Cardiac Magnetic Resonance T1 Mapping in Adolescent and Young Adult Survivors of Childhood Cancers: A Case-Control Study

Short title: T1 Mapping for Long-Term Childhood Cardiotoxicity

Xiaowan Tong, MBBS[1]*; Vivian Wing-yi Li, MPhil[2]*; Anthony Pak-yin Liu, MBBS[2]; Edwina Kam-fung So, BSc[2]; Queenie Chan, PhD[3]; Karin Kar-huen Ho, MBBS[4]; Jeffrey Ping-wa Yau, MBBS[5]; Daniel Ka-leung Cheuk, MBBS[2]; Yiu-Fai Cheung, MD[2#]; Ming-Yen Ng, BMBS, FRCR[1#]

[1]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong, [2]Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, [3]Philips Healthcare, Hong Kong, China, [4]Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong, [5]Department of Paediatrics, Queen Elizabeth Hospital, Hong Kong

* Contributed equally

[#] Co-Corresponding authors: Dr Ming-Yen Ng

Department of Diagnostic Radiology
Queen Mary Hospital
The University of Hong Kong
102 Pokulam Road
Hong Kong
China
Tel: 852-22554524
Fax: 852-28551652
Email: myng2@hku.hk

Prof Yiu-Fai Cheung

Division of Paediatric Cardiology
Department of Paediatrics and Adolescent Medicine
Queen Mary Hospital
The University of Hong Kong
102 Pokfulam Road
Hong Kong
China
Tel: 852-22554090
Fax: 852-25539491
E-mail: xfcheung@hku.hk

Subject terms: Magnetic Resonance Imaging (MRI); Imaging; Fibrosis

Key words: cardiotoxicity; cardiovascular magnetic resonance imaging; T1 mapping; extracellular matrix; myocardial fibrosis

Additional key words: Childhood survivors, Anthracycline, Extracellular volume

Total word count: 880 words

There is a paucity of cardiac magnetic resonance (CMR) T1 mapping data in childhood cancer survivors (CCS). Furthermore, the available data appears inconclusive. One study showed negative correlations between native T1/ extracellular volume (ECV) and exercise capacity in CCS but healthy controls (HC) were not included.[1] In another study, native T1 was similar between CCS and HC, although ECV was shown to be higher in female than male survivors.[2] Our goal was to determine if CMR native T1 and ECV are altered in CCS, and if sex difference of these myocardial fibrosis markers exists in long-term CCS.

CCS aged ≥13yrs who had completed anthracycline-based chemotherapy regimens for >5yrs were recruited from three hospitals. All subjects provided written informed consent. Age- and sex-matched normotensive healthy volunteers with no history of cardiovascular disease, normal electrocardiograms and blood tests were recruited. Haematocrit of all subjects was determined within 48 hours of CMR examination. A 3T CMR Scanner acquired T1 mapping images using a modified Look-Locker Inversion Recovery (MOLLI) sequence 5s(3s)3s (spatial resolution 1.17mm x 1.17mm x 10mm) in the left ventricular (LV) short axis at the base, mid and apex, pre-contrast and 15 minutes post-contrast injection. T2 mapping was performed in the same T1 mapping positions. T1 and T2 mapping contouring was performed on the mid-ventricular slice. Late gadolinium enhancement (LGE) areas were excluded. LGE was performed 8 to 15 minutes after intravenous injection of 0.2mmol/kg gadolinium-DOTA. Two observers independently evaluated LGE presence and location. LGE was quantified semi-automatically using a signal intensity threshold of >6 standard deviations above the normal myocardium. Study was approved by the Institutional Review Board of University of Hong Kong/ Hospital Authority and participants' informed consent was obtained for all participants. Study database is available from the corresponding author upon reasonable request.

Kolmogorov-Smirnov test was applied to determine appropriate parametric or non-parametric tests. Continuous variables were compared between CCS and HC as a group and by sex using two-sided Student's t-test and Mann-Whitney U test where appropriate. Categorical variables were compared by Fisher's exact test. Multivariable linear regression analyses were performed to explore associations between native T1, ECV, LGE and clinical parameters.

54 CCS and 42 HC (25±7yrs vs 26±8yrs, p=0.66; 34 males vs 19 males, p=0.11) were recruited for study. CCS were diagnosed at 7±4yrs and studied at 17±7yrs after chemotherapy completion. Cancer diagnoses were leukaemia (n=34), lymphoma (n=12), Wilms' tumour (n=3), Ewing sarcoma (n=3) and others (n=2). Median cumulative anthracycline dose and duration of treatment were 220mg/m^2 (interquartile range 155 to 280mg/m^2) and 0.5yr (interquartile range 0.3 to 0.6yr), respectively. No CCS had cardiac symptoms. None were receiving cardiac medications. CCS and HC had similar haematocrit (0.41±0.03g/dL vs 0.41±0.05g/dL, p=0.76), weight, height and body surface area. CCS had lower LV ejection fraction (p=0.008) and right ventricular end-diastolic (p=0.008) and end-systolic (p=0.029) volumes.

