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Impaired right ventricular function in long-term survivors of allogeneic haematopoietic stem-cell transplantation

Richard John Massey ⬤ ,[1,2] Phoi Phoi Diep,[2,3,4] Marta Maria Burman,[2,3,4] Anette Borger Kvaslerud ⬤ ,[1,2] Lorentz Brinch,[4] Svend Aakhus,[5,6] Lars Gullestad ⬤ ,[1,2,7] Ellen Ruud ⬤ ,[2,8] Jan Otto Beitnes[1]

Correspondence to
Dr Richard John Massey;
massey_richard@hotmail.com

ABSTRACT

Aims Survivors of allogeneic haematopoietic stem-cell transplantation (allo-HSCT) are at higher risk of cardiovascular disease. We aimed to describe right ventricular (RV) systolic function and risk factors for RV dysfunction in long-term survivors of allo-HSCT performed in their youth.

Methods and results This cohort included 103 survivors (53% female), aged (mean±SD) 17.6±9.5 years at allo-HSCT, with a follow-up time of 17.2±5.5 years. Anthracyclines were used as first-line therapy for 44.7% of the survivors. The RV was evaluated with echocardiography, and found survivors to have reduced RV function in comparison to a group of healthy control subjects: Tricuspid annular plane systolic excursion, (TAPSE, 20.8±3.7 mm vs 24.6±3.8 mm, p<0.001), RV peak systolic velocity (RV-s', 11.2±2.3 cm/s vs 12.3±2.3 cm/s, p=0.001), fractional area change (FAC, 41.0±5.2% vs 42.2±5.1%, p=0.047) and RV free-wall strain (RVFWS, −27.1±4.2% vs −28.5±3.3%, p=0.043). RV systolic dysfunction (RVSD) was diagnosed in 14 (13.6%), and was strongly associated with progressive left ventricular systolic dysfunction (LVSD). High dosages of anthracyclines were associated with greater reductions in RV and LV function. Multivariable linear regressions confirmed global longitudinal strain to be a significant independent predictor for reduced RV function.

Conclusion Impaired RV function was found in long-term survivors of allo-HSCT who were treated in their youth. This was associated with progressive left ventricle dysfunction, and pretransplant therapies with anthracyclines. The occurrence of RVSD was less frequent and was milder than coexisting LVSD in this cohort.

INTRODUCTION

Allogeneic haematopoietic stem-cell transplantation (allo-HSCT) is increasingly used as a curative therapy for severe malignant and non-malignant disorders in young patients. Advances in treatment strategies have improved survival in the immediate years after transplantation.[1] A growing concern in long-term survivors is a 2–4 times higher cardiovascular mortality compared with the general population.[2 3] Acquired heart disease can be attributed to pretransplant chemotherapy, transplant-related conditioning, graft-versus-host disease (GVHD) and elevated levels of cardiovascular risk factors.[2–5]

Chemotherapy-induced cardiotoxicity in the form of left ventricle systolic dysfunction (LVSD) is well acknowledged. In contrast, information regarding the therapeutic consequences of HSCT to right ventricular (RV) function is scarce,[6] and to our knowledge, is absent in those exposed during childhood, adolescence and young adulthood (CAYA). The level of functional impairment after chemotherapy is reported to differ between the ventricles.[6–8] Moreover, RV function has been shown to be a strong predictor for progression and mortality in heart failure.[9 10]

This observational study aimed to evaluate RV function, determine the prevalence

Key questions

What is already known about this subject?
► Survivors of allogeneic haematopoietic stem-cell transplantation (allo-HSCT) are at elevated risk of heart disease due to high-dose chemotherapies, graft-versus-host disease and high rates of cardiovascular risk factors. Despite this, there is scarce information on right ventricular (RV) function.

What does this study add?
► This study demonstrates that RV function is reduced in survivors of allo-HSCT.
► The occurrence of RV systolic dysfunction is strongly associated with co-existing left ventricular systolic dysfunction.

