Multi-modality imaging in ischemic heart disease, arrhythmia and cardiac-mechanics

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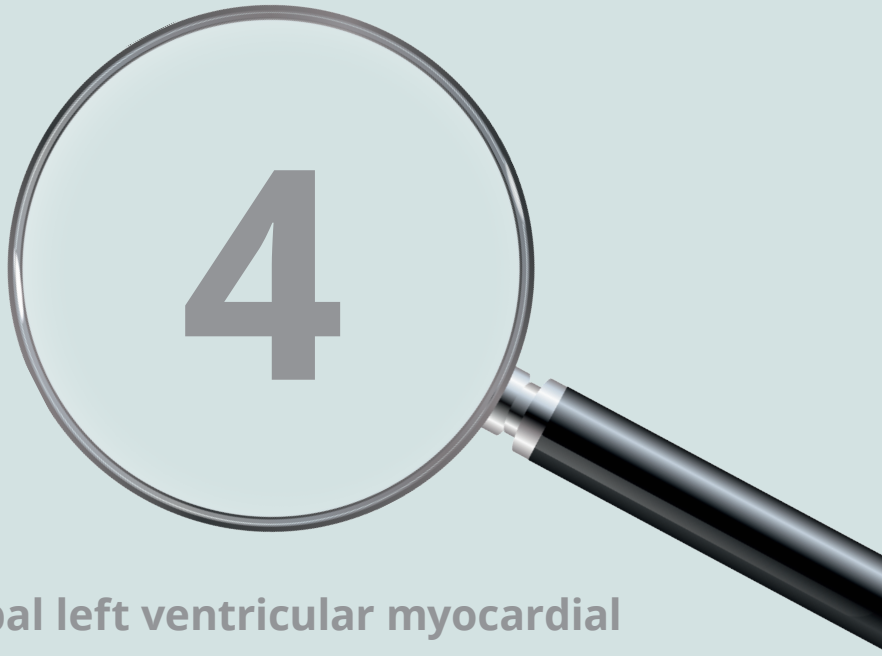

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Global left ventricular myocardial work efficiency in healthy individuals and patients with cardiovascular disease

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ABSTRACT

Global left ventricular (LV) myocardial work efficiency, the ratio of constructive to wasted work in all left ventricular segments, reflects the efficiency by which mechanical energy is expended during the cardiac cycle. Global LV myocardial work efficiency can be derived from LV pressure-strain loop analysis incorporating both non-invasively estimated blood pressure recordings and echocardiographic strain data. The aim of this study was to characterize global LV myocardial work efficiency in healthy individuals and patients with cardiovascular risk factors or overt cardiac disease. We retrospectively included healthy individuals without structural heart disease or cardiovascular (CV) risk factors were selected from an ongoing database of normal individuals, and matched for age and sex with: i) individuals without structural heart disease but with CV risk factors, ii) post-infarct patients without heart failure and iv) heart failure patients with reduced ejection fraction (HFrEF). Global LV myocardial work efficiency was estimated with a proprietary algorithm from speckle tracking strain analyses, as well as non-invasive blood pressure measurements. In total, 120 individuals (44% male, 53±13 years) were included (n=30 per group). In healthy individuals without structural heart disease or CV risk factors, global LV myocardial work efficiency was 96.0% (IQR 95.0-96.3). Myocardial efficiency of the LV did not differ significantly between individuals without structural heart disease and those with CV risk factors (96.0% vs. 96.0%; p=0.589). Global LV myocardial work efficiency however, was significantly decreased in post-infarct patients (96.0% vs. 93.0%, p<0.001) and those with HFrEF (96.0% vs. 69.0%; p<0.001). In conclusion, while global LV myocardial work efficiency was similar in normal individuals and those with CV risk factors, it was decreased in post-infarct and HFrEF patients. The global LV myocardial work efficiency values presented here show distinct patterns in different cardiac pathologies.

