

Advances in the Research Application of Ultrasound Non-Invasive Stress-Strain Loop Technology in Cardiovascular Diseases

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Abstract

The ultrasound pressure-strain loop (PSL) technique is a non-invasive method of examining myocardial work, which takes into account the effect of cardiac afterload on deformation and combines the overall longitudinal strain force of the left ventricle with the changes in the left ventricular pressure, allowing earlier detection of possible subclinical cardiac damage in patients, and a more accurate and non-invasive assessment of the patient's myocardial work performance. In this article, we will discuss the progress of PSL applications in cardiovascular diseases.

Keywords

Echocardiography, Speckle Tracking, Non-Invasive Myocardial Work, Pressure-Strain Loop, Left Ventricular Pressure

1. Introduction

How to accurately assess patients' myocardial systolic and diastolic function plays a very important role in clinical applications. Left ventricular ejection fraction (LVEF) is the most commonly used clinical index to assess patients' systolic function, but traditional echocardiography is easily affected by doctors' subjective consciousness and operating experience, and is dependent on load, heart rate, and asynchronous contraction, which has low sensitivity to subclinical myocardial damage. Two-dimensional speckle tracking echocardiography (2D-STE) overcomes the angular dependence, and by tracking the displacement of scattered speckles during the cardiac cycle, it can quickly and non-invasively obtain regional and global longitudinal strain (GLS), which is the most common strain in the myocardium

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[1]. GLS can be used to assess myocardial deformation and ventricular systolic and diastolic kinetics, but it does not reflect myocardial oxygen consumption and has a load-dependent effect on the accuracy of myocardial function assessment. Some studies [2] [3] have shown that LV myocardial strain measurements decrease with increasing afterload, leading to misjudgment of true systolic function. Pressure-volume loops (PVLs), as the “Gold standard” for evaluating left ventricular function, have no load dependence and can reflect the relationship between end-systolic and end-diastolic pressure and volume, due to the invasive and complex nature of the method, which is left ventricular pressure and volume obtained by cardiac catheterization or cardiogram, it has not been applied in clinical practice [4] [5].

In recent years, the concept of non-invasive “myocardial work” (MW) has been proposed by Russell *et al.* [6], which takes into account the effects of deformation and afterload. It combines the peak LV pressure estimated by brachial artery cuff pressure with the longitudinal strain force of the LV in STE to obtain an LV strain-pressure curve, whose level changes help to understand the mechanical changes of the whole LV and segments under different loading conditions. The cardiac contractile function could be more accurately assessed by quantifying the overall and segmental myocardial work done, reflecting the relationship between intracardiac pressure and myocardial contraction. The curve is based on echocardiographic judgment of the actual valve opening and closing times of the patient’s relevant cardiac cycle, adjusting the time intervals of isovolumic systole, ejection, and isovolumic diastole, matching the time axis of the curve to the actual period of the cardiac cycle by stretching or compressing the curve, and then non-invasively estimating the peak LV pressure based on the brachial arterial blood pressure to make adjustments to the pressure axis of the average pressure curve to obtain a patient-specific non-invasive LV pressure curve [6]-[8]. It has been validated in both animal models and human subjects [6]. The area of the myocardial pressure-strain loop represents an index of regional left ventricular work and also serves as a mechanical index of regional myocardial oxygen consumption. What’s more, myocardial oxygen consumption has a high correlation and concordance with regional myocardial glucose metabolism as assessed by 18F-deoxyglucose positron emission tomography (PET) [6]. Because of its non-invasiveness, high reproducibility, and simpler operation, it has been used to judge myocardial metabolism and myocardial work in a variety of cardiovascular diseases.

2. Main Parameters of Myocardial Work

1) Global myocardial work index (GWI): The total work done in the region of all segments of the left ventricular PSL from mitral valve closure to mitral valve opening, *i.e.*, the area under the PSL curve.

