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MINIREVIEWS

Nuclear imaging in detection and monitoring of cardiotoxicity

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Abstract

Cardiotoxicity as a result of cancer treatment is a novel and serious public health issue that has a significant impact on a cancer patient's management and outcome. The coexistence of cancer and cardiac disease in the same patient is more common because of aging population and improvements in the efficacy of antitumor agents. Left ventricular dysfunction is the most typical manifestation and can lead to heart failure. Left ventricular ejection fraction measurement by echocardiography and multigated radionuclide angiography is the most common diagnostic approach to detect cardiac damage, but it identifies a late manifestation of myocardial injury. Early non-invasive imaging techniques are needed for the diagnosis and monitoring of cardiotoxic effects. Although echocardiography and cardiac magnetic resonance are the most commonly used imaging techniques for cardiotoxicity assessment, greater attention is focused on new nuclear cardiologic techniques, which can identify high-risk patients in the early stage and visualize the pathophysiologic process at the tissue level before clinical manifestation. The aim of this review is to summarize the role of nuclear imaging techniques in the non-invasive detection of myocardial damage related to antineoplastic therapy at the reversible stage, focusing on the current role and future perspectives of nuclear imaging techniques and molecular radiotracers in detection and monitoring of cardiotoxicity.

Key words: Cardiotoxicity; Cardiac nuclear imaging; Early diagnosis; Scintigraphy; Positron emission tomography

Core tip: Cardiomyopathy is a potential complication of various anticancer drugs, such as anthracyclines and biological therapy. Left ventricular dysfunction is the most common manifestation of cardiotoxicity and is monitored with left ventricular ejection fraction measurement, but it is a late manifestation of myocardial injury. Thus, the cardiologist and oncologist should collaborate to identify new non-invasive techniques to detect cardiac dysfunction at an early and potentially reversible stage, before the onset of clinical manifestation. To achieve this aim, nuclear imaging techniques may offer good future perspectives for early detection of myocardial damage using novel molecular tracers.

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INTRODUCTION

Over the last few decades, early diagnosis and development of new antitumor agents have significantly improved the survival of cancer patients. However, conventional and new oncologic drugs frequently have a wide range of cardiac adverse effects, in particular myocardial toxicity. Anthracyclines (doxorubicin, epirubicin), cyclophosphamide, monoclonal antibodies (trastuzumab) and other tyrosine kinase inhibitors (TKIs) are antineoplastic drugs more frequently associated with cardiotoxicity[1]. These drugs may cause irreversible damage, such as that induced by anthracyclines, through free radical production, adrenergic function alteration and cardiac myocyte death due to calcium overload[2,3], or potential completely reversible dysfunction, like that related to TKI administration[4].

Left ventricular (LV) dysfunction is the most typical manifestation of cardiotoxicity and it contributes to increased mortality during chemotherapy[5]. Cardiotoxicity has been defined by the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials[6] as: (1) a decrease in cardiac LV ejection fraction (EF), either globally or more severe in the septum; (2) the onset of symptoms associated with congestive heart failure (HF); (3) the presence of signs associated with congestive HF; and (4) a reduction in LVEF from baseline of at least 5% to below 55% with signs and symptoms of congestive HF, or a decline in LVEF of at least 10% to below 55% without signs and symptoms of congestive HF. The serial assessment of LVEF is the most common modality for detection of cardiotoxicity and a reduction more than 10% from baseline or a decrease in LVEF below 50% are considered interruption criteria for anticancer drugs administration[7-9]. Notwithstanding, guidelines do not specify the timing and the duration of follow-up and what technique is preferable to assess LV function during and after cancer treatment[10].

Echocardiography (ECHO) plays an important role in evaluation and monitoring of cancer patients treated with cardiotoxic antineoplastic drugs due to its availability and repeatability. Conversely, inter- and intra-observer variability during serial measurement of LVEF and underestimation of myocardial contractile dysfunction should be considered. To overcome these limitations, novel echocardiographic techniques, such as tissue velocity imaging and strain imaging, could be used to detect the presence of myocardial contractile dysfunction before impairment of LVEF[11].

