Impaired Right Ventricular Function in Long-Term Lymphoma Survivors

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Background: Cardiotoxicity from anthracyclines or cardiac radiation therapy is detrimental to left ventricular (LV) function. However, the long-term effects on right ventricular (RV) performance are largely unknown. The aim of this study was to investigate the long-term impact of cardiotoxic treatment on RV function among adult cancer survivors.

Methods: Adult lymphoma survivors (LSs) who underwent autologous hematopoietic stem cell transplantation in Norway from 1987 to 2008 were invited to undergo cardiovascular evaluation by echocardiography and cardiopulmonary exercise testing. In total, 274 LSs participated. The mean age was 56 ± 12 years, and the mean follow-up time since lymphoma diagnosis was 13 ± 6 years. Echocardiographic parameters were compared with those of age- and gender-matched control subjects from an existing large Norwegian database. RV systolic dysfunction was indicated by two or more abnormal RV systolic parameters according to current recommendations. LV systolic dysfunction was indicated by LV global longitudinal strain > −17%.

Results: All parameters of RV systolic function were impaired in LSs compared with control subjects ($P < .01$ for all). The most pronounced difference was observed for tricuspid annular plane systolic excursion: 22.9 ± 4.1 versus 27.1 ± 4.2 mm. Greater cardiotoxic treatment burden was associated with larger RV functional impairment. Tricuspid annular plane systolic excursion correlated with peak oxygen consumption ($r = 0.23$, $P = .001$). RV systolic performance was associated with LV systolic function ($r = 0.49$, $P < .001$ for tricuspid annular plane systolic excursion vs LV global longitudinal strain), but a greater proportion of patients had LV dysfunction (30.8%) compared with RV dysfunction (6.2%) ($P < .001$).

Conclusions: RV systolic function was impaired in LSs. The association between RV and LV function indicates a global, long-term cardiotoxic effect. However, RV dysfunction was less prevalent than LV dysfunction. (J Am Soc Echocardiogr 2016;29:528-36.)

Keywords: Anthracyclines, Echocardiography, Lymphoma survivors, Radiotherapy, Right ventricle

Lymphoma survivors (LSs) are at increased risk for cardiovascular complications because of treatment with cardiotoxic drugs, such as anthracyclines,[1] as well as cardiac radiation therapy (RT), including direct and/or scattered irradiation. Anthracyclines dose-dependently induce cardiomyocyte apoptosis,[2] eventually leading to overt heart failure.[3] Cardiac RT causes both micro- and macrovascular damage[4] and is associated with increased risks for valvular disease, myocardial infarction, and heart failure.[5]

Multiple studies have assessed left ventricular (LV) function after cardiotoxic treatment among LSs, showing that LV function is reduced during or shortly after lymphoma treatment[6-8] as well as in long-term survivors.[9] However, less is known regarding the effects on right ventricular (RV) function. The lack of available data on RV function and the fact that RV function has not been adequately studied in cancer survivors was also acknowledged in a recent expert consensus report on cardiac imaging in adult cancer patients.[10] A

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This study was supported by the South-Eastern Norway Regional Health Authority and Extrastiftelsen and received no funding from the medical industry. Håvard Dalen has a position at MI Lab, a Centre of Research-based Innovation that is funded by the Research Council of Norway and industry. One of the industry partners is GE Vingmed Ultrasound. GE had no role in this manuscript, such as planning of the study, data acquisition, drafting or revision of the manuscript or supply of ultrasound equipment. All the other authors declare no conflict of interest.

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2016.02.014

Abbreviations

Auto-HCT = Autologous hematopoietic stem cell transplantation

FAC = Fractional area change

GLS = Global longitudinal strain

LS = Lymphoma survivor

LV = Left ventricular

RA = Right atrial

RIMP = Right ventricular index of myocardial performance

RT = Radiation therapy

RV = Right ventricular

TAPSE = Tricuspid annular plane systolic excursion

Vo_2 = Oxygen uptake

subclinical decline in RV function has been observed shortly after completion of anthracycline-containing chemotherapy for breast cancer,[11] but no available data describe RV function in adult LSs. In the general population, RV systolic dysfunction is associated with increased mortality from systolic heart failure,[12] but its prognostic value in cancer survivors is unknown.

In the present study, we aimed to assess the long-term effect of cardiotoxic treatment on RV systolic function in adult LSs treated with autologous hematopoietic stem cell transplantation (auto-HCT).

