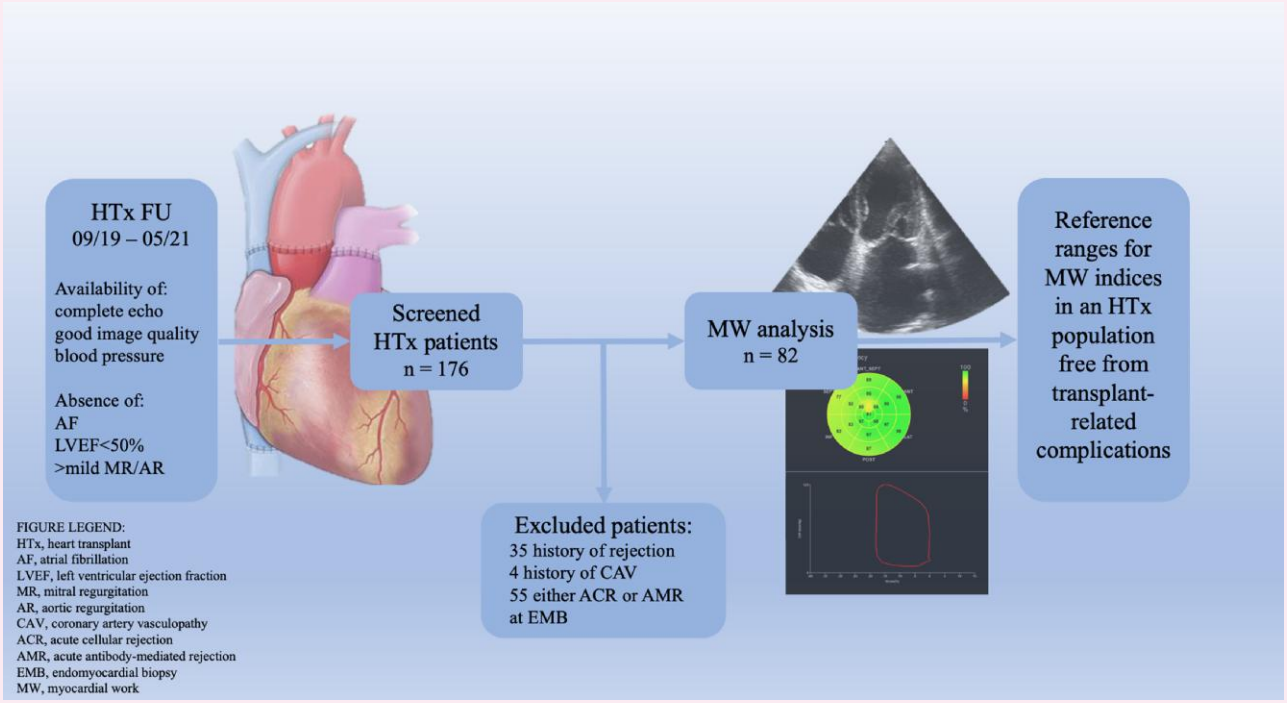
Graphical Abstract



Study design. Heart transplant patients undergoing EMB at follow-up were screened for myocardial work analysis. HTx, heart transplant; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; AR, aortic regurgitation; CAV, coronary artery vasculopathy; ACR, acute cellular rejection; AMR, acute antibody-mediated rejection; EMB, endomyocardial biopsy; MW, myocardial work.

Keywords myocardial work • heart transplant • reference values • echocardiography • speckle tracking strain

Introduction

The prevalence of individuals affected by heart failure worldwide is incessantly increasing, counting now over 60 million.[1] Heart transplantation (HTx) remains the gold-standard therapeutic option in the advanced heart failure. Data from recent years show that the median survival time after HTx currently exceeds 10 years.[2] Therefore, the world population of HTx patients is increasing with more than 6000 heart transplants performed annually worldwide.[3] Following international recommendations, HTx patients undergo periodic clinic visits for blood tests, electrocardiogram, and echocardiographic examination with the aim of monitoring potential complications or drug-related adverse events and titrating immunosuppressive therapy. For the same reason, HTx patients typically follow a specific protocol of endomyocardial biopsy (EMB) surveillance to detect potentially subclinical episodes of rejection. Even though studies in the last years have tried to identify early predictors of such events, EMB remains the gold-standard investigation to rule out rejection in the early post-transplant phase and in symptomatic patients.[4–6]

Myocardial work (MW) is a relatively novel non-invasive echocardiographic method to estimate pressure–volume loops by speckle tracking echocardiography.[7] MW has already emerged as a promising tool for various pathological conditions, but its role in HTx patients has been poorly tested so far. Even though a sound rationale for the implementation of MW in HTx patients during follow-up visits to unveil potentially subclinical alterations in left ventricular function, the absence of normal reference ranges for this special population cannot be disregarded.[8–10] To the best of our knowledge, normal reference ranges of MW indices are currently available only in healthy volunteers, derived from the European Association of Cardiovascular Imaging (EACVI) Normal Reference Ranges for Echocardiography (NORRE) study.[11] As normal ranges of MW indices in HTx patients may differ from those of healthy people, this study aims to obtain the reference ranges for 2D echocardiographic (2DE) indices of MW for adult HTx patients and to compare them with the EACVI NORRE healthy population.

