Imaging for Cardiotoxicity: Many Issues, Many Questions

Sebastian Szmit, MD, PhD

Department of Pulmonary Circulation and Thromboembolic Diseases, Centre of Postgraduate Medical Education, Poland

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INTRODUCTION

Cardiac imaging is a key area of interest in cardio-oncology. Early diagnosis of myocardial damage in the course of antineoplastic treatment makes it possible to predict further cardiovascular events, including the ones which occur many years after the treatment has been completed. Thus, the diagnosis becomes an indication for appropriate preventive measures. Some of the questions that remain to be answered include these of which imaging method should be selected, how sensitive echocardiography is in comparison with magnetic resonance, whether it is necessary to establish an independent central laboratory, and whether all patients undergoing anti-HER2 therapy should be subject to follow-up cardiac imaging tests performed every 3 months.

MAIN TEXT

Dinesh Thavendiranathan from the University of Toronto presented "The use of strain and newer echocardiography imaging techniques"

In the first part of his lecture, Thavendiranathan presented the role of 3D echocardiography and strain imagining in the diagnostics of cardiotoxicity. In the second part of his presentation, he initiated a discussion aimed at explicating the pathomechanism behind the abnormalities in strain during anti-cancer treatment. He also proposed different interventions to improve the prognosis of patients with diagnosed abnormalities in strain imaging.

For a long time now, there have been attempts at creating an optimum algorithm for the prediction of cardiotoxicity in breast cancer females treated with anthracyclines, taxanes and trastuzumab. Predictive models based on the findings of phase III clinical trials take into consideration patient age and baseline LVEF values [1]:

$$\frac{[7{,}0 + (0{,}04 \times \text{AGE IN YEARS}) - (0{,}1 \times \text{BASELINE PERCENT LVEF})] \times 100}{4{,}76}$$

Correspondence:
Sebastian Szmit, MD, PhD
Department of Pulmonary Circulation and Thromboembolic Diseases,
Centre of Postgraduate Medical Education, ECZ-Otwock
05-400 Otwock, ul. Borowa 14/18

Recent findings demonstrate that borderline baseline LVEF (LVEF ≤ 5 percentage points above the lower limits of normal) indicates a high risk of cardiotoxicity, especially in elderly patients and in patients with haematological conditions [2]. One can easily conclude that even minor changes in LVEF impact cardiotoxicity prediction and prognostication. Hence, 3D echocardiography is becoming a method of choice, being the least invasive and the most accurate tool for the assessment of LVEDV (end-diastolic volume), LVESV (end-systolic volume), and LVEF [3]. Compared with magnetic resonance imaging and MUGA (multiple-gated acquisition), 3D echocardiography offers satisfactory diagnostic accuracy for the diagnosis of cardiotoxicity in the course of breast cancer treatment [4]. LVEF assessment in 3D echocardiography has lower inter-rater, intra-rater, and test-retest variability than contrast 3D echo or 2D LVEF assessment methods (2D-biplane Simpson's method, 2D-triplane) [5].

Thavendiranathan paid attention to how imperfect LVEF is as a marker of positive prognosis of oncological patients. Cardinale's observations indicate that once cardiotoxicity has been reported as a result of significant decrease in LVEF, only some of the patients have a chance of achieve normalization of their left ventricular systolic function [6, 7]. Therefore, there is an evident need for more sensitive and earlier cardiotoxicity markers in echocardiography so as to avoid the later cardiovascular adverse events. It has long been proven that in the course of anthracycline treatment, significant abnormalities are reported in myocardial bioptates, while LVEF remains normal [8]. A reflection of the structural changes observed in the bioptates could be the myocardial strain assessed in echocardiography.

Thavendiranathan demonstrated that based on the baseline GLS (global longitudinal strain) one can prognosticate symptomatic heart failure as well as overall survival in patients treated with anthracyclines [9]. Saway et al. indicate that in anthracycline- and trastuzumab-treated breast cancer patients, GLS changes reported 3 months into treatment predict the risk of cardiotoxicity in 6-month follow-up [10]. Similar findings of Negishi et al., involving a similar population, go to prove that GLS changes reported 6 months into treatment predict cardiotoxicity in 12-month follow-up [11]. Thavendiranathan performed an accurate analysis of the sensitivity, specificity, PPV and NPP for GLS as a cardiotoxicity predictor, considering it a highly promising parameter [12]. He emphasised that strain abnormalities are observed several years after anthracycline and trastuzumab treatment for breast cancer, and in smoking patients in particular [13]. Similar findings pertain to children on anthracyclines [14]. Abnormal GRS/GCS (global radial strain/global circumferential strain) is reported regardless of the normal LVEF values.

