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Review article

Emerging Cardiac Imaging Modalities for the Early Detection of Cardiotoxicity due to Anticancer Therapies

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ABSTRACT

The undeniable advances in the field of oncology have finally led to a decrease in overall cancer-related mortality. However, this population of long-term cancer survivors is now facing a shift toward a substantial increase in cardiovascular morbidity and mortality. Because the development of overt cardiotoxicity can be associated with poor outcomes, preclinical identification of cardiac toxicity is important. This will promote early instauration of treatments to prevent overt heart dysfunction and allow oncologists to continue cancer therapy in an uninterrupted manner. Surveillance strategies for the early detection of cardiac injury include cardiac imaging and biomarkers during treatment. In this review, we outline existing cardiac imaging modalities to detect myocardial changes in patients undergoing cancer treatment and in survivors, and their strengths and limitations.

Nuevas técnicas de imagen cardiaca en la detección precoz de cardiotoxicidad secundaria a tratamientos oncológicos

Palabras clave:
Cardiotoxicidad
Quimioterapia
Insuficiencia cardiaca
Ecocardiografía

RESUMEN

Los indudables progresos en el campo de la oncología han disminuido la mortalidad secundaria al cáncer. Sin embargo, esta población de larga supervivencia se enfrenta ahora a un aumento de la morbimortalidad cardiovascular. Dado que la aparición de cardiotoxicidad se asocia con mal pronóstico, identificarla en una fase subclínica es importante para promover el inicio precoz de tratamientos cardioprotectores y evitar interrupciones del tratamiento oncológico. Las estrategias de detección precoz de la cardiotoxicidad incluyen el uso de biomarcadores y técnicas de imagen cardiaca. Este artículo revisa las técnicas de imagen disponibles, con sus ventajas y limitaciones, para detectar alteraciones precoces de la función miocárdica de pacientes en tratamiento antitumoral y en supervivientes al cáncer.

INTRODUCTION

Advances in the early detection and treatment of malignancies have resulted in a 20% decline in cancer mortality.[1] However, cardiovascular disease (CVD) has become an important competing risk for morbidity and mortality in cancer survivors.[2] For example, in breast cancer survivors older than 66 years who survived more than 5 years, CVD exceeds breast cancer as the leading cause of death.[2] This heighted risk of CVD is due to a combination of shared risk factors for cancer and CVD, the direct impact of cancer therapy on the cardiovascular system, and the gap in the cardiac care of patients with cancer.[3–5] Optimization of preexisting conditions before treatment is important, but is unlikely to be sufficient as a sole strategy to prevent CVD. Particularly for the prevention of cancer therapy-related heart failure (HF), strategies to identify early myocardial injury are needed so that targeted therapy can be instituted to prevent overt HF. Cardiac imaging and serum biomarkers have been demonstrated to be key strategies in identifying early myocardial injury. Serum biomarkers have shown tremendous promise but have some limitations, including the lack of clarity on the best biomarker to use, the timing of measurements, and the thresholds to define abnormality.[6] There has been increasing enthusiasm for the use of cardiac imaging to detect cardiac injury as it provides direct assessment of myocardial function.[7] In this review, we outline existing cardiac imaging modalities to detect myocardial changes in patients undergoing cancer treatment and in survivors and their strengths and limitations. We also provide some practical suggestions for clinicians involved in the cardiac care of patients with cancer.

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Abbreviations

2DE: 2-dimensional echocardiography
3DE: 3-dimensional echocardiography
CMR: cardiac magnetic resonance
CT: computed tomography
CTRCD: cancer therapy related cardiac dysfunction
CVD: cardiovascular disease
GLS: global longitudinal strain
LVEF: left ventricular ejection fraction

3D ECHOCARDIOGRAPHY

Controversies in the Definition of Cardiotoxicity

Different definitions of cardiotoxicity have been used historically with practical implications for how patients are managed.[8] The strongest controversy concerns the definition of cancer therapy-related cardiac dysfunction (CTRCD) both in clinical trials and consensus documents.[3,9] In the modern era, overt clinical HF and cardiac death occur in 5% to 6% of treated patients.[10,11] Asymptomatic deterioration in left ventricular ejection fraction (LVEF), associated with a higher incidence of symptomatic HF is documented in as many as 20% of patients depending on the cancer treatment.[12–14]

All definitions of CTRCD are based on a serial decline in LVEF. Unfortunately, there are no universal threshold changes to define CTRCD. The American Society of Echocardiography Consensus document defines CTRCD as a LVEF drop $\geq$ 10% to a value of $<$ 53%,[15] based on new American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) recommendations for chamber quantification.[16] These recommendations have been endorsed by the Canadian Cardiovascular Consensus Statement.[17] Recently, the European Society of Cardiology 2016 position paper considers the lower limit of normal LVEF by echocardiography as 50%, in line with the definition commonly used in registries and trials in patients with cancer.[18]