In addition, cardiac magnetic resonance imaging (CMR) is a well recognized imaging technique to screen chemotherapy-related cardiomyopathy[12]. It provides reproducible and noninvasively assessment of LV volume, mass and function[13,14]. Moreover, several studies[13,15,16] emphasized its role in early detection of myocardial damage, however high cost and low availability limit clinical routine use.

Although ECHO and CMR are the two most commonly used imaging techniques for non-invasive chemioterapic myocardial toxicity assessment, nuclear imaging may still have a role in the evaluation and monitoring of cancer patients treated with cardiotoxic drugs. Besides providing sensitive and accurate estimation of LVEF, nuclear imaging techniques using specific radiotracer molecules represent an emerging tool for non-invasive detection of biological processes preceding anatomical involvement and physiological consequences of myocardial damage induced by antineoplastic drugs (Tables 1 and 2).

In this review we will summarize the role of nuclear cardiology in the non-invasive detection of myocardial damage related to antineoplastic therapy, focusing on the current role and future perspectives of nuclear imaging and molecular radiotracers in the assessment of cardiac toxicity.

^{99M}TC-MUGA

Multigated radionuclide angiography (MUGA) is a non-invasive technique using ^{99m}Tc-erythrocytes to visualize the cardiac blood pool through a γ camera with gated acquisition[17]. The series of heart planar images at each stage of the cardiac cycle permit accurate and highly reproducible quantification of LV volumes and LVEF during cancer therapy[18]. However, its use may be hampered by soft tissue attenuation artifacts and may expose patients to ionizing radiation[14,19]. In 28 patients treated with increasing cumulative doses of doxorubicin for non-Hodgkin lymphoma, Nousianen *et al*[20] documented that a MUGA scan had 90% sensitivity and 72% specificity for predicting development of chronic HF. However, the results of this little prospective study were not confirmed by a large retrospective study[21] conducted on 630 patients randomized to increasing dose of doxorubicin or placebo. In fact, Swain *et al*[21] observed that 66% of patients experiencing doxorubicin-related chronic HF showed no clinically relevant decline in LVEF value assessed by MUGA scan from baseline levels (ranging from 0 to 30% of the absolute value), suggesting that it is not accurate in HF prediction.

^{99m}TC GBPS

^{99m}TC gated blood-pool SPECT (single photon emission computed tomography) is a nuclear technique enabling acquisition of 3-dimensional scanned images. ^{99m}TC gated blood-pool SPECT provides information on LVEF, right ventricular EF and wall motion useful for monitoring and personalizing therapy in HF patients[21]. A good cor-

Table 1 Radiotracer for cardiac nuclear imaging

Technique	Tracer	Action
SPECT		
	^{99m}Tc-erythrocyte	Contractile function
	^{111}In-antimyosin	Imaging necrosis/cell death
	^{123}I-MIBG	Neuronal imaging(presynaptic uptake and storage)
	^{111}In-Tz	Therapeutic target imaging
	^{99m}Tc-annessin V	Imaging necrosis/cell death
	^{123}I-BMIPP	Fatty acid use
PET		
	^{18}F-FDG	Glucose metabolism
	Presynaptic tracers	Visualize inhibition of neurotransmission
	true catecholamines	
	^{18}F-6-fluorodopamine	
	^{11}C-epinephrine	
	catecholamine analogs	False neurotransmitters
	^{11}C-HED	
	^{11}C-phenylephrine	
	^{18}F-6-fluoro-metaraminol	
	Postsynaptic tracers	Visualize transmission of sympathetic signal to target tissue
	^{11}C-CGP12177	
	^{11}C-CGP12388	
	^{11}C-GB67	

SPECT: Single photon emission computed tomography; PET: Positron emission tomography; HED: Hydroxyephedrine; FDG: Fluorodeoxyglucose; ^{123}I-BMIPP: ^{123}I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid.

relation between gated blood-pool SPECT and MUGA in LVEF estimation was documented[22]. However, gated blood-pool SPECT tends to underestimate LVEF values (33% ± 13%)[23] compared with MUGA (41% ± 14%, P = 0.001), first-pass radionuclide ventriculography (45% ± 13%, $P < 0.0001$) and echocardiography (37% ± 15%, P = 0.004).