Thavendiranathan was optimistic about the predictive role of GLS changes triggered by anti-cancer drugs. Results published by Negishi et al. demonstrate that it may become the basis for the protective administration of beta-adrenolytics, which is efficacious in terms of preventing further development of the left ventricular systolic dysfunction [15].

Thavendiranathan underlined that the definition of stage B heart failure should be changed. In cardio-oncology, the definition should be based on GLS assessment. High-risk patients should thus be defined as those with GLS changes in the course of chemotherapy, and they should be on cardioprotective drugs.

Sanjeev Francis presented "MRI: Utility for evaluation of cardiotoxicity"

In daily practice, cardiotoxicity of oncological treatment is diagnosed based on imaging tests, and the diagnosis impacts the patient's further prognosis, including the potential withdrawal of anti-cancer drugs and initiation of cardiovascular therapy. What may be problematic here is the differentiation of subclinical cardiotoxicity from clinically significant cardiotoxicity (tab. 1).

Francis paid attention to the possibility of diagnosing myocardial oedema or inflammation on the basis of MRI. Observation of small groups of patients treated with chemotherapeutics demonstrates that such lesions can be reported as early as between day 3 and month 3 from the administration of cytostatics. Larger studies are needed to confirm the usefulness of the method (Tissue characterisation T2) for the prediction of clinically significant heart failure. Fibrosis of the myocardium may also be diagnosed with the use of MRI. Associated with poor prognosis, it is a manifestation of an advanced stage in many different conditions [16]. Gadolinium distribution observed under MRI reflects the hyperplasia of fibrous tissue in the interstitial space. Extensive fibrosis and its progression in time may be monitored with the technique of T1 mapping (Tissue characterisation T1). The method appears to be useful for the monitoring of anthracycline-related cardiotoxicity [17]. An increase in the myocardial extracellular volume (ECV), measured using T1 measurements, is observed in those cases. Such abnormalities may even be reported in long-term follow-up, several years after the chemotherapy has been completed [18]. Focal fibrosis may be monitored with the assessment of LGE (late gadolinium enhancement). It is, however, rarely observed in the context of

TABLE 1.
Spectrum of cardiotoxicity by Dr. Sanjeev Francis.

	Sub-clinical cardiotoxicity	Clinical cardiotoxicity
Clinical findings	Asymptomatic	Symptomatic
Echocardiographic findings	Preserved EF	Reduced EF
Morphological findings	Possible ultrastructural changes	Myocardial fibrosis
MRI findings	Oedema/inflammation – T1 – T2 Increase in LV mass Arterial stiffness	Focal fibrosis (LGE) Diffuse fibrosis (T1 mapping, ECV) Decrease in LV mass Reduced EF

anthracyclines, and more likely associated with other cytostatics affecting the patient's cardiovascular status.

Bearing in mind how "subtle" the definition of cardiotoxicity is, based on symptomatic LVEF changes of 5 percentage points, and asymptomatic LVEF changes of 10 percentage points, one should remember that MRI remains the golden standard. Only MRI ensures reliable repeatability and compatibility of LVEF assessment results. It has been proven that MRI offers significantly higher diagnostic accuracy in the diagnostics of cardiomyopathy in paediatric oncological patients than 2D and 3D echocardiography [19]. Additionally, MRI makes objective assessment of the left ventricular mass possible, which is important, as the mass changes with the administered anthracycline dose, offering prognostic value, too [20]. The list of useful prognostic parameters also includes the left ventricular end-systolic volume, left ventricular strain, and pulse wave velocity [21].

There are ongoing studies (PRADA, MANTICORE) aimed at confirming the role of MRI in qualifying patients for pharmacological prevention of cardiotoxicity. Its negative aspects include the cost-effectiveness ratio, low availability of MRI in daily practice, and contraindications for MRI scans (e.g. claustrophobia, implanted stimulators, artificial limbs etc.). On the other hand, its assets include the remarkable possibilities of differential diagnostics, and sensitivity of the method in detecting early stages of numerous diseases. MRI may thus be highly useful for individual monitoring of high-risk patients [22].

Michel Khouri from Duke University Medical Center presented "Is it the *best practice* to use imaging core labs for all major studies?"

The future of cardio-oncology seems to be based on clinical trials that focus on cardiac imaging. Such trials should always aim to identify the prognostic value of abnormalities detected by imaging tests. Thanks to the technological progress, we are now equipped with new tools for cardiovascular imaging, and we are capable of detecting ever more subtle abnormalities. What is necessary is to make sure that the new tools are standardized, and offer high repeatability and reliability of results. It is also of key importance that their clinical usefulness be defined.

Establishment of a core laboratory will contribute to the reduction in inter-rater, inter-centre and test-retest variability. The chief goal is control of study quality and minimization of the risk of erroneous diagnosis. Such a laboratory increases the reliability of study results. Thanks to that, the power of a clinical trial is higher, even if it involves a smaller cohort of patients. Improvement in the accuracy of the generated data may be so significant that the trial's primary endpoint and final conclusions may be changed completely.