How might this impact on clinical practices?
► Examination of the right ventricle with echocardiography should be performed in survivors of high-dose anthracyclines and coexisting left ventricular dysfunction.
► Allo-HSCT survivors identified with reduced RV function may benefit from more frequent surveillance and assertive cardioprotective interventions.

of RV systolic dysfunction (RVSD), and identify factors predicting its occurrence in a cohort that underwent allo-HSCT at a young age.

METHODS

Study design

Oslo University Hospital is Norway's national centre for allo-HSCT. A complete nationwide cohort was identified by browsing the hospital registry. The eligibility criteria were allo-HSCT at Oslo University Hospital, <30 years at transplantation, >16 years at inclusion and a minimum observation time of 5 years. Survivors with Hurler syndrome were excluded due to multi-organ pathology as a part of their primary disease.

Clinical assessment

Anthracycline cumulative dosage was calculated by recommended conversion rates to isotoxic doses of doxorubicin.[11] Dyspnoea was classified according to the New York Heart Association (NYHA).[12] Blood pressures were measured after ≥30 min in the supine position, immediately after echocardiography, as the average of three measurements. Blood samples were collected after overnight fasting and analysed at the hospital's laboratory. N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) concentrations were determined by an electrochemiluminescence immunoassay (Roche Diagnostics, Switzerland). The lowest detectable NT-pro-BNP value was 5 ng/L, and elevated levels were defined by age-specific and gender-specific cut-offs as recommended by the manufacturer. Diabetes mellitus type II was classified as haemoglobin glucose >6.5% (48 mmol/mol) or use of glucose-lowering medication. Hypothyroidism was defined by the use of thyroid replacement medication or serum thyroid-stimulating hormone >4 mg/L and free thryroxine-4 <9 pmol/L. Hypertension was defined as current use of anti-hypertensive drugs, systolic blood pressure >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg. Hypercholesterolaemia was defined as low-density lipoprotein >4.1 mmol/L (160 mg/dL) or use of lipid-lowering medication. Acute GVHD and chronic GVHD (cGVHD) were graded by the Glucksberg and Shulman criteria.[13 14] Bronchiolitis obliterans syndrome (BOS) was defined as recommended.[15]

Echocardiography

Transthoracic echocardiography was performed using Vivid-E9 scanners and software (V.113.1.3-EchoPAC, GE-Vingmed Ultrasound, Norway). A comprehensive protocol was designed to evaluate cardiac function, and data from this cohort were used to describe LV and RV function. All echocardiograms were acquired and analysed by the same experienced investigator (RJM). Analyses were conducted en bloc after completion of the last inclusion, on deidentified images, in random order and blinded to patient's medical records. RV and LV indices were measured at separate occasions to reduce bias. Twenty-five echocardiograms from patients and

controls were randomly selected for intraobserver variability tests.

The study followed European Association of Cardiovascular Imaging (EAVCI) recommendations for image acquisition and analyses.[16 17] Scanner settings were optimised and measurements made from three consecutive heart cycles. Internal RV dimensions, right atrium (RA) area/volume, and measures of RV function were performed on modified apical four-chamber view focused on the RV. Particular care was made to ensure appropriate orientation and without foreshortening. Further adjustments to sector width and depth of grey-scale images increased resolution. Average frame rate was 69/s. For fractional area shortening (FAC), the RV's borders were traced in end-diastole and end-systole, with consideration of trabeculations. RV posterior-wall thickness was measured in diastole on a dedicated subcostal four-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was measured with anatomical M-mode placed between the annulus and apex, and parallel to the free-wall. Tissue velocity imaging (TVI) with Doppler was recorded from the annulus to calculate RV peak systolic velocity (RV-s') and RV index of myocardial performance (RIMP). Speckle tracking echocardiography (STE) was used to obtain RV free-wall strain (RVFWS) as the average peak systolic value from three free-wall segments. Region of interest was manually adjusted for apex, annular plane and myocardial borders. Tracking was visually controlled. Results were only included if reliable values were acquired from all segments.

Current EAVCI guidelines were used to define the cut-offs for reduced RV function: FAC <35%, TAPSE <17 mm, RV-s'<9.5 cm/s, RVFWS >−20% and RIMP >0.54.[16] In the absence of a consensus for definition of RVSD, we considered RVSD to be present when at least two of these parameters were abnormal.

