Scientific Research Publishing

Journal of Biosciences and Medicines, 2024, 12, 351-360
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Progress in the Application of Noninvasive Myocardial Work to Evaluate Chemotherapy-Related Cardiotoxicity

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How to cite this paper: Guo, L., Zhang, Q., Wang, J.S. and Hao, X.Y. (2024) Progress in the Application of Noninvasive Myocardial Work to Evaluate Chemotherapy-Related Cardiotoxicity. *Journal of Biosciences and Medicines*, **12**, 351-360.
https://doi.org/10.4236/jbm.2024.1212028

Received: November 5, 2024
Accepted: December 16, 2024
Published: December 19, 2024

Abstract

Due to advances in modern tumor treatments, patients can survive long-term. However, cardiotoxicity caused by tumor therapy poses a significant challenge to both physicians and patients. Early detection and accurate assessment of cardiovascular toxicity from tumor therapy are crucial for guiding clinical treatment and improving patient prognosis. A noninvasive myocardial workup can monitor and assess the development of tumor chemotherapy-related cardiotoxicity. In monitoring oncology chemotherapy-related cardiac injury, a significant decrease in left ventricular ejection fraction (LVEF) of left ventricular systolic function (LVSCF) often indicates severe cardiac injury, making it challenging to monitor early cardiac injury. 3D-STI (three-dimensional speckle tracking imaging) can evaluate early cardiac injury, but its load dependence reduces the accuracy of myocardial function evaluation. In contrast, the noninvasive evaluation of myocardial work using left ventricular pressure-strain loops (PSL), which considers both myocardial deformation and left ventricular pressure, avoids the effect of load dependence on myocardial contractile function and improves the accuracy of myocardial function evaluation. This article reviews the noninvasive evaluation of myocardial work to assess cardiotoxicity associated with tumor chemotherapy.

Keywords

Noninvasive Myocardial Work, Cardiotoxicity, Anthracycline Chemotherapy, Pressure-Strain Loop, Left Ventricular Pressure

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1. Clinical Features of Chemotherapy-Related Cardiotoxicity

Cardiotoxicity in tumor patients is mainly affected by three factors: 1) the patient's own cardiovascular disease risk factors, such as age, diabetes, and hypertension; 2) the tumor's direct or indirect effects on the cardiovascular system; and 3) cardiovascular injuries caused by chemotherapy, targeted therapy, and radiotherapy. Currently, the diagnosis of cancer therapy-related cardiac dysfunction (CTRCD) is mainly based on cardiac systolic dysfunction. Measurement of left ventricular ejection fraction (LVEF) reflects the overall contractile function of the left ventricle (LV), and a decrease in LVEF indicates impaired cardiac systolic function. The latest guidelines from the British Society of Echocardiography and the British Society of Cardiac Oncology define definitive cardiotoxicity as a 10% to 50% decrease in LVEF [1]. However, a decrease in LVEF is a late manifestation of chemotherapy-related cardiotoxicity, often resulting in irreparable cardiac damage before it is detected [2]. Tumor-related cardiovascular toxicity (cancer therapy-related cardiovascular toxicity, CTR-CVT) encompasses a wide range of cardiovascular diseases (CVD), classified into several major categories: heart dysfunction caused by cancer treatment, including cardiac injury, cardiomyopathy, and heart failure; myocarditis; vasculotoxicity; arterial hypertension; and arrhythmias. CTRCD can be divided into two categories: 1) asymptomatic CTRCD, which can be subdivided into a) mild: left ventricular ejection fraction (LVEF) ≥50% with a >15% decrease in global longitudinal strain (GLS) from baseline and/or elevated cardiac biomarkers; b) moderate: ≥10% reduction in new LVEF to 40% - 49% or a 15% reduction in new LVEF from baseline or new elevations in cardiac biomarkers; c) severe: reduction in new LVEF to <40%; and 2) symptomatic CTRCD (*i.e.*, heart failure), categorized as mild, moderate, severe, or very severe based on symptoms and the need for treatment and/or hospitalization [3].

