Cardiotoxicity in Cancer Therapy – the Role of Cardiovascular Magnetic Resonance

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Introduction

Cardiovascular magnetic resonance (CMR) imaging has become a mainstay in the assessment of various cardiac pathologies including ischemic and non-ischemic cardiomyopathies. Beyond the sole aspect of functional deterioration, CMR has convincingly demonstrated to provide further information on the underlying cause contributing sufficient information to narrow the differential diagnosis. Furthermore, insight into the myocardial composition may shed light into the risk prediction of certain diseases and may also allow monitoring of therapeutic interventions and their effects on the heart.

In recent years, the link between tumor therapies and cardiac disease has gained substantial attention and is currently focus of multiple ongoing large-scale studies. With the continuous improvement of survival rates of patients with various malignancies, potential detrimental effects on cardiac function and outcome including increased morbidity and mortality has become the center of such investigations. Outside study settings, major centers with large oncology and cardiac programs have started to establish Cardio-Oncology clinics, in order to help guide oncologists in their treatment planning in patients with pre-existing cardiac disease as well as taking care of patients with potential tumor therapy regimen related cardiovascular effects and potential development of heart failure (HF).

Tumor therapy and heart failure

Todays' therapy regimens in patients with malignant neoplasms may be based on surgical approaches, local or extended radiation therapy (RT) as well as systemic tumor therapies or a combination thereof. While surgical approaches and RT generally affect structures within the application field, systemic therapies may not only result in anti-tumor effects but may also affect otherwise normal body tissue, including the heart. Such negative effects of tumor-related therapy on the heart are generically referred to as cardiotoxicity. The known impact of anthracycline (AC) related tumor therapy possibly resulting in HF may often also be referred to as anthracycline induced heart failure (AIHF).

While modern personalized medicine approaches result in the continuous development of new anti-tumor drugs amongst different drug classes, AC still remain a mainstay of modern tumor therapy regimens. They are commonly used in treatment of breast malignancies, sarcomas and also hematologic malignancies. It is estimated that up to 60% of childhood cancer survivors have been exposed to AC therapy regimens and/or chest radiation [1; 2].

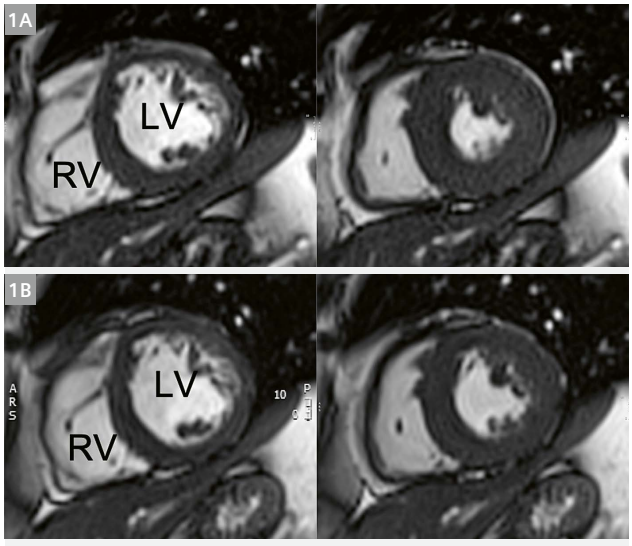

Figure 1:
Standard cine imaging in a patient with breast cancer **(1A)** prior to chemotherapy and **(1B)** one year after the end of anthracycline/trastuzumab combination therapy. Images demonstrate almost identical slice positioning (Cardiac Dot Engine) in diastole (left), but already visually a clear reduction in global ejection fraction is seen in systolie (right). The ejection fraction had dropped by ≥ 10% to < 50%.

LV = left ventricle; RV = right ventricle

Up to ~20% of patients undergoing AC based tumor therapy (with or without combination therapy) may experience AC related cardiotoxicity with the development of HF. The incidence generally increases with increasing cumulative AC dosing. Specifically designed studies employing short interval imaging (echocardiography) based monitoring of the ventricular function, the vast majority (up to 98%) of cardiotoxicity related HF developed either during the systemic cancer therapy or within one year after the end of therapy [3] (Fig. 1). Among patients experiencing such detrimental effects, the vast majority of patients will not entirely recover their cardiac function despite initiation of HF therapy [3]. The risk of cardiac events in this population is significantly increased and in case of confirmed AIHF, mortality may exceed 50% within two years.