INTRODUCTION

Non-invasive myocardial work is a relatively new parameter for assessing left ventricular (LV) systolic function, derived from LV pressure-strain loop analysis incorporating both non-invasively estimated blood pressure recordings and echocardiographic strain data.[1] Russell et al. demonstrated that non-invasive LV pressure-strain loops corresponded well with invasively-measured LV pressure-strain loops,[1,2] and these results have been confirmed in subsequent studies.[3] Non-invasive myocardial work has been shown to be a strong predictor of response to cardiac resynchronization therapy (CRT)[4,5] and superior to LV ejection fraction (LVEF) and LV global longitudinal strain (LV GLS) in identifying patients with acute coronary syndromes.[6] Despite showing great clinical potential, there are few data on normal values of global LV myocardial work efficiency in different cardiac pathologies.
The aim of this study is to characterize global LV myocardial work efficiency in four groups: i) normal individuals without structural heart disease or cardiovascular (CV) risk factors, ii) individuals without structural heart disease but with CV risk factors, iii) post-infarct patients without heart failure and iv) heart failure patients with reduced ejection fraction (HFrEF).

METHODS

Study population

We retrospectively included healthy individuals without structural heart disease or CV risk factors selected from a database of normal individuals,[7] and matched for age and sex with: i) individuals without structural heart disease but with CV risk factors, ii) post-infarct patients without heart failure (from an ongoing registry of patients with ST-segment elevation myocardial infarction (STEMI), treated with primary percutaneous coronary intervention)[8] and iii) HFrEF (from an ongoing registry of cardiac resynchronization therapy recipients).[9] Heart failure etiology was considered ischemic in the presence of significant coronary artery disease and/or a history of prior myocardial infarction or revascularization. Demographics and clinical data were collected from the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands), as well as electronic medical records (HiX; ChipSoft, Amsterdam, The Netherlands). For retrospective analysis of clinically acquired data, the institutional review board

waived the need of written patient informed consent. All data used for this study were acquired for clinical purposes and handled anonymously.

Echocardiographic data acquisition

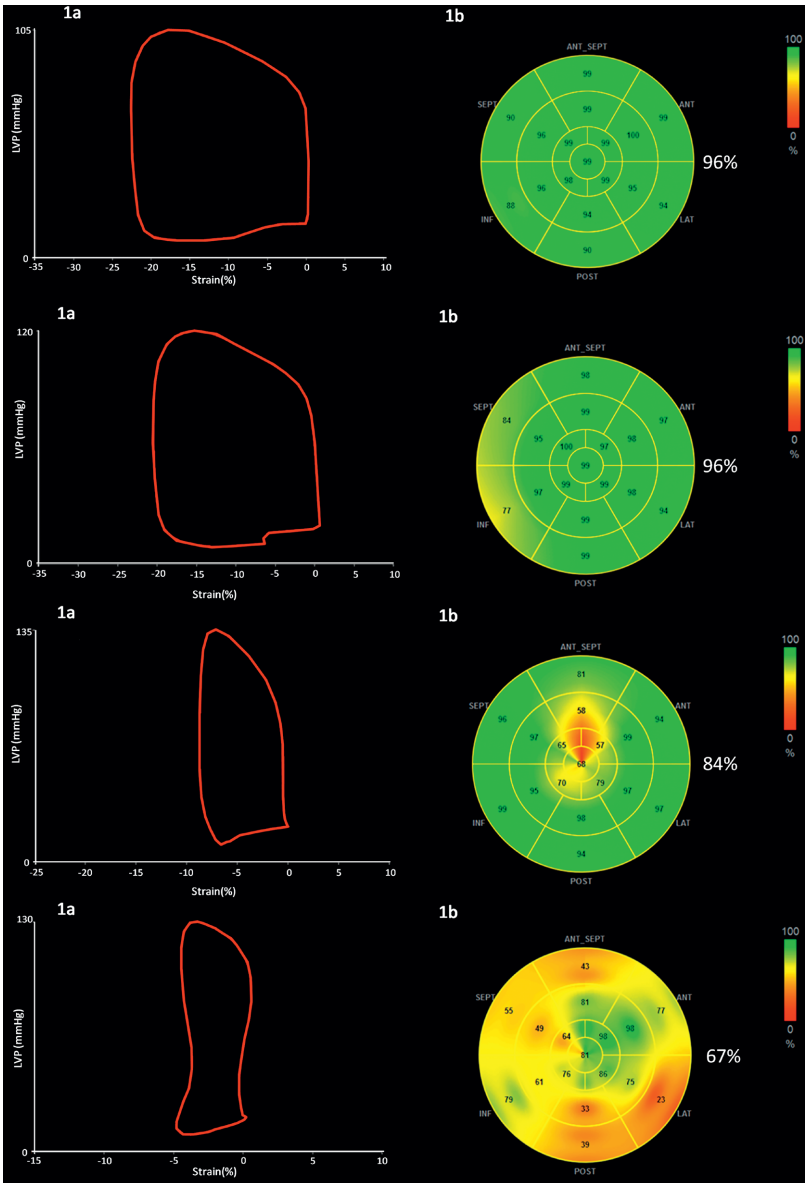
Transthoracic echocardiographic images were recorded using a Vivid 7 or E9 ultrasound system (General Electric Vingmed Ultrasound, Milwaukee, USA) with patients at rest, in the left lateral decubitus position. ECG-triggered echocardiographic data were acquired with 3.5 MHz or M5S transducers and digitally stored in cine-loop format for offline analysis with EchoPac (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, USA).[10] LV end-diastolic and end-systolic volumes were measured in the apical 2- and 4-chamber views, and the LVEF calculated using the biplane Simpson's method.[10]