The pathogenesis of anthracycline-associated cardiotoxicity has been extensively studied, with the most widely accepted mechanism being the "oxidative stress theory" [4]: increased production of reactive oxygen species (ROS) and peroxidation of membrane lipids lead to the destruction of the collagen fiber network and cardiomyocytes, affecting myocardial energy metabolism and cardiac diastolic function. Additionally, the role of 2β-topoisomerase (TOP2β) in anthracycline-mediated cardiotoxicity has been widely recognized in recent years [5]: blockade of the TOP enzyme by anthracyclines leads to DNA double-strand breaks and transcriptome alterations, followed by mitochondrial biosynthesis disorders and increased production of oxygen free radicals. Pathologically, this results in mitochondrial swelling, sarcoplasmic reticulum breakage, cellular vacuolization, myofibrillar arrangement disorder, cardiomyocyte apoptosis, myofibrillar lysis, and myocardial fibrosis in the late stage. The occurrence of trastuzumab-related myocardial toxicity is associated with the blockade of epidermal growth factor receptors in cardiomyocytes, resulting in reduced ATP synthesis and decreased myocardial contractile function. Some chemotherapeutic drugs and the effects of radiotherapy can also cause atherosclerosis and myocardial ischemia and

infarction by promoting vasospasm, damaging vascular endothelial cells, or causing long-term lipid metabolism abnormalities. Chemotherapeutic agents generally do not directly damage valves, but valve fibrosis and calcification can occur in those treated with combined radiotherapy. Inflammation in the heart may also lead to microvascular injury, as anthracycline therapy has been shown to activate inflammatory cells such as macrophages and neutrophils, which can damage small arteries and capillaries [6].

2. Inspection Methods

The current non-invasive screening methods for cardiotoxicity include biomarker tests, CMR, and Speckle Tracking Echocardiography (STE). The main imaging tests are echocardiography (UCG), CMR, and radionuclide angiography (MUGA). The 2022 ESC Guidelines for Cardiac Oncology recommend [7]: for the diagnosis and management of asymptomatic CTRCD during cancer treatment, TTE (including 3D-LVEF and GLS assessment) is the preferred technique for detecting and confirming cardiac dysfunction. Although 3D speckle-tracking echocardiography has made progress in assessing cardiotoxicity, it is highly affected by afterload. In contrast, noninvasive myocardial work-up techniques are not limited by afterload and are superior for the early detection of cardiotoxicity.

2.1. CMR

CMR has excellent precision and accuracy in measuring LVEF and is considered the gold standard for screening [8]. CMR effectively compensates for the lack of sound window and resolution in ultrasound examinations. Magnetic resonance myocardial labeling (myocardial tagging) technology was first used to study myocardial strain, but it is challenging to use widely in clinical practice due to the need for specific sequences, complex post-processing, and long breath-holding times. The new generation of tissue feature tracking technology makes measuring stress parameters more automated, stable, and less time-consuming, with promising clinical applications. Existing studies have reported the feasibility of continuously monitoring subclinical myocardial functional changes in chemotherapy patients. [9] The CMR late gadolinium enhancement (LGE) sequence has long been considered the "gold standard" for detecting myocardial fibrosis and scar tissue. Although anthracycline-based chemotherapeutic agents cause significant changes in cardiac structure, they are not easily detected in LGE imaging, whereas trastuzumab-induced CTRCD is relatively obvious in LGE imaging. Using MR to evaluate cardiac function in oncology patients who received anthracycline-based chemotherapy in childhood (after an average of 7.8 years), one investigator found that approximately 18% of patients had an LVEF of less than 45%, and about 27% had abnormal right ventricular function [10]. Although CMRI is more sensitive and accurate than echocardiography in LVEF assessment, it is still not sensitive enough for CTRCD screening. Wadhwa [11] and others have shown that anthracycline-induced CTRCD is characterized by diffuse fibrosis with a relatively low probability of LGE.