2) Global constructive work (GCW): The work done in favor of the left ventricle ejection to the aorta, the work done by the left ventricle in systole for the left ventricular ejection, *i.e.*, isovolumic systolic myocyte shortening and diastolic myocyte

lengthening work.

3) Global wasted work (GWW): Work that is detrimental to LV ejection, as opposed to GCW, *i.e.*, work done by isovolumic systolic myocyte lengthening (rather than shortening) and diastolic myocyte shortening.

4) Global work efficiency (GWE): $GWE = GCW / (GCW + GWW)$; reflects the work efficiency of mechanical energy throughout the cardiac cycle, and the GWE of a healthy person is close to 100%.

Through myocardial work analysis, 17-segment regional myocardial work index (RMWI) and 17-segment regional myocardial work efficiency (RMWE) bull's-eye diagrams can also be obtained, and the color of the bull's-eye diagrams can be used to assess the magnitude of the values with the naked eye, with green indicating normal myocardial work, red indicating increased myocardial work, blue indicating decreased myocardial work, negative myocardial work segments indicated by dark blue [9].

3. Application of PSL in the Healthy Human Body

The determination of normal reference ranges for MW parameters is a landmark in clinical and research settings. Manganaro *et al.* [10] were enrolled according to the European Association of Cardiovascular Imaging (EACVI) study with 226 healthy subjects in the Normal Reference Ranges for Echocardiography (Norre) Echocardiography, it was found that the minimum expected MW index of GWI, GCW and GWE was 1270 mmHg% (male) and 1310 mmHg% (female), 1650 mmHg% (male) and 1544 mmHg% (female), 90% (male) and 91% (female), respectively.

The highest GWW expectation was 238 mmHg% in men and 239 mmHg% in women. Multivariate analysis showed that GWI and GCW were significantly associated with systolic blood pressure only, with little correlation with age and sex [10]. Galli *et al.* [11] in a population of 115 healthy volunteers, derived reference ranges for all LV myocardial work: GWI was (1926 ± 247) mmHg% (95%CI: 1534 - 2356); GCW was (2224 ± 229) mmHg% (95% CI: 1894 - 2647); GWW of 90 (61 - 123) mmHg% (95% CI: 38 - 195); and GWE 96% (94% - 97%) (95% CI: 91 - 98), and also showed that MV was not affected by age. Tretter *et al.* [12] and Pham *et al.* [13] calculated reference ranges of MV parameters for each group of children using 52 healthy adolescents and 221 children as study populations, respectively. Yanase *et al.* [14] studied 113 neonates and found that all MCW parameters in neonates were lower than the previously reported normal ranges in children and adults. GWI and GCW correlated more closely with BP, suggesting that MW is promising for use in screening for neonatal prevalent heart disease. As the research continues, this technique is being explored and applied more widely in various populations, and its value is in the process of being discovered.

4. Application of PSLs in CRTs

Cardiac resynchronization therapy (CRT) is currently an effective treatment for

asynchronous heart failure (HF), wide QRS waves, and reduced ejection fraction. However, nearly 30% of CRT patients have a poor response to therapy, and it has become a clinical challenge to identify non-responders [15], and how to identify non-responders has become a major clinical challenge. Zhu *et al.* [16] included 106 heart failure (HF) patients scheduled to undergo CRT in a MW analysis and found that GWI and GCW were significantly higher in CRT responders than in non-responders, and multifactorial analysis showed that lower septal mid-segment GWE (OR 0.975, 95% CI: 0.959 - 0.990, $P = 0.002$) and higher lateral mid-segment GWI (OR 1.003, 95% CI: 1.002 - 1.004, $P < 0.001$) were independent predictors of CRT responsiveness. The study confirmed that CRT resulted in a more balanced distribution of asynchronous cardiac work, leading to a significant improvement in overall cardiac function, and demonstrated that the improvement in overall left ventricular function stemmed primarily from the increased efficiency of septal work after CRT. Galli *et al.* [17] their other study found that GCW and GWW were associated with CRT responders, that GCW and GWW were significantly increased in responders compared to non-responders, and that a $GCW > 1057$ mmHg% and $GWW > 384$ mmHg% was a valid and significant predictor of CRT-positive responders, showed a good specificity (100%) and positive predictive value (100%) but a low sensitivity (22%), negative predictive value (41%). These results support the hypothesis [18] that differences in GCW detected by pre-CRT PSL may correspond to residual myocardial metabolic activity and contractile reserve, and thus may explain the role of GCW in predicting CRT responders and validate that GWW can be used as a measure of myocardial energy loss during the cardiac cycle. Therefore, the PSL technique is not only helpful in identifying CRT responders but also more accurate and sensitive in identifying the efficacy before and after CRT treatment.

