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Value of Left Ventricular Pressure–Strain Loops in the Quantitative Assessment of Myocardial Function in Patients with Nonobstructive Hypertrophic Cardiomyopathy

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Abstract

Purposes: The purposes of this study were to use noninvasive Left ventricular pressure-strain loops (LV-PSLs) to compare the various myocardial work indices in patients with noninvasive hypertrophic cardiomyopathy (NHCM) and to evaluate the clinical application of myocardial work to the evaluation of NHCM patients.

Method: 80 NHCM patients and 45 healthy subjects were enrolled. All the selectors underwent Echocardiography examination. Dynamic images of standard apical three-chamber, four-chamber, and two-chamber view were collected, the myocardial work indices of left ventricle were measured by LV-PSLs. The difference in myocardial work indices between two groups and various myocardial work indices in different types of hypertrophic cardiomyopathy were compared.

Results: There were no significant difference in the general clinical data between the NHCM group and control; myocardial work indices of HCM were lower compared with control group except global work waste (GWW); The myocardial work between all three types of NHCMs was also different, particularly in global construction work (GCW); the intra- and inter observer consistency of myocardial work indices were good.

Conclusion: Myocardial work assessed by the LV-PSLs could reflect myocardial work in NHCM patients at the early stage and quantitatively assess regional and global myocardial function, providing an accurate and convenient imaging method for early detection of the subclinical status of NHCM patients.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common cardiomyopathy and is related to mutations in more than 1,400 genes that influence cardiac sarcomeres[1, 2]. It has obvious heritability and familial aggregation and often causes frequent adverse events, dominated by a familial history of sudden cardiac death, syncope, severe ventricular hypertrophy, and left ventricular outflow tract obstruction[3]. Autopsy shows myocardial wall thickening, cardiomyocyte hypertrophy, interstitial fibrosis, cardiomyocytes with disordered arrangement, and thickening of intramyocardial small arteries in HCM patients[4–6]. When these changes are in the metastable state, myocardial systolic and diastolic dysfunction cannot be revealed by conventional echocardiography (ECG)[3]. The annual incidence of sudden cardiac death in HCM patients is 0.8%, and it is the most common cause of sudden death in adolescents as well as an important cause of heart failure, atrial fibrillation, and cerebral infarction. Therefore, early assessment of myocardial function in these patients is particularly important[7].

Myocardial work (MW) is a means to quantify myocardial function through left ventricular pressure–strain loops (LV-PSLs), an extension of the concept of strain that can be used to comprehensively evaluate the strain and load[8, 9]. MW used to be obtained through invasive pressure measurement, which limited the feasibility of MW clinical application. Russel et al. demonstrated that the LV-PSL can evaluate left ventricular function noninvasively, and the corresponding area of the PSL is directly related to the myocardial metabolic activity assessed by F^{18}-fluorodeoxyglucose positron-emission tomography (FDG-PET)[10]. Noninvasive LV-PSLs have been used in the diagnosis of myocardial ischemia and in the evaluation of left ventricular myocardial function after receiving cardiac resynchronization therapy, and they have shown high sensitivity and specificity[11–14].

This study aimed to evaluate noninvasive LV-PSLs (1) to evaluate MW in patients with nonobstructive HCM (NHCM); (2) to compare the various MW indices in patients with different types of HCM; and (3) to evaluate the clinical application of MW to the assessment of NHCM patients.

Materials And Methods

Patient population

A total of 80 patients with NHCM treated at the First Affiliated Hospital of Nanchang University between October 2019 and October 2020 were selected, including 62 male patients (62/80, 78%) and 18 female patients, aged 20–68 years (mean 49 ± 18 years). The inclusion criteria were (1) NHCM diagnosed according to the latest diagnostic guideline of hypertrophic cardiomyopathy [3], with interventricular septal thickness (IVST) ≥ 15 mm, left ventricular outflow tract pressure gradient (LVOT PG) < 30 mmHg at rest or after physiological exercise; (2) LV ejection fraction (LVEF) > 50%; (3) a diameter of stenosis in all three coronary arteries of < 50% on coronary angiography; and (4) sinus rhythm. The exclusion criteria were (1) HCM caused by hypertension, diabetes mellitus, or renal failure; (2) New York Heart Association (NYHA) class III or above; (3) severe pericardial and heart valve disease.

NHCMs were divided into HCM with ventricular septal hypertrophy (ventricular HCM) which is asymmetric atrophy of the interventricular septum, which apical HCM that is defined as hypertrophy confined to the apical segment, and HCM with concentric hypertrophy (concentric HCM), which is characterized by symmetric hypertrophy of the left ventricular wall segments. Forty-five healthy people, 28 males (28/45,63%) and 12 females, aged 20–65 years (mean 48 ± 12 years), matched for age and sex with the patients in the NHCM group, were included in the study as the control group. These healthy people had no history of cardiac macrovascular disease and normal results on electrocardiography and conventional echocardiography. All subjects in this study signed informed consent forms. The study was approved by the ethics committee of The First Affiliated Hospital of Nan Chang University.

Equipment and scanning method

Clinical data including age, sex, height, weight, body mass index (BMI), and brachial arterial pressure of the subjects were collected before Echocardiography examination.

The GE Vivid E95 ultrasound system with the M5Sc-D probe was used, with a frequency of 1.5-4.6MHz. Echo PAC 203 software was used for postprocessing offline on images. All subjects were placed in the left lateral decubitus position with a limb lead electrocardiogram (ECG) attached. After their respiration and heart rate had stabilized, dynamic images of the left ventricular apical three-chamber view, four-chamber view, and two-chamber view in five cardiac cycles were stored continuously. The left ventricular diameter diastole (LVEDd), left ventricular diameter systole (LVEDs), and left atrial anteroposterior diameter (LAD) were sequentially measured in the two-dimensional plane. The LVEF was measured using the Simpson method. The forward flow velocity of the aortic valve (AV) was measured on the apical five-chamber view, and early diastolic mitral inflow velocity (E peak), and early diastolic mitral annular velocity (e') were measured in the apical four-chamber view. MVT and the different morphologies of the left ventricular wall were determined from short-axis views of basal and apical segments of the LV. All images were saved in files for analysis. All dynamic images and 2D images were stored by the same experienced radiologists.

