JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 7, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.01.019

EDITORIAL COMMENT

Expanding CT Application to Myocardial Tissue Characterization*

Igor Klem, MD[a,b]

Computed tomography (CT) has evolved into a powerful diagnostic tool, and since the advent of 64-detector row scanners, it has been demonstrated as a promising noninvasive method for coronary artery stenosis imaging (1). Although the basic physical principle of CT is unidimensional, a function of x-ray attenuation detected from multiple orientations around the imaged object, exciting new technical developments have opened the avenue for novel research applications such as myocardial infarct imaging with late post-contrast CT (2), assessment of cardiac function and volume changes (3), and even hemodynamic assessment of coronary stenosis significance with CT-derived fractional flow reserve using computational fluid dynamic principles (4). One such technical advance is dual-energy CT, which uses the photoelectric effect of CT to exploit the energy-dependent attenuation of tissues when exposed to 2 different photon energy levels. This technique allows the characterization of tissues on the basis of attenuation profiles of 3 known materials, such as iodine (in CT contrast), soft tissue, and fat at 2 levels of energy (e.g., 100 kV and 140 kV) (5). One recently introduced cardiac application uses the ability of dual-energy CT to map regional myocardial iodine distribution as a quantitative marker of blood volume, which is a surrogate for myocardial perfusion and can be used to detect ischemia (6).

SEE PAGE 836

In this issue of *iJACC,* Hong et al. (7) report on the novel use of dual-energy CT to characterize myocardial tissue changes in an animal model of doxorubicin-induced cardiotoxicity. Based on the iodine maps of the myocardium and blood pool, they determined the extracellular volume (ECV) fraction before and during doxorubicin treatment. They report a pre-treatment ECV fraction of 28.5%, which increased after 6 weeks of doxorubicin treatment by 6.8 percentage points to 35.3%, after 12 weeks by an additional 6.6 percentage points to 41.9%, and after 16 weeks remained unchanged at 42.1%. Notably, doxorubicin has been discussed to induce apoptotic and necrotic cell death through multiple mechanisms, mostly leading to oxidative stress by generation of several reactive oxidation species and disruption of the cardiac sarcomere structure, with some reparative but mostly reactive fibrosis, with increased deposition of collagen and extracellular matrix in the interstitium (8,9). Thus, the ECV fraction is only in part composed of collagen fibers in the extracellular space, which were quantified by Hong et al. (7) on histologic examination to represent the reference standard for comparison to CT ECV measurements. Not surprisingly, therefore, the baseline collagen volume fraction was smaller than the CT ECV fraction at 3.3%, but tracked the ECV fraction changes over time and increased after 6 weeks of doxorubicin treatment by 9.4 percentage points to 12.4%, after 12 weeks by an additional 7.4 percentage points to 20.1%, and increased further after 16 weeks by 9.2% percentage points to 29.3%, resulting in an excellent correlation between histological characteristics and CT measurements ($r = 0.925$).

The CT ECV fraction measurements were also compared with myocardial ECV fraction assessed with cardiac magnetic resonance (CMR) T1 mapping. In the past few years, this technique has received considerable attention in the CMR imaging field, and CMR ECV measurements were shown in pathological validation to correlate with the histological collagen volume fraction in explanted human hearts with ischemic and dilated cardiomyopathy (10). Notably, similar to the present study, the CMR ECV measurements were shown to be larger compared with the collagen volume fraction by histological examination. Hong et al. (7) report a CMR ECV of 28.8% at baseline,

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the [a]Duke Cardiovascular Magnetic Resonance Center, Duke University Medical Center, Durham, North Carolina; and the [b]Division of Cardiology, Duke University Medical Center, Durham, North Carolina. Dr. Klem has reported that he has no relationships relevant to the contents of this paper to disclose.

which increased after 6 weeks of doxorubicin treatment by 3.8 percentage points to 32.6%, after 12 weeks by an additional 3.2 percentage points to 35.8%, and after 16 weeks increased further by 5.5 percentage points to 41.3%. Overall, both CT ECV fraction and CMR ECV fraction tracked the changes seen on histological collagen volume fraction. Of interest though, unlike CMR and on histologic examination, the CT ECV fraction did not further increase from 12 to 16 weeks.

Similar to CT, equilibrium CMR ECV fraction quantification requires image acquisitions before and after contrast administration to determine its concentration in the myocardium and blood pool. At contrast-agent equilibrium, the contrast concentration is equal in both compartments, and because the volume of distribution (or ECV) in blood is known from the hematocrit, myocardial ECV can be calculated. Whereas in CT, the Hounsfield units are the measured input, in CMR the T1-relaxation times are determined using a specific T1-weighted pulse sequence (11).

What is the potential role of measuring the ECV fraction in improving the current clinical practice of cardiotoxicity surveillance? With increasing numbers of cancer survivors with modern chemotherapy regimens, a pivotal aim of the "cardio-oncology" field is to reduce the increasing risk of heart failure morbidity and mortality associated with treatments including potentially cardiotoxic agents. Even in more recent recommendations of the societies of oncology and cardiac imaging, serial measurements of left ventricular ejection fraction (LVEF) with echocardiography and multigated acquisition scans remains the cornerstone surveillance parameter during anthracycline treatments, with the addition of troponin measurements to detect acute myocardial injury (12,13). Both the recognition of a reduction in LVEF, which is typically required to be >10% to 15% or drop to below <50%, and a troponin rise represent already clinically manifested effects of anthracycline cardiotoxicity. A novel marker that has the potential to detect cardiotoxicity at an earlier stage, *before* overt dysfunction or heart failure symptoms occur, would hence have great importance. In that respect, the findings of Hong et al. (7) from ECV measurements during anthracycline treatment (both with CT and CMR) demonstrate that an increase in ECV fraction occurs *simultaneously* with substantial clinical changes consisting of a drop in LVEF of >10% already after 6 weeks of treatment to a mean LVEF of 32% at the end of 12 weeks. Future studies will be needed to demonstrate that sizeable ECV changes can be detected and are sensitive enough for the prediction of future reductions in LVEF or clinical symptoms before these changes occur. Furthermore, the relative merit of ECV measurements (with CT or CMR) for this purpose versus other emerging imaging tests such as myocardial strain imaging with echocardiography or CMR will need to be established (14).