5. PSL in Coronary Artery Disease

Coronary artery disease (CAD) has a variety of onsets and is overlooked by patients in the early stages due to the lack of obvious symptoms, however, about 20-25% of patients start the disease with sudden cardiac death, so early detection and timely diagnosis and treatment can greatly improve the survival rate of patients [19]. A recent study [20] showed that PSL, which can demonstrate single or multiple coronary lesions, is superior to GLS (AUC = 0.693) in predicting patients without segmental ventricular wall motion abnormalities and with normal EF. It is also shown that MW (AUC = 0.786) is the strongest predictor of severe CAD, the optimal cut-off value for predicting MW severe CAD is 1810 mmhg% (sensitivity of 92%; specificity of 51%). Boe *et al.* [21] using PSL in 126 patients with acute non-ST-segment elevation myocardial infarction, found that regional GWI indices were significantly lower in patients with concomitant acute coronary occlusion, and that ≥ 4 adjacent dysfunctional segments as assessed by GWI were significantly superior to the overall strain and ejection fraction ($P < 0.05$) in detecting the development of acute coronary occlusion. Therefore, PSL can be used as an

important tool to select patients for emergency percutaneous coronary intervention. Percutaneous coronary intervention (PCI) can re-dilate narrowed coronary arteries and restore myocardial blood supply, and it is the mainstay of treatment for CAD. Cui *et al.* [22] a study of myocardial work index before and after coronary artery bypass grafting in patients with coronary artery disease found that GWI and GWE were higher at 3 months postoperatively than before surgery, and GWI, GCW, and GWE were higher at 3 months postoperatively than at 1 month postoperatively ($P < 0.05$), which suggests that the PSL can quantitatively assess the changes in left ventricular myocardial function before and after PCI in patients with CAD. Zhang *et al.* [23] showed that myocardial function was significantly improved in CAD patients in the short term after PCI. Luo *et al.* [24] showed that the PSL technique can be used to assess myocardial work in CAD patients with single or multivessel disease. All these studies indicated that PSL provided a new non-invasive method for the diagnosis and treatment of coronary artery disease and the assessment of LV function before and after PCI.

6. PSL in Cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common clinical cardiomyopathy, often accompanied by systolic and diastolic dysfunction of the left ventricle or both ventricles, and with the progression of the disease, heart failure caused by the reduction of left ventricular systolic function is the direct cause of death in most DCM patients. A study by Cui *et al.* [25] found that GWI was elevated in patients with DCM after treatment compared to before treatment and that GWI, GCW, and GWE before and after treatment in the case group were lower than those in the normal control group, and GWW were higher than those in the normal control group. Their study also found that there were differences in the values between different segments, and the MWI and MWE were lower in 17 regions in the case group compared with the control group, and there was a significant correlation between GMW values and LVEF and GLS values ($P < 0.01$), which was in line with the results of the study by Chan *et al.* [3].

