CMR Tissue Characterization by T1 and T2 Mapping: A Moving Target in Need of Stable References

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Word count: 1496

The Hamburg City Health Study (HCHS) is a population-based study in the city of Hamburg, Germany that started enrolling participants in 2016 to study important risk and prognostic factors in major chronic diseases, including cardiovascular diseases. Like other recent population studies with similar goals, including the Multi-Ethnic Study of Atherosclerosis (MESA) [1] and UK Biobank [2], HCHS includes CMR imaging studies for evaluation of structure and function of the heart and myocardial tissue characterization by T1 and T2 mapping without and with contrast enhancement. The myocardial tissue characteristics revealed by T1, T2 and ECV have turned these magnetic resonance parameters into biomarkers of increasing relevance to uncover pathological changes in myocardial tissue that are not discernible by more conventional imaging tests, like late gadolinium enhancement. As a population-based prospective study, HCHS can further the aim of establishing reference ranges for myocardial biomarkers based on T1 and T2 mapping.

In the current issue of Circulation CVi, Cavus et al report on reference ranges for the native myocardial relaxation times T1 and T2 and on the effects of sex and cardiovascular risk factors on T1 and T2 in 1576 HCHS participants imaged with CMR at 3 Tesla field-strength. Native T1 and T2 (i.e. the T1 and T2 relaxation times measured without any gadolinium contrast) depend on the magnetic field strength at which a CMR scanner operates, but also on the pulse sequence technique being used, including their parameter settings. The HCHS study used optimized versions of the modified Look-Locker T1 and T2-preprared mapping techniques, which are effectively standards today, but these standards still are a source of variation as multiple technical aspects can affect the measured T1 and T2 values. This includes details such whether one uses a “front-loaded” MOLLI acquisition scheme as in HCHS, which is thought to reduce the heart rate dependence of native T1 [3]. Establishing reference ranges has in the past been challenging as noted in a recent meta-analysis of native T1 mapping in healthy individuals[4] which concluded that the “relatively high degree of heterogeneity may preclude the derivation of a normal

range for native T1". More than 80% of the studies included in the meta-analysis had groups of healthy controls with 50 or fewer subjects, with a median of 20 subjects for studies at 3 Tesla. The study by Cavus with 1576 participants all scanned at 3 Tesla, provides therefore valuable data for T1 and T2 reference ranges for a much larger cohort.

Establishing reference ranges would certainly not be enough justification for using a relatively costly resource like CMR imaging on a large scale in a population-based study, because continuous technical advances render reference ranges a moving target. Arguably, it is at least equally important to obtain a better understanding of how cardiovascular risk factors impact myocardial structure and function, as this will aid in the interpretation of clinical studies that use T1 and T2 mapping. Questions such as how one should factor in a history of hypertension in a patient being evaluated for a cardiomyopathy, which includes T1 and T2 mapping, remain largely unanswered. Reference ranges, if stratified by common cardiovascular risk factors, are a first step to improve diagnostic certainty.

The study by Cavus corroborates the previous finding in the multi-ethnic study of atherosclerosis (MESA) of significant differences of T1 and ECV between men and women and the positive association of T1 and T2 in women with advancing age [5]. Other cardiovascular risk factors like hypertension and diabetes were not associated in HCHS native T1, though in MESA participants treated for diabetes had a higher native T1. Part of the lingering uncertainty about the effects of CV risk factor on myocardial imaging biomarkers may also depend on how risk factor burden is assessed: In MESA Yi et al considered the compound effect of risk factors by looking at risk scores rather than individual risk factors [6]. Furthermore, some of the more recent cardiovascular risk scores include inflammatory markers like CRP which increases their prognostic value. Cavus et al do not report on any association with inflammatory

markers, though myocardial fibrosis quantified by T1 and ECV have been linked to systemic inflammation markers[7].

In MESA, investigators found native T1 to be slightly elevated in participants treated for diabetes and ECV was higher in smokers. The fact that in HCHS current or past smokers were not found to have a higher ECV may be because post-contrast T1 and ECV were only available in less than 40% of the imaging studies. The awareness of long-term adverse side-effects from gadolinium contrast administration has certainly increased since the early days of the MESA imaging studies and led to the exclusion of gadolinium contrast in the CMR protocols of more recent population-based studies, like UK Biobank. {Petersen, 2016 #5} This has to be balanced with the fact that some of non-biological factors that confound the interpretation of native T1 and T2, like field strength and pulse sequence technique, have a lesser effect on ECV, as noted in the meta-analysis by Gottbrecht et al. [4] or aid in the interpretation of native T1 as changes of extra- and intra-cellular volumes can have opposite effects on native T1.

A salutary aspect of the study by Cavus et al is the inclusion of native T2 in the imaging protocol. T2 mapping has been somewhat neglected compared to T1 mapping and was not included in the MESA imaging protocol or mentioned in a previously published report about the UK Biobank CMR imaging protocol [8]. The CMR community now has at its disposal good techniques for T2 mapping and Cavus et al provide an encouraging first example in a population-based study of individuals without overt cardiovascular disease. In the HCHS, native T2, but not T1 and ECV, was significantly different between the subgroups with and without CV risk factors.

Now that Cavus et al have provided important reference ranges, one must hope that for other 3T scanner platforms one may be able establish some type of conversion to make these reference ranges more widely useful. It is unrealistic to expect that these large studies are repeated for different scanner platforms! Our understanding of how to interpret the sex-related differences and the effects of cardiovascular risk factors also needs to improve. The observation of sex-related differences is interesting, but the causes of a higher native T1 in females compared to males remain speculative. Is this related to other sex-related distinction of myocardial characteristics, like the fact that resting blood flow in pre-menopausal females is higher than in males [9, 10]? How do the differences change with the onset of menopause and does it confound the interpretation of the effects of advancing age?

We conclude that the HCHS study provides nearly one decade after the initial publications of the results on native T1 in MESA an authoritative and needed update, including reference ranges for 3 Tesla for 46-78 year olds. These data from HCHS will serve the CMR community well, but it will also be necessary to think about efficient strategies to further standardize the acquisition of T1 and T2 data and avoid too much "heterogeneity" from use of different T1 and T2 mapping techniques, while still leaving room for technical innovation.

Disclosures: MJH has no disclosures. SEP is consultant for Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada

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