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● *Original Contribution*

LEFT ATRIAL MECHANICS AND INTEGRATED CALIBRATED BACKSCATTER IN ANTHRACYCLINE-TREATED LONG-TERM SURVIVORS OF CHILDHOOD CANCERS

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Abstract—We tested the hypothesis that left atrial (LA) mechanics and myocardial calibrated integrated backscatter (cIB) are altered in anthracycline-treated long-term survivors of childhood cancers. Forty-nine survivors and 25 controls were studied. Survivors had significantly smaller maximal ($p = 0.009$) and minimal ($p = 0.017$) LA volumes and lower peak negative LA strains ($p = 0.011$). For left ventricular (LV) indices, survivors had significantly lower shortening fraction ($p < 0.001$), ejection fraction ($p < 0.001$) and mitral annular late diastolic velocity ($p = 0.003$). Myocardial cIB of the LA posterior wall, ventricular septum and LV posterior wall was significantly greater in survivors than controls (all p values <0.05). Peak negative LA strain was related to late diastolic mitral annular velocity ($r = 0.27, p = 0.018$), whereas LA cIB was related to the average of septal and LV posterior wall cIB ($r = 0.54, p < 0.001$). In conclusion, LA remodeling as characterized by contractile dysfunction and increased cIB suggestive of fibrosis occurs in adult survivors of childhood cancers. (E-mail: xfcheung@hku.hk) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Ultrasound, Left atrial mechanics, Calibrated integrated backscatter, Childhood cancer survivors.**

INTRODUCTION

Long-term cardiac sequelae of pediatric cancer survivors, including reduced ventricular mass (Lipshultz et al. 2005), increased afterload (Lipshultz et al. 2005) and impaired left ventricular (LV) global function and mechanics (Cheung et al. 2010; Ganame et al. 2007), are well-documented. Optimal performance of the heart requires normal functioning not only of the ventricles, but also of the atria. Physiologically, the atrium acts as a reservoir during ventricular systole, functions as a conduit during opening of the atrioventricular valve in early ventricular diastole and performs as a pump at late ventricular diastole (Todaro et al. 2012). Previous studies in anthracycline-treated long-term survivors of childhood cancers have, however, focused on functional assessment of the ventricles. Nonetheless, there is evidence to suggest potential involvement of the atria in anthracycline cardiotoxicity.

In an ovine model of anthracycline-induced cardiomyopathy, significant left atrial (LA) remodeling as characterized by atrial enlargement, dysfunction and increased fibrosis has been reported (Lau et al. 2011). With accumulation of collagen, as part of either the reactive fibrosis or reparative process to replace degenerating myocardial tissue (Silver et al. 1990), deformation of the atrial wall might be affected. Nevertheless, data on atrial function and its significance in long-term survivors of childhood cancer have hitherto not been reported. The absence of data on atrial function in anthracycline cardiotoxicity may in part be related to the laborious methods required previously for its assessment.

Recent advancements in speckle tracking echocardiography (STE) have enabled convenient and comprehensive evaluation of LA function (Todaro et al. 2012). Determination at different phases of the cardiac cycle of LA strain and strain rate, which represent respectively the magnitude and rate of atrial myocardial deformation, provides functional assessment of atrial reservoir, conduit and pump function. Additionally, there has also been increasing clinical application of 2-D echocardiography-derived calibrated integrated backscatter (cIB) analysis in the assessment of LA

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fibrosis (den Uijl et al. 2011; Kubota et al. 2012; Wang et al. 2009).

Given the aforementioned experimental data on possible alteration of atrial substrate and function in anthracycline-induced cardiomyopathy, we hypothesized that LA mechanics and myocardial cIB are altered in anthracycline-treated long-term survivors of childhood cancers. The aims of this study were to test the hypothesis by assessment of LA mechanics, in terms of global atrial strain and strain rates using STE, and LA myocardial cIB as a marker of fibrosis in long-term childhood cancer survivors and to explore their relationships with left ventricular (LV) function.