Hypertrophic cardiomyopathy (HCM), characterized by asymmetric myocardial hypertrophy, is the leading cause of sudden death after exercise in young adults. Zeng [26] in her study found that in patients with HCM, even if LVEF was normal, GWI, GCW, GWE, and GLS were significantly reduced, and GWW was significantly increased, indicating that PSL technology assessed LV myocardial work in patients with HCM in a more advanced manner than LVEF [27]. In a study, Galli's team found that a GCW cutoff value of 1623 mm Hg% was a sensitive predictor of LV fibrosis [28]. In a later study, they also found that a GCW cut-off value of ≤ 1550 mm Hg% was strongly associated with significant cardiac fibrosis, with a sensitivity of 91% and a specificity of 84%, which were higher than that of GLS, and further demonstrated that GCW was associated with significant left ventricular myocardial fibrosis on cardiac magnetic resonance, PSL is expected to be a

useful predictor of LV fibrosis in certain cardiomyopathies in patients who cannot be fitted with a pacemaker, prosthetic valve, or cochlear implant, cardiac stents, electronic cochlear implants, etc. that cannot undergo cardiac MRI. In a study of pediatric cardiomyopathy [29], GWI and GWE were found to be significantly lower than normal in pediatric patients with DCM and HCM. The PSL technology can provide multi-regional myocardial motion parameters and can be used as a new non-invasive examination of myocardial function in patients with various types of cardiomyopathies and patients of all ages.

Clemmensen's team [30] [31] in their study on cardiac amyloidosis (CA) found that CA patients with inefficient myocardial work and poor exercise capacity had poorer overall myocardial performance. This study showed that the difference between healthy and CA patients during exercise was more pronounced in LVMWI than in GLS, and LVMWI differed more significantly between NYHA Class I and II patients and between NYHA Class III and IV patients compared with GLS, suggesting that MWI may be of clinical value in identifying CA patients with advanced disease and poor prognosis and in predicting major adverse cardiac events (MACEs) and all-cause mortality, which cannot be assessed by LVGLS.

7. PSL in Other Secondary Myocardial Damages

Most diseases affect the heart at a later stage, increasing the workload of the heart, which may eventually lead to heart failure, worsening of the condition, or even death. However, most patients with secondary heart disease are already at a late stage of cardiac involvement by the time they are diagnosed, so early detection of potential myocardial damage may be effective in improving the patient's prognosis and increasing the survival rate. Several studies have demonstrated that PSL can provide an earlier evaluation of LV function in different levels of increased hypertensive load and is superior to conventional echocardiography [3] [32] and is superior to conventional echocardiography and STE [33]-[35]. Huang *et al.* [34] showed that segmental myocardial work analysis provides a reliable means of investigating the distribution of myocardial injury at different stages of LV remodeling in hypertensive patients. Tadic *et al.* [35] after analyzing hypertensive patients with or without diabetes mellitus, glycated hemoglobin (HbA1c) and systolic blood pressure were associated with GWI and GCW in hypertensive patients, and diabetes mellitus had an additional negative effect on GCW in hypertensive patients, but no significant effect on GWI. Cheng *et al.* [36] the team utilized a 6-month follow-up of diabetic patients treated with empagliflozin, LV GWI, GCW, and GWE were lower than those of healthy subjects, GWW was higher than those of healthy subjects, and changes in troponin cTnI were negatively correlated with GWE, suggesting that the improvement in non-invasive myocardial work after empagliflozin treatment may indirectly reflect the improvement in myocardial energy utilization. Hence, the PSL technique not only allows for the unifactorial and multifactorial assessment of myocardial damage in patients with different stages of the disease in single-factor and multi-factor ways, but also evaluate the efficacy

of patients' treatment, which can help clinicians to understand patients' disease progression more clearly and provide the basis for patients to develop a more reasonable treatment plan.