METHODS

Study Design and Participants

Patients were enrolled in a cross-sectional Norwegian multicenter study.[13] The eligibility criteria were auto-HCT treatment for Hodgkin or non-Hodgkin lymphoma in Norway between 1987 and 2008, age ≥ 18 years at auto-HCT, and being alive at the time of the survey. The only exclusion criterion was current treatment for relapsed lymphoma. In total, 274 LSs participated, constituting 69% of all eligible LSs. Patient recruitment has previously been described.[14] Participants and nonparticipants ($n = 125$) did not differ with regard to the primary diagnosis (non-Hodgkin or Hodgkin lymphoma), gender, mean cumulative doxorubicin dose, proportion receiving cardiac RT, age at survey, or time from auto-HCT ($P > .05$ for all, data not shown). Echocardiographic examinations were performed between March 2012 and March 2014. All participants provided written informed consent. The Regional Committee for Medical and Health Research Ethics approved the study.

Treatment

On the basis of the median cumulative anthracycline dose and a previously reported cutoff for high-dose cardiac RT,[15] we categorized the LSs into four groups: low-dose anthracyclines (<300 mg/m^2), higher dose anthracyclines (≥300 mg/m^2), anthracyclines and low-dose cardiac RT (≤30 Gy), and anthracyclines and high-dose cardiac RT (>30 Gy). Details concerning treatment regimens have been described elsewhere.[14]

Control Group

We recruited control subjects from a large Norwegian cross-sectional population study (the Nord-Trøndelag Health Study), which includes an echocardiographic database of 1,266 participants without known cardiovascular disease, hypertension, or diabetes mellitus.[16] The control subjects were matched 1:1 with study participants according to age, gender, systolic blood pressure, and body mass index.

Echocardiography

After a minimum of 5 min of rest, patients assumed a left lateral decubitus position for ultrasound examinations. As recommended, examinations were performed using parasternal, apical, and subcostal projections, including dedicated RV views.[17] Ultrasound recordings were obtained using echocardiographic scanners (Vivid 7 or E9; GE Vingmed Ultrasound, Horten, Norway) with standard settings, second-harmonic imaging, and optimal gain and contrast. The frame rates were >90 and >40 frames/sec during tissue Doppler recordings and grayscale imaging, respectively. We obtained at least three consecutive cine loops (more than five for patients in arrhythmia), which were stored for offline analysis using dedicated software (EchoPAC version 112; GE Vingmed Ultrasound).

RV dimensions and functional measurements were obtained as recommended.[18] RV wall thickness was measured at end-diastole from the subcostal view or the parasternal long-axis view. RV basal, mid, and longitudinal diameters and right atrial (RA) area were indexed to body surface area. We measured tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC), RV peak systolic velocity at the lateral tricuspid annular plane (RV S′) by pulsed Doppler tissue imaging, and RV index of myocardial performance (RIMP)[19] by pulsed Doppler tissue imaging at the lateral tricuspid annulus. Peak systolic longitudinal RV strain was measured using two-dimensional speckle-tracking echocardiography.[20,21] We estimated RV strain (average of six segments, including the interventricular septum) and RV free wall strain (average of three segments, excluding the interventricular septum) in a dedicated four-chamber view.

On the basis of previous studies in healthy individuals, we defined the following cutoff values as indicators for abnormality: TAPSE < 17 mm, RV FAC < 35%, RV S′ < 9.5 cm/sec, RIMP > 0.54, and absolute RV free wall strain < 20%.[18] Lacking a validated global definition of impaired RV systolic function, we considered RV systolic dysfunction to be present when at least two of these parameters were below the cut points. We considered a peak velocity of tricuspid valve regurgitation of >2.8 m/sec to indicate elevated pulmonary arterial pressure.[22] The right atrium was considered enlarged when RA area indexed to body surface area was >10.4 cm^2/m^2.[23] LV systolic function was estimated using two-dimensional speckle-tracking echocardiography in the three standard apical image planes to obtain LV global longitudinal strain (GLS) in a 16-segment model. LV GLS > −17.0% was taken to indicate abnormal LV systolic function.[24]

When comparing the numbers of patients with abnormal RV and LV function, in addition to the aforementioned definitions, we also used another set of cutoff values derived from the matched healthy control population. For the latter analyses, abnormality was defined as values below the lower limits of normal (<2 SDs) for TAPSE and LV GLS. As a surrogate for LV end-diastolic pressure, we used the E/e′ ratio, where E is the early transmitral inflow velocity by pulsed Doppler and e′ is the mean of the peak early diastolic velocities at the lateral and septal mitral annulus by Doppler tissue imaging.

A single experienced echocardiographer (K.M.), who was blinded to patient treatment, performed all echocardiographic analyses in the LSs. The control subjects were all examined by an experienced cardiologist (H.D.) using a Vivid 7 scanner. All of the original recordings were reassessed by one investigator (K.M.).

Measurement of Peak Oxygen Uptake

We used an ergometer bicycle for maximal, upright, symptom-limited exercise testing. We used an individualized, stepwise protocol in which the workload was increased every minute to reach the age-, gender-,