Quantification of global LV myocardial work efficiency

Global LV myocardial work efficiency was quantified using a novel, non-invasive method which employs echocardiographic strain data as well as brachial cuff blood pressure recordings.[1] This method has been validated in different patient subgroups.[1,2,4,6,11,12] Strain was measured using 2-dimensional speckle tracking echocardiography by manually tracing the LV endocardial border in the apical long-axis, 2- and 4-chamber views. A non-invasively estimated LV pressure-strain loop curve was then constructed using the strain and blood pressure data, and a normalized reference curve adjusted according to the duration of the different cardiac cycle phases (defined by the timing of aortic and mitral valve events).[1] LV myocardial work was subsequently computed segmentally by differentiation of the strain values over time, giving the segmental shortening rate, which was then multiplied by the instantaneous LV pressure. Instantaneous power (the result) was integrated over time to yield the segmental (as well as the global) LV myocardial work values as a function of time.

Constructive work was defined as work performed during segmental shortening in systole or during lengthening in isovolumic relaxation. Wasted work was then defined as work performed during segmental lengthening in systole or work performed during segmental shortening against a closed aortic valve in isovolumic relaxation. Global LV myocardial work efficiency was calculated as the sum of constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, expressed as a percentage (Figure 1).

Figure 1. Global LV myocardial work efficiency in a healthy individual (panel A), a patient with cardiovascular risk factors (panel B), a post-infarct patient (panel C) and a heart failure patient with reduced ejection fraction (panel D).



On the left, the pressure-strain loop (1a) is depicted and the global LV myocardial work efficiency presented as a parametric map (1b) is shown on the right. Note the progressive reduction in global LV myocardial work as the LV damage increases: from 96% in the healthy individual (panel A) to 67% in the patient with heart failure with reduced ejection fraction (panel D).
LVP: left ventricular pressure.

Statistical analysis

Categorical data are presented as frequencies and percentages. Continuous variables are reported as mean±standard deviation if normally distributed, and as median and interquartile range (IQR) if non-normally distributed. Categorical data were compared with the $\chi 2$ test, followed by post-hoc analysis of subgroups. Continuous data were compared using the Student's *t* test if normally distributed or the Mann-Whitney U test or the Kruskal-Wallis test if non-normally distributed. Pearson correlation was used to investigate the relationship between LVEF and global LV myocardial work efficiency. Twenty random individuals were selected for inter- and intra-observer agreements and analyzed using Bland-Altman plots and the intraclass correlation coefficient (ICC). Intra-observer measurements were performed after a 2-week interval. The second observer was blinded to the measurements of the first observer, as well as to all previous measurements, when performing the inter-observer assessments. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 23.0 (SPSS, Armonk, NY, USA).

RESULTS

Clinical characteristics

A total of 120 individuals (44% male, age 53±13 years) were included. Clinical characteristics are shown in Table 1. The left anterior descending (LAD) was the culprit vessel in 20 (67%) post-infarct patients. The etiology of heart failure was non-ischemic in 17 (57%) patients.