2.2. 3D-STE

Before the advent of 3D-STI, some scholars used two-dimensional speckle tracking imaging (2D-STI) to monitor anthracycline-induced cardiotoxicity and found that 2D-STI could detect subclinical cardiotoxicity at an early stage [12]. In contrast, 3D-STI can track the motion of endocardial borders in three dimensions, allowing for better quantitative identification of normal and abnormal myocardium, especially for minor segmental motion abnormalities [13]. A study showed that the left ventricular global area strain (GAS), global longitudinal strain (GLS), and right ventricular global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) were significantly reduced after chemotherapy compared to those before chemotherapy ($P < 0.05$), which was negatively correlated with the cumulative dose of anthracyclines. Another study evaluated LV strain after different doses of anthracycline chemotherapy. The results showed that, compared to the pre-chemotherapy period, patients' LV global longitudinal strain (LVGLS), LV global circumferential strain (LVGCS), and left atrial global longitudinal strain (LAGLS) were significantly reduced ($P < 0.001$). Compared to the low-dose group, the rate of change in LVGCS at the end of chemotherapy was significantly higher in the high-dose group [21.12 (6.52, 35.37) vs. 5.49 (−14.73, 27.01); $P = 0.03$] [14]. However, 3D-STI suffers from load dependence, reducing the accuracy of myocardial function evaluation.

3. Advances in the Application of Noninvasive Myocardial Work to Assess Cardiac Injury Associated with Tumor Therapy

PSL was more objectively reflective of myocardial mechanics than GLS and LVEF. To obtain the myocardial work index, brachial artery blood pressure was measured at rest. The patient was then positioned on the left side and connected to an electrocardiogram, while maintaining calm breathing. In practice, the quality of images and blood pressure are crucial to the data. The software performs automatic frame-by-frame depiction of the epicardium and endocardium. Check for issues in the endocardial and outer membrane boundaries depicted by the system, as a more accurate heart contour can be obtained with reasonable manual adjustment. After that, it will automatically calculate the overall area strain of the GAS, GLS, GRS, and GCS. In addition, the 17-segment bullseye map and the corresponding strain-time image can be obtained. In the bullseye chart, the system independently divides the left ventricular myocardium into 17 segments in the same plane. Different segments will show the actual strain parameters and color, allowing for the assessment of ventricular wall movement.

LVEF obtained by conventional echocardiography and LV longitudinal strain (GLS) obtained by STI technology can assess ventricular changes in patients undergoing oncologic chemotherapy, but both have certain limitations. PSL is a widely used technology in recent years. It combines peripheral brachial artery pressure with the cardiac cycle to mimic the cardiac pressure-volume ring and

construct the LV pressure and myocardial strain area ring. The area of the ring represents the work of the heart muscle. GWI represents the total work done by the myocardium since the mitral valve closure interval. GCW represents the work contributing to ventricular ejection done by myocardial systolic shortening and diastolic lengthening of cardiac fibers. GWW represents the futile work done by the myocardium during systolic lengthening and isovolumetric diastolic shortening. GWE represents the useful work. Non-invasive PSL based on the STI technique includes both GLS and LV pressure to obtain myocardial function parameters, objectively evaluating changes in LV systolic function in terms of myocardial motion and work. It is also suitable for monitoring cardiac function after chemotherapy with anthracyclines, where the PSL area is reduced compared to the pre-chemotherapy area, indicating reduced LV myocardial work.