Image analysis

The original image was imported into the Echo PAC workstation for offline analysis. First, the spectral Doppler images of the aortic valve and the mitral valve were selected successively, and the event timing was marked. Then, the automated functional imaging analysis mode was entered, and the dynamic images of the LV apical from the three-chamber, four-chamber, and two-chamber views were sequentially selected. The software automatically recorded the endocardial and left ventricular wall contours, and the segments that were not satisfactory for tracing could be manually adjusted. We clicked on “Process” to complete the image analysis of the corresponding section, and the system automatically derived the strain parameters [global longitudinal strain (GLS), peak strain time dispersion (PSD)] of the whole LV and each segment. We chose “Myocardial Work” and then input the brachial arterial pressure of the patient and clicked “Advanced” to obtain both the pressure–strain loop and the global myocardial work index along with the bull's-eye plot pattern of each segment. MW indices such as the global work index (GWI), global work waste (GWW), global constructive work (GCW), and global work efficiency (GWE) of each segment were observed on the bull's-eye plot pattern.

Consistency test

A total of 20 subjects were randomly selected for analysis. MW analysis was performed by two radiologists with similar experience. All analyses were performed without knowledge of the patient’s other test results or the results of the other party's analysis, to test inter-observer repeatability. Image analysis was performed again after a one-week interval by the same observer to test intra-observer repeatability.

Statistical methods

SPSS 23.0 software was used for statistical analysis. The continuous variables are expressed as mean ± standard deviation ($\bar{x} \pm S$) when they followed a normal distribution and as median (IQR) when they did not. Categorical variables are expressed as absolute number and percentage. Comparison between the NHCM group and the control group in terms of general data and conventional echocardiographic parameters was performed using Student’s t test, the Mann-Whitney U test, or the χ^2 test. The comparison of MW parameters between the NHCM group and the control group was performed using one-way analysis of variance. The pairwise comparisons of different NHCM types were performed using the least significant difference t test. A total of 20 subjects in the NHCM group and the control group were randomly selected for the consistency test. The inter- and intra-observer consistency tests for left ventricular GWI, GCW, GWW, and GWE were performed by Bland-Altman analysis. $P < 0.05$ was considered statistically significant.

Results

Comparison of general clinical data

The general clinical data and ECG characteristics of the NHCM group and the control group are shown in Table 1. The results showed no significant difference in age, sex, height, weight, BMI, brachial artery systolic pressure, and diastolic pressure between the NHCM group and the control group ($P > 0.05$). All subjects had sinus rhythm.

Comparison of conventional two-dimensional echocardiography parameters

When we compared the conventional two-dimensional echocardiographic parameters of the NHCM group and the healthy control group, LVEDd, LVEDs, LVEF, and AV had no significant difference ($P>0.05$). The LAD was significantly higher ($P<0.05$) and E/e' non-significantly higher in the NHCM group. Although the diastolic function of the NHCM group was impaired, this group no significant difference compared with the control group. Moreover, their LVOT PG was in the normal range. The majority of NHCM patients presented with ventricular septal HCM (37/80,46%), followed by apical HCM (27/80,33.7%) and, in few patients, concentric HCM (16/80,20%). The maximum wall thickness (MWT) of the NHCM group was significantly different from that of the control group (19.53±3.40 vs 9.68±1.59, $P<0.05$). as shown in Table 1.

Comparison of indices of myocardial strain and Myocardial Work

The GLS of the NHCM group was significantly lower than that of the control group (-13.58 ±3.26% vs -19.23±2.58%, $P<0.001$), and the PSD was longer than that of the control group (73.34±21.65ms vs 39.65±14.98ms, $P<0.001$). The GWI and GCW of the NHCM group were lower than those of the control group (1206.88±304.9mmHg% vs 1866.89±192.89mmHg%; 1304.85±325.5mmHg% vs 2208.74±207.94mmHg%, $P<0.001$). GWE was decreased (90.39% [IQR: 88.75-93.21%] vs 96.02% [IQR: 94.45-96.65%]) and GWW (351 ± 179 mmHg% vs 77.84 ± 19.18 mmHg%, $P = 0.012$) was increased in the NHCM group (Fig.1).

Comparison of the MW indices of different types of NHCMs

As presented in table 2, The GWI, GCW, GWE, and GWW of patients with the three different types of NHCM were significantly different from those of the control group ($P < 0.01$) (Fig.2). The GWI, GCW, and GWE of patients with concentric HCM (Fig.3) were significantly lower than those of apical HCM (Fig.4) patients (all $P < 0.05$). The GWI, GCW, GWE of patients with ventricular septal HCM (Fig.5) were all lower than those of the apical HCM patients, and there was a significant difference in GCW between two types of patients ($P < 0.01$). The GWI, GCW, and GWE of the patients with concentric HCM were all lower than those of patients with ventricular septal HCM, but the difference was only significant for GWW ($P < 0.01$). There was no significant difference in GWW between the three types of NHCM.

Consistency test

The results of Bland-Altman consistency analysis showed that the inter- and intra- observer consistency of GWI, GCW, GWW, and GWE were good (Fig.6, Fig.7).

Discussion

This study found that (1) the left ventricular global MW indices of NHCM patients, GLS, PSD, GCW, GWW, GWE, and GWI, were all impaired compared with those of healthy individuals; (2) there were differences in the global MW of the different types of NHCM patients, and a significant difference in GCW was observed; and (3) the MW indices derived from LV-PSLs can be used to assess myocardial function in NHCM patients.

HCM is an inherited cardiomyopathy characterized by increased myocardial mass. Most NHCM patients do not have obvious symptoms or signs at the early stage. As the disease progresses, abnormal myocardial hypertrophy and disordered myocardial fibers are observed in HCM patients, which can cause cardiomyocyte contractile dysfunction and impaired overall myocardial deformation capacity[15–17], ultimately leading to left ventricular diastolic and systolic dysfunction[18, 15–17]. LVEF reflects changes in left ventricular volume. When cardiac hypertrophy is not sufficient to cause a significant left ventricular volume change, LVEF loses its significance in the evaluation of the changes in left ventricular volume. Moreover, LVEF only significantly falls when there is severe hypertrophy or complications in the myocardium. Even though the body can maintain a positive level of LVEF through a compensatory mechanism, some patients may have cardiovascular events such as sudden cardiac death, malignant arrhythmias, and heart failure[19]. Among young people with sudden cardiac death, more than half suffer from pumping dysfunction due to HCM[20]. Accurate assessment of myocardial function in NHCM patients can provide valuable clinical information that will help us determine the prognosis of patients and take precautionary treatment measures as soon as possible.