Table 1. Clinical characteristics

	Normal (n=30)	With CV risk factors (n=30)	Post-infarct (n=30)	HFrEF (n=30)
Age (years)	56 (41-64)	54 (35-69)	55 (48-63)	54 (51-57)
Male, n (%)	13 (43)	13 (43)	13 (43)	14 (47)
BSA (m^2)	1.9 (1.8-2.0)	1.8 (1.7-2.1)	2.0 (1.8-2.1)	1.9 (1.7-2.1)
BMI (kg/m^2)	24.6 (21.9-26.9)	24.2 (21.5-26.7)	26.7 (24.7-29.5)*†	26.1 (22.7-28.8)
Systolic blood pressure (mmHg)	128 (110-139)	127 (110-141)	120 (110-135)	120 (107-129)
Diastolic blood pressure (mmHg)	75 (70-85)	78 (70-90)	73 (69-80)	72 (69-79)
Mean arterial pressure (mmHg)	93 (86-101)	95 (85-107)	90 (81-96)	88 (82-93)
CV risk factors				
Hypertension, n (%)	0 (0)	7 (23.3)*	18 (60.0)*†	12 (40.0)*
Hypercholesterolemia, n (%)	0 (0)	4 (13.3)	6 (20.0)	9 (30.0)*
Diabetes, n (%)	0 (0)	4 (13.3)	5 (16.7)	2 (6.7)
Current smoking, n (%)	0 (0)	7 (23.3)*	15 (50.0)*	14 (46.7)*
Family history of CVD, n (%)	0 (0)	20 (66.7)*#	9 (30.0)*	12 (40.0)*
Medication, n (%)				
Aspirin	1 (3.3)	2 (6.7)	28 (93.3)*†‡	10 (33.3)
Thienopyridine	0 (0)	0 (0)	26 (86.7)*†‡	1 (3.3)
β-blocker	0 (0)	2 (6.7)	28 (93.3)*†	26 (86.7)*†
Statin	0 (0)	3 (10.0)	30 (100.0)*†‡	17 (56.7)*†
Diuretic	0 (0)	3 (10.0)	9(30.0)*	25 (83.3)*†#
ACE-I/ARB	0 (0)	5 (16.7)	29 (96.7)*†	28 (93.3)*†

ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, BMI: body mass index, BSA: body surface area, CV: cardiovascular, CVD: cardiovascular disease, HFrEF: heart failure with reduced ejection fraction. Data are presented as mean ± standard deviation if normally distributed or median (25^{th}-75^{th} percentile) if not normally distributed. * $p<0.05$ compared to normal individuals, † $p<0.05$ compared to individuals with CV risk, # $p<0.05$ compared to post-infarct patients, ‡ $p<0.05$ compared to HFrEF patients

Conventional echocardiographic parameters

Conventional echocardiographic findings are summarized in Table 2. Patients with HFrEF had larger cavity sizes and worse LVEF, compared to all other groups. In addition, the post-infarct patients had worse LVEF compared to the healthy individuals without CV risk factors and those with CV risk factors.

Table 2. Echocardiographic characteristics

	Normal (n=30)	With CV risk factors (n=30)	Post-infarct (n=30)	HFrEF (n=30)
Heart rate (bpm)	69 (61-76)	68 (63-75)	63 (57-70)	73 (62-85) ǂ
Left ventricular mass index (g/m²)	92 (72-112)	90 (74-99)	102 (87-122)	158 (139-191)*†ǂ
Interventricular septal thickness (mm)	10 (8-11)	10 (9-12)	12 (10-12)	10 (8-11)
Left ventricular posterior wall thickness (mm)	10 (9-12)	10 (8-11)	10 (9-12)	11 (10-12)
Left ventricular end-diastolic volume (ml)	109 (96-133)	112 (88-124)	112 (85-150)	234 (160-304)*†ǂ
Left ventricular end-systolic volume (ml)	44 (37-54)	42 (33-55)	56 (43-80)†	186 (120-250)*†ǂ
Left ventricular ejection fraction (%)	58 (56-63)	61 (58-65)	50 (45-53)*†	24 (17-30)*†ǂ
Left ventricular global longitudinal strain (%)	-19.3 (-20.5 to -18.3)	-18.8 (-20.4 to -17.0)	-14.4 (-18.0 to -11.8)*†	-6.2 (-7.2 to -5.0)*†ǂ