Methods

Patient selection

All the consecutive HTx patients admitted at our institution (University Hospital of Siena, Italy) for a planned follow-up between September 2019 and May 2022 who underwent EMB were considered. Those without complete available echocardiographic examination or with insufficient image quality to perform a speckle tracking echocardiography analysis of the left ventricle or those without brachial artery–cuff pressure availability were not considered. Patients with a known history of rejection, a history of coronary artery vasculopathy (CAV), either acute cellular rejection (ACR) or acute antibody-mediated rejection (AMR) at EMB, and donor-specific antibodies (DSA) were excluded. Additional exclusion criteria were atrial fibrillation, more than mild mitral or aortic regurgitation, and reduced or mildly reduced left ventricular ejection fraction (LVEF, <50%). In the case of multiple EMB performed during the inclusion period in a single patient, only the first one was considered for the analysis. The study was performed in accordance with the Declaration of Helsinki and approved by the local scientific ethics committee.

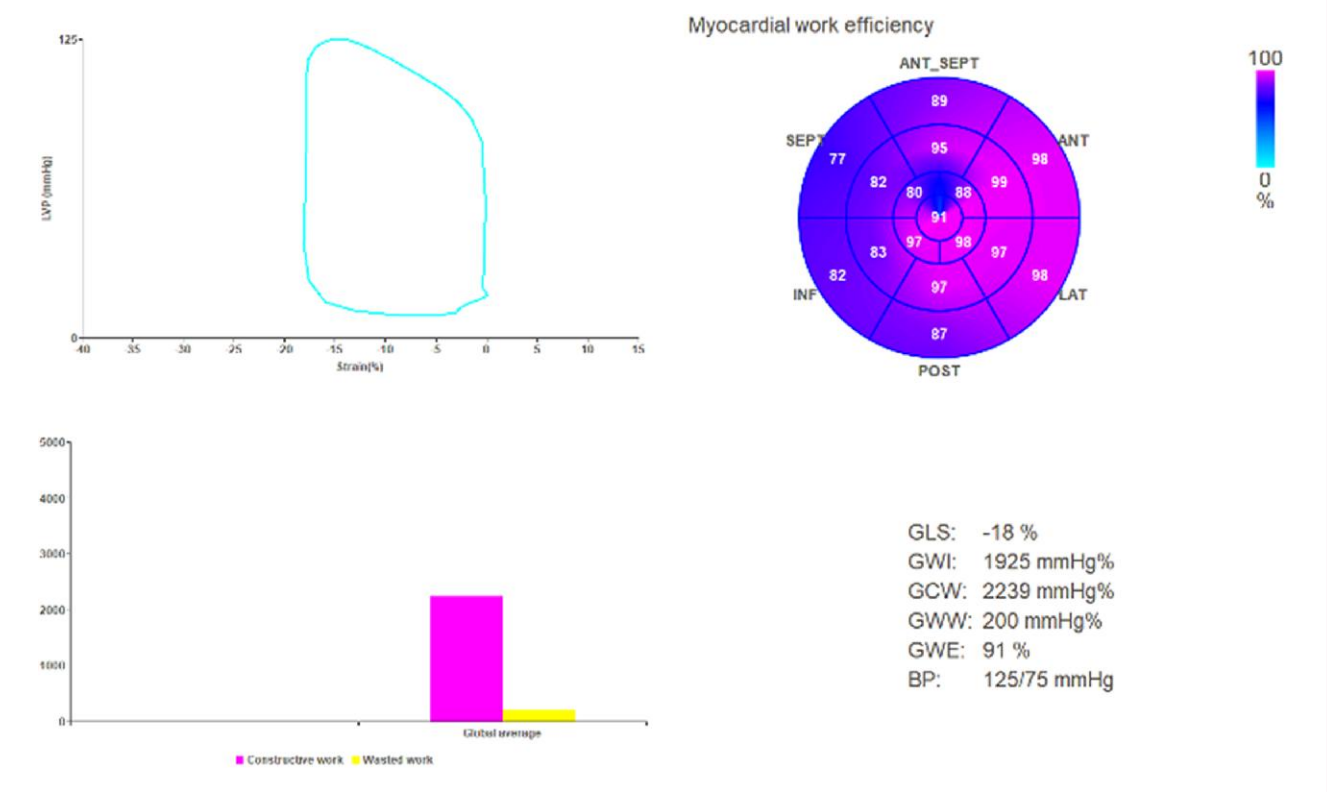


Figure 1 An MW analysis. Software's output after completion of MW analysis.