In recent years, ECG has continuously advanced in the evaluation of cardiac function. Conventional M-mode ultrasound is affected by the sampling line, so the error is very large[21]. Many studies have used speckle-tracking imaging (STI) to evaluate LV myocardial function. STI is not affected by the sampling line and is noninvasive and convenient. However, due to the impact of afterload, it cannot reflect true myocardial contractile function, and its specificity is low[18]. Suga et al.[22, 23] studied invasive left ventricular pressure–volume loops and showed that regardless of the contractile state of the left ventricle, the pressure–volume area was linearly correlated with myocardial oxygen consumption. Recently, Russell et al.[10] replaced invasive measurement of left ventricular pressure by blood pressure measurement combined with left ventricular deformation parameters to construct the noninvasive LV-PSLs, used the LV-PSLs area to represent MW, and verified the feasibility of applying noninvasive LV-PSLs to evaluate MW. MW is a new parameter that takes into account cardiac afterload, largely eliminates the impact of afterload on myocardial strain, and can more realistically reflect left ventricular myocardial function. The effectiveness of noninvasive LV-PSLs in assessing left ventricular myocardial function has been confirmed in dog models and in screens of patients with acute coronary syndrome and cardiac resynchronization therapy response[24, 13, 8, 25].

Conventional echocardiography and two-dimensional STI of NHCM patients

LVEDd, LVEDs, and LVEF are commonly used to measure left ventricular global systolic function. GLS reflects myocardial contractile function by quantifying the degree of myocardial deformation. In this study, there was no significant difference in LVEF between the NHCM group and the control group, but the left ventricular GLS in the NHCM group was significantly lower than that in the control group, indicating that myocardial compliance had been reduced in the presence of no change in the LVEF of NHCM patients. On the one hand, during normal left ventricular wall contraction, the degree of myocardial thickening gradually decreased from the endocardium to the epicardium, 58% of which was endocardial fibrous thickening[26]. Subendocardial myocardium is composed of longitudinal myocardial fibers. On the other hand, the coronary flow reserve of HCM patients is insufficient, and the endo-myocardium is more sensitive to hypoxia. Therefore, when there is no change in LVEF, GLS shows a significant decrease[27–29]. The PSD represents synchronous myocardial contraction, and the PSD in the NHCM group was significantly prolonged. PSD can be prolonged because the cardiomyocyte hypertrophy in HCM patients and the extensive and uneven proliferation of myocardial interstitial cells lead to reduced elasticity during systole, which affects synchronous myocardial contraction, leading to prolonged peak contraction time. These results indicate that myocardial dysfunction is already present in NHCM patients before LVEF has changed.

Noninvasive MW of NHCM

The left ventricular wall gradually becomes thinner from the basal to the apical ventricular side in healthy people. Compensatory thickening occurs when the myocardium of NHCM patients cannot meet the needs of normal myocardial function. This thickening is not an increase in the number of cardiomyocytes but an increase in the volume of cardiomyocytes. Galli et al. [30]evaluated MW in HCM patients, and the results showed that the GCW of HCM patients was significantly lower than that of the control group (1599 ± 432 vs 2248 ± 249 mmHg%, $P < 0.001$), while the GWW of the two groups was not significantly different (141 ± 125 vs 101 ± 88 mmHg%, $P = 0.18$). In our study, GCW, GWI, and GWE were significantly lower in the NHCM group than in the control group, and the GWW level in NHCM group was higher than that of the control group, in line with the results of Hiemstra et al[31].These changes may be related to myocardial pathological changes in these patients. Irregular arrangement of myocardial fibers, interstitial proliferation, and an increase in stiffness resulted in weakened myocardial elasticity and deformability, leading to global MW failure. Changes in coronary artery structure in myocardial hypertrophy sites, insufficient microcirculation perfusion, and reduced capillary distribution density result in insufficient blood supply in the corresponding segments. In addition, myocardial hypertrophy causes reduced myocardial compliance, further affecting the synchronicity of myocardial contraction, thereby causing disorders of myocardial contraction, which may also GCW, GWE, and GWI to decrease and GWW to increase. The asynchronous contraction of the myocardium and reduced myocardial deformation capacity affect the global MW, increase myocardial oxygen consumption, and even aggravate myocardial remodeling, eventually leading to impaired myocardial work.

Differences in the MW of patients with different types of NHCMs

In this study, NHCMs were divided into three types, apical HCM, ventricular septal HCM, and concentric HCM, and the MW in patients with the different types of NHCM was analyzed. The global MW of patients with either of the three types of NHCM was not as good as that of the control group, especially the patients with concentric HCM. A significant difference in GCW was observed between all three types of NHCMs. The GCW of apical HCM was significantly higher than that of ventricular septal HCM and concentric HCM. However, GWW was not significantly different between three types of NHCMs, which may be related to the fact that GWW is mainly affected by bundle branch block and is consistent with the study of Galli et al[30]. Patients with apical HCM have more limited hypertrophy, which less affects the left ventricular systolic and diastolic function. Therefore, apical HCM has a weaker effect on global MW than the other two types. Ventricular septal HCM involves more segments, and the arrangement of cardiomyocytes in the hypertrophic site is disordered. The shortening rate of sarcomeres during contraction is significantly reduced compared to that of normal myocardium, and the regional myocardial strain rate is decreased. These greatly impact left ventricular contraction synchronization and fibrosis. In contrast, the overall left ventricular wall was thickened in patients with concentric HCM, and their cardiomyocytes were more hypertrophic and irregularly arranged than those of normal people, resulting in narrowing of the microvascular lumen within the ventricular wall under pressure, impaired microvascular perfusion, more severe cardiomyocyte ischemia, and more obvious myocardial fibrosis. These changes may have caused the lower GCW and GWW and the more obvious increase in GWW in patients with concentric HCM.