3.1. Monitoring of Chemotherapy-Related Early Cardiac Injury

The time window for the onset of myocardial toxicity varies among different chemotherapeutic agents, with anthracycline-related cardiotoxicity being the most studied. With anthracyclines, injury can occur at the onset of chemotherapy, but symptoms may not appear immediately due to the heart's compensatory mechanisms. Although the incidence of significant ventricular dysfunction and heart failure in patients is less than 5%, the incidence of subclinical left ventricular dysfunction is as high as 42%. The parameter of left ventricular myocardial work (LVMW) can be a useful indicator for determining early myocardial toxicity [15] [16]. Studies by KE [17] *et al.* and Galli [18] *et al.* have indicated that myocardial do-it-yourself is a more sensitive method for detecting left ventricular dysfunction in cardiomyopathic patients compared to LVEF dysfunction. It also detects subclinical dysfunction in chronic kidney disease with normal LVEF. Noninvasive myocardial work is also suitable for monitoring cardiac activity with other chemotherapeutic agents. Liu Xi [19] and Deng [20] have shown that paclitaxel can induce severe lipid peroxidation, nitroxide stress, and cationic metabolites that damage mitochondrial DNA. This directly affects cardiac protein metabolism, leading to abnormal cardiac conductivity and excitability, resulting in arrhythmias, acute myocardial infarction, chronic cardiomyopathy, and myocarditis. Liao Yuanyuan [21] *et al.* studied the left ventricular functional changes in 28 nasopharyngeal carcinoma patients receiving paclitaxel combination chemotherapy using the stress-strain loop technique. They found that changes in work parameters were correlated with GLS, GWI, and GCW, which were positively correlated, while GWW was negatively correlated with GLS. This further indicated that the myocardial work parameters obtained by the PSL technique could be more sensitive in detecting the damage of chemotherapy drugs on myocardial function.

3.2. Monitoring of Local and Global Myocardial Activity

The 17 segments of the left ventricle typically produce very little ineffective work due to high contraction synchronization. However, when cardiac function is

impaired, causing desynchronization of myocardial contraction in different segments, a large amount of ineffective work is produced. This occurs when some segments of the myocardium are prolonged during systole or shortened during diastole [22]. In healthy individuals, MW parameters vary in a gradient from apical to basal levels; specifically, GWI (global work index), GCW (global constructive work), GWE (global work efficiency), and GWW (global wasted work) increase progressively from basal to apical levels [23]. One study of myocardial alterations in 27 patients undergoing anthracycline-based chemotherapy for breast cancer found that the basal, intermediate, and apical myocardial work indexes (MWI-B, MWI-M, and MWI-AP) and myocardial work efficiencies (MWE-B, MWE-M, and MWE-AP) were lower in the case group than in the pre-chemotherapy group after 4 cycles of chemotherapy ($P < 0.05$). MWI and MWE at T0 (pre-chemotherapy), T1 (2 cycles of chemotherapy), and T2 (4 cycles of chemotherapy) in both healthy control and case groups showed an increase from the base of the heart toward the apex [24]. The results showed that the overall cardiac function of patients with early breast cancer receiving anthracycline chemotherapy was mainly characterized by a reduction in left ventricular longitudinal myocardial fiber strain and a decrease in overall myocardial work index and efficiency. Another study indicated that the decrease in myocardial work was primarily in the apical segment [25]. This suggests that noninvasive myocardial work can not only monitor myocardial injury at an early stage but also reflect myocardial changes in various segments of the ventricle.

Abnormal myocardial electromechanical activity caused by anthracycline chemotherapeutic drug cardiotoxicity and ventricular wall motion dyssynchrony affects ventricular systolic function [26], leading to wasted myocardial work, inefficient pumping, and an increase in myocardial GWW, consistent with the findings of Russell [27] *et al*. Increased useless work further affects the efficiency of myocardial work in the left ventricle. In contrast, the study by Moya [28] *et al*. showed that the reason for decreased MWE in patients with moderate CTRCD is not higher waste work (WW) but lower useful work (constructive work, CW). Patients with normal preexisting GLS but lower CW are at higher risk of developing CTRCD. In addition to lower baseline CW, patients with moderate CTRCD had significantly higher WW at follow-up. Therefore, MW assessment may be an additional validated marker for patient risk stratification and subsequent CTRCD detection. Myocardial work index (PSI) is a new assessment parameter based on a 2D speckle tracking technique that considers deformation and afterload by interpreting strain associated with noninvasive LV pressures.