Population characteristics

Clinical, demographic, and laboratory data of all included patients were retrospectively collected from the institutional electronic records and recorded in a dedicated database. Echocardiographic data from examinations performed just before EMB were also collected. All echocardiographic examinations were performed by experienced operators using a GE Vivid E80/E95 equipped with an adult 1.5–4.3 MHz phased-array transducer and with an ECG continuously traced, according to the American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations.[12–15] For speckle tracking echocardiography analysis, endocardial borders and myocardium of all segments from the apical views (four chambers, two chambers, and apical long axis) had to be clearly visualized throughout the whole cardiac cycle. The analysis was retrospectively performed offline using EchoPAC software v204 (GE Healthcare).[14] A brachial artery–cuff pressure was measured 15 minutes after the end of the echocardiographic examination with the patient lying in a calm and comfortable position.[16]

MW analysis

A left ventricular speckle tracking strain analysis was semiautomatically performed by EchoPAC software v204 (GE Healthcare) in the three apical views and adjusted by the operator in terms of region of interest (ROI) width and positioning to optimize endomyocardial tracking.[6,16,17] Markers for aortic and mitral valves opening and closure were required to set the beginning and the end of each main phase of the cardiac cycle, and they were visually set from the apical long-axis view (see Supplementary data online, *Video S1*). Moreover, the brachial cuff blood pressure (BP) was needed to adapt in time and amplitude the reference curve for left ventricular pressure estimation. Finally, the software output displays a series of indices which depict the PS loop from various perspectives and also provides a graphic representation of the PS loop[6,16,17] (*Figure 1*). The following are the main MW indices: global work index (GWI) which is the total work performed by the heart between mitral valve closure to mitral valve opening; global constructive work (GCW) which is the work performed during shortening in systole adding work during lengthening in isovolumetric relaxation; global wasted work (GWW) which is the work performed during lengthening in systole adding work performed during shortening in isovolumetric relaxation; and global work efficiency (GWE) which is the constructive work divided by the sum of constructive and wasted work. An MW analysis was performed by two experienced operators.

Endomyocardial biopsy

EMBs were performed as a day hospital regimen. Vascular access for EMB was obtained with ultrasound guidance at the right internal jugular vein under local anaesthesia with Seldinger's technique. Guidance and confirmation of correct positioning of the bioptome at the mid-septum level was verified by fluoroscopy before the biopsy specimens were withdrawn. Usually, four or more samples were taken from each patient. Immediately after the completion of the procedure, biopsy specimens were sent to the pathology department for analysis. Haematoxylin and eosin staining was used for analysis, and additionally, trichrome staining was used in selected cases. A local biopsy surveillance protocol usually lasted for 8 years following heart transplantation. Immunofluorescent/immunoperoxidase staining was used to detect AMR along with solid-phase assay and/or cell-based assays to determine the presence of DSA. The ISHLT definitions and diagnostic criteria for ACR and AMR were used.[18,19]

Statistical analysis

Continuous data are presented as mean and SD or as median and interquartile range, as appropriate. The Kolmogorov–Smirnov test was used to verify the normal distribution of variables. Continuous variables were compared using the unpaired *t*-test for normally distributed variables and the nonparametric Mann–Whitney *U* test for non-normally distributed variables. Lower normal limits were calculated as mean − 2 × SD or 2.5th percentile,

