Future CARDIOLOGY

COMMENTARY

Special Focus Issue: Cardio-oncology

Strain imaging to detect cancer therapeutics-related cardiac dysfunction: are we there yet?




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Cardio-oncology

With increasing survival of patients with cancer, an important cause of morbidity and mortality has become cancer therapeutics-related cardiac dysfunction [1]. This has inspired new collaborative efforts between doctors interested in addressing the cardiovascular side effects of cancer therapy and maximizing cardiovascular outcomes for cancer survivors. Now, multidisciplinary teams have been forged including cardiologists, oncologists and radiation oncologists who have come together in a formal way to address these emerging trends and the field of cardio-oncology has emerged. This already broad intersection between heart disease and cancer will continue to grow because of shared risk factors – both disease groups show rising prevalence with age while there is also an increasing awareness of the oncological hazard of 'traditional cardiovascular risk factors' such as obesity, physical inactivity and smoking.

Cancer therapeutics-related cardiac dysfunction

Type I chemotherapeutic agents (e.g., anthracyclines) cause cumulative dose-related permanent cardiac damage, with cellular death observable on biopsy specimens [2]. In contrast, type II chemotherapeutic agents (e.g., trastuzumab) cause reversible cellular dysfunction in a nondose-related manner, without distinct changes in biopsy specimens [3]. There are also newer chemotherapeutic agents coming on stream such as tyrosine kinase inhibitors and VEGF inhibitors, which may cause severe systemic arterial hypertension and ischemic events [4].

Prevalence of heart failure with chemotherapy varies somewhat in the literature depending on the population studied – in general, rates are higher in those with conventional risk factors, those with established heart disease and those receiving adjuvant radiotherapy. In one study, the increase in risk of heart failure with anthracyclines was in the order of 29% (hazard ratio = 1.8; $p < 0.01$) with an adjusted congestive heart failure-free survival rate of 74 versus 79% in untreated patients, 8 years after treatment [5]. A paper reviewing the major adjuvant trastuzumab trials found that up to 4% of enrolled patients experienced severe congestive heart failure during treatment [6]. In such patients, the

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rate of asymptomatic left ventricular (LV) dysfunction varied between 14 and 24% (higher in those with conventional risk factors), with the difference in LV ejection fraction (LVEF) often detectable within 3 months and typically associated with subepicardial linear delayed enhancement of the lateral wall of the left ventricle on cardiac MRI within 6 months follow-up [6–8]. Biomarkers also have the potential to provide value in the early detection of cardiotoxicity; for example, in patients exposed to trastuzumab, troponin-I was useful as a means to identify LVEF recovery which occurred less frequently in troponin-I-positive patients (35 vs 100%; $p < 0.001$) [9]. Similarly, in patients exposed to anthracyclines, brain natriuretic peptide levels could significantly predict subsequent hospitalization with heart failure and overall death [10].

Adding further complexity to assessment of the cardiac dysfunction is the fact that many cancer patients may receive type I and type II agents either sequentially or concurrently followed by adjuvant radiotherapy. Among patients who have received radiotherapy, cardiovascular disease is the most common nonmalignant cause of death [11]. The effects of radiation exposure on the heart are myriad and include complex latent effects such as valvular disease, pericardial disease, myocardial disease (diastolic dysfunction, fibrosis, dilated or restrictive cardiomyopathy), vascular disease (epicardial and microvascular coronary artery disease) and conduction system disease that combine to cause pancarditis and heart failure. A characteristic echo finding that should alert toward prior radiation exposure and radiation-induced cardiotoxicity is thickening of the aorto-mitral curtain, the extent of which has been shown to have strong adverse prognostic utility [12]. Risk factors for radiation-induced cardiotoxicity include total dose >30–35 Gy (>2 Gy/day), the volume of heart irradiated (direct vs tangential), younger age at treatment, longer time since exposure, concomitant cardiotoxic chemotherapy and the presence of conventional risk factors. In the past, radiation beams were directed at tumors with little awareness of potential cardiotoxicity so that the effects of prior radiation exposure especially in patients with left breast cancer and lymphoma continue to be seen. The prevalence of heart failure associated with radiotherapy is difficult to ascertain because heart-sparing techniques are now used to minimize the heart dose. The apparent increase in prevalence seen currently is likely attributable to the fact that radiation effects on the heart may not be evident for decades after treatment.