METHODS

Patients

This is a prospective study of anthracycline-treated survivors of childhood cancers who had been off treatment for at least 5 y and were consecutively recruited from the oncology clinic. The following data were collected from the case notes: diagnosis, age at diagnosis, dates of start and completion of chemotherapy, surgical interventions, cumulative dose of anthracyclines and the need for cardiac irradiation and current cardiac medications. The echocardiographic findings of patients were compared with those of healthy control patients, who were hospital staff, healthy siblings and children attending the cardiac clinic with functional heart murmur, non-specific chest pain or palpitation, and for which no underlying organic causes were identified. Weight and height of all patients were measured, and body mass index and body surface area were calculated accordingly. Ethical approval was obtained from the institutional review board of the University of Hong Kong/Hospital Authority West Cluster, Hong Kong, and written informed consent was provided by patients before examinations.

Assessment of left atrial function and remodeling

All echocardiographic assessments were performed using a M4 S transducer transduced to the Vivid 7 ultrasound machine (GE Medical Systems, Horten, Norway). Data were stored digitally and analyzed offline using EchoPAC software (GE Medical Systems). Average values of echocardiographic indices based on readings from three cardiac cycles were used for statistical analyses.

Left atrial volume was measured using biplane Simpson's method and normalized for body surface area. Left atrial volumes were assessed just before mitral valve opening (maximal LA volume, Vol_{max}), at mitral valve closure (minimal LA volume, Vol_{min}) and at P-wave onset just before atrial contraction (pre-A LA volume, Vol_p). As described previously, LA reservoir function was assessed by calculation of LA expansion index ($Vol_{max} - Vol_{min}/Vol_{min} \times 100\%$), conduit function by LA passive emptying fraction ($Vol_{max} - Vol_p/Vol_{max} \times 100\%$), and contractile function by LA active emptying fraction ($Vol_p - Vol_{min}/Vol_p \times 100\%$) (Debonnaire et al. 2013).

From the apical four-chamber view, global LA myocardial deformation was assessed using 2-D STE based on tracking of the entire endocardial contour of the left atrium by the EchoPAC software (Hou et al. 2015; Li and Cheung 2015; Saraiva et al. 2010; Todaro et al. 2012). The onset of P wave was taken as the reference point for determination of the following parameters of global atrial deformation: peak positive strain, peak negative strain, total strain and atrial strain rate at ventricular systole (aSRs), early diastole (aSRed) and atrial contraction (aSRac) (Fig. 1). Our group has previously reported on the reproducibility of assessing LA deformation using STE, the intra- and inter-observer variability in measurements of LA total strain being 5.6% and 7.0%, SRs 7.6% and 11.1%, SRed 5.7% and 10.5% and SRac 8.1% and 9.2%, respectively (Hou et al. 2015).

Integrated backscatter of the posterior LA wall from the parasternal long-axis view was measured at atrial diastole as the difference between the region of interest and that of the pericardium as described previously (Fig. 2) (den Uijl et al. 2011; Wang et al. 2009). The ultrasound settings, including frequency, frame rate and time gain compensation, were standardized to remain constant throughout the study to limit their influence on integrated backscatter values. Placement of the sample volume may affect the analysis and values. Hence, a sample volume 2 to 3 mm in diameter was tracked manually to maintain its location in the same region throughout the heart cycle. Care was taken to avoid bright specular reflection, and output power settings were adjusted to ensure that signals were not saturated in both the pericardium and atrial wall.

Assessment of left ventricular function and cIB

From the parasternal short-axis views, the following M-mode measurements were made: LV end-systolic and end-diastolic dimensions and thickness of the interventricular septum and posterior LV wall. The fractional shortening and LV mass were calculated according to standard formulas. Pulsed-wave Doppler examination was performed to obtain peak mitral inflow velocities at early (*E*) and late (*A*) diastole, *E* deceleration time and *E/A* ratio. Tissue Doppler echocardiography was performed with the sample volume positioned at the basal LV free wall–mitral annular junction to determine the following parameters: peak systolic (*s*), early diastolic (*e*) and late diastolic (*a*) myocardial tissue velocities and *e/a* and E/*e* ratios.