Hiemstra et al[31]. studied myocardial function in each segment of HCM patients, and the results showed that constructive work (CW) of the apical segments of patients with apical HCM was significantly reduced, septal CW was reduced in patients with ventricular septal HCM, and segmental CW (except for the apical segments) was reduced in patients with concentric HCM. The fibrosis and disordered arrangement of myocardium in hypertrophic segments of HCM is more obvious than those of non-hypertrophic segments[32], and the hypertrophic segment has weakened myocardial contractility due to severe lesions, while the myocardial contractile function in non-hypertrophic segments may be enhanced due to compensatory mechanisms to maintain the overall contraction strength. Therefore, studying the changes in MW in different types of HCM may provide a reference for the treatment options for different types of NHCM patients.

Conclusion

Noninvasive LV-PSLs can be used to quantify the relationship between left ventricular reconstruction and wall stress under different loading conditions. The noninvasive MW indices quantitatively assess regional and global myocardial function, providing an accurate and convenient imaging method for early detection of the subclinical status of NHCM patients. NHCM patients had low MW, and the MW was different in patients with different types of HCM. This difference was the most obvious in GCW. Evaluation of GCW was helpful in identifying patients with different types of HCM.

Declarations

Conflict of Interest Statement-There is no potential conflict of interest to study participants.

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Tables

Table 1. Clinical and Echocardiographic parameters of patients with HCM and control subjects

	Control Subjects (n=45)	Patients with HCM (n=80)	P
Clinical characteristics			
Age(year)	48±12	49±18	0.063
Sex(male)	63% (28)	78% (62)	0.061
BMI	23.68±2.33	24.56±2.65	0.053
Systolic BP (mmHg)	112±19	134±23	0.057
Diastolic BP (mmHg)	69±11	78±15	0.063
Heart rate (beats/min)	75±16	72±13	0.076
Echocardiographic parameters			
MWT (mm)	19.53±3.40	9.68±1.59	<0.001
LVEDd (mm)	43.74±4.37	43.67±5.54	0.056
LVEDs (mm)	28.83±2.23	28.76±2.43	0.051
LAD (mm)	37.53±5.24	29.65±4.12	0.025
E/e´[M(QR)]	8.88(8.34,9.14)	6.56(5.24,8.67)	0.043
LVEF (%)	62.71±5.19	63.13±4.78	0.065
LVOT (cm/s)	99.86±14.41	98.56±12.22	0.057
AV (cm/s)	120.43±26.97	119±25.43	0.052
HCM phenotype			
Septa HCM		46% (37)	
Apical HCM		33.7% (27)	
Concentric HCM		20% (16)	

BMI=body mass index, MWT=maximum wall thickness, LAD=left atrial anteroposterior diameter, LVOT= left ventricular outflow valve, AV= the aortic valve

Table 2. Comparison of Myocardial Work parameters in HCM Patients with different phenotypes

Group	Value	GWI （mmHg%）	GCW （mmHg%）	GWW（mmHg%）	GWE（%）[M(QR)]
Control Subjects	45	1988±35	2089±214	79(45-99)	96(94-97)
Apical HCM	37	1665±398	1768±503	114(78-134)	94(89-97)
Septa HCM	27	1281±479	1313±472[a]	132(67-137)	92(86-98)
Concentric HCM	16	959±586[b]	1078±637[bc]	147(88-178)[b]	90(85-95)[b]

Apical HCM vs Septa HCM, [a] *P*＜0.01; Apical HCM vs Concentric HCM, [b] *P*＜0.05; Septa HCM vs Concentric HCM, [c] *P*＜0.01.GWI=global work index, GCW=global constructive work, GWW= global work