Data collected in multi-centre clinical trials on echocardiographic assessment of cardiac function following myocardial infarction have been published and made available. They go to show that measurements performed in a core laboratory offer a significantly higher prognostic value than those performed in regional centres [23]. It is worth comparing two interesting studies: PROSPECT [24] and E-VALVE [25]. The PROSPECT trial may be considered unsuccessful, as regardless of an optimum echocardiographic training, and despite core lab assessment, assessment of the 12 echocardiographic parameters failed to predict clinical benefits following CRT implantation, with sensitivity ranging from 6 to 74%, and specificity of 35–91%. The variability was too high for it to be acceptable in a clinical trial. On the other hand, the E-VALVE study confirmed the usefulness of a central laboratory for echocardiographic assessment of mitral regurgitation, both in terms of qualification for intervention

as well as in terms of the assessment of its efficacy. Khouri emphasised that for a core lab to be able to increase the diagnostic strength of a clinical trial, it has to be organized in an optimum way, with appropriate data archiving, transfer and interpretation [26]. That appears to be the key to success of a multi-centre clinical trial.

Correct interpretation of the cardiac image may have significant impact on further clinical decisions. In cardio-oncology it may be the grounds for the initiation of a potentially cardiotoxic chemotherapy or for the termination of an efficacious anti-cancer treatment. In the field of classical cardiology, usefulness of a core lab has been demonstrated in prospective studies, when randomizing and assessing patients with dilated cardiomyopathy, qualified for mitral valve surgical treatment with potential implantation of the CorCap cardiac support device [27], when qualifying patients with aortic valve stenosis for surgery in the PARTNER I study [28], and when qualifying patients with ischaemic heart failure for cardio-surgical treatment in the STICH trial [29, 30]. It is only thanks to the assessment performed in a core laboratory that researchers may rest assured that restrictive echocardiographic study inclusion criteria have been met. However, it is important that central assessment generates no unnecessary delays in patient randomization and further clinical decisions. Moreover, core lab assessment successfully eliminates the possibility of making a mistake, when qualifying patients for a procedure [31]. Additionally, a core lab should verify the accuracy and repeatability of measurements performed in the centres involved in the trial. If the agreement is lower than 80%, additional training sessions should be organised [32].

Khouri discussed the advantages and limitations of establishing a core lab for cardio-vascular imagining in multi-centre clinical trials.

Advantages: it facilitates creation of homogenous patient groups, guarantees high reliability and repeatability of results, minimizing subjectivization.

Disadvantages: it complicates the study pattern, prolongs recruitment of study subjects, and increases the cost.

Echocardiographic core laboratory is essential in the case of small clinical trials aimed at delivering an unequivocal answer pertaining to a significant diagnostic problem.

Juan Carlos Plana & Clifford Hudis held the Keynote Debate entitled "Should all HER2-positive breast cancer patients still undergo serial imaging every 3 months?"

Cardiologist Juan Carlos Plana presented arguments for stringent recommendations concerning imaging of heart and vessels in patients with HER2-positive cancer. He claimed, for instance, that in oncology practice, where our patients are frequently elderly people with different concomitant diseases, the risk of cardiotoxicity is truly high. Plana discussed a publication presenting the trastuzumab-induced cardiotoxicity risk stratification algorithm [33]. The more points scored, the higher the risk, with 6 and more points amounting roughly to a 40% risk. The method has been validated, with individual points scored for the type of prior chemotherapy, patient age, and comorbidities, including coronary heart disease, atrial fibrillation, diabetes, arterial hypertension, and renal dysfunction. Plana pointed out that contemporary expert recommendations are rather ambitious, pointing not only to the need of LVEF assessment performed every 3 months, but also to the usefulness of echocardiographic strain-rate imaging and troponin assessment [34]. Oncologist Clifford Hudis was in opposition. He proposed to reduce the frequency of follow-up echocardiography tests, referring to the recent results of clinical trials demonstrating that the risk of trastuzumab-induced cardiotoxicity is not high in long-term follow-up [35]. The findings are similar for anthracyclines with cyclophosphamide, possibly combined with bevacizumab [36]. According to Huddis, the key question to be answered is why we keep monitoring our patients so closely. Evidence is missing for the association of such close monitoring with better cardiovascular prognosis of the patients involved. Thus, we need to validate the current programme that requires repeating the tests every 3 months. The present recommendations are based on expert opinions. Those opinions are transferred from large phase III clinical trials, which means that they are not class I recommendations [37].

CONCLUSIONS

Imaging diagnostics will determine the progress in cardio-oncology in the nearest future. We should hope that the ever more advanced methods for the detection of early stages of cardiotoxicity will facilitate effective cardioprotection.

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