^{111}IN-ANTIMYOSIN SPECT

The immunoscintigraphic agent ^{111}In-antimyosin is a specific marker for myocardial cell injury and necrosis, binding to intracellular myosin when sarcolemma disruption occurs and the cell is irreversibly damaged. It has been studied in myocardial infarction, myocarditis, cardiac transplant rejection and anthracycline cardiotoxicity[24].

^{111}In-antimyosin SPECT can play a role in subclinical assessment of LV dysfunction as documented in several studies[24,25]. Estorch *et al*[25] showed an increased uptake of ^{111}In-antimyosin after anthracycline chemotherapy (doxorubicin or mitoxantrone) in breast cancer patients without cardiovascular risk factors or previous chemotherapy or mediastinal radiotherapy, and the degree of myocardial antimyosin uptake was associated with changes in LVEF. Moreover, the presence in some patients of radiotracer uptake not associated with a significant reduction in LVEF after chemotherapy suggested the potential use of this technique to detect cellular damage before the onset of LV functional impairment, allowing the identification of patients at risk of HF. Similar results have also been obtained by Carrió *et al*[24], who documented a significant reduction in LVEF after chemotherapy in patients treated with an anthracycline dose of 420-600 mg/m^2 ($P < 0.001$) and no significant change in patients treated with a dose of 240-300 mg/m^2. Moreover, patients with heart-to-lung ratio (HLR) $\geqslant$ 1.90 at a cumulative anthracycline dose of 240-300 mg/m^2 developed a reduction in LVEF greater than 10% at a subsequent cumulative doxorubicin dose of 420-600 mg/m^2. These data encouraged the use of antimyosin scintigraphy to identify patients with a high risk of developing systolic LV dysfunction when treated with an increasing dose of chemotherapeutic drugs. In addition, Valdés Olmos *et al*[26] observed that patients with a persistent reduction in LVEF after chemotherapy had a significantly higher HLR value (1.83 ± 0.37) than patients with transient LVEF decrease (1.52 ± 0.21; $P < 0.01$), revealing that cardiac uptake of ^{111}In-antimyosin could also be useful in discriminating between patients with transient and persistent LV dysfunction and in guiding clinical decisions about discontinuation of anthracycline therapy.

^{123}I-METAIODOBENZYLGUANIDINE SPECT

^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) SPECT is a promising technique for detection of early anthracycline injury and for identification of patients at high risk of developing cardiotoxicity.

Chemotherapy-induced cardiomyopathy activates a compensatory response that increases adrenergic sympathetic and renin-angiotensin system activity to preserve organ perfusion[27]. In patients with chronic HF, increased norepinephrine (NE) release, depletion of NE deposits and downregulation of human NE transporter (hNET1)

Table 2 Techniques used for detection of anticancer therapy cardiomiopathy

Methods	Advantages	Limits
Echocardiography	Non-invasive	Inter- and intra-observer variability
	Absence of adverse effects	Low sensitivity of EF assessment for early diagnosis
	Analysis of systolic and diastolic function	
	Tissue velocity imaging and strain imaging useful for early detection of subclinical alteration	
Magnetic resonance imaging	Accurate heart anatomic description	Limited availability
	Absence of radiation exposure	High costs
	Accurate and reproducible EF assessment	Not applicable in patients with metallic device
	Cardiac innervation assessment	Low information about its role in the early detection
Multiple-gated acquisition scintigraphy	High sensitivity and specificity EF assessment	Low sensitivity of EF for early diagnosis
	No inter- and intra-observer variability	Less information about diastolic function
		Radiation exposure
Positron emission tomography	Myocardial metabolic and perfusion evaluation	Limited availability

EF: Ejection fraction.

have been shown[28]. ^{123}I-MIBG is a norepinephrine analogue, showing the same uptake, storage and release mechanisms of NE. Unlike NE, MIBG is not metabolized by catechol-o-methyl transferase and monoamine oxidase[29]; so, labelled with ^{123}I, it can be used to generate scintigraphic images of cardiac efferent sympathetic innervation. After ^{123}I-MIBG administration, early (15 min) and late (4 h) post injection images are acquired to determinate heart to mediastinal ratio (H/M) and washout rate (WR). Consequently, increased NE in the cardiac synaptic space and a reduction in the presynaptic space, induced by HF, reduced MIBG cardiac uptake and accelerated the washout rate.