Data are presented as mean ± standard deviation if normally distributed or median (25^{th}-75^{th} percentile) if not normally distributed.
bpm = beats per minute, CV = cardiovascular, HFrEF = heart failure with reduced ejection fraction.
* p<0.05 compared to normal individuals
† p<0.05 compared to individuals with CV risk
ǂ p<0.05 compared to post-infarct patients
‡ p<0.05 compared to HFrEF patients

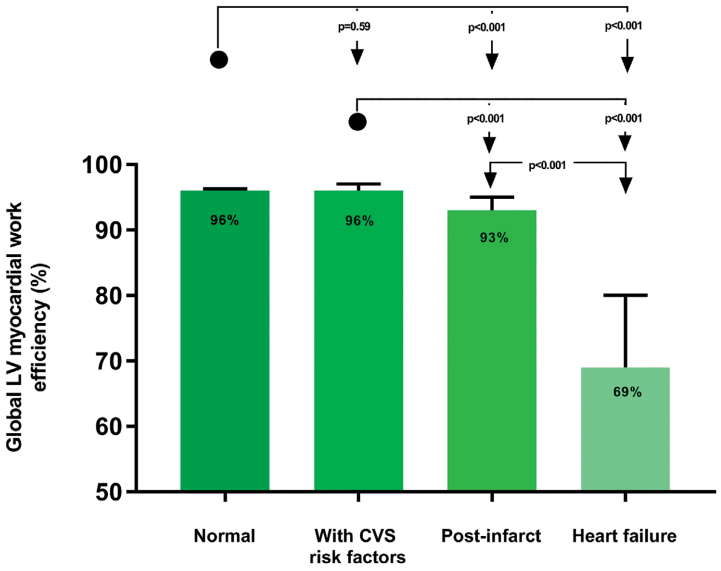
Two-dimensional speckle tracking data: global LV longitudinal strain and myocardial work efficiency

HFrEF patients showed the most impaired LV GLS values as compared to post-STEMI patients, patients with CV risk factors and healthy individuals (Table 2). In healthy individuals without structural heart disease or CV risk factors, the median

global LV myocardial work efficiency was 96.0% (IQR 95.0-96.3) (Figure 1), which did not differ significantly from individuals with CV risk factors 96.0% (IQR 95.0-97.0) (p=0.59, Figures 1 and 2). Compared to healthy individuals, median global LV myocardial work efficiency was significantly worse in post-STEMI patients (93.0%, IQR 88.5-95.0, p<0.001, Figures 1 and 2), and HFrEF patients (69.0%, IQR 63.8-80.0, p<0.001, Figures 1 and 2). The median global LV myocardial work efficiency was also significantly more impaired in post-STEMI patients and HFrEF patients as compared to individuals with CV risk factors (p<0.001, Figure 2). In comparison to post-STEMI patients, median global LV myocardial work efficiency was significantly lower in HFrEF patients (p<0.001, Figure 2). The global LV myocardial work efficiency did not differ between men and women (94.0% vs. 95.0%; p=0.489) in the overall population. There was a significant correlation between global LV myocardial work efficiency and LVEF in the total population (r=0.80, p<0.001). However, this correlation was non-significant when analyzing patients with CV risk factors (r=-0.03, p=0.876), post-STEMI patients (r=-0.226, p=0.231) and HFrEF patients (r=0.324, p=0.081) separately (Figure 3).