Anthracyclines (e.g. doxorubicin, epirubicin) have been known from early use to potentially cause HF and still remain the drug class most commonly related to HF. However, also other drug classes may result in negative cardiovascular effects or may increase the risk of HF in combination with AC based therapy schemes. These classes include monoclonal anti-bodies (MAB) such as trastuzumab, tyrosine kinase inhibitors (TKI) as well as immune checkpoint inhibitors (ICI).

Meanwhile, guidelines have been developed helping to identify patient populations who are specifically at risk for cardiotoxicity related HF [4]. In general, the risk is specifically depending on the dosage of AC therapy, but also the amount of potentially applied additional radiation, potential cardiovascular risk factors as well as the combination of certain drug classes (e.g. anthracycline-trastuzumab combination therapy) [4].

Of specific interest is also the class of aforementioned ICI's, a group of agents that has generally demonstrated lower rates of cardiotoxicity, but that may specifically cause autoimmune myocarditis in rare instances resulting in high complication rates [5].

Cardiovascular magnetic resonance and cardiotoxicity

The breadth of techniques available in CMR for assessment of cardiac function, myocardial deformation and myocardial tissue characterization makes it a potentially ideal tool for assessment and monitoring of patients with increased risk of developing cancer therapy related cardiotoxicity.

Functional cardiac imaging

Today's definitions of cardiotoxicity are almost exclusively based on the assessment of the left ventricular (LV) ejection fraction (EF). As such, the known high accuracy and precision of CMR in the assessment of cardiac volume and function is perfectly suited to guide clinicians according to current definitions of cardiotoxicity [6]. With little variation, published criteria of cardiotoxicity follow a change in LVEF with main cut-offs at a drop of ≥ 10% to under 50% or 55%/53% respectively (Fig. 1) [7–9]. More subtle changes in LVEF (≥ 5%) should be considered as possibly related to cardiotoxicity in patients with symptoms of heart failure (HF) [8]. However, it is important to keep in mind that such thresholds are generally based on echocardiography or multigated acquisition (MUGA) radionuclide ventriculography, modalities that generally suffer from a higher inter-scan and inter-observer variability. Although there is no separate cut-off criterion based on CMR, recent study data suggests that MUGA results may potentially result in misclassification of patients [10].

In any of the above LVEF based definitions of cardiotoxicity, proper baseline assessment and follow scans are required; single time assessment of the cardiac function would not allow adequate judgement. In addition to standard imaging approaches, CMR may play an increasingly important role in the monitoring of such patients. Various clinical experiences report cases where echocardiography based functional assessment would have missed a significant drop in LVEF.

However, from decades of imaging experience it is known that LVEF changes may only occur as a delayed relation to local changes. Therefore, assessment of myocardial deformation may provide a more sensitive and earlier insight into myocardial changes. In the field of echocardiography, the application of speckle tracking echocardiography (STE) has pushed the use of strain imaging towards clinical use including assessment of cardiotoxicity. CMR offers various techniques for myocardial deformation imaging including myocardial tagging, sensitivity encoding (SENC) and displacement encoding with stimulated echoes (DENSE). However, such techniques have never been established on a larger scale in clinical routine CMR.

Most recently, developments of techniques that allow assessment of myocardial strain in routinely acquired cine balanced steady state free precession (bSSFP) data sets have opened a whole new avenue of myocardial deformation assessment. The different available techniques rely either on feature tracking algorithms or employ motion correction techniques for calculation of deformation in cine bSSFP [11–15]. Especially, prototype deformation map-based techniques such as TrufiStrain[1] (Siemens Medical Imaging Technologies, Princeton, US) demonstrated promising and highly

[1] *WIP, the product is currently under development and is not for sale in the US and in other countries. Its future availability cannot be ensured.*

reproducible results compared to accepted standard of reference such as myocardial tagging (Figures 2–4) [12; 14]. In the application of cardiotoxicity evaluation, CMR based strain has also demonstrated great promise aiming at early detection of changes.