Studies[30,31] conducted in asymptomatic patients treated with anthracyclines revealed that ^{123}I-MIBG was useful for assessment of myocardial adrenergic derangement and identification of patients at risk of developing cardiotoxicity. In addition, in 36 patients undergoing MIBG scintigraphy who had a diagnosis of sarcoma and no history of cardiac disease or previous cancer treatment, Carrió *et al*[30] found an insignificant decrease in LVEF and MIBG uptake at an intermediate cumulative dose of doxorubicin (240-300 mg/mg^2). However, when a high cumulative dose of doxorubicin 420-600 mg/m^2 was used, the experimenters documented a significant impairment of ^{123}I-MIBG uptake ($P < 0.001$) and a reduction in LVEF ($P < 0.05$), and proposed that the degree of H/M reduction was also correlated with the dose of anthracycline administrated.

^{111}IN-TRASTUZUMAB SPECT

In cancer patients, anthracyclines can increase the levels of human epidermal growth factor receptor 2 (HER2) expressed by myocytes. In patients pre-treated with anthracyclines, trastuzumab, a chemotherapic agent with a direct effect on HER2, often causes cardiotoxicity, likely as a result of the inhibition of cardiac HER2 that activates the apoptotic pathways and amplifies anthracycline oxidative stress. Thus, ^{111}In-trastuzumab (^{111}In-Tz) SPECT can be used to evaluate the myocyte HER2 expression and the risk of development LV dysfunction in patients treated with this drug[32].

In a small study, Behr *et al*[33] investigated ^{111}In-Tz scintigraphy in 20 patients with metastatic breast cancer expressing the HER2/neu receptor, pre-treated with anthracyclines and scheduled for administration of Tz as second-line therapy. They documented myocardial ^{111}In-Tz uptake prior to Tz in 7 patients; of these, 6 developed clinical HF (II-IV NYHA class), whereas none of 13 patients without uptake had adverse cardiac events, suggesting that pre-treatment scanning with ^{111}In-Tz could predict cardiotoxicity. In contrast to these results, Perik *et al*[34] documented increased ^{111}In-Tz uptake at the start of trastuzumab therapy only in 1 of 17 studied patients, who had received extensive anthracycline pre-treatment, and normal ^{111}In-Tz uptake at baseline scintigraphy in 3 patients who developed Tz-induced cardiomyopathy.

^{99M}TC-ANNEXIN V SPECT

Apoptosis of myocardial cells plays a critical role in the onset of cardiomyopathy and has been observed in several conditions, such as hypoxia, ischemia, cardiac overload, acute myocardial infarction, anthracycline-induced cardiomyopathy and end-stage HF. In apoptotic cells, the early stage is characterized by activation of proteases and sphingomyelinases and consequent exposure of phosphatidyldserine molecules on the outer surface of the cell membrane. ^{99m}Tc-annexin V has a high affinity for the exposed phosphatidylserine molecule and thus allows imaging of apoptotic cell death[35].

In animals, annexin V scintigraphy has been used to assess acute and chronic doxorubicin-induced cardiomyopathy based on early apoptosis. Increased ^{99m}Tc-annexin V uptake was observed in the myocardium of doxorubicin-treated animals and cardiac oxidative stress was confirmed by histological analysis[36,37].

Further studies are needed of the clinical use of this radiotracer, in particular early identification of myocardial

damage related to antineoplastic drugs.