Tricuspid regurgitation pressure (TRP) was measured with continuous wave Doppler from multiple views. Pulmonary artery systolic pressure (PASP) was calculated from TRP using the Bernoulli equation plus RA pressure estimated by size and respiratory variation of the inferior vena cava.[17] Elevated PASP was defined as TRP >2.8 m/s and/or PASP >35 mm Hg.[17] In survivors without adequate TR or signs of pulmonary hypertension, PASP of 23.3 mm Hg (group mean) was allocated.

LVSD was defined as reduced 2D-LVEF (male <52%, female <54%) and/or reduced global longitudinal strain (GLS) ≥−17%. Diastolic function was evaluated according to guideline algorithms.[18] Tricuspid and pulmonary valve pathology were graded according to recommendations.[19] Pericardial pathology was defined as increased pericardial fluid >0.5 cm, and/or presence of abnormal thickening or fusion of the visceral and parietal membranes.

Control group

Calculations of sample size were made for TAPSE, RV-s', RVFWS and FAC, using EACVI reference values for means and SD in controls.[16] To identify a 10% difference

in group means with α=0.05 (two sided) and power >0.8, a minimum of 48 controls were required. To accommodate for eventual missing data, 55 healthy controls of similar race and ethnicity were recruited from advertisements. Efforts were made to obtain control group with a comparative patient characteristics. The only exclusion was established cardiovascular disease.

Statistical analyses

Statistical analyses were performed with SPSS V.26 (SPSS), and p<0.05 was considered significant. Shapiro-Wilk test was used to assess normality. Continuous data are presented as mean±SD, or as median (25th, 75th percentile) in cases of asymmetric distribution. Categorical data are presented as number (percentage). Allo-HSCT survivors (n=103) and controls (n=55) were compared with Student's t-test and Mann-Whitney U-test for continuous data, and χ^2 or Fisher's exact test for categorical data. Inverse probability of treatment weighting method (propensity scoring) was used to adjust for imbalances between the groups in covariates that potentially influence RV function: Age at examination, heart rate (HR) and DBP.

Predictors for RV function (TAPSE, RV-s', RVFWS) were determined by multivariable linear regression analyses. Continuous variables were standardised. The final prediction model included priori selected variables considered to be important determinants for RV function and covariates with p<0.20 in univariable regression. Assumption testing included histograms, residual plots and multicollinearity assessed by Pearsons correlations, tolerance and variance inflation factor (VIF). Over-fitting was avoided. Likewise deletion was used to handle the few randomly missing data.

Dose-dependent effects from anthracyclines on RV function were tested by allocating survivors into three groups according to dosage: none, low ($<300\,mg/m^2$) and high ($300\,mg/m^2$). Allocation of dosage cut-offs was based on median values, and was comparative to previous studies. Analysis of covariance (ANCOVA) with age at examination, HR, body mass index and DBP as covariates, and χ^2, both with Bonferroni post hoc analysis, were used in these in-group comparisons.