Tissue characterization

Qualitative tissue characterization techniques such as T2-weighted imaging or Late Gadolinium Enhancement (LGE) imaging have long played a role in the assessment of various cardiomyopathies and inflammatory changes such as myocarditis [16, 17]. However, the use of LGE imaging in assessment of cardiotoxicity appears limited. As an exception, LGE may play a role in assessment of possible autoimmune myocarditis/pericarditis which may occur during ICI therapy and is considered a bad prognostic marker (Fig. 5).

As a potential new marker of cardiotoxicity related tissue level changes, cardiac relaxometry techniques such as T1 mapping, T2 mapping as well as derived markers such as extracellular volume fraction (ECV) have been proposed and evaluated in various experimental and clinical studies predominately focused on the effects of anthracycline therapy.

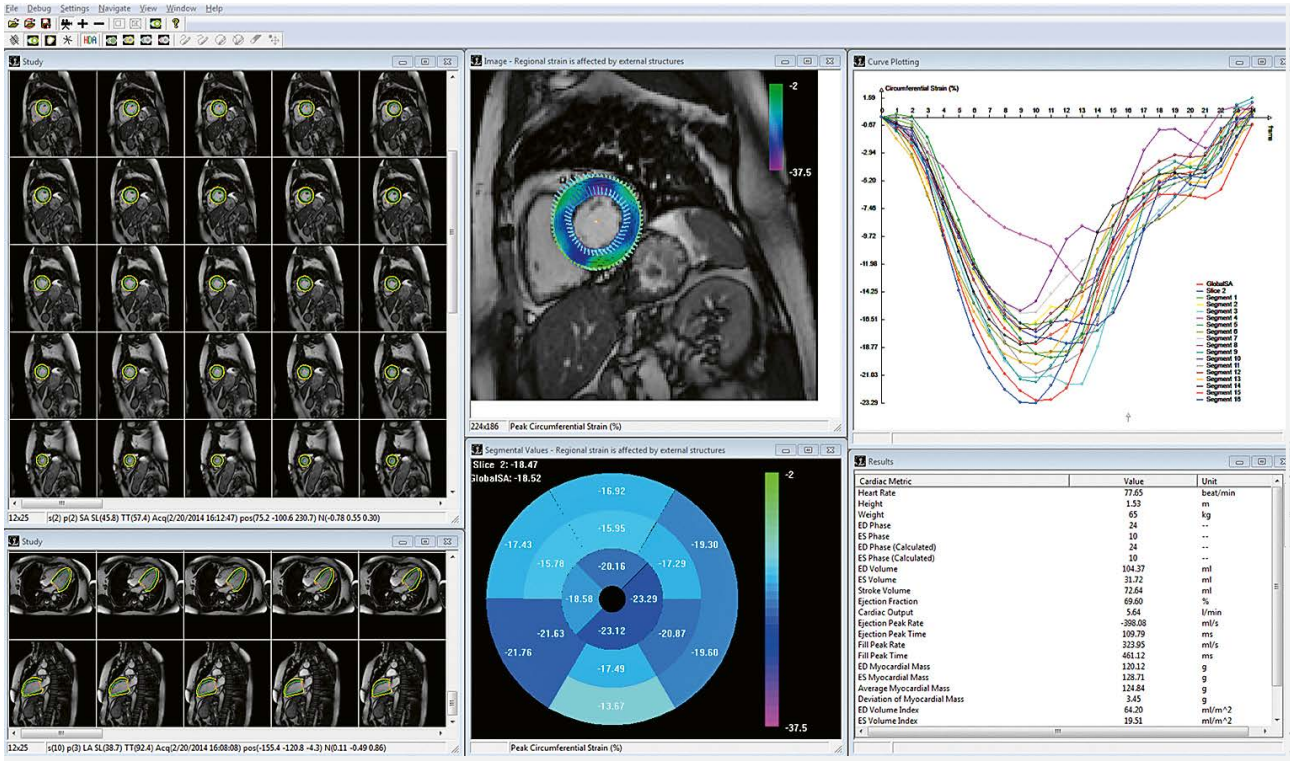

Figure 2:
Standard screen overview of TrufiStrain[1], a prototype software for cine derived strain analysis. The left part of the layout demonstrates the fully automated (short axis) and semiautomated (long axis) segmentation of the endo- and epicardial contours. The center part highlights a visual overlay of strain data onto cine data as well as a bullseye plot of AHA segment strain results. On the right, a visual display of the strain curves (circumferential in this case) for all 16 AHA segments as well as the entire slice with additional results of automated functional analysis at the bottom.