4. Conclusion and Discussion

In conclusion, with the continuous progress of noninvasive myocardial work-up technology in studying tumor chemotherapy-related cardiotoxicity, noninvasive myocardial work can measure various functional and structural parameters more accurately and sensitively. It can also identify changes in myocardial activity at an

early stage, providing comprehensive information for diagnosing, monitoring, assessing efficacy, and prognosing tumor-related cardiotoxicity. This has important clinical value and application prospects. On the other hand, myocardial work is developed based on two-dimensional STI. Under the influence of STI, the imaging quality is poor when the heart rate is high, making it difficult for the software to clearly depict the endocardial boundary in a high heart rate state [29]. Compared to GLS, PSL excludes the artifact of altered myocardial contractile function due to changes in afterload, allowing for a more accurate assessment of myocardial contractile function. PSL does not consider myocardial curvature thickness but only represents an index of work, rather than directly measuring the value of work [30]. The current domestic and foreign studies on myocardial work technology to evaluate cardiac injury mostly target the left ventricle, with few studies on right ventricular injury. The PSL, provided by the supplier and specifically designed to assess LV myocardial work, may be less accurate for the RV due to its complex geometry. In the future, it may be necessary to verify with the invasive right ventricular pressure-volume ring and design professional analysis software for the right ventricular myocardium. In conclusion, PSL obtains left ventricular myocardial work parameters—GWI, GCW, GWW, GWE—and each parameter, combined with GLS analysis, can quickly, effectively, non-invasively, and accurately quantify the early detection of breast cancer using anthracycline chemotherapy drugs. Subclinical myocardial toxicity provides advanced information for cancer-related cardiac dysfunction and contributes to early clinical protection and treatment.

Conflicts of Interest

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

References

[1] Dobson, R., Ghosh, A.K., Ky, B., Marwick, T., Stout, M., Harkness, A., *et al.* (2021) BSE and BCOS Guideline for Transthoracic Echocardiographic Assessment of Adult Cancer Patients Receiving Anthracyclines And/or Trastuzumab. *JACC*: *CardioOncology*, **3**, 1-16. https://doi.org/10.1016/j.jaccao.2021.01.011

[2] Santoro, C., Arpino, G., Esposito, R., Lembo, M., Paciolla, I., Cardalesi, C., *et al.* (2017) 2D and 3D Strain for Detection of Subclinical Anthracycline Cardiotoxicity in Breast Cancer Patients: A Balance with Feasibility. *European Heart Journal—Cardiovascular Imaging*, **18**, 930-936. https://doi.org/10.1093/ehjci/jex033

[3] Lyon, A.R., López-Fernández, T., Couch, L.S., Asteggiano, R., *et al.* (2022) 2022 ESC Guidelines on Cardio-Oncology Developed in Collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society. International Cardio-Oncology Society (IC-OS). *European Heart Journal*, **43**, 4229-4361.

[4] Ky, B., Vejpongsa, P., Yeh, E.T.H., Force, T. and Moslehi, J.J. (2013) Emerging Paradigms in Cardiomyopathies Associated with Cancer Therapies. *Circulation Research*, **113**, 754-764. https://doi.org/10.1161/circresaha.113.300218

[5] Zhang, S., Liu, X., Bawa-Khalfe, T., Lu, L., Lyu, Y.L., Liu, L.F., *et al.* (2012) Identification of the Molecular Basis of Doxorubicin-Induced Cardiotoxicity. *Nature*

Medicine, **18**, 1639-1642. https://doi.org/10.1038/nm.2919

[6] Todorova, V.K., Wei, J.Y. and Makhoul, I. (2021) Subclinical Doxorubicin-Induced Cardiotoxicity Update: Role of Neutrophils and Endothelium. *American Journal of Cancer Research*, **11**, 4070-4091.