RESULTS

In total, 290 patients were treated with allo-HSCT in the time frame specified for this study. Of these, 131 (45.2%) died prior to study start and two were excluded due to incomplete patient files. One-hundred and fifty-seven were eligible for inclusion, and 104 (66.2%) survivors were initially included and examined with echocardiography (figure 1). One patient had previous heart surgery to remove a benign tumour from the left atrium and was excluded from statistical analyses. The cohort consisted of 103 survivors, 55 (53.4%) females, aged 17.6±9.5 years at allo-HSCT, and with a follow-up time to examination with echocardiography of 17.2±5.5 years. Non-participants (n=54) were younger (27.7 years), had shorter follow-up
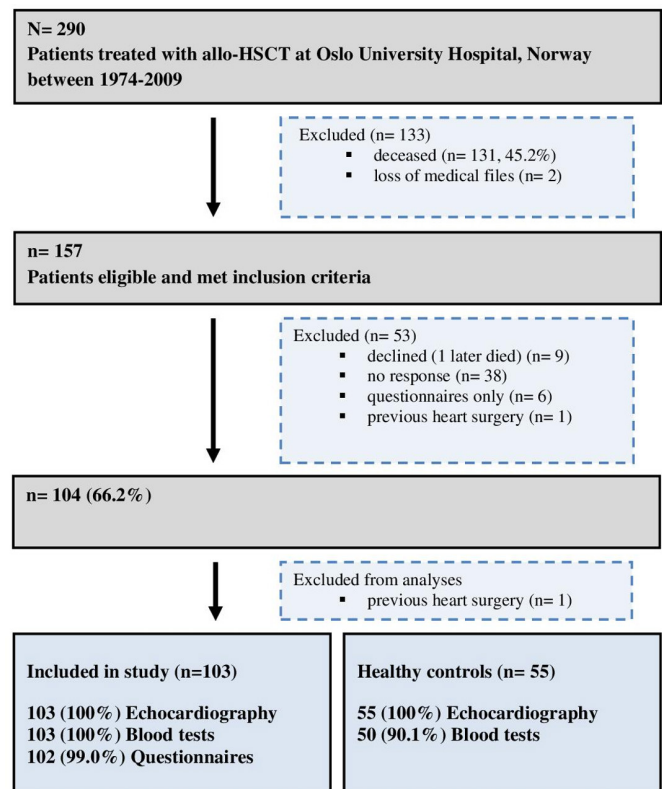

Figure 1 Flow chart of study participants. allo-HSCT, allogeneic haematopoietic stem-cell transplantation.

time (13.2 years), and were more commonly male (68.5%).

Survivor characteristics and treatments

Survivor characteristics are shown in table 1. Malignancy was the primary disease in 76 (73.8%, 55.3% were female), and was the indication for anthracyclines in 46 (44.7%, 58.7% were female) and mediastinal radiotherapy in two (1.9%). Median cumulative anthracycline dosage was $270\,mg/m^2$ ($45–585\,mg/m^2$). The majority received myeloablative conditioning consisting of busulfan (4–5 mg/kg/day/po administered over 4 days) in combination with cyclophosphamide (50 mg/kg/day/intravenously over 4 days or 60 mg/kg/day/intravenously over 2 days). Seven (6.8%) received fractionated total body irradiation (TBI, 1,3 Gy × 2 over 5 days). History of GVHD was identified in 67 (65.0%) survivors. Ten (9.7%) were diagnosed with BOS, of which 80% also had chronic GVHD. Currently used medication included ACE-inhibitors and/or angiotensin receptor blockers in 20, calcium blockers in 13, beta-blockers in two and statins in four. In comparison to controls, survivors had a higher prevalence of cardiovascular risk factors (table 1), and a higher DBP (72 mm Hg vs 66 mm Hg, p<0.001). Risk factors in survivors were distributed equally between sexes, with the exception of hypertension (17 female vs 24 male, p=0.048) and hypothyroidism (8 female vs 1 male, p=0.025).

Table 1 Survivor characteristics

Variable	Allo-HSCT	Controls	P value
Number	103	55	
Gender (female)	55 (53.4)	29 (52.7)	0.936
Body mass index (kg/m^2)	24.5±5.1	24.1±3.4	0.478
Age at allo-HSCT (years)	17.6±9.5		
Time to follow-up (years)	17.2±5.5		
Age at examination (years)	34.8±11.6	36.4±10.6	0.401
Systolic blood pressure (mm Hg)	123±19	117±11*	**0.036**
Diastolic blood pressure (mm Hg)	72±13	66±8*	**<0.001**
Heart rate (bpm)	69±11	68±12	0.59
Malignant/non-malignant disease	76 (73.8)/27 (26.2)		
Mediastinal radiotherapy	2 (1.9)		
Anthracyclines	46 (44.7)		
Cum. dosage (mg/m^2)	270 (130, 435)		
Myeloablative conditioning:			
Chemotherapy (Bu/Cy)	94 (91.3)		
Chemotherapy+TBI	7 (6.8)		
None	2 (1.9)		
Graft-versus-host disease (GVHD)	67 (65.0)		
Acute GVHD	27 (26.2)		
Chronic GVHD	12 (11.7)		
Acute and chronic GVHD	28 (27.2)		
New York Heart Association			
Class-I	74 (73.3)†	55 (100.0)	**<0.001**
Class-II	16 (15.8)†	0 (0)	**0.002**
Class-III	11 (10.7)†	0 (0)	**0.008**
Class-IV	0 (0)†	0 (0)	
Risk factors:			
Hypertension	41 (39.8)	1 (1.8)	**<0.001**
Diabetes mellitus	3 (2.9)	0 (0)	**0.552**
Hypothyroidism	9 (8.7)	0 (0)	**0.028**
Hypercholesterolaemia	15 (14.9)†	0 (0)	**0.003**
Bronchiolitis obliterans syndrome	10 (9.7)	0 (0)	**0.015**
Smoking (current/previous)	10 (9.9)/17 (16.5)†	2 (3.6)/11 (20.0)	**0.216/0.622**
Laboratory parameters:			
NT-pro-BNP (ng/L)§	47 (22, 84)	5 (5,52)¶	**<0.001**
Elevated levels**	16 (15.5)	2 (4.0)¶	**0.038**