Figures

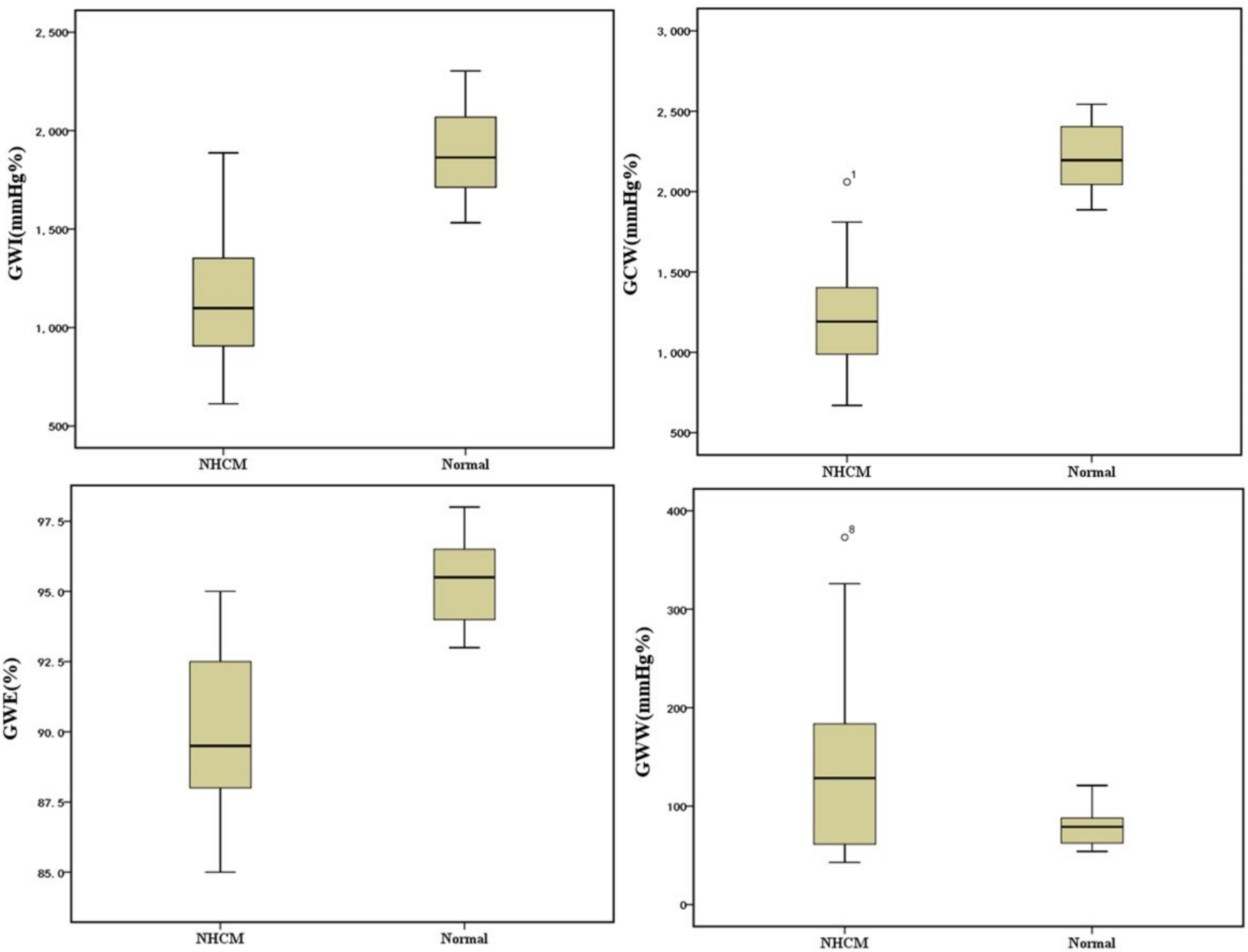
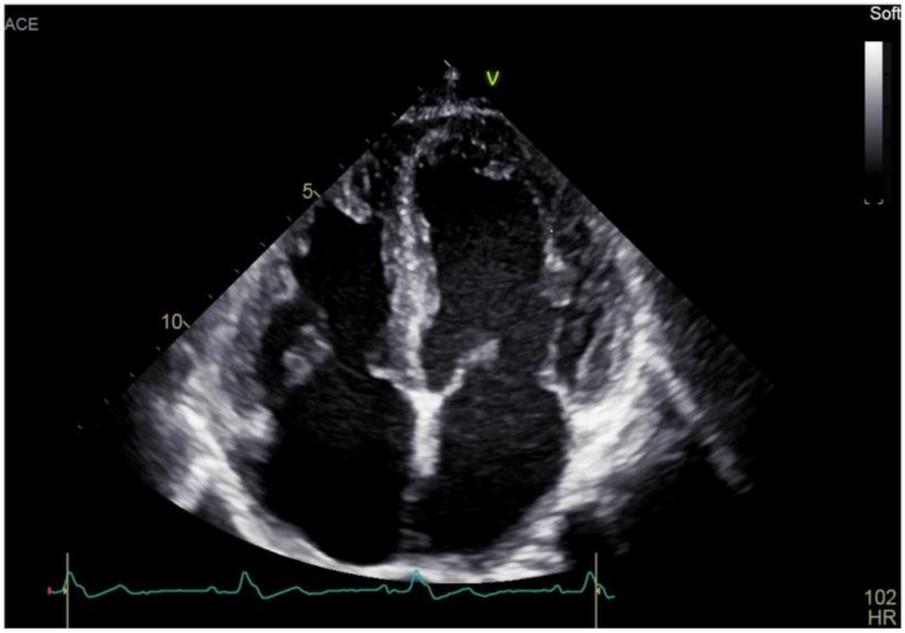
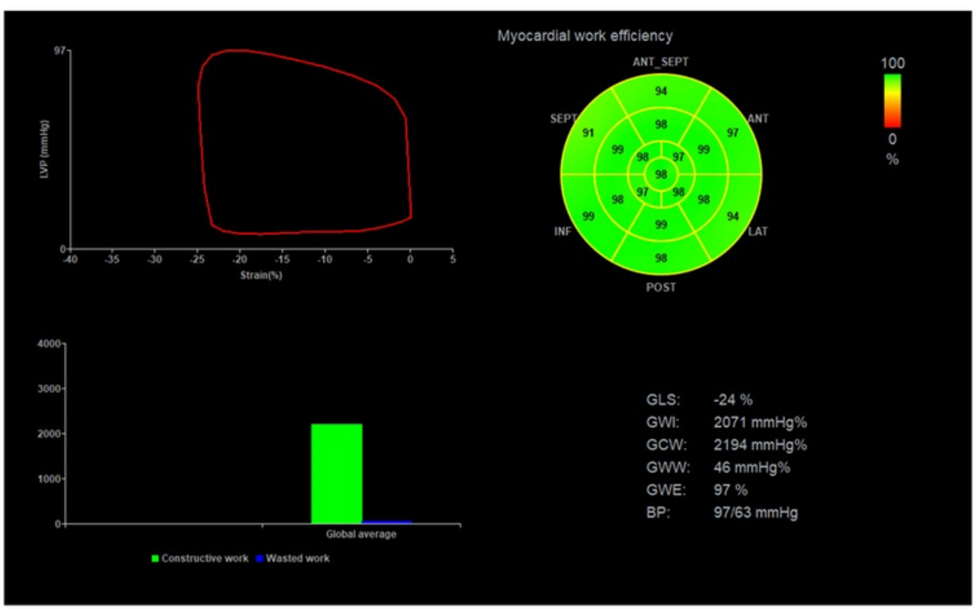


Figure 1

Box plots of GWI, GCW, GWE, GWW in 80 patients with noninvasive hypertrophic cardiomyopathy (NHCM) and 45 healthy controls.



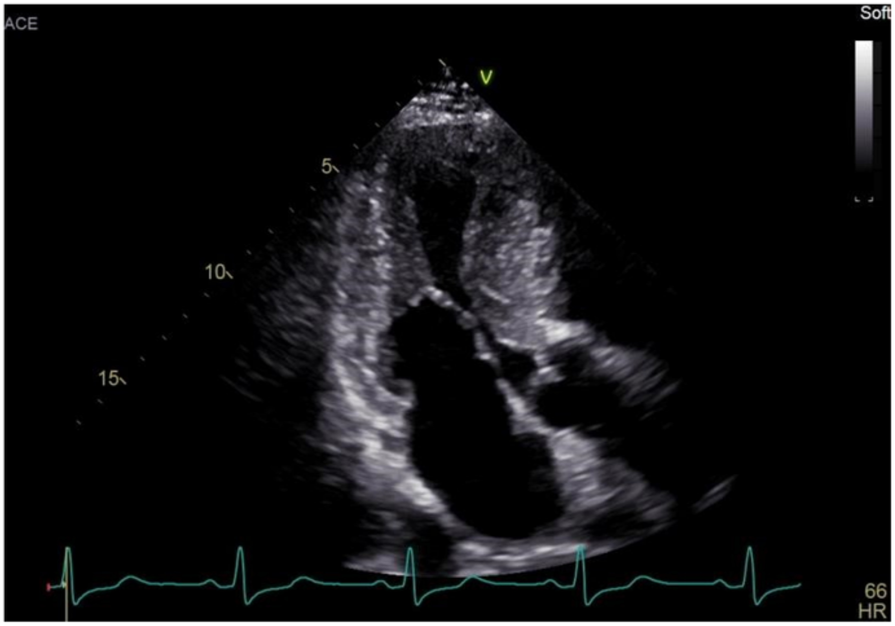
A)