[7] Lyon, A.R., López-Fernández, T., *et al*. (2022) 2022 ESC Guidelines on Cardio-Oncology Developed in Collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the Task Force on Cardio-Oncology of the European Society of Cardiology (ESC). *European Heart Journal*, **43**, 4229-4361. https://doi.org/10.1093/eurheartj/ehad196

[8] Yin, G., Cui, C., An, J., Zhao, K., Yang, K., Li, S., *et al*. (2022) Assessment of Left Ventricular Systolic Function by Cardiovascular Magnetic Resonance Compressed Sensing Real-Time Cine Imaging Combined with Area-Length Method in Normal Sinus Rhythm and Atrial Fibrillation. *Frontiers in Cardiovascular Medicine*, **9**, Article 896816. https://doi.org/10.3389/fcvm.2022.896816

[9] Lunning, M.A., Kutty, S., Rome, E.T., Li, L., Padiyath, A., Loberiza, F., *et al*. (2015) Cardiac Magnetic Resonance Imaging for the Assessment of the Myocardium after Doxorubicin-Based Chemotherapy. *American Journal of Clinical Oncology*, **38**, 377-381. https://doi.org/10.1097/coc.0b013e31829e19be

[10] Ylänen, K., Poutanen, T., Savikurki-Heikkilä, P., Rinta-Kiikka, I., Eerola, A. and Vettenranta, K. (2013) Cardiac Magnetic Resonance Imaging in the Evaluation of the Late Effects of Anthracyclines among Long-Term Survivors of Childhood Cancer. *Journal of the American College of Cardiology*, **61**, 1539-1547. https://doi.org/10.1016/j.jacc.2013.01.019

[11] Wadhwa, D., Fallah-Rad, N., Grenier, D., Krahn, M., Fang, T., Ahmadie, R., *et al*. (2008) Trastuzumab Mediated Cardiotoxicity in the Setting of Adjuvant Chemotherapy for Breast Cancer: A Retrospective Study. *Breast Cancer Research and Treatment*, **117**, 357-364. https://doi.org/10.1007/s10549-008-0260-6

[12] Stoodley, P.W., Richards, D.A.B., Hui, R., Boyd, A., Harnett, P.R., Meikle, S.R., *et al*. (2011) Two-Dimensional Myocardial Strain Imaging Detects Changes in Left Ventricular Systolic Function Immediately after Anthracycline Chemotherapy. *European Journal of Echocardiography*, **12**, 945-952. https://doi.org/10.1093/ejechocard/jer187

[13] Song, H.N., Qin, Z.Y., Zhou, Q., *et al*. (2015) Application of Three-Dimensional Speckle Tracking Technology to Construct a Multiparameter Diagnostic Model to Improve the Efficiency of Early Diagnosis of Coronary Artery Stenosis. *Chinese Journal of Ultrasound Imaging*, **24**, Article No. 10.

[14] Han, M.X., Li, Z., Zhang, Q.L., *et al*. (2024) Left Ventricular Strain after Anthracycline Chemotherapy with Different Doses of Anthracyclines Assessed by Three-Dimensional Speckle Tracking Imaging. *China Clinical Medicine*, **31**, 559-564.

[15] Plana, J.C., Galderisi, M., Barac, A., Ewer, M.S., Ky, B., Scherrer-Crosbie, M., *et al*. (2014) Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*, **27**, 911-939. https://doi.org/10.1016/j.echo.2014.07.012

[16] Chen, T.Q., Fu, S.P., Ruan, H.D., *et al*. (2021) Three-Dimensional Speckle Tracking Imaging Combined with Myocardial Work to Evaluate the Effect of Anthracyclines on Left Ventricular Function in Breast Cancer Patients. *Chinese Journal of Ultrasound Medicine*, **37**, 539-542.

[17] Ke, Q., Xu, H., Bai, J., Xiong, L. and Li, M. (2020) Evaluation of Global and Regional Left Ventricular Myocardial Work by Echocardiography in Patients with Chronic Kidney Disease. *Echocardiography*, **37**, 1784-1791. https://doi.org/10.1111/echo.14864

[18] Galli, E., Vitel, E., Schnell, F., Le Rolle, V., Hubert, A., Lederlin, M., *et al*. (2018) Myocardial Constructive Work Is Impaired in Hypertrophic Cardiomyopathy and Predicts Left Ventricular Fibrosis. *Echocardiography*, **36**, 74-82. https://doi.org/10.1111/echo.14210

[19] Liu, X., Jiang, F., Zhong, X.Q., *et al*. (2020) The Value of Serum sST-2 and Galectin-3 in Monitoring Cardiotoxicity of Paclitaxel Combined with Platinum-Based Chemotherapy. *Journal of Practical Cancer*, **35**, 2080-2084.