Table 1 Characteristics of the study population

Parameters	Total ($n = 82$)	Female ($n = 26$)	Male ($n = 56$)	*P*-value
Age (years)	53 (46–62)	47 (46–55)	55 (44–63)	0.163
Weight (kg)	76 ± 13	70 ± 11	78 ± 12	0.008
Height (cm)	172 ± 10	162 ± 4	178 ± 7	<0.001
Systolic BP (mmHg)	120 (110–135)	115 (110–131)	122 (115–135)	0.195
Diastolic BP (mmHg)	80 (70–80)	80 (70–80)	80 (70–83)	0.870
Months from HTx	5 (2–22)	5 (3–31)	6 (2–18)	0.689
WBC (10^9/μL)	7.0 (5.5–8.6)	6.8 (4.6–8.4)	7.2 (5.6–8.8)	0.265
Hb (g/dL)	13.4 ± 1.4	12.5 ± 1.3	13.8 ± 1.3	<0.001
Creatinine (mg/dL)	1.10 ± 0.35	0.94 ± 0.35	1.17 ± 0.33	0.004
HbA1c (%)	6.39 ± 1.00	6.99 ± 0.65	6.12 ± 1.03	0.005
LDL-C (mg/dL)	95 ± 38	105 ± 49	91 ± 32	0.198
Immunosuppression				
Corticosteroids	73 (89.0)	23 (88.5)	50 (89.3)	0.912
Cyclosporine	5 (6.1)	1 (3.8)	4 (7.1)	0.562
Tacrolimus	77 (93.9)	25 (96.2)	52 (92.3)	0.562
Mycophenolate	66 (80.5)	23 (88.5)	43 (76.8)	0.214
Everolimus	12 (14.6)	1 (3.8)	11 (19.6)	0.060
LV EDD (mm)	44.82 ± 4.31	42.50 ± 3.89	45.89 ± 4.09	0.001
LV EF (%)	60 (60–60)	60 (60–60)	60 (60–60)	0.060
RV EDD (mm)	30.83 ± 3.28	30.19 ± 2.91	31.12 ± 3.41	0.233
TAPSE (mm)	15.84 ± 3.12	15.73 ± 2.54	15.89 ± 3.37	0.831
sPAP (mmHg)	29.7 ± 5.8	29.6 ± 6.2	30.0 ± 5.2	0.841
LV GLS (%)	−16.1 ± 3.5	−16.7 ± 2.8	−15.9 ± 3.7	0.312

Data are expressed as the mean ± SD or as median (interquartile range) and as number (percentage).
Hb, haemoglobin; WBC, white blood cell; LV EDD, left ventricular end-diastolic diameter; LV EF, left ventricular ejection fraction; RV EDD, mid-cavity right ventricular end-diastolic diameter; sPAP, systolic pulmonary artery pressure; LV GLS, left ventricular global longitudinal strain.

according to the distribution of variables. Echocardiographic measures were compared with previously reported distributions in the EACVI NORRE study[11] using Welch's unequal-variance *t*-tests. A linear regression analysis was performed to examine associations between MW indices and baseline parameters [at the time of echocardiographic assessment, including age, months from HTx, gender, weight, height, systolic BP, diastolic BP, haemoglobin, white blood cells, creatinine, HbA1c, and low density lipoprotein cholesterol (LDL-C)]. Inter-observer and intra-observer agreement for indices of MW was assessed in 30 randomly selected patients using the Bland–Altman analysis and intra-class correlation coefficients (ICCs) using the MW analysis performed by two experienced operators blinded to the other's results. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Population characteristics

Out of the 176 screened HTx patients, 35 patients were excluded because of a previous history of rejection, 4 patients because of a history of CAV, and 55 patients because of either ACR or AMR at EMB. Therefore, the final study population consisted of 82 HTx patients [68.3% male, median age 53 (46–62) years] (*Graphical Abstract*). All patients underwent HTx with bicaval technique. The median age from HTx was 5 (2–22) months. Weight, height, haemoglobin, creatinine, and HbA1c significantly differed between male and female ($P < 0.05$). Complete demographic and clinical characteristics of the study population, divided by gender, are summarized in *Table 1*.

Reference ranges for MW indices in HTx

Values of MW indices in the overall population were given as follows: mean GWE 84 ± 8%, GWI 1447 ± 409 mmHg%, GCW 2067 ± 423 mmHg%, and median GWW 310 (217–499) mmHg%. No differences between genders were found (*Table 2*).

Comparison of MW indices with the EACVI NORRE results

Comparison of MW indices with results from the EACVI NORRE study in healthy volunteers revealed statistically significant differences for each of the MW indices. In particular, transplanted hearts had lower GWI, GCW, and GWE and higher GWW values, irrespective of gender. *Table 3* describes the complete results of the comparison and stratified for genders.

Association of MW indices with patient characteristics

GWE was associated with weight, systolic BP, diastolic BP, and HbA1c at univariate analysis. At multivariate analysis, only weight ($\beta = -0.410$, *P*-value = 0.002) and HbA1c ($\beta = -0.375$, *P*-value = 0.005) showed a significant association. GWI was associated with weight, systolic BP, and diastolic BP at univariate analysis. At multivariate analysis, only weight ($\beta = -0.205$, *P*-value = 0.031) and systolic BP ($\beta = 0.529$, *P*-value=<0.001) confirmed a significant association. GCW was associated with systolic BP and diastolic BP at univariate analysis and with

Table 2 2DE parameters of MW of the study population

Parameters	Total	Lower normal limit	Female	Lower normal limit	Male	Lower normal limit	*P*-value
GWI (mmHg%)	1447 ± 409	645	1538 ± 415	725	1407 ± 403	617	0.189
GCW (mmHg%)	2067 ± 423	1238	2143 ± 281	1592	2034 ± 470	1113	0.293
GWW (mmHg%)	310 (217–499)	104	296 (209–501)	104	315 (222–426)	76	0.894
GWE (%)	84 ± 8	68	84 ± 9	66	84 ± 8	68	0.897

Data are expressed as the mean ± SD or as median (interquartile range).