Data presented as mean±SD, median (25th, 75th) or n (%). Calculated with Student's t-test, Mann-Whitney and χ^2/Fisher's exact test. Statistically significant values in boldface p<0.05.
*n=54.
†n=101.
‡
§Lowest recordable value=5 ng/L.
¶n=50.
**18–44 years: male >86 ng/L, female >130 ng/L, 45–54 years: male >121 ng/L, female >249 ng/L.
allo-HSCT, allogeneic haematopoietic stem-cell transplantation; NT-pro-BNP, N-terminal pro-brain-type natriuretic peptide; TBI, total body irradiation.

RV morphology and function

The RV and RA were structurally similar between survivors and controls, with the exception of indexed RV mid-wall diameter that was mildly, but significantly larger in survivors (table 2). Male survivors had larger heart chambers, and significantly greater values for RV-s' (male 12.0±2.4 cm/s vs female 10.4±1.8 cm/s, p<0.001) and larger values for TAPSE (male 21.5±3.3 mm vs

Table 2 Comparisons of right ventricular function in survivors and controls

Variable	Allo-HSCT (n=103)	Control (n=55)	P value	Adjusted P value*
RA morphology				
RA area (cm/m²)	8.0±1.5	8.3±1.4	0.254	0.445
RA-EDV-index (mL/m²)	22.2±6.8	22.8±4.9	0.560	0.833
Dilated RA-EDV†	14 (13.6)	5 (9.1)	0.407	
RV morphology				
RVIDd basal (cm/m²)	2.0±0.3	2.0±0.2	0.133	0.092
RVIDd mid-wall (cm/m²)	1.7±0.3	1.6±0.2	**0.005**	**0.001**
RVIDs basal (cm/m²)	1.6±0.2	1.5±0.2	0.391	0.158
RVIDs mid-wall (cm/m²)	1.3±0.2	1.1±0.2	**0.001**	**<0.001**
RV length (cm/m²)	4.1±0.5	3.9±0.4	0.119	0.145
RV wall-thickness (mm)	39±4 (n=90)	38±4 (n=48)	0.111	0.168
RV-EDA (cm/m²)	11.0±2.3	10.8±1.0	0.538	0.428
Dilated RV-EDA‡	32 (31.1)	9 (6.4)	**0.045**	-
RV-ESA (cm/m²)	6.5±1.4	6.2±1.1	0.227	0.068
RV function				
Fractional area change (%)	41.0±5.2	42.2±5.1	0.175	**0.047**
FAC <35%	11 (10.7)	2 (3.6)	0.222	-
TAPSE (mm)	20.8±3.7	24.6±3.8	**<0.001**	**<0.001**
TAPSE <17mm	13 (13.0)	1 (1.8)	**0.020**	-
RV s' (cm/s)	11.1±2.3	12.3±2.3	**0.005**	**0.001**
RV-s' <9.5cm/s	26 (25.5)	8 (14.8)	0.124	-
RV-e' (cm/s)	10.0±2.7	11.7±2.5	**<0.001**	**<0.001**
RV-e' <7.8cm/s	18 (17.6)	1 (1.9)	**0.004**	-
RIMP	0.45±0.09	0.45±0.07	0.851	0.649
RIMP >0.54	17 (17.2)	3 (5.6)	**0.042**	-
RVFWS (%)	−27.1±4.2	−28.5±3.3	0.052	**0.043**
RVFWS ≥20%	3 (3.2)	0 (0)	0.553	-
TRP (mm Hg)	18.1±4.0	16.7±2.6	**0.034**	0.125
PASP >35 mm Hg	3 (2.9)	0 (0)	0.552	-
LV function				
2D-LVEF (%)	55.2±5.9	59.0±2.9	**<0.001**	**<0.001**
GLS (%)	−17.5±2.2	−19.7±1.4	**<0.001**	**<0.001**
E/e'	6.6±2.2	5.7±1.4	**0.003**	**0.011**