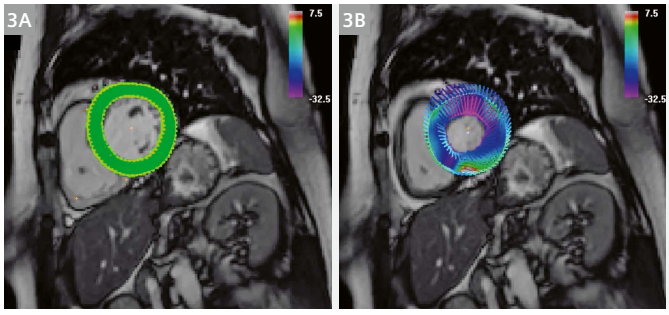

Figure 3:
Single short axis slice in a healthy volunteer in **(3A)** diastole and **(3B)** systole with time point related strain result overlay; the colored lines on the systolic display visualize the direction and magnitude of endo- as well as epicardial motion from diastole to systole.

In animal studies, the repeated application of anthracycline doses lead to a continuous increase in native T1 values over the course of 12–14 weeks while other studies have demonstrated that T2 values are increased in the early phase (~4–6 weeks) suggesting myocardial edema [18, 19]. However, the later study also demonstrated that despite elevated T2 values in early stages, ECV was not elevated until later stages. A possible explanation of elevated T2 and normal ECV might be the occurrence of intracellular edema.

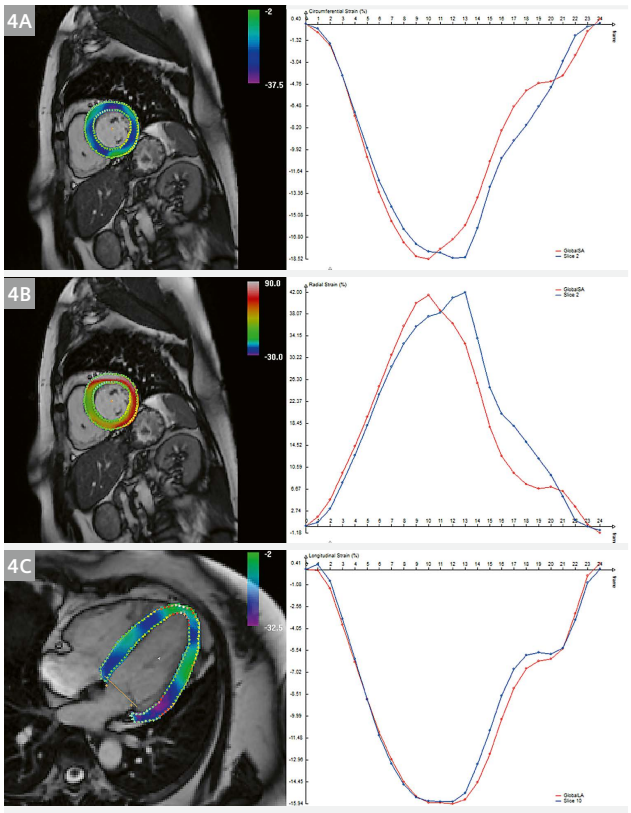

Figure 4:
Demonstration of three major directions/orientations of myocardial strains typically evaluated; **(4A)** circumferential strain, **(4B)** radial strain and **(4C)** longitudinal strain. As strain is a measure of length changes in relation to an applied force, the typical shortening in evaluation on circumferential and longitudinal strain result in negative strain values while the thickening during systole results in positive values for radial strain.