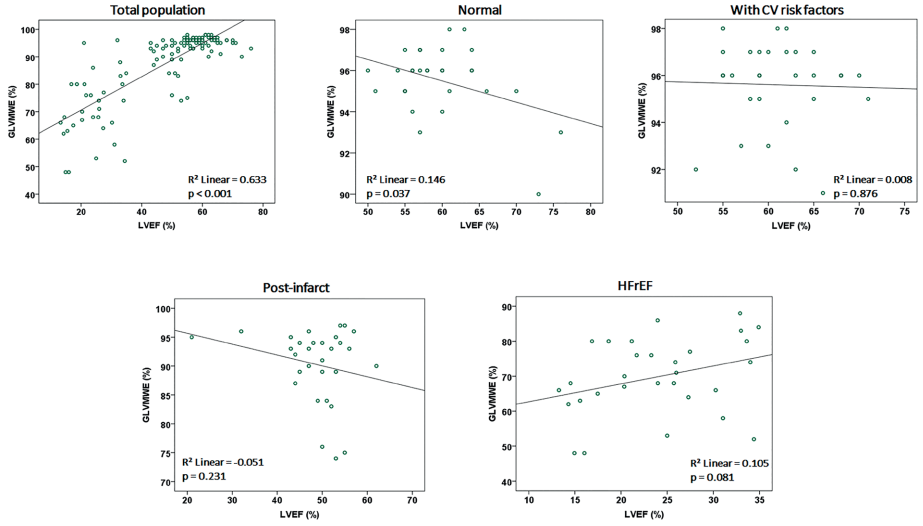
The ICC for intra-observer variability was 0.645 (p<0.001) and that for inter-observer variability 0.737 (p<0.001, Figure 4). Bland-Altman analysis for assessing intra-observer variability showed a bias of 0.55 with 95% limits of agreement ranging from -1.407 to 2.507 and for inter-observer variability a bias of 0.84 with 95% limits of agreement ranging from -1.950 to 3.634 (Figure 4).

Figure 2. Median global left ventricular myocardial work efficiency, compared across the different groups.



Columns represent median values, and T-bars the upper quartile. CV: cardiovascular, LV: left ventricular

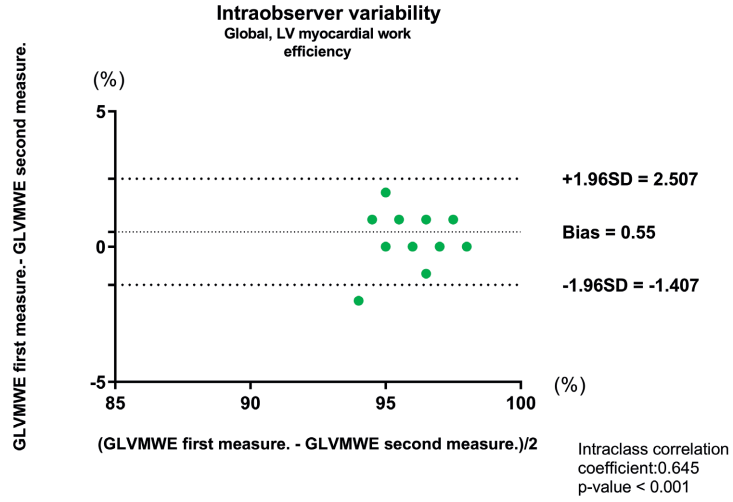
Figure 3. Relation between global left ventricular myocardial work efficiency and left ventricular ejection fraction.



GLVMWE: global left ventricular myocardial work efficiency, LVEF: left ventricular ejection fraction, CV: cardiovascular, HFrEF: heart failure with reduced ejection fraction.

Figure 4. Bland-Altman plots depicting intra-observer (A) and inter-observer (B) variability of global left ventricular myocardial work efficiency.

A



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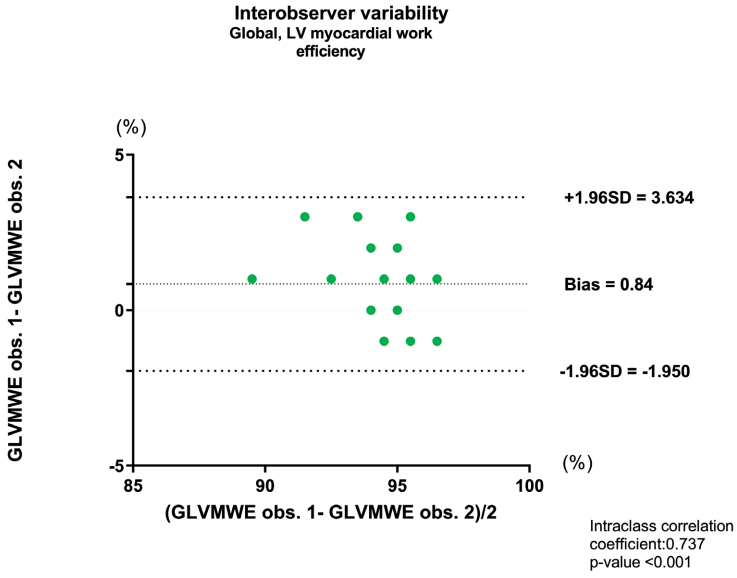