*Adjusted p values by propensity scoring. Statistically significant values in boldface (p<0.05).
†Dilated RA in males if >32 mL/m² and in females if >27 mL/m².
‡Dilated RV-EDA in males if >12.6 cm²/m² and in females if >11.5 cm²/m².
Allo-HSCT, allogeneic haematopoietic stem-cell transplantation; 2D, two dimensions; E/e', ratio of early-diastolic velocity to mean early-diastolic myocardial velocity; FAC, fractional area change; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure; RA, right atrium; RA-EDV, RA-end-diastolic volume; RIMP, Right Ventricular Index of Myocardial Performance; RV, right ventricular; RV-e', RV early-diastolic velocity; RV-EDA, RV-end-diastolic area; RV-ESA, RV-End-Systolic Area; RVFWS, RV-free-wall strain; RVIDd, RV-internal dimension in diastole; RVIDs, RV-internal dimension in systole; RV-s', RV-peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TRP, tricuspid regurgitation pressure.

female 20.1±3.3 mm, p=0.056). Measured parameters on systolic RV function were clearly lower in survivors of allo-HSCT as compared with controls, with the exception of RIMP: TAPSE (20.8±3.7 mm vs 24.6±3.8 mm, p<0.001), RV-s' (11.1±2.3 cm/s vs 12.3±2.3 cm/s, p=0.001), FAC (41.0%±5.2% vs 42.2±5.1%, p=0.047) and RVFWS (−27.1±4.2% vs −28.5±3.3%, p=0.043) (table 2 and figure 2). Significant linear correlations were found between parameters of RV and LV function

(see online supplemental table 1). Higher anthracycline dosages corresponded with greater biventricular functional impairments, and more cases of elevated filling pressures, indicating a dose-dependent relationship (table 3). RVSD was found in two survivors whom had received high-dose (>300 mg/m²) anthracyclines and TBI conditioning. Neither of the two survivors whom had received mediastinal radiotherapy had registered RVSD.
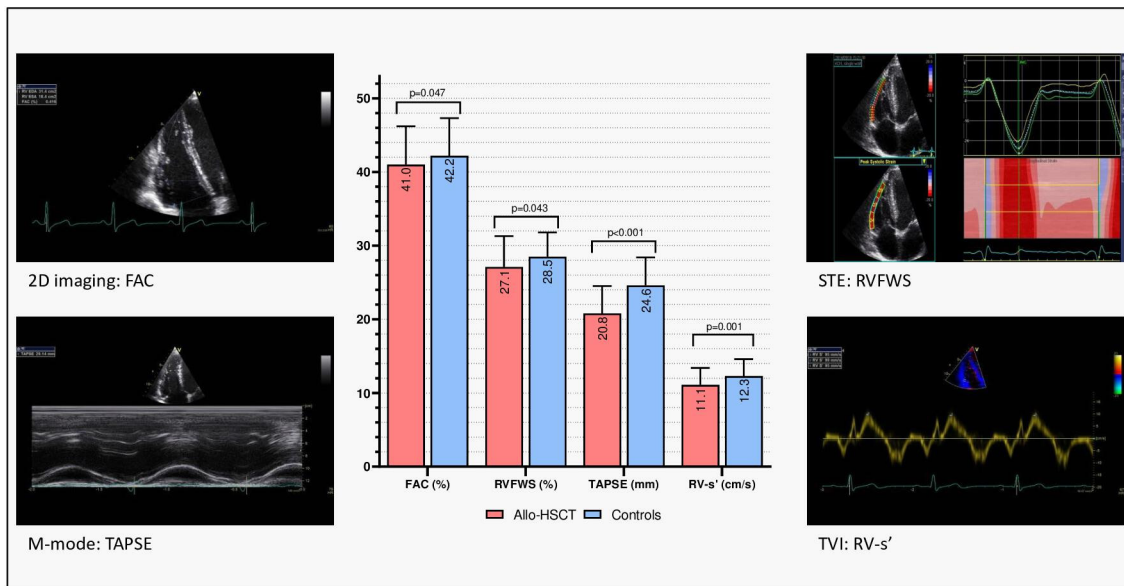
Figure 2 Comparison of right ventricular systolic function between allo-HSCT survivors and healthy controls. Presented with means±SD and adjusted p values. 2D, two dimensions; allo-HSCT, allogeneic haematopoietic stem-cell transplantation; FAC, fractional area change; M-mode, motion-mode ultrasound; RVFWS, Right ventricular Free-Wall Strain (absolute value), RV-s', right ventricular peak systolic velocity; STE, speckle tracking echocardiography; TAPSE, tricuspid annular plane systolic excursion; TVI, tissue velocity imaging.