Changes in myocardial T1 as well as ECV values have also been demonstrated in patient studies. As in many other cardiomyopathies, pre-contrast T1 values as well as ECV increase after chemotherapy, likely related to development of interstitial fibrosis [20]. However, hyperacute reactions within the myocardium may result in an initial T1 value decrease possible indicating worse outcome [21]. Currently, there is still limited data from prospective longitudinal studies available to clearly describe potential differences in quantitative cardiac relaxometry in patients with and without development of functional deterioration after chemotherapy. Similar to functional analysis, likely sequential longitudinal imaging, including pre-therapy assessment of T1 and T2 data, is required to identify and differentiate true tissue changes from imaging related variability. A possibly even more promising use of cardiac relaxometry techniques may again relate to patients under ICI therapy with possible autoimmune myocarditis changes (Fig. 5). Similar to recent recommendations regarding the diagnosis of myocarditis in general, changes in quantitative tissue markers may help earlier and more accurate diagnosis [22].

Conclusion

While the playing field of potentially cardiotoxic tumor therapy generally hasn't substantially changed, decades of study results have helped to better understand risk factors and relationships between tumor therapy and cardiac failure. Furthermore, there is a much-increased awareness of the potential interaction between tumor

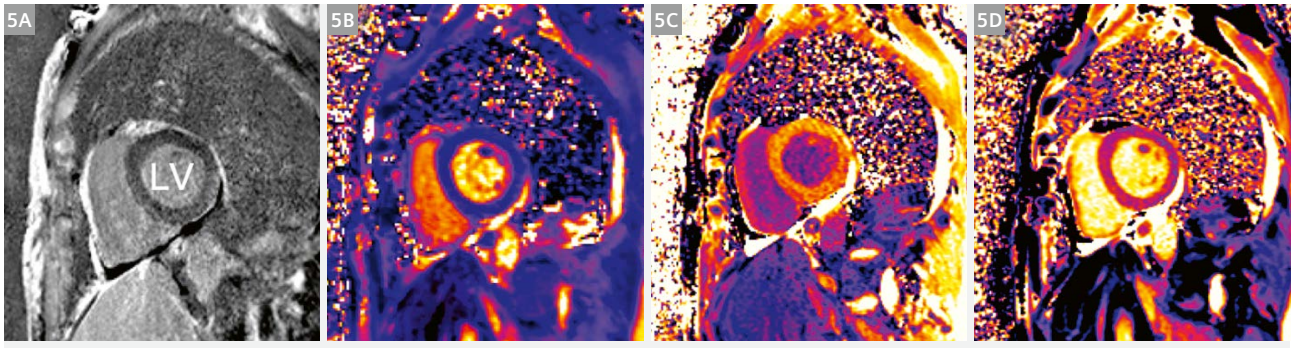

Figure 5:
Patient undergoing immune checkpoint inhibitor (ICI) cancer therapy with troponin elevation and suspicion of immune myocarditis. While **(5A)** LGE imaging possible demonstrates very faint diffuse enhancement, cardiac relaxometry with T1 and T2-mapping (1.5T) provides further information. **(5B)** T2 mapping reveals a T2 time of 55 ms while **(5C)** pre-contrast T1 values were 1184 ms and **(5D)** post-contrast T1 values 519 ms (0.15 mmol/kg Gadobutrol). Based on the patient's hematocrit the ECV is calculated to 38%.

therapy and heart failure resulting in the new subspecialty of 'Cardio-Oncology'. While imaging has long played a role in cancer patients undergoing chemotherapy, CMR is rapidly entering the field and is more frequently being employed. The accuracy and precision of CMR functional assessment proves beneficial in early identification of functional deterioration. Added information might be gathered from cine CMR based strain analysis and quantitative myocardial tissue markers (T1/T2/ECV mapping). However, the timing and specific application of CMR during the course of cancer therapy, especially in patients at risk, has yet to be determined. For a better understanding of that role, additional data on the general test-retest variability of such quantitative markers is still required. Furthermore, society guidelines and definitions of cardiotoxicity would need to further extend beyond the sole criteria of cardiac function.

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