GLVMWE: global LV myocardial work efficiency, measure.: measurement, obs: observe

DISCUSSION

The values of global LV myocardial work efficiency were similar for normal individuals without structural heart disease or CV risk factors, and for individuals with CV risk factors. In contrast, global LV myocardial work efficiency was decreased in post-STEMI and HFrEF patients, compared to normal individuals and those with CV risk factors.

Non-invasive estimation of myocardial work efficiency

Myocardial work, estimated using non-invasive pressure-strain loops, is a novel approach to assess LV systolic function.[1] It overcomes the load-dependency of LVEF and global LV strain by integrating afterload into an LV function parameter. In a LV with preserved systolic function, increased afterload may lead to decreased global LV strain, which does not necessarily signify impaired contraction. In a preclinical model, aortic constriction decreased global LV strain, whereas no change was seen in the area of the non-invasive pressure-strain loop.[6] By integrating afterload, Russell et al. introduced a technique whereby non-invasively estimated blood pressure recordings are integrated with echocardiographic, speckle tracking strain values to construct pressure-strain loops of the LV.[1] The principle was tested in a canine model under a wide range of hemodynamic conditions and validated in 18 patients with chronic heart failure. An excellent correlation was found between non-invasive LV pressure-strain loop areas and invasively-measured equivalents. Similar results were shown by Hubert et al., in 9 patients with CRT, under 5 different conditions: CRT-off, right ventricular-pacing only, LV-pacing only, standard biventricular pacing and multipoint, biventricular pacing.[3] Russell et al. also demonstrated a strong correlation between myocardial glucose utilization (measured with ^{18}F-fluorodeoxyglucose positron emission tomography) and regional LV myocardial work (using non-invasive pressure-strain loops).[1] Combining cine cardiovascular magnetic resonance imaging (CMR) volumetry with quantitative phosphorus (^{31}P) magnetic resonance spectroscopy (MRS), Gabr et al. investigated the relation between non-invasive LV mechanical work and creatine kinase (CK) flux in 14 healthy subjects and 27 patients with heart failure.[13] LV mechanical efficiency was highly correlated with CK flux, supporting non-invasive LV work as valid measure of myocardial energetics. Although there is a strong correlation between LVEF and global LV myocardial work efficiency in the total population in our study, the absence of a significant correlation in the patients with CV risk

factors, post-STEMI patients and HFrEF patients, provides further support to the unique characterization of systolic function by global LV myocardial work efficiency.

Since LV work can be reliably estimated by means of a non-invasive methodology, global LV myocardial work efficiency can be derived from LV wasted and constructive work with the following formula: (constructive work / (constructive work + wasted work)) x 100%. Constructive work is defined as work performed during segmental shortening in systole or during lengthening in isovolumic relaxation, while wasted work is defined as work performed during segmental lengthening in systole or work performed during segmental shortening against a closed aortic valve in isovolumic relaxation. Unlike global LV work index, which measures the total amount of work performed (area within the LV pressure-strain loop), global LV myocardial work efficiency represents the ratio between effectively performed work and wasted work of the LV.

This technique can be applied to examine the effects of cardiac pathologies, e.g. myocardial infarction and heart failure, on myocardial energetics.

Global LV myocardial work efficiency: normal values

If all LV segments contract and relax synchronously during the cardiac cycle, with normal deformation and against an optimized afterload, global LV myocardial work efficiency should theoretically be close to 100%. Such a high level of efficiency is almost never achieved in a biological system, and we found a mean global LV myocardial work efficiency of 96.0% (IQR 95.0-96.3%) in healthy individuals. One of the reasons can be mild LV dyssynchrony as documented in healthy individuals.[14,15] Furthermore, limitations of the technique itself may cause some variation in the normal values: blood pressure values are measured sphygmomanometrically, and modelled onto reference curve, i.e. the value of global LV myocardial work remains an estimate, and not a direct measurement of cardiac efficiency.[3] Recently, Manganaro and colleagues presented normal values of global LV myocardial work efficiency in a population of 226 healthy subjects.[16] Our results are in close agreement with those of Manganaro et al., i.e. a median global LV myocardial work efficiency of 96% (IQR 94-97) in healthy individuals.