RVSD was identified in 14 survivors (64.3% were female) and one control (13.6% vs 1.8%, p=0.016), and was less common than LVSD 46 (44.7%). Thirteen (92.9%) survivors with RVSD had coexisting LVSD. The survivors with RVSD had significantly worse LV function than survivors without LVSD (2D-LVEF 48.6±7.1% vs 56.2±5.0%, p<0.001 and GLS –14.3±2.4% vs –17.9±1.8%, p<0.001). The median value for NT-pro-BNP was significantly higher in survivors with RVSD, compared with survivors without RVSD (71 ng/L (46,281) vs 43 ng/L (22,82), p=0.043).

Despite these findings, the frequency of dyspnoea (NYHA class ≥II) did not differ in survivors with RVSD compared with survivors without RVSD (21.4% vs 27.6%, p=0.754). Elevated LV filling pressure was identified in 22 (21.4%) survivors with LVSD. E/e' remained significantly higher in survivors than in controls (6.6±2.2 vs 5.7±1.4, p=0.011) after controlling for age at examination, HR and DBP. In survivors, E/e' correlated with TRP (R=0.357, p<0.001). Diastolic dysfunction in the absence of LVSD was present in seven (6.8%) survivors. Individuals with BOS did not

Variable	None	Low-dose <300 mg/m²	High-dose >300 mg/m²	Adjusted p value*
Number	57 (55.3)	24 (23.3)	22 (21.4)	
FAC (%)	41.6±4.2	42.0±4.3	38.3±7.6	**0.033**[d]
TAPSE (mm)	21.3±3.6	20.4±3.5	20.0±4.0	0.303[a]
RV-s' (cm/s)	11.7±2.1	10.8±2.4 (n=23)	10.2±2.3	**0.045**[a]
RIMP	0.45±0.09 (n=55)	0.46±0.09 (n=23)	0.44±0.11	0.955[a]
RVFWS (%)	−27.7±3.6 (n=50)	−27.7±4.6 (n=23)	−25.2±4.7	**0.034**[b,d]
TRP (mm Hg)	17.8±3.6 (n=44)	18.7±3.8 (n=15)	18.3±5.3 (n=17)	0.656[a]
2D-LVEF (%)	57.0±4.7	54.5±7.1	51.1±5.0	**<0.001**[b,d]
GLS (%)	−17.9±2.1 (n=55)	−17.0±2.2 (n=23)	−16.8±2.2 (n=21)	**0.024**[d]
Elevated filling pressures	10 (17.5)	2 (8.3)	10 (45.5)	**0.002**[b,d]