Table 3 2DE parameters of MW compared with those from the EACVI NORRE study

Parameters	Study population ($n = 82$) Total	EACVI NORRE ($n = 226$) Total	*P*-value	Study population ($n = 56$) Male	EACVI NORRE ($n = 85$) Male	*P*-value	Study population ($n = 26$) Female	EACVI NORRE ($n = 141$) Female	*P*-value
GWI (mmHg%)	1447 ± 409	1896 ± 308	<0.001	1407 ± 403	1849 ± 295	<0.001	1538 ± 415	1924 ± 313	<0.001
GCW (mmHg%)	2067 ± 423	2232 ± 331	0.002	2034 ± 470	2228 ± 295	0.007	2143 ± 281	2234 ± 352	0.154
GWW (mmHg%)	310 (217–499)	79 (53–122)	<0.001	315 (222–426)	94 (62–131)	<0.001	296 (209–501)	74 (50–111)	<0.001
GWE (%)	84 ± 8	96 (94–97)	<0.001	84 ± 8	95 (94–97)	<0.001	84 ± 9	96 (94–97)	<0.001

Data are expressed as mean ± SD or as median (interquartile range).

systolic BP (β = 0.497, *P*-value=<0.001) at multivariate analysis. GWW was associated with weight and HbA1c at univariate analysis. At multivariate analysis, only HbA1c (β = 0.406, *P*-value = 0.006) showed a significant association. The results of univariate and multivariate analyses are shown in *Table 4*.

MW measurement reproducibility

The results of intra-observer and inter-observer variability analyses for MW indices are shown in *Table 5*. The Bland–Altman plots for assessing the inter- and intra-observer variability of the indices of MW are shown in *Figures 2* and *3*, respectively. The ICCs for the inter-observer variability demonstrated good reliability, while those for the intra-observer variability indicated excellent reliability.

Discussion

This study provides contemporary reference ranges for 2DE indices of MW in a wide cohort of adult HTx patients without a prior history of rejection or CAV and with negative EMB. The results proved to be significantly different from those obtained in healthy volunteers from the EACVI NORRE study.[11]

MW is a relatively novel non-invasive echocardiographic method to estimate pressure–volume loops by speckle tracking echocardiography with increasing fields of application.[6] Its role in HTx patients has been poorly investigated, presumably because of the absence of normal reference ranges for this special population of patients. In fact, few studies have been published regarding its potential applications in HTx, either adults or paediatric, each necessitating an internal control group to compare MW values.[8–10] As a matter of fact, normal reference ranges of MW indices have only been determined in a population of healthy volunteers so far.[11]

In this study, we performed the MW analysis in a wide population of adult HTx patients with preserved LVEF. Of note, patients with a history of rejection, a history of CAV, and either ACR or AMR at EMB were excluded from the analysis. Furthermore, echocardiographic examinations and estimation of BP data used for MW calculation were performed on the same day of EMB. Applying these strict criteria makes the included patients reliably considerable as free from HTx-related complications.

The results from the MW analysis revealed that values of all indices significantly differed from those reported in the EACVI NORRE study of healthy volunteers.[11] Particularly, GWI, GCW, and GWE showed lower values, while GWW showed higher values in our HTx population. In the first instance, these findings could be explained by the reduced values of left ventricular global longitudinal strain known in HTx patients, possibly because of the surgical procedure, pericardiotomy, ischaemic time, and myocardial fibrosis.[17] Other specific HTx peculiarities differentiate these patients from patients undergoing traditional cardiac surgery, such as donor heart and recipient characteristics and various degrees of donor–recipient mismatch.[20,21] However, the impact of cardiac surgery alone on MW indices needs specific investigation. On the contrary, systemic hypertension is a well-known condition in patients receiving immunosuppressive therapy, potentially mitigating the reduction in GWI, GCW, and GWE due to decreased speckle tracking echocardiography strain values.[22] Moreover, conduction disturbances, which have long been described in HTx patients, may lead to various degrees of dyssynchrony which could explain higher GWW and consequently lower GWE.[23]

Univariate and multivariate analyses showed some association of MW indices and patient characteristics. Particularly, systolic BP, diastolic BP, weight, and HbA1c were the variables which showed the closest association. Only systolic BP remained positively associated with GWI and GCW on multivariate analysis, an observation which has already been described and appears logical due to its accounting into MW calculation.[11] Weight showed a negative association only with GWE and GWI on multivariate analysis, possibly because of the abovementioned various degrees of donor–receiver mismatch.[21] Finally, a HbA1c