In patients that have developed cardiotoxicity, LVEF recovery and cardiac event reduction may be achieved if the cardiac dysfunction is detected early and modern heart failure treatment is promptly initiated [9]. There are limited data to suggest that continuous use of beta-blocker therapy is associated with a lower risk of new heart failure events [13]. The decision to withhold or reduce the dose of lifesaving chemotherapy or radiotherapy should be made in a careful and a collaborative way with other members of the multidisciplinary team including the treating oncologist/radiation oncologist.

Guidelines addressing imaging evaluation in cardio-oncology

Two guideline papers have recently been published offering expert consensus opinions regarding how to evaluate adult patients during and after cancer therapy as well as how to evaluate the cardiovascular complications of radiotherapy [14,15]. Cancer therapeutics-related cardiac dysfunction has been defined as a decrease in LVEF of >10% to a value <53% confirmed by repeated cardiac imaging 2–3 weeks later. Subclinical LV dysfunction has been defined as a relative decrease in global longitudinal strain of >15% confirmed by repeated cardiac imaging 2–3 weeks later.

These guidelines recommend baseline echocardiographic evaluation of LVEF prior to initiation of both type I and type II chemotherapeutic agents; with anthracyclines such as doxorubicin, repeat echo is recommended after a cumulative doxorubicin dose of 240 mg/m [2], every 50 mg/m [2] thereafter and 6 months after completion of therapy; with trastuzumab, repeat echo is recommended every 3 months during therapy and 6 months after completion of therapy [15].

After radiation exposure, screening echo is recommended at 10 years with reassessment thereafter at 5 yearly intervals. For patients considered at higher risk (left chest radiation, higher cumulative dose, younger patients, concomitant chemotherapy, cardiovascular disease or risk factors), screening with echo together with an ischemia evaluation (such as stress echo) is recommended to begin 5 years after radiation exposure with reassessment also at 5 yearly intervals [14].

The most widely used method to assess LV function in current practice is 2D echocardiography, through measurement of volumes during systole and diastole. It is, however, well-recognized that the measurement of LVEF is subject to measurement variability, which comes close to and on occasion may even be higher than the thresholds used to define cardiotoxicity. For this reason, in circumstances where two or more LV segments are not adequately visualized, the use of echo contrast to enhance endocardial definition and to allow more precise LVEF assessment is recommended. Indeed, LVEF calculation using 3D echocardiography offers optimal interobserver, intraobserver and test re-test variability so that this is the method of choice for serial echo assessment to detect cancer therapeutics-related cardiac dysfunction [16]. Because of the limitations associated with LVEF assessment, there is growing interest in other echocardiographic parameters primarily myocardial deformation or strain as a means to routinely screen for subclinical ventricular dysfunction in at-risk patients.

Strain imaging

Strain is defined as the magnitude of regional change in myocardial deformation (percent change in dimension). Strain assessment via speckle-tracking echocardiography utilizes the method in which natural acoustic markers in gray scale images form interference patterns within the myocardial tissue. After filtering out random noise, small segments of myocardium with temporarily stable and unique speckle patterns called kernels are identifiable which can then be tracked on an automatic frame-to-frame basis during the cardiac cycle. Speckle-tracking technology involves measurement of the instantaneous distance between two kernels, that allows for regional assessment in a relatively angle-independent manner. By using an average value from multiple regions, a more global measure of LV function can be evaluated. Most notably, global longitudinal strain is obtained by averaging values of longitudinal strain from three standard apical projections and has increasing validation as a relevant clinical marker for LV dysfunction.