Nonetheless, the addition of ECV measurements to LVEF assessment may be helpful to detect myocardial tissue damage outside the diagnostic window provided by troponin measurements. The value of this additional computed tomographic imaging study and possible integration into current imaging schedules in oncologic patients has yet to be determined. ECV measurements could possibly be performed in conjunction with studies performed for cancer staging or in the future possibly with LVEF surveillance with CT, which is currently not performed.

From a practical perspective, ECV measurements require intravenous access, contrast administration, and hematocrit determinations, which are not routinely required in serial LVEF surveillance imaging with echocardiography and CMR. However, intravenous administration of radiolabeled erythrocytes is necessary if LVEF is measured with multigated acquisition scans, which is currently used in up to 50% of patients according to a recent report on more than 2,000 patients with breast cancer undergoing chemotherapy in the United States (15). An alternative approach obviating the requirement of intravenous access and contrast administration is the assessment of native tissue characteristics. Hong et al. (7) did measure pre-contrast T1 times, which increased after initiation of anthracycline from 1,068 ms to 1,110 ms at 6 weeks. Unfortunately, previous studies have found no correlation of native T1 with histological collagen volume fraction in humans, thus limiting the expectations for this simple approach (10). The CT-Hounsfield unit measurements showed an increase from 58.0 to 68.4, although not before 12 weeks; at 6 weeks there was no significant change in computed tomographic signal. Moreover, these were post-contrast data, and it remains unclear if a dual-energy assessment of native tissue composition can potentially provide useful information.

In summary, Hong et al. (7) present a novel technique for tissue characterization with dual-energy CT, which is an exciting development expanding further the facets of cardiac CT. The future of this technique in cardio-oncology will vastly depend on its ability to detect myocardial injury from potentially cardiotoxic agents early before clinically manifested changes

JACC: CARDIOVASCULAR IMAGING, VOL. 9, NO. 7, 2016
JULY 2016:846–8

have occurred, how it will compare to other emerging tests (e.g., strain imaging, CMR T1 mapping) for that purpose, and its smooth integration into the already busy imaging test schedules oncologic patients are subject to.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Igor Klem, Duke Cardiovascular MRI Center, DUMC-3934, Trent Drive, Durham, North Carolina 27710. E-mail: igorklem@duke.edu.

REFERENCES

1. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med 2008;359:2324–36.

2. Gerber BL, Belge B, Legros GJ, et al. Characterization of acute and chronic myocardial infarcts by multidetector computed tomography: comparison with contrast-enhanced magnetic resonance. Circulation 2006;113:823–33.

3. Yamamuro M, Tadamura E, Kubo S, et al. Cardiac functional analysis with multi-detector row CT and segmental reconstruction algorithm: comparison with echocardiography, SPECT, and MR imaging. Radiology 2005;234:381–90.

4. Yoon YE, Choi JH, Kim JH, et al. Noninvasive diagnosis of ischemia-causing coronary stenosis using CT angiography: diagnostic value of transluminal attenuation gradient and fractional flow reserve computed from coronary CT angiography compared to invasively measured fractional flow reserve. J Am Coll Cardiol Img 2012;5:1088–96.

5. McCollough CH, Leng S, Yu L, Fletcher JG. Dual- and multi-energy CT: principles, technical approaches, and clinical applications. Radiology 2015;276:637–53.

6. Blankstein R, Shturman LD, Rogers IS, et al. Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. J Am Coll Cardiol 2009;54:1072–84.

7. Hong YJ, Kim TK, Hong D, et al. Myocardial characterization using dual-energy CT in doxorubicin-induced DCM: comparison with CMR T1-mapping and histology in a rabbit model. J Am Coll Cardiol Img 2016;9:836–45.

8. Feridooni T, Hotchkiss A, Remley-Carr S, Saga Y, Pasumarthi KB. Cardiomyocyte specific ablation of p53 is not sufficient to block doxorubicin induced cardiac fibrosis and associated cytoskeletal changes. PloS One 2011;6:e22801.

9. Sawyer DB, Peng X, Chen B, Pentassuglia L, Lim CC. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? Prog Cardiovasc Dis 2010;53:105–13.

10. Miller CA, Naish JH, Bishop P, et al. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. Circ Cardiovasc Imaging 2013;6:373–83.

11. Messroghli DR, Walters K, Plein S, et al. Myocardial T1 mapping: application to patients with acute and chronic myocardial infarction. Magn Reson Med 2007;58:34–40.

12. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Ann Oncol 2012;23 Suppl 7:vii155–66.

13. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2014;15:1063–93.

14. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63:2751–68.

15. Chavez-MacGregor M, Niu J, Zhang N, et al. Cardiac monitoring during adjuvant trastuzumab-based chemotherapy among older patients with breast cancer. J Clin Oncol 2015;33:2176–83.

KEY WORDS cardiac imaging techniques, cardiomyopathy, dual-energy scanned projection, magnetic resonance imaging, mapping, radiography