Table 4 Univariable and multivariable analyses for 2DE parameters of MW

Parameters	Univariate analysis coefficient	*P*-value	Multivariate analysis coefficient	*P*-value
GWE				
Age	0.092	0.418		
Months from HTx	−0.006	0.962		
Male gender	−0.015	0.897		
Weight	−0.337	0.002	−0.410	0.002
Height	0.276	0.139		
Systolic BP	0.350	0.002	0.317	0.077
Diastolic BP	0.281	0.012	0.001	0.994
Hb	−0.034	0.768		
WBC	−0.080	0.496		
Creatinine	−0.126	0.270		
HbA1c	−0.365	0.016	−0.375	0.005
LDL-C	−0.026	0.838		
Corticosteroids	−3.478	0.241		
Cyclosporine	0.268	0.073		
Tacrolimus	−0.268	0.942		
Mycophenolate	2.194	0.325		
Everolimus	−2.947	0.237		
GWI				
Age	0.106	0.353		
Months from HTx	0.007	0.951		
Male gender	−0.149	0.189		
Weight	−0.227	0.045	−0.205	0.031
Height	0.062	0.746		
Systolic BP	0.551	<0.001	0.529	<0.001
Diastolic BP	0.410	<0.001	0.021	0.876
Hb	−0.059	0.612		
WBC	−0.158	0.179		
Creatinine	−0.007	0.953		
HbA1c	−0.055	0.726		
LDL-C	−0.179	0.157		
Corticosteroids	−268.757	0.078		
Cyclosporine	−41.324	0.828		
Tacrolimus	41.324	0.828		
Mycophenolate	−48.721	0.673		
Everolimus	41.808	0.746		
GCW				
Age	0.065	0.568		
Months from HTx	0.071	0.534		
Male gender	−0.120	0.293		
Weight	−0.051	0.652		
Height	0.061	0.748		
Systolic BP	0.567	<0.001	0.497	<0.001
Diastolic BP	0.453	<0.001	0.099	0.461
Hb	−0.043	0.708		
WBC	−0.144	0.220		
Creatinine	0.181	0.113		
HbA1c	0.171	0.272		
LDL-C	−0.207	0.102		
Corticosteroids	−215.708	0.173		
Cyclosporine	0.976	0.996		
Tacrolimus	−0.976	0.996		
Mycophenolate	−78.202	0.512		
Everolimus	118.634	0.374		
GWW				
Age	−0.074	0.517		
Months from HTx	0.096	0.402		
Male gender	−0.093	0.413		
Weight	0.251	0.026	0.249	0.080
Height	−0.270	0.149		
Systolic BP	−0.151	0.184		
Diastolic BP	−0.105	0.355		
Hb	−0.045	0.694		
WBC	0.004	0.974		
Creatinine	0.220	0.053		
HbA1c	0.414	0.006	0.406	0.006
LDL-C	−0.052	0.686		
Corticosteroids	83.667	0.472		
Cyclosporine	−19.824	0.891		
Tacrolimus	19.824	0.891		
Mycophenolate	−50.542	0.563		
Everolimus	80.490	0.410		

Hb, haemoglobin; WBC, white blood cell.

negative association with GWE and a positive association with GWW could be explained on the basis of an ongoing subclinical left ventricular systolic dysfunction previously observed in asymptomatic diabetic patients.[24] Of note, immunosuppressive regimens may lead to iatrogenic diabetes in otherwise non-diabetic patients.[25] In our study population, there was not significant association between immunosuppressive regimen and MW indices.

Finally, a reproducibility analysis was deemed necessary due to the possible operator dependency of MW calculation. Therefore, the reproducibility analysis was performed in 30 randomly selected patients by two experienced operators blinded to each other's results. The results were satisfactory in terms of both intra-observer and inter-observer variability with excellent and good reliability, respectively. These results are in line with those from the EACVI NORRE study regarding a population of healthy volunteers.[11]

Clinical perspectives

MW is an emerging echocardiographic method with many potential applications in various contexts due to more insightful information regarding myocardial performance than other traditional parameters. Only few studies on MW role in HTx patients have been published so far; however, promising results have already emerged with important implications in identifying long-term complications such as CAV,