Independent of normal reference ranges, relative changes between baseline and follow-up LVEF are needed to appropriately identified CTRCD. If LVEF decreases $>$ 10% to a value below the lower limit of normal, angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) in combination with beta-blockers are recommended (unless contraindicated) to prevent further left ventricular (LV) dysfunction or symptomatic HF.[15,17,18] If LVEF decreases $>$ 10%, to a value that does not drop below the lower limit of normal, patients should undergo repeat assessment of LVEF promptly. In addition, these patients should be considered for advance echo imaging monitoring to avoid delays in HF therapy initiation.[15,17,18]

This article focuses on the ASE definition of CTRCD (lower limit of normal considered as an LVEF $<$ 53%) to improve the early detection and prompt therapy of cardiotoxicity, which are crucial for substantial recovery of cardiac function.[19,20] In fact, Wang et al.[11] demonstrated that even normal LVEF within 5 points of the lower limits of normal was associated with a near-to-3 fold increase in the rate of cardiac events in patient treated with anthracyclines

We Need Precise LVEF Measurements: Pros and Cons of 3DE-LVEF

In cancer patients, serial evaluation of LVEF must be reliable enough to identify true changes in ventricular function leading to subsequent clinical and therapeutic decisions.[21] While the imaging modality for monitoring should be based on local institutional expertise, 2-dimensional echocardiography (2DE) is increasingly used due to its widespread availability and safety. This modality allows for characterization of systolic and diastolic function, pulmonary pressures, valvular function, right ventricular function, and the pericardium. Digital storage of images is advisable to allow visual comparison in doubtful cases. The recommended method for 2DE-LVEF quantification is the modified Simpson's biplane method.[16] However, due to various factors (reader experience, geometrical assumptions or suboptimal endocardial border definition), 2DE-LVEF has low sensitivity for the detection of small changes in LV function and has a reported test-re-test variability ranging from 9% to 10.8%, which is higher than the threshold used to define CTRCD.[22] Contrast agents and automated contour detection may be used to reduce variability. In fact, in the study by Cannesson et al.,[23] automated 2DE-LVEF measurements had lower interobserver variability (3.4%) than the manual biplane method (9.8%).

Three-dimensional echocardiography (3DE) provides a compelling alternative with many advantages similar to cardiac magnetic resonance (CMR) imaging.[16] It increases the ability to detect smaller changes in LVEF, with a higher reproducibility than 2DE when compared with CMR.[24] Three-dimensional echocardiography volume measurements are independent of LV geometric assumptions or apical foreshortening (Table 1). The reduced observer and test-re-test variability in 3DE is at least partially attributable to the automated endocardial tracing.[25] In a recent study, Thavendiranathan et al.[26] followed up 56 women undergoing chemotherapy by 2DE and 3DE at 3 monthly intervals for 1 year to determine the technique with the least variability. The use of noncontrast 3DE provides lower temporal variability than 2D-LVEF (5.8 vs 9.8%), which is of the utmost importance in these patients.

The reproducibility of 3DE may be of particular importance in patients with low normal LVEF. In 114 adult survivors of childhood malignancies treated with chest radiation and/or anthracyclines, 16 (14%) were found to have LVEF $<$ 50% by CMR as the reference standard, but 10 of the 16 were misclassified by 2DE as having preserved LVEF by the biplane method.[27] On average, 2DE overestimated LVEF by 5% (mean LVEF 56% in CMR, 55% in 3DE, and 61% in 2DE by biplane) and had wider ranges and limits of agreement. 3DE-measured LVEF was the most sensitive echocardiography parameter to identify a LVEF $<$ 55% with CMR. Based on these results, it was suggested that 2DE-LVEF at the lower limits of normal (range of 50%-59%) warrants particular attention and may require further cardiac evaluation to rule out cardiac dysfunction.[28]

The ASE, the EACVI, the European Society of Cardiology and the Canadian Cardiovascular Consensus Statement recommend serial imaging with calculated LVEF by the best method available in an echocardiography laboratory.[15,17,18] Today 3DE is the preferred technique for the longitudinal monitoring of LVEF in cancer patients.[26,29] Fully automated software decreases 3DE-LVEF measurement variability, is timesaving and will help facilitate the integration of 3DE into clinical practice.[30] Operator expertise, standardized approaches, and quality improvement initiatives within the echocardiography laboratory are required to achieve the superiority of 3DE-LVEF.[16,24] The latter is particularly important given that changes as small as 10% in LVEF are commonly used to define CTRCD and to initiate cardioprotective therapies.[15,17,18]

Tips and Tricks for Daily Practice

Image acquisition in 3DE is similar to 2DE with a 1 to 2 minute acquisition time from the apical position (Table 2).[16,25] Two to

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