New advances in medical imaging technology for the evaluation of anthracycline-induced cardiotoxicity

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To *the Editor:* Anthracycline antibiotics are the core treatment strategy for breast cancer, hematological malignancies, and sarcomas. The main clinical drugs are daunorubicin and doxorubicin. Unfortunately, cumulative doses of anthracyclines can induce cardiac dysfunction in patients with tumors, such as cardiotoxicity, myocardial ischemia, or infarction, which in turn affects the tumor treatment.[1,2] Researchers found that anthracycline-in-duced cardiotoxicity (AIC) develops during or after treatment; however, the exact mechanism is unclear. Therefore, the optimal use of non-invasive cardiac examinations is necessary to control the drug side effects. Medical imaging technology has been reckoned to be the most effective method for the non-invasive detection of AIC. Therefore, to minimize the cardiac risk, a brief overview of the latest advances in medical imaging technology has been provided in this article.

Echocardiography has become the most commonly used monitoring method for cardiovascular complications during chemotherapy. The left ventricular ejection fraction (LVEF) is currently the most commonly used parameter for the detection and monitoring of AIC and is mainly determined using echocardiography. The American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) recommend the determination of LVEF. These recommendations mention two-dimensional echocardiography (2DE) left ventricular volumetric and LVEF calculations as an improvement over the Simpson technique. If at least two myocardial segments among the 16 myocardial segments do not adequately display the endocardial border, the ASE and EAE guidelines recommend the application of contrast agents. In addition, three-dimensional (3D) echocardiography LVEF seems superior to 2DE LVEF in terms of analysis time and reproducibility. In 1997, Otterstad *et al*[1] reported that 2DE could recognize differences in the measured values of LVEF up till 8.9%. In a recent study of cancer patients undergoing repeated echocardiography, the upper limit of the 95% confidence interval for longitudinal variability in 2DE LVEF measurements was 9.8%. In contrast, 3D LVEF provides 5.6% of the required longitudinal reproducibility level, making it the preferred method for the sequential measurement of LVEF during cancer treatment [Supplementary Table 1, http://links.lww.com/CM9/B20].

Cardiac magnetic resonance (CMR) was able to detect early changes in myocardial contrast and mild deterioration of cardiac function during anthracycline therapy. CMR places the natural magnetic rotation of atomic nuclei in an external magnetic field, and then disturbs the magnetic rotation of these nuclei by applying radio frequency pulses to produce a static and moving heart image. Magnetic resonance imaging (MRI) is safe and has excellent spatial resolution and time resolution with no radiation exposure, and the guidelines support the use of CMR for the assessment of cardiac response to chemotherapy. It is the gold standard technique for the non-invasive measurement of ventricular volume, quality, and function in a large patient population. Moreover, it can be used for the monitoring of patients who are away from chemotherapy or longitudinal detection of anthracycline-induced changes during treatment. However, CMR is limited by cost, availability, the application of metal devices, or the presence of advanced renal failure.

The exploration of biomarkers such as troponin T and/or pro-brain natriuretic peptide (BNP) can be used in conjunction with imaging techniques to diagnose early congestive heart failure or predict the risk of LV systolic dysfunction (LVD). Azambuja *et a1*[2] found elevated BNP followed by LVD in patients treated with anthracyclines. Unfortunately, there were no values for cardiac biomarkers before or during treatment to determine predictors of late LVD. However, they found that the trend of increased

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pro-BNP in patients receiving anthracycline therapy may support cardiac MRI findings.

CMR is a gold standard imaging technique for detecting myocardial edema and myocardial fibrosis. Farhad *et al*[3] studied the characterization of cardiac structure and function in mice treated with anthracyclines by using CMR imaging. The purpose of the study was to test whether CMR can be used to detect AIC. The authors found that anthracyclines are associated with acute cardiac edema, subacute myocardial fibrosis, edema, and fibrosis. The extent of early edema and subacute fibrosis may be associated with late doxorubicin-induced mortality in mice. They also evaluated the conventional cardiac structure and function in mice treated with anthracycline antibiotics. CMR is a powerful imaging technique for reliable and repeatable measurement of LVEF and is recommended for cardiac monitoring. It has been reported that baseline LVEF and LVEF reduction after anthracy-cline therapy could predict clinical cardiotoxic events. LVEF measurements are readily available with powerful markers but are associated with limitations in terms of AIC monitoring. In patients treated with anthracyclines, LVEF is usually normal despite extensive pathological evidence of cardiomyocyte injury. Furthermore, Hong[4] and his team demonstrated CMR to be a reliable non-invasive diagnostic method for myocardial T1 mapping, especially the determination of extracellular volume (ECV) values, and for the early diagnosis and continuous monitoring of chemotherapy cardiotoxicity.

Jordan *et al*[5] attempted to determine whether T1- and T2-weighted measurements of signal intensity are associated with decreased LVEF in patients receiving potentially cardiotoxic chemotherapy and enhanced myocardial contrast echocardiography. An increase in T1-weighted signal intensity is associated with cardiomyocyte injury and a decrease with the LVEF. These data indicate that changes in T1-weighted signal intensity can serve as early markers of subclinical lesions associated with the administration of potentially cardiotoxic chemotherapy in humans.