Table 5 Repeatability and reproducibility of 2DE indices of MW

Indices	Mean ± SD Operator 1	Mean ± SD Operator 2	Bias	*P*-value	95% LOA	ICC	95% CI
Inter-observer							
GWI (mmHg%)	1480 ± 342	1389 ± 367	90.5	0.109	−496.5–677.5	0.784	0.545–0.897
GCW (mmHg%)	2005 ± 343	1953 ± 365	52.0	0.338	−520.3–624.2	0.796	0.571–0.903
GWW (mmHg%)	327 ± 160	343 ± 189	−16.2	0.496	−267.9–235.6	0.844	0.673–0.926
GWE (%)	85 ± 6	85 ± 6	0.1	0.962	−7.5–7.5	0.897	0.783–0.951
Intra-observer							
GWI (mmHg%)	1389 ± 367	1414 ± 347	−24.7	0.311	−281.8–232.4	0.965	0.927–0.983
GCW (mmHg%)	1953 ± 365	1975 ± 384	−21.4	0.417	−301.1–258.3	0.962	0.921–0.982
GWW (mmHg%)	343 ± 189	345 ± 193	−2.1	0.908	−193.0–188.9	0.931	0.854–0.967
GWE (%)	85 ± 6	85 ± 6	0.3	0.548	−5.0–5.6	0.952	0.900–0.977

CI, confidence interval; LOA, limits of agreement.

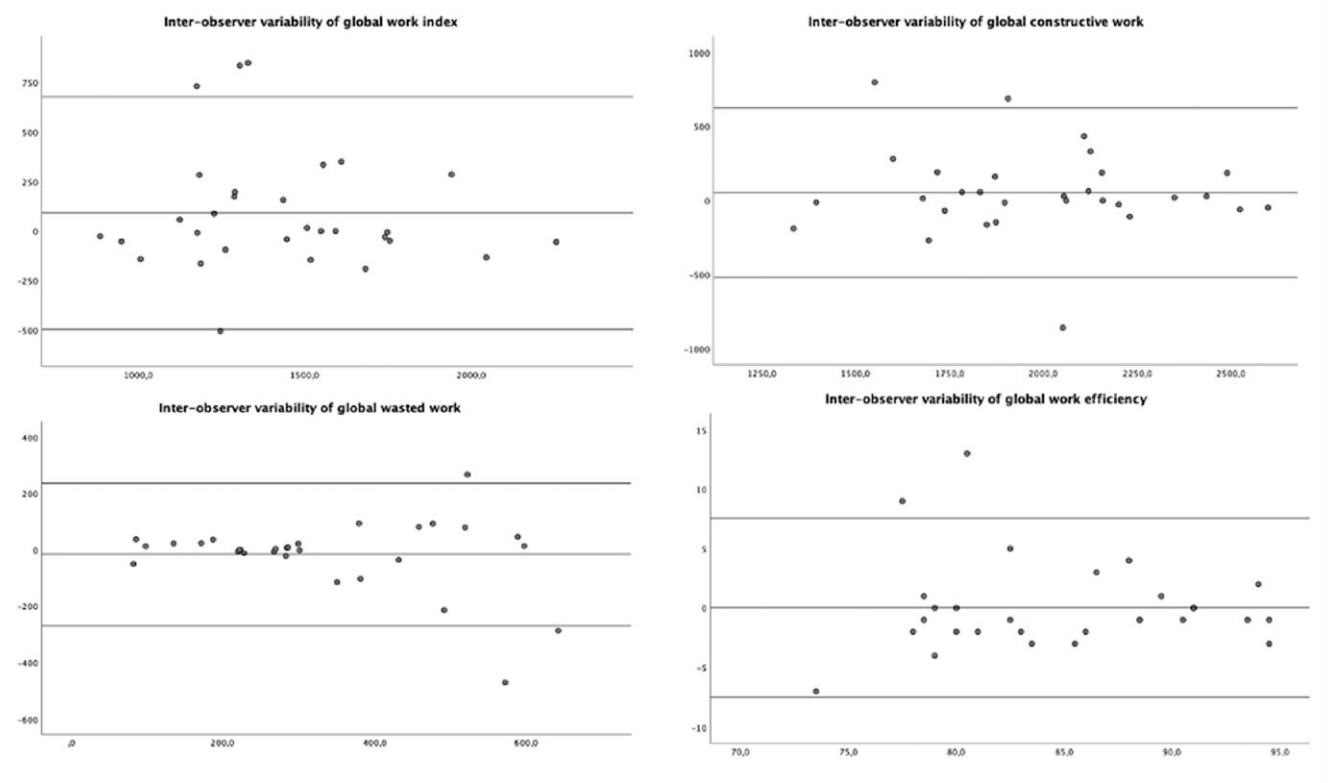


Figure 2 The inter-observer variability. The Bland–Altman analysis for assessing inter-observer variability of GWI, GCW, GWW, and GWE. The dotted lines represent the bias and 95% limits of agreement for measurements taken in 30 patients.

acute rejection, and ventricular disfunction.[8–10] Therefore, this study aims to further support clinical investigation of this promising tool in HTx patients.