As the number of cancer survivors rises, cancer therapy-related cardiac dysfunction (CTRCD) is gradually attracting clinical attention [37]. Chemotherapy may have an indirect effect on the heart, such as heart failure, coronary artery disease, peripheral artery disease, myocarditis, etc. One of the definitions for CTRCD published by the European Society of Cardiology in 2022 was based on the relative change in LVEF reduction (<50%, or at a critical 50% - 54%) and relative changes in LVGLS [38]. In recent years, several scholars [39] [40] have made relevant studies using PSL technology in patients undergoing chemotherapy for malignant tumors, showing that MWI may be more sensitive than GLS for detecting early cardiac damage. It was found that non-invasive assessment of LV myocardial work by stress-strain analysis may be of clinical value in oncology cardiology and can identify early signs of cardiotoxicity during anticancer therapy.

In addition to this, the pressure-strain loop technique has been studied and applied in more and more areas, such as patients with pulmonary hypertension [41], patients with liver cirrhosis [42], renal failure and dialysis [43], rheumatic immunology [44] and so on. Furthermore, stress-strain loop technology has been studied and applied in more and more aspects, such as patients with pulmonary hypertension, liver cirrhosis, renal failure and dialysis, rheumatoid immunity, etc. The advantages of stress-strain loop technology have been demonstrated to varying degrees, and it is capable of detecting systolic and diastolic dysfunction at a much earlier stage than conventional echocardiography and 2D speckle tracking, which provides an effective way to detect subclinical myocardial damage.

8. Limitations of PSL and Outlook

The PSL technique non-invasively assesses the patient's myocardial work more reproducibly and effectively than the invasive PVL technique, as has been verified in several scientific studies. However, PSL technology still has certain limitations: firstly, the afterload of the heart contraction also includes vascular stiffness, resistance, etc., which cannot completely replace the left ventricular wall pressure, so the accuracy of using cuff pressure to replace the left ventricular pressure is not as good as the invasive method, there is a certain degree of error. Secondly, when the peripheral pressure and left ventricular pressure are not equal, such as when the patient has left ventricular outflow tract obstruction or aortic stenosis, brachial artery pressure is not able to replace when peripheral pressure and left ventricular pressure are not equal, such as when the patient has left ventricular outflow tract obstruction or aortic stenosis, brachial artery pressure cannot be used as a substitute for left ventricular pressure. Thirdly, PSL is based on a two-dimensional speckle tracking technique, which requires a higher quality of the image, and the analysis of the work performed is limited by the quality of the image.

In recent years, Owashi *et al.* [45] constructed a new cardiovascular system to

evaluate myocardial work in aortic stenosis, showing that there is a good match between experimental and simulated left ventricular and aortic pressures, which provides a new way of thinking for patients with aortic stenosis. Another scholar, Taconne *et al.* [46] evaluated patients with aortic stenosis using both models and showed a high correlation between LV myocardial work and that measured by invasive methods. Ribic *et al.* [47] showed that when the aortic orifice pressure was matched to diastolic pressure in the original model, the accuracy of the estimated LV pressure curve improved, reflecting the accuracy of the aortic stenosis-specific model. Various researchers are gradually overcoming the limitations of PSL and building appropriate models based on PSL to accommodate other restrictive diseases, reduce technical or experimental errors, expand the range of disease applications, and improve diagnostic accuracy.

In summary, LV stress-strain loop technology combines afterload and myocardial strain, which can non-invasively, sensitively, and effectively assess myocardial oxygen consumption and myocardial work in primary or secondary cardiovascular disease, can detect potential myocardial damage in patients at a much earlier and more sensitive stage than conventional echocardiography and 2D-STE, and is more reproducible and convenient than cardiac magnetic resonance imaging and PET. They are more reproducible and convenient than cardiac magnetic resonance imaging and PET technology. Furthermore, they have superior validation and application in the early diagnosis of patients, assessment of disease progression, estimation of clinical efficacy, and prevention and treatment of complications. However, this technology is still in the exploratory stage, supported by only one equipment supplier, GE, and has not been widely carried out in the clinic. It is believed that with the deepening of the research, PSL will appear in the clinic more accurately, adding a novel and reliable option for clinicians and patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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