Jordan[6] and his team comparatively evaluated 54 cancer survivors who received either anthracycline-based ($n = 37$) or non-anthracycline-based ($n = 17$) chemotherapy and 236 cancer-free participants. All study participants underwent CMR examinations on a 1.5 T Siemens Avanto scanner with phased array chest coils for the assessment of native T1 time, LV volume, and LV mass. Myocardial endocardial and epicardial borders were manually drawn on the T1 and T2 maps to ensure exclusion of the LV blood pool and epicardial fat. The results of the study indicated that the ECV, measured using CMR, abnormally increased after 3 years of anthracycline-based chemotherapy. The study also showed an increase in ECV and subclinical myocardial fibrosis, consistent with LVEF and myocardial mass loss in adult cancer survivors.

Multiple blood pool imaging (MUGA) technology has been used to monitor LV function in patients receiving anthracycline therapy since the late 1970s. MUGA consistently outperforms standard 2DE in terms of the accuracy and repeatability of LVEF measurements, and one of the advantages of MUGA techniques is that they can facilitate the identification of most patients with poor echocardiographic windows. Notably, an early MUGA study reported that these studies were performed using a single-head small-field gamma camera that allowed optimal patient positioning to achieve optimal separation between the two ventricles, as well as tail tilt to avoid overlap with the left atrium. In contrast, current gamma cameras primarily have a large field of view or use dual-head systems that do not allow optimal patient positioning for patients. In addition, MUGA does not provide comprehensive information about right ventricular function, left atrial and right atrial size, and the presence of valve or pericardial disease; however, the biggest drawback of MUGA is radiation exposure.

Anthracycline cardiomyopathy is a major drawback of tumor chemotherapy. Although the underlying mechanisms of this adverse effect have not yet been fully elucidated, the interference of the drug with the respiratory chain and the subsequent oxidative stress appear to play important roles. This effect is ultimately accompanied by an increase in glucose consumption, characterized by increased uptake of fluorodeoxyglucose (FDG) by cardiomyocytes. However, the potential association between this uptake index and anthracycline cardiotoxicity has only been described in one case report, and its clinical potential remains uncertain. Therefore, Bauckneht *et al*[7] conducted a transformation study based on this report to verify whether evaluation of doxorubicin uptake based on cardiac FDG can predict advanced cardiotoxicity. To this end, they first validated the dose dependence of the effects of doxorubicin on myocar-dial metabolism, and analyzed a series of cancer mouse models previously studied by micro-positron emission tomography scans in the laboratory; they also evaluated a group of continuous PET/computed tomography (CT) scans obtained in Hodgkin's disease patients to determine the chronological order of the metabolic effects of doxorubicin and to verify their possible clinical relevance. The results of this study demonstrate that doxorubicin affects myocardial glucose consumption. The dose dependence of these effects is very pronounced and reproducible in animal experiments, and patients show largely heterogeneous effects depending on the baseline metabolic patterns. The relatively retained cardiac FDG findings suggest that the cardiac metabolism shows minimal response to doxorubicin. In contrast, patients with a low baseline tracer intake showed a systemic metabolic response to doxorubi-cin: the myocardial normalized standardized uptake value gradually increased during treatment, which increased glucose consumption status after treatment for several months. This metabolic pattern is associated with the onset of advanced electrocardiographic or echocardiographic abnormalities. Multivariate analysis confirmed that a low myocardial FDG uptake before treatment was the most effective predictor of subsequent cardiac changes, and its efficacy even exceeded the predicted values of recognized risk factors, such as mediastinal irradiation or total doxorubicin dose. The results of this study prove that ^{18}F-FDG PET/CT evaluations to observe the effect of doxorubicin on myocardial metabolism can not only predict an increase in

cardiac glucose consumption and cardiac abnormalities during and after chemotherapy but also optimize studies of myocardial metabolism. No further scans are required to select candidates for alternative or cardioprotective treatments. Other studies have also described that a significant increase in myocardial FDG uptake on PET/CT after treatment may be a potential imaging biomarker for doxorubicin-induced cardiotoxicity.

Some recent studies have used CT to detect diffuse myocardial fibrosis. These studies were primarily based on the theory that iodine contrast agents in CT and guanidine reagents in CMR have similar kinetics, molecular weights, and ECV distribution despite their different molecular structures. Dual-energy CT is an advanced imaging technique that provides additional information about material composition using two different X-ray spectral datasets. No previous reports have described ECV quantification by dual-energy CT in patients with diffuse myocardial fibrosis. Dual-energy CT[8] has been used to verify and evaluate the value of CT ECV in extracting the iodine component of the myocardium. One study compared CT ECV and parallel contrast-enhanced CMR measurements and assessed the histological collagen volume fraction in a rabbit model of adriamycin-induced dilated cardiomyopathy. The study also developed a color-coded graphics software with a percentage scale, which can be used to outline ECV on the map. This CT ECV map can reveal the changes in ECV at a glance. The study was a rare study to use dual-energy CT to evaluate CT ECV. To determine the appropriate scan parameters and the stable point of CT ECV, scans were performed at 3, 5, 7, 9, 11, 13, and 20 min after contrast injection. No significant changes were observed in the CT ECV values across the entire scan of all participants, and MR ECV also showed stable findings 3 min after contrast injection.

This study aimed to explore the progress in medical imaging technology used for the evaluation of AIC. Unfortunately, some of the latest research results have not been applied to clinical diagnosis on a large scale. However, the results described above indicate the applicability of imaging medical technology in diagnosing and monitoring the cardiotoxicity of chemotherapeutic drugs, providing more hope for researchers and a broader development space for future clinical applications.

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Conflicts of interest

None.

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