^{123}I-15-(P-IODOPHENYL)-3-(R,S)-METHYLPENTADECANOIC ACID SPECT

Taxanes are used in the treatment of breast, lung and ovarian cancer, and they can cause ischemia, arrhythmias and HF. Taxanes can impair the microtubular transport system in cardiomyocytes, resulting in failure to store free fatty acids in the cytosol lipid pool and impairment of mitochondrial free fatty acid uptake for beta-oxidation. ^{123}I-15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (^{123}I-BMIPP) scintigraphy has been used to assess this biochemical perturbation in free fatty acid oxidation[38]. Saito *et al*[38] showed significantly lower BMIPP uptake scores after chemotherapy than those before treatment (23.4 ± 3.4 *vs* 26.6 ± 0.8, $P < 0.001$). Moreover, 6 of 25 studied patients, who developed LV dysfunction, also had a significant decrease in total BMIPP uptake scores, suggesting the use of ^{123}I-BMIPP SPECT for detecting of taxane-induced cardiotoxicity. The value of ^{123}I-BMIPP in prediction of cardiotoxicity was also documented in 36 patients with various malignancies treated with doxorubicin[39]. In this study, Saito *et al*[39] showed a significant dose-related reduction in ^{123}I-BMIPP uptake (0.095 ± 0.25 *vs* 0.071 ± 0.019; $P < 0.001$) after doxorubicin chemotherapy and a higher rate of LV dysfunction development in patients with decreased uptake, but with normal LVEF at echocardiography.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is the gold standard technique to assess myocardial metabolism and perfusion due to its high spatial and temporal resolution and high diagnostic sensibility and accuracy. Cardiac PET radiotracers are divided into two categories, those evaluating myocardial perfusion and those evaluating myocardial metabolism.

In the cardio-oncologic field, PET is useful for the diagnosis of metastatic lesion and assessment of the response to chemotherapy. However, fluorine-18-fluorodeoxyglucose (^{18}F-FDG)-PET imaging is used to monitor the response to treatment of primary cardiac lymphoma[40,41] and to evaluate metastatic pericardial involvement[42]. The role of PET in the early detection of cardiotoxicity is still debated. Nony *et al*[43] showed a significant decrease in LVEF ($P = 0.046$) assessed by radionuclide angiography after treatment with doxorubicin, but no significant effect was observed in myocardial blood flow evaluated with PET in 6 female cancer patients without heart disease. Recently, Borde *et al*[44] analyzed changes in myocardial glucose metabolism using FDG-PET and suggested increased glucose utilization was evidence of cellular alteration preceding the cardiotoxicity cascade in patients treated with adriamycin.

Like SPECT, PET imaging can play a key role in the evaluation of cardiac autonomic dysfunction associated with HF[45]. PET provides several advantages over SPECT, with higher spatial and temporal resolution and routinely available attenuation correction. In addition, PET radiotracers more closely resemble the endogenous neurotransmitters than ^{123}MIBG used for SPECT imaging, and the variety of available tracers may allow for more detailed analysis of neuronal signalling[46]. There are two types of presynaptic positron-emitting tracers to assess the presynaptic sympathetic integrity in the heart, radiolabeled catecholamines and radiolabeled catecholamine analogs. The first type behaves identically to endogenous neurotransmitters, thus it is metabolically active and can complicate kinetic data analysis. Catecholamine analogs work as false neurotransmitters and are incapable of following the entire metabolic pathway of true catecholamines. Instead, postsynaptic tracers transmit the sympathetic signal to target tissue. Compared with the availability of presynaptic tracers, only a small number of tracers for postsynaptic neuronal imaging are clinically used. Experimental studies showed a significant reduction in the amount of LV β-adrenoceptors[47] and ^{11}C-hydroxyephedrine in HF catecholamine uptake[48,49] associated with LV dysfunction. Thus, studies are needed to validate this new radiotracer in the cardio-oncology field.

However, the complexity of most of the radiolabeling ligands, the requirement of laborious and specific knowledge, the high cost and the low availability limit clinical use of PET.

CONCLUSION

Cardiotoxicity is one of the principal adverse effects of anticancer therapy of clinical and prognostic importance. LVEF reduction is the most valid criterion to assess the presence of myocardial damage during or after chemotherapy. However, changes in LVEF occur when a critical amount of myocardial damage has taken place and compensatory mechanisms are exhausted[50]. Thus, cardiologists and oncologists should work together to identify new non-invasive, sensitive and non-expensive diagnostic tools that can accurately recognize cardiotoxicity at the subclinical stage to reduce cardiac morbidity and mortality in cancer patients. Further interesting future perspectives in early detection of myocardial damage are offered by nuclear imaging using new molecular tracers which may be able to identify patients at high risk of developing LV dysfunction during and after cancer treatment. Several studies are needed to validate the clinical application of new molecular markers for the identification of early cellular damage.

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