Empowering the Imagers with 3D-Speckle Tracking Echocardiography to Detect Subclinical Cancer Therapy-Related Myocardial Dysfunction

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Short Editorial related to the article: Empowering the Imagers with 3D-Speckle Tracking Echocardiography to Detect Subclinical Cancer Therapy Related Myocardial Dysfunction

Despite the expansion of the cardio-oncology field, defining cardiotoxicity to guide therapeutic decisions and impact prognosis is still a work in progress. The most widely recognized diagnosis of cardiotoxicity is based on serial changes in the left ventricular ejection fraction (LVEF). The ESC Position Paper recommends that if LVEF decreases by 10% to a value below the lower limit of normal (considered as an LVEF >50%), angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) in combination with beta-blockers are recommended to prevent further left ventricular (LV) dysfunction or the development of symptomatic heart failure.[1] However, different LVEF thresholds have been proposed by different authors and guidelines,[2,3] and the 2-dimensional (2D)-echocardiography LVEF depends on loading conditions (fluid status varies significantly in cancer patients), has low sensitivity for detecting small LV function changes, is subject to intra- and interobserver variability and relies on geometrical assumptions.[4] Hence, due to the limited availability of cardiac magnetic resonance imaging, 3D echocardiography is the preferred technique for monitoring cardiotoxicity in oncological patients, and the 3D-LVEF is the method of choice for cardiotoxicity surveillance.[5]

Because any grade of cancer therapy-induced myocardial dysfunction matters, a growing body of literature has explored the role of myocardial deformation analysis in patients receiving cancer therapy for early detection of myocardial damage before LVEF starts declining.[3] Speckle-tracking echocardiography (STE) allows quantitative assessment of global and segmental LV myocardial function by measuring strain in a manner largely independent of angle and ventricular geometry.[6] Compared with 2D-strain, 3D-strain has the advantage of tracking the speckle patterns in any direction and out-of-the imaging plane, offering additional deformation parameters (such as area strain) and a more comprehensive quantitation of LV geometry and function.[7,8]

Albeit a young technique, recent studies have already demonstrated the reliability and feasibility of 3D-echocardiography strain to assess the global and regional LV function in ischemic and non-ischemic heart diseases, to evaluate LV mechanical dyssynchrony and, to detect subclinical cardiac dysfunction in conditions at risk of overt heart failure, such as in cancer patients.[9] Differences between studies related to the technology, commercial software, and vendors (despite industry efforts for standardization), oncology drug regimes and dosages, type of cancer, and genetic background unable a fair judgment of the 3D-strain value in cardio-oncology.

In this issue of the *Arquivos Brasileiros de Cardiologia (ABC Cardiol)*, Y Guan et al.[10] reported the combined data of 9 prospective cohort studies, including 650 cancer patients (71% female) from China, Portugal, Romania, and Greece that assessed the value of 3D-STE to detect myocardial dysfunction related to oncological treatment.[10] The performance of 3D-global longitudinal, circumferential, and radial strains (GLS, GCS, GRS, respectively) and 3D-global area strain (GAS) against a gold standard definition of cardiotoxicity based on an LVEF decrease (thresholds varying from 5 to 10%) was summarized. Evidence on GLS is, undoubtedly, more abundant than for the other parameters, with 8 (out of 9) studies providing consensual data on its good performance; GLS sensitivity and specificity values that were pointed out in this meta-analysis were achieved, making it a potential candidate for immediate clinical use. However, GAS, a less studied 3D-strain metric, shined in this meta-analysis with a higher sensitivity (0.85, 95% CI: 0.70-0.93) and specificity (0.82, 95% CI: 0.78-0.86) than GLS (sensitivity of 0.81 [95% CI: 0.74-0.86] and specificity was 0.81 [95% CI: 0.68-0.90]. The better performance of GAS is not entirely surprising; GAS reflects the relative area change, and because it combines both the longitudinal and circumferential myocardial shortening, it can be regarded as an integrative parameter of myocardial deformation. Its particularly high sensitivity makes it an attractive measure to detect subtle myocardial dysfunction. The main limitation is still lacking data (only 4 studies reported data on GAS). Given their poor individual performance, it seems consistent that GCS and GRS may be out of this game.

Keywords

Tridensional Echocardiography/methods; Myocardium/diagnosis imaging; Cardiotoxicity; Myocardial Deformation; Left Ventricular Function

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A meta-analysis of studies in a growing field is always welcome. However, we, the readers, must be attentive to some aspects. First, the level of heterogeneity and source of bias; in this meta-analysis, the authors explicitly reflected on reasons for heterogeneity and assessed its impact on the summarized data by a meta-regression; no significant differences in 3D-STE performance were attributed to the type of cancer, cardiotoxicity definition, geographical area, and vendors. Second, no matter how promising the newer parameters look, they will never outperform the gold standard ("the LVEF master"); thus, these results cannot be interpreted as a prove that GLS/GAS are better than LVEF. Such a conclusion could only be made by a randomized controlled trial comparing side-by-side GLS *versus* LVEF. In the SUCCOUR trial (cardioprotection using strain-guided management of potentially cardiotoxic cancer therapy), a total of 331 anthracycline-treated patients were randomly allocated to cardioprotective therapy guided by a 12% reduction in GLS (n=154) or a 10% reduction in LVEF (n=153) groups; at 1-year follow-up, 3D-GLS-guided cardioprotective treatment significantly minimized the fall of 3D-LVEF to the abnormal range (no difference on baseline LVEF and GLS between groups).[11] These results support the use of 3D-GLS to start cardioprotective treatment. More problematic would be the decision to modify the cancer therapy and the impact that this action can have on patient outcomes. Currently, no established cut-off value for LVEF drop indicates the need to withdraw cancer treatment. This is, however, the level of myocardial damage that we want to avoid by detecting LV dysfunction at earlier minimal stages by super sensitive (and specific) imaging methods.

In this regard, the implementation of cardio-oncology programs is vital to enable risk stratification, treatment of established cardiovascular disease, early and late monitoring of cardiotoxicity, and adoption of cardioprotective strategies to complete oncological treatment without the need to withhold it because of cardiac impairment. Finally, we cannot forget that imaging captures only one aspect of the myocardial damage related to oncological drugs – myocardial dysfunction. Serum biomarkers (such as troponin and brain natriuretic peptides) as a first step even before imaging can be an alternative option to universally screen for myocardial dysfunction related to cancer therapy. For cardiovascular imagers, 3D-STE and GAS will certainly be the spotlight of future studies!

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