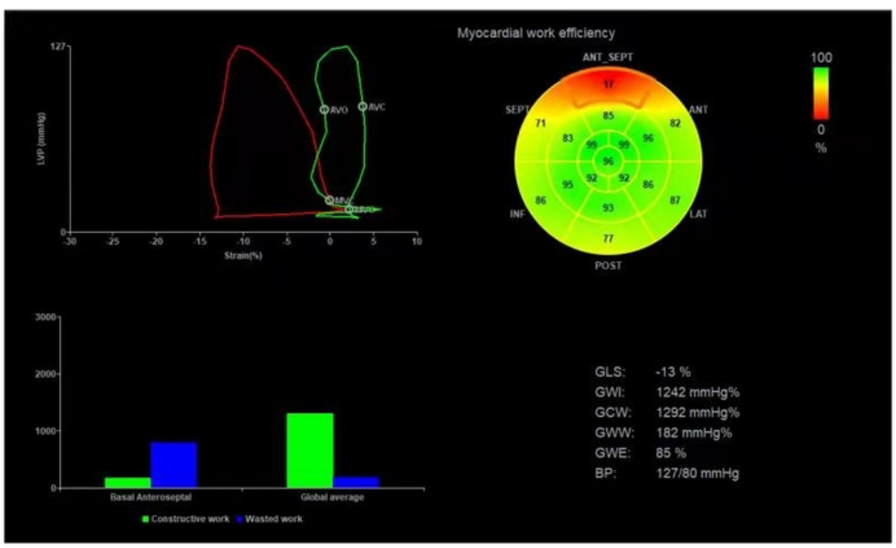
B)

Figure 2

Healthy People: A 42-year-old woman has no history of cardiac macrovascular disease. No left ventricular hypertrophy is evident at transthoracic echocardiography(a), The red curve represents a normal LV PSL, The bull´s-eye plot on the right shows segments myocardial work efficiency, The global constructive work and wasted work is showed in the bottom left(b).



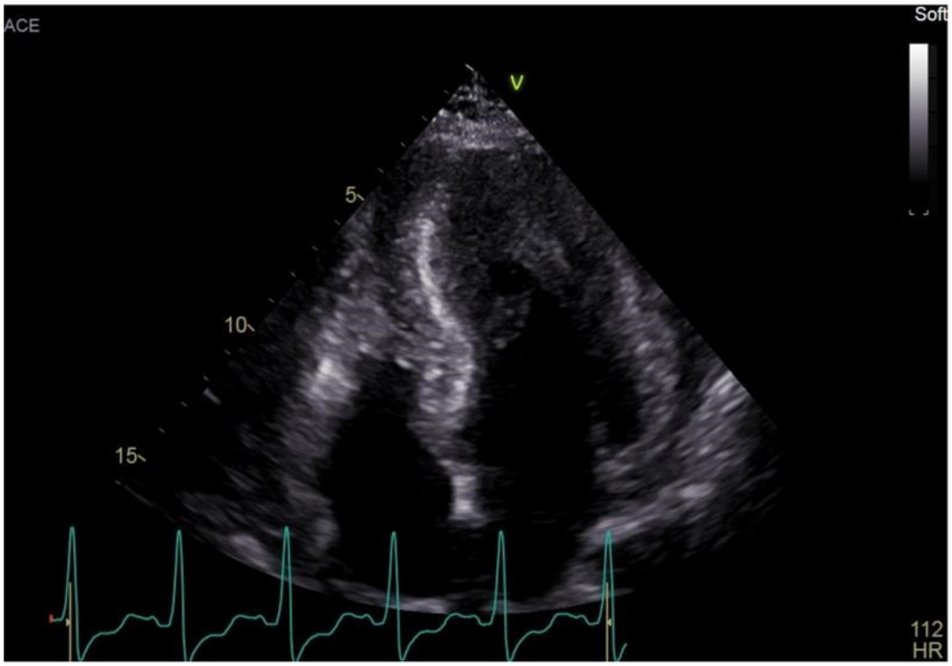
A)



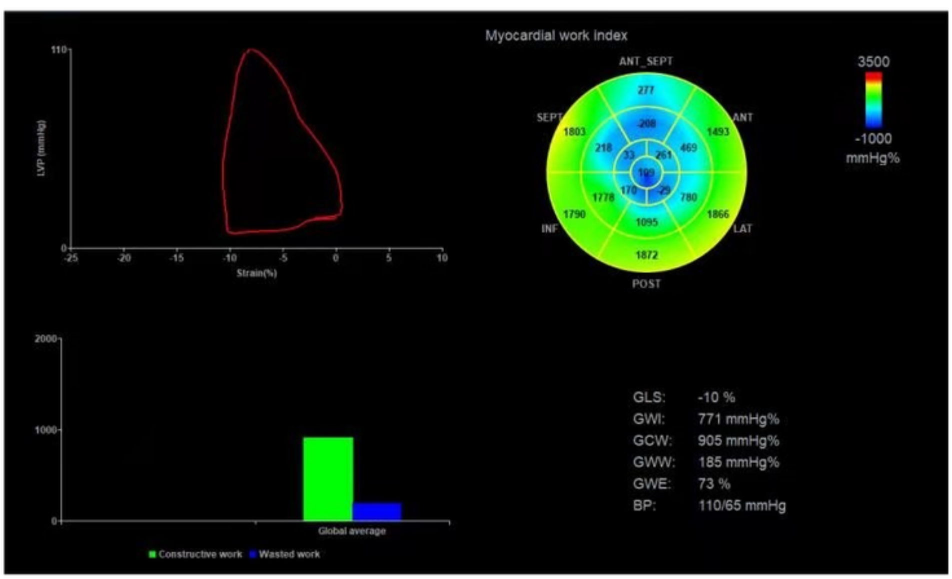
B)

Figure 3

Septal HCM Patient: A 28-year-old man is septal HCM patient, predominant asymmetric septal hypertrophy is evident at transthoracic echocardiography(a), The red curve represents the global LV PSL, while the green curve reflects the deviating PLS of an anterior septal segment in this patient. The bull´s-eye plot on the right show segments myocardial work efficiency, The global average constructive work and wasted work and the basal anteroseptal average constructive work and wasted work are showed in the bottom left(b).