Native T1 (1222±23ms vs 1226±19ms, p=0.31), ECV (22.9±2.2% vs 23.8±2.4%, p=0.06) and T2 values (57±4ms vs 58±6ms, p=0.22) were similar between CCS and HC (Fig. 1A). Female CCS had significantly higher native T1 (1232±19ms vs 1216±23ms, p=0.012) and ECV (24.5±1.8% vs 22.0±1.9%, p<0.001) than male survivors. Similarly, among HC, females had significantly higher ECV (25.1±1.8% vs 22.4±2.1%, p<0.001) and lower T2 values (56±3ms vs 61±6ms, p=0.002) than males. When stratified by sex, there were no significant differences in all of these parameters between CCS and HC (all p>0.05) (Fig. 1B). Multiple linear regression analyses confirmed that sex is the only significant independent variable of both native T1 (p=0.01) and ECV (p<0.001) after adjustment for CCS/ HC status, age at diagnosis, years post-chemotherapy, cumulative anthracycline dose, and T2 mapping. Median LGE volume was 0.0% in CCS (range, 0.0% to 5.8%) and HC (range, 0.0% to 3.1%). LGE volume was similar between CCS and HC (0.92%±1.32% vs 0.46%±0.96%, p=0.07).

Our study demonstrates the absence of statistically significant increase in myocardial fibrosis as assessed by CMR native T1, ECV and LGE in relatively young CCS. The higher native T1 and ECV in female survivors are probably related to an intrinsic sex difference. Our findings are consistent with

Toro-Salazar et al who showed no significant increase in native T1 and ECV in CCS compared to HC.[2] Tham et al's study on T1 mapping in CCS did not include a normal reference.[1] However, a subsequent paper from the same group[3] showed that native T1 and ECV were lower compared to normal reference values (native T1 1155.3±56.5ms vs 1177±27ms; ECV 20.7±3.6% vs 22.2±3.1%). Thus, our findings are consistent with those of previous publications. While increased ECV was also reported by Tham et al to correlate with decreased LV mass/volume ratio and peak oxygen consumption during exercise testing,[1] there was no adjustment for sex as a possible confounder. Further analysis of our data did not reveal significant correlations between native T1 or ECV and LV mass/LV end-diastolic volume after adjustment for sex. Limitations of our study include the small sample size, potential survivor selection bias, and the lack of formal exercise testing.

Our findings contrast with those in adult cancer survivors, in whom T1 mapping showed elevated levels.[4] Possible explanations include differences in underlying malignancies and hence chemotherapeutic regimens, need for additional radiotherapy that accentuates the myocardial fibrotic process, and different age at the time of treatment.[4] Sex difference in native T1 and ECV are now recognized in different myocardial diseases.[5]

Sources of Funding

This study is supported by the Children's Cancer Foundation (Hong Kong).

Disclosure Statement

None.

References:

1. Tham EB, Haykowsky MJ, Chow K, Spavor M, Kaneko S, Khoo NS, Pagano JJ, Mackie AS,

Thompson RB. Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. *J Cardiovasc Magn Reson*. 2013;15:48.

2. Toro-Salazar OH, Gillan E, O'Loughlin MT, Burke GS, Ferranti J, Stainsby J, Liang B, Mazur W, Raman SV, Hor KN. Occult cardiotoxicity in childhood cancer survivors exposed to anthracycline therapy. *Circ Cardiovasc Imaging*. 2013;6:873-880.
3. Thompson RB, Chow K, Khan A, Chan A, Shanks M, Paterson I, Oudit GY. T1 mapping with cardiovascular MRI is highly sensitive for Fabry disease independent of hypertrophy and sex. *Circ Cardiovasc Imaging*. 2013;6:637-645.
4. Jordan JH, Vasu S, Morgan TM, D'Agostino RB, Jr., Melendez GC, Hamilton CA, Arai AE, Liu S, Liu CY, Lima JA, Bluemke DA, Burke GL, Hundley WG. Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors. *Circ Cardiovasc Imaging*. 2016;9.
5. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017;19:75.

Figure 1: (A) Scatter plots showing the distribution of native T1 (top), ECV (middle) and T2 (bottom) values in patients and controls. Solid lines represent the mean values. (B) Boxplots showing sex differences and group comparison of native T1 (top), ECV (middle) and T2 (bottom) values. *$p<0.01$ for sex differences in survivors; #$p<0.01$ for sex differences in controls. ECV=extracellular volume fraction.