Global LV myocardial work efficiency: influence of CV risk factors

In a recent study by Chan et al. there was no difference in global LV myocardial work efficiency between patients with hypertension and normal controls.[17] Similarly, CV risk factors (including hypertension) did not lead to a decrease in LV myocardial efficiency in our cohort. The presence of CV risk factors alone, in the absence of structural or functional cardiac changes, does not seem to impact global LV myocardial work efficiency negatively. In the study of Chan and co-workers, patients with hypertension had proportionally higher values of global constructive work, which was balanced by increased amount of global wasted work.[17] The resulting global LV myocardial work efficiency was therefore similar to controls, which is in agreement with our results.

Global LV myocardial work efficiency in post-STEMI and HFrEF patients

Decreased segmental, LV myocardial work was superior to LV global longitudinal strain and LVEF in identifying coronary artery occlusion in patients with non-STEMI, in a study of 126 patients.[6] This is consistent with our results: we found lower global LV myocardial work efficiency in patients who underwent primary percutaneous coronary intervention for STEMI (generally held to indicate complete coronary artery occlusion), compared to those with CV risk factors and normal controls. Acute coronary syndromes have the ability to induce LV dyssynchrony,[18] regional decreases in longitudinal LV strain[19,20] and dynamic changes in LV afterload,[21] which can all lead to a decrease in LV mechanical efficiency. The prognostic role of measuring global LV myocardial work efficiency in patients with acute coronary syndromes, remains to be explored.

In the current study, the lowest global LV myocardial work efficiency values were seen in patients with HFrEF (with indications for cardiac resynchronization therapy). In a population of 97 HFrEF patients, with both ischemic and non-ischemic etiologies, the mean global LV myocardial work efficiency pre-CRT was 76%, which is comparable to the values we observed in the current analysis.[5] Likewise, in a pilot study of 21 HFrEF patients receiving CRT, the mean global LV myocardial work efficiency was 61%.[4] The markedly decreased global LV myocardial work efficiency in HFrEF patients may originate in the substantial degree of LV dyssynchrony experienced by these patients,[22] as well as reduced global or regional LV strain values, reflecting impaired systolic function.[23]

Several preliminary studies have shown the capacity of non-invasive derivation of myocardial work efficiency to identify CRT response.[4,5] Global LV myocardial work efficiency could therefore be a useful tool in assessing CRT candidates, although its incremental value to current CRT selection criteria remains to be proven.

Study Limitations

This study is subject to the inherent limitations of a single-center, retrospective analysis. CV risk factors were adjudicated on the basis of medical records, including patient history. The inclusion of only revascularized STEMI patients and HFrEF patients with indications for cardiac resynchronization therapy, might limit the generalizability of our results to these specific groups. Since global LV myocardial work efficiency is predicated on the measurement of speckle tracking strain echocardiography, it is not a vendor-independent measure. Currently, commercial software for the measurement of global LV myocardial work efficiency is only provided by a single vendor. For the assessment of non-invasive myocardial work, systemic arterial pressure is used as a substitute for LV pressure. This technique can therefore not be applied when systemic arterial pressure and LV pressure are discordant, e.g. in patients with LV outflow obstruction and significant aortic stenosis.[1]

CONCLUSION

Speckle tracking strain echocardiography and sphygmomanometric blood pressure measurements can be integrated to estimate global LV myocardial work efficiency non-invasively. Individuals with CV risk factors, but without structural heart disease, had global LV myocardial work efficiencies similar to normal controls. Lower myocardial efficiency was found in patients with previously revascularized STEMI who did not develop heart failure, while HFrEF patients had the lowest global LV myocardial work efficiency. The values presented here clearly demonstrate distinct profiles of myocardial efficiency in different cardiac pathologies, which may inform further studies. The echocardiographic evaluation of LV mechanical efficiency is a promising tool for both diagnosis and prognostication of various cardiac diseases.

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