[20] Deng, J.-H., Deng, J., *et al*. (2015) Clinical Outcome of Cisplatin-Based Chemotherapy Is Associated with the Polymorphisms of GSTP1 and XRCC1 in Advanced Non-Small Cell Lung Cancer Patients. *Clinical and Translational Oncology*, **17**, 720-726. https://doi.org/10.1007/s12094-015-1299-6

[21] Liao, Y.Y., You, Y.G., *et al*. (2023) Clinical Significance of Left Ventricular Stress-Strain Loop Technique in Assessing Left Ventricular Myocardial Function in Nasopharyngeal Carcinoma Chemotherapy Patients. *Chinese Journal of Modern Medicine*, **33**, 79-85.

[22] Papadopoulos, K., Özden Tok, Ö., Mitrousi, K. and Ikonomidis, I. (2021) Myocardial Work: Methodology and Clinical Applications. *Diagnostics*, **11**, Article 573. https://doi.org/10.3390/diagnostics11030573

[23] Galli, E., John-Matthwes, B., Rousseau, C., Schnell, F., Leclercq, C. and Donal, E. (2019) Echocardiographic Reference Ranges for Myocardial Work in Healthy Subjects: A Preliminary Study. *Echocardiography*, **36**, 1814-1824. https://doi.org/10.1111/echo.14494

[24] Jia, X.H., Kang, C.M., Shen, Y.M., e*t al*. (2024) Changes in Local Myocardial Function after Chemotherapy in Breast Cancer Patients Evaluated by Ultrasound Myocardial Performance. *Clinical Medicine Research and Practice*, **9**, 14-18.

[25] Jaber, M., Armand, A., Rochette, E., Monzy, S., Greze, V., Kanold, J., *et al*. (2024) Anthracycline-Induced Cardiotoxicity on Regional Myocardial Work and Left Ventricular Mechanical Dispersion in Adolescents and Young Adults in Post-Lymphoma Remission. *Cancer Medicine*, **13**, e6857. https://doi.org/10.1002/cam4.6857

[26] Liu, F.Q., Ren, J.L. and Wang, Z.G. (2015) Research Progress of Echocardiographic Assessment of Cardiac Function in Patients with Metabolic Syndrome. *Chinese Journal of Medical Imaging*, **23**, 790-793.

[27] Russell, K., Eriksen, M., Aaberge, L., Wilhelmsen, N., Skulstad, H., Gjesdal, O., *et al*. (2013) Assessment of Wasted Myocardial Work: A Novel Method to Quantify Energy Loss Due to Uncoordinated Left Ventricular Contractions. *American Journal of Physiology-Heart and Circulatory Physiology*, **305**, H996-H1003. https://doi.org/10.1152/ajpheart.00191.2013

[28] Moya, A., Buytaert, D., Beles, M., Paolisso, P., Duchenne, J., Huygh, G., *et al*. (2023) Serial Non-Invasive Myocardial Work Measurements for Patient Risk Stratification and Early Detection of Cancer Therapeutics-Related Cardiac Dysfunction in Breast Cancer Patients: A Single-Centre Observational Study. *Journal of Clinical Medicine*, **12**, Article 1652. https://doi.org/10.3390/jcm12041652

[29] Roemer, S., Jaglan, A., Santos, D., Umland, M., Jain, R., Tajik, A.J., *et al*. (2021) The Utility of Myocardial Work in Clinical Practice. *Journal of the American Society of Echocardiography*, **34**, 807-818. https://doi.org/10.1016/j.echo.2021.04.013

[30] Donal, E., Galli, E., Hubert, A. and Bouzille, G. (2017) New Indices of Left Ventricular Function: Let's Move from Ejection Fraction to More Physiological Parameters. *The Journal of Physiology*, **595**, 3959-3960. https://doi.org/10.1113/jp274108