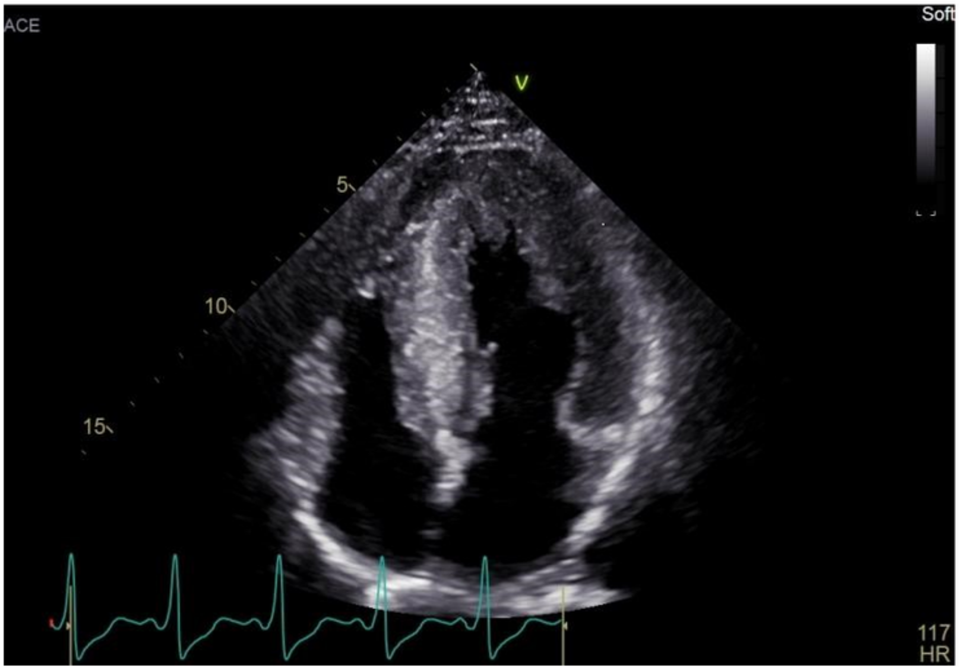
A)



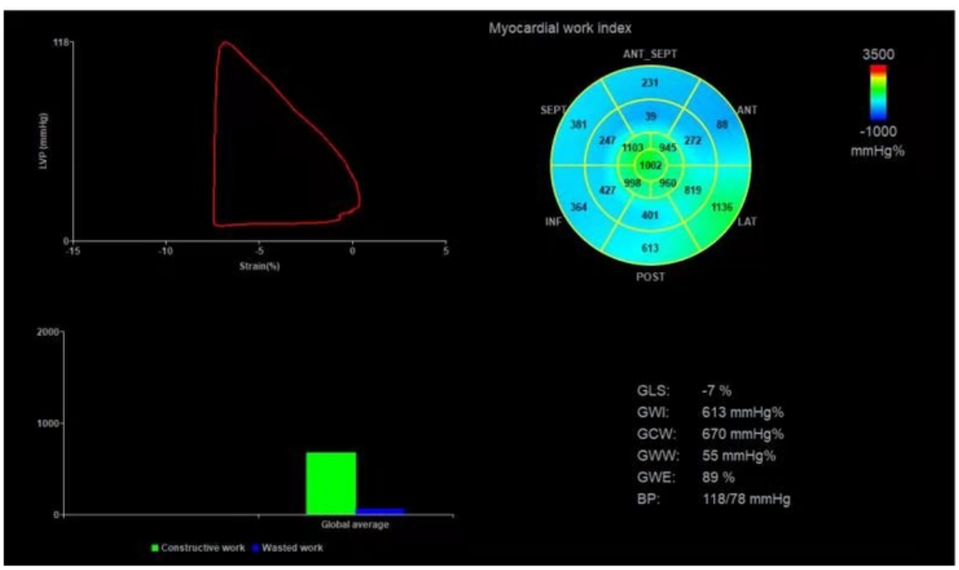
B)

Figure 4

Apical HCM Patient: A 56-year-old man is apical HCM patient, localized apical hypertrophy is evident at transthoracic echocardiography(a), The red curve represents the global LV PSL. The bull´s-eye plot on the right show segments myocardial work index, The global average constructive work and wasted work is showed in the bottom left(b). Myocardial work index of apex is significantly lower than other segments.



A)



B)

Figure 5

Concentric HCM Patient: A 38-year-old man is Concentric, symmetric HCM patient, characterized by symmetric hypertrophy of the left ventricular wall segments at transthoracic echocardiography(a), The red curve represents the global LV PSL. The bull´s-eye plot on the right show segments myocardial work index, The global average constructive work and wasted work is showed in the bottom left(b). The myocardial work index of each segment on the bull's-eye plot is significantly reduced.