Study limitations

This study has some limitations. First, this was the single-centre retrospective nature of the study. However, we performed a reproducibility analysis to control for potential bias due to operator dependency of the calculation. Secondly, the study has a limited number of patients included the majority of whom was Caucasians, even though similar to or higher than the previous papers involving heart-transplanted subjects.[26,27] We had to exclude a big number of patients to achieve a highly selected population suitable for the purpose of the study. The median time from HTx was relatively short, considering that a baseline echocardiographic assessment was usually recommended to be performed at 6 months from HTx,[28] and information regarding the donor heart prior to HTx is lacking, limiting further analysis. However, the wide

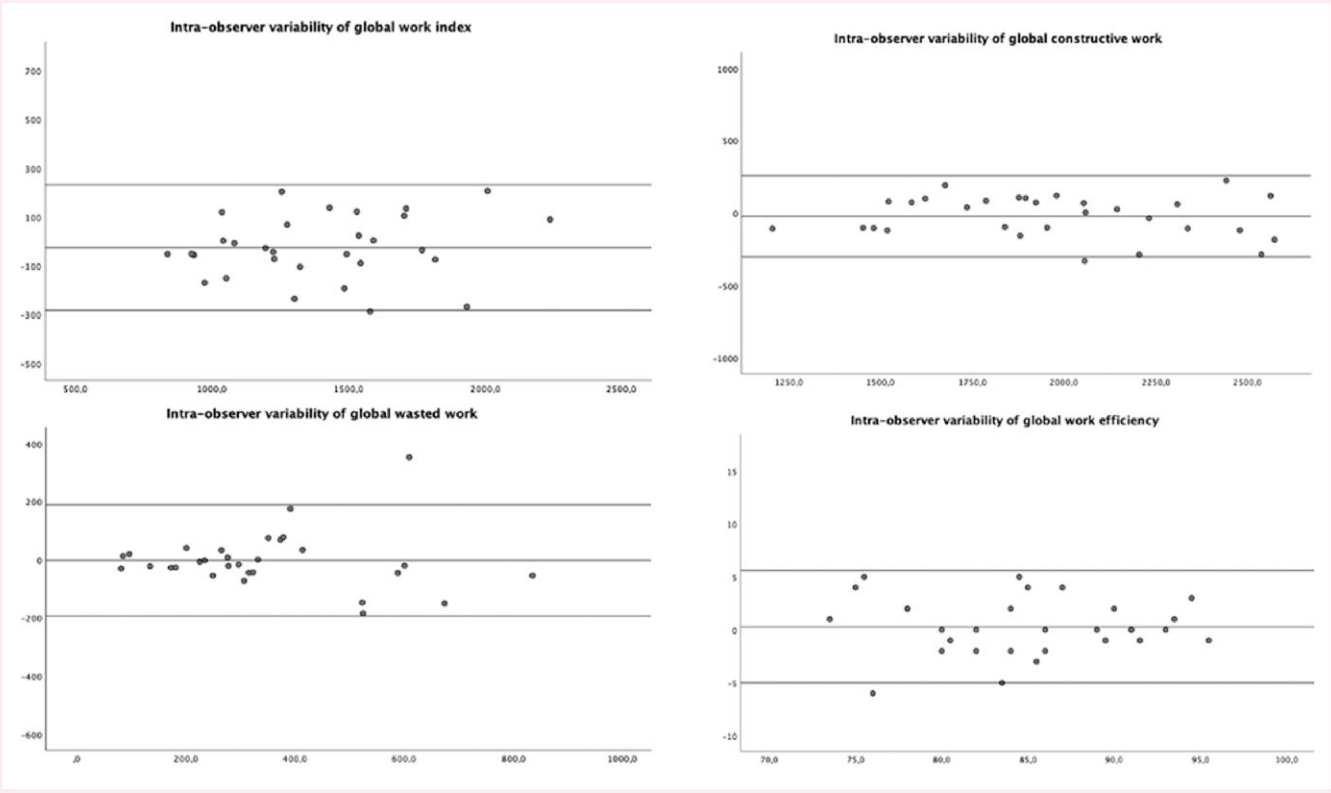


Figure 3 The intra-observer variability. The Bland–Altman analysis for assessing intra-observer variability of GWI, GCW, GWW, and GWE. The dotted lines represent the bias and 95% limits of agreement for measurements taken in 30 patients.

range of timings from HTx, on the other hand, could provide widely applicable values even in patients in the early post-HTx period when acute rejection is more frequent.[20] Finally, a feasibility analysis was not performed because patients with image quality deemed insufficient for a speckle tracking echocardiography analysis were not considered from the beginning.

Conclusions

This study provides applicable 2DE reference ranges for non-invasive MW indices in adult HTx patients. Comparing results with normal individuals from the EACVI NORRE study shows that HTx patients had lower GWI, GCW, and GWE and higher GWW values.

Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

Consent

Each patient gave its written informed consent for the participation to the study.

Acknowledgements

None.

Conflict of interest: none declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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