Negishi *et al.* measured global longitudinal strain via speckle tracking in breast cancer patients and showed that strain was an independent predictor of reduction in LVEF and was incremental to established predictors for chemotherapy-induced cardiotoxicity [17].

Thavendiranathan *et al.* recently published an important systematic review concluding that strain indeed had value for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy [18].

Strain imaging has also been used to detect subclinical radiation therapy-induced cardiotoxicity in modern day breast cancer patients. Although no changes were observed with conventional echocardiography, a decrease in global strain and anterior wall strain (regional site of largest mean dose) was observed at all postradiation treatment time points for left-sided patients but not for right-sided patients [19].

Interpretation of the strain data

In our lab, we consider a value of -18% to be a typical normal value using EchoPAC (GE) software with -14.5% representing more than two standard deviations below normal. In order to try and eliminate inter-vendor differences, we try and do repeat studies on the same type of machine as on the prior study if possible. In general, the variability of strain seems to compare favorably to serial LVEF measurements – with an average coefficient of interobserver variation <4% and an average coefficient of intraobserver variation <6% [20].

When significant differences between serial studies are encountered, it is important that a careful side-by-side comparison of the current and prior echoes is performed to review for other potential confounding sources of variation. Given the limitations of LVEF and strain assessment, the treating physician needs to have an in-depth knowledge of potential sources of measurement variability as well as other possible clinical sources of variation including but not limited to volume status, hemodynamics (such as heart rate and blood pressure) and the presence of anemia. Indeed, in the setting of cancer patients undergoing cancer therapies, there may be an even greater likelihood that such potential confounding effects may be present and/or subject to change.

Limitations of strain

Normal values for strain are not universally accepted, while strain values are known to vary with age, gender and race. There is a learning curve in the measurement and interpretation of strain for both sonographers and physicians alike, making dedicated training and quality monitoring essential. Currently strain assessment

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via speckle-tracking echocardiography is mainly been used as a clinical utility in experienced echocardiographic laboratories and there is limited knowledge of the performance characteristics of strain in nonacademic centers where chemotherapeutic agents may also be administered. Adequate endocardial definition is an absolute requirement and in contrast to 2D imaging, the use of echo contrast typically interferes with strain assessment. Another impediment to strain measurement is heart rate variability – an averaged value for global longitudinal strain is not obtainable should heart rate vary excessively. Optimization of image acquisition parameters such as frame rate (40–60 frames/s is recommended) is important to ensure adequate image quality for optimal tracking. Inter-vendor variability also needs to be taken into account – this is accounted for by differences in image post-processing algorithms including the extent of the myocardial wall included in the analysis which unfortunately has resulted in discordant inter-vendor results for 2D strain measurements and some heterogeneity in the published literature.

Future perspective

The current guidelines to diagnose cancer therapeutics-related cardiac dysfunction stress the need for the drop in LVEF or strain to be sustained (confirmed by repeated cardiac imaging 2 to 3 weeks later). In an era of proposed multiple testing, the need to be able to distinguish 'noise' from 'real change' has become increasingly important. It is cautionary to note that intertest variability of echo parameters such as LVEF and strain to date has generally only been performed assessing differences between two time points. But what is the true intertest variability when a test is performed multiple times? The high frequency of echocardiographic retesting as currently recommended by guidelines mandates that larger prospective trials not just be performed to assess intertest variability for multiple testing, but also to assess the variability of such parameters outside academic settings.

Equally, the intensive monitoring and high frequency of repeat testing endorsed by the current guidelines comes at high cost. Whether screening as currently recommended followed by intervention where necessary can deliver a reduction in hard end points like heart failure and death in this population is currently unproven. Cancer survivors that have had chemotherapy or radiotherapy clearly represent a vulnerable population. It is important that doctors who take care of such patients are not overzealous in their approach and continue to acquire more data to specifically address the utility and cost–effectiveness of these recommendations.

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