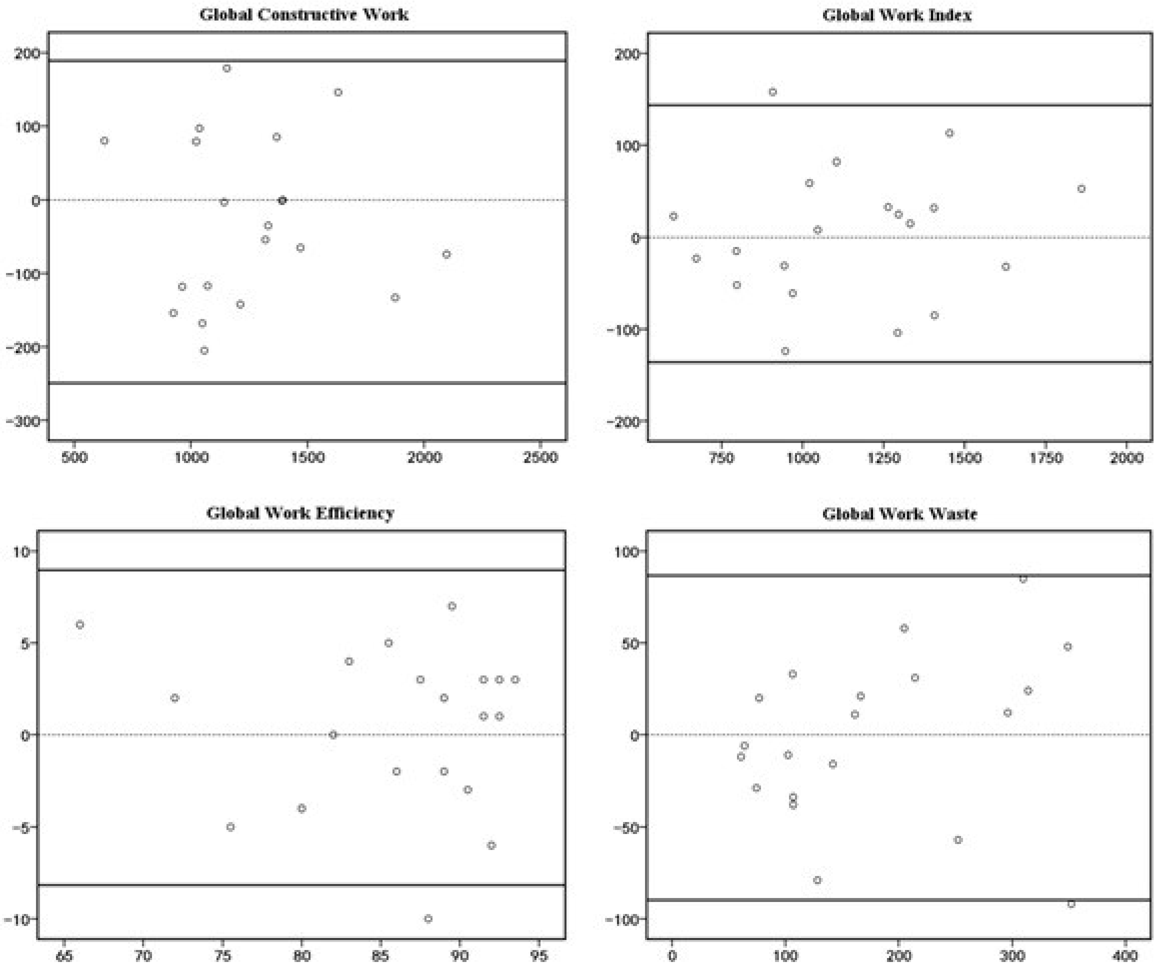


Figure 6

Bland-Altman analysis of inter-observer variability of global work index, global constructive work, global work waste, and global work efficiency.

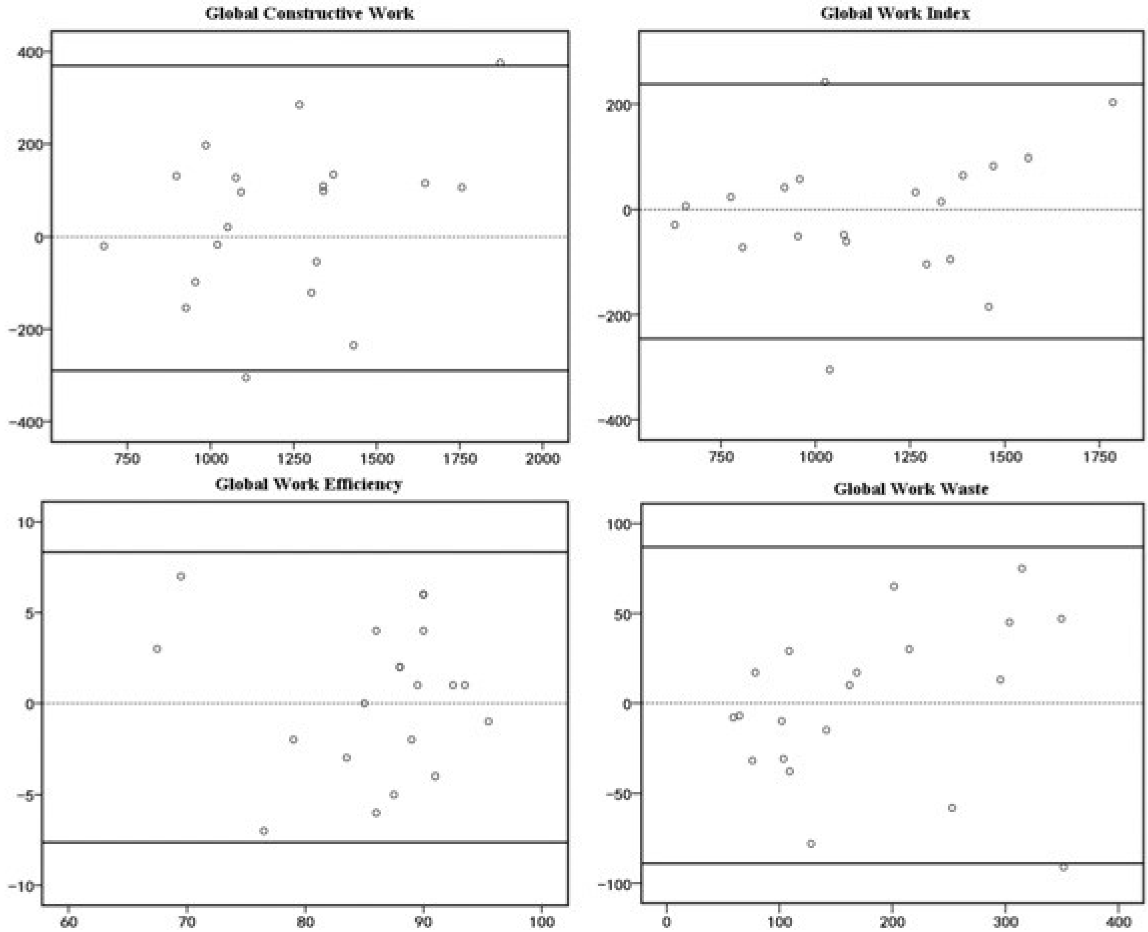


Figure 7

Bland-Altman analysis of intra-observer variability of global work index, global constructive work, global work waste, and global work efficiency.