Table 3 Dose-related effects of anthracyclines on right ventricular function

Data presented as mean±SD, or n (%). Calculations with χ^2.
*Analysis of covariance (ANCOVA) adjusted for age at examination, heart rate, body mass index, diastolic blood pressure. Statistically significant values in boldface (p<0.05). Post hoc Bonferroni: [a]No significant difference between treatment groups. [b]Significant difference (<0.05) between 'high dose >300 mg/m²' and 'low dose <300 mg/m²'. [c]Significant difference (<0.05) between 'high dose >300 mg/m²' and 'low dose <300 mg/m²' with 'no anthracycline'. [d]Significant difference (<0.05) between 'high dose >300 mg/m²' and 'no anthracycline'.
2D, two dimensions; FAC, fractional area change; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; RA, right atrium; RIMP, Right ventricular index of myocardial performance; RV, right ventricular; RVFWS, RV-free-wall strain; RVIDd, RV-Internal Dimension in diastole; RV-s', RV-peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TRP, tricuspid regurgitation pressure.

statistically differ in RV function, and none had RVSD (p=0.350).

Predictors of RV function

Linear regressions to identify predictors of TAPSE, RV-s' and RVFWS are presented in table 4. Assumptions for regressions were satisfied; Pearsons correlations were <0.6, tolerance was >0.6 and VIF <1.5 indicating no multicollinarity. In the multivariable analyses, LV systolic function by GLS (statistically more significant than 2D-LVEF) was identified as a strong, independent predictor for reduced RV function.

Valve disease, pulmonary hypertension and pericardial abnormalities

Trivial or mild TR was found in 82 survivors and 37 controls (79.6% vs 67.3%, p=0.087). Moderate TR was found in only five survivors (4.9% vs 0%, p=0.164), and no severe regurgitations were observed. Trivial or mild pulmonary regurgitation (PR) was found in 80 survivors and in 40 controls (78.4% vs 72.7%, p=0.422). Moderate PR was found in five survivors and in two controls (4.9% vs 3.6%, p=1.000).Severe PR was not observed. Mildly elevated PASP (≤40 mm Hg) was found in three survivors (2.9%, two with RVSD). Abnormal pericardium seen as localised fibrotic thickening without haemodynamic consequences was observed in eight (7.8%) survivors. Statistical comparisons after exclusion of these individuals did not alter the significance of the results (see online supplemental table 2). Seven cases were associated with cGVHD, and none were found in survivors with RVSD. One had a medical history of recurrent pericarditis, two were previously diagnosed by echocardiography, but none had received invasive treatment like pericardiocentesis or pericardectomy.

Measurement variability

Good image quality allowed high feasibility: FAC and TAPSE in 100%, RV-s' in 99.0%, RIMP in 97.1%, RVFWS in 92.2% and TRP in 73.8%. For intraobserver variability, the same images were analysed >6 months apart by the same observer and software, blinded to the previous result. The average value of three repeated measurements was used to calculate intraclass correlation coefficient (ICC). The ICC-type A (two-way mixed and absolute agreement) and mean difference±SD were: FAC (0.93, 1.6±0.3%), TAPSE (0.98, 0.1±0.4 cm), RV-s' (0.98, 0.1±1.7 cm/s) and RVFWS (0.94, 0.1±0.1%).

DISCUSSION

In this study, we showed that long-term survivors of allo-HSCT treated as CAYA can acquire biventricular dysfunction. To our knowledge, this is the first study assessing RV function in allo-HSCT survivors. RVSD was diagnosed in 14%, of which 93% had coexisting LVSD. LV systolic function by GLS was the strongest independent predictor of RV function.

Literature on the effects of chemotherapy on the RV is scarce, especially after HSCT. Tanindi et al reported

on subclinical changes in RV function by echocardiography in adults, shortly after the completion of therapies including anthracyclines.[20] Christiansen et al found reduced RV function by echocardiography in 30% of long-term survivors of childhood lymphoma or acute leukaemia treated with anthracyclines and radiotherapies.[7] In comparison, Ylänen et al used cardiac magnetic resonance and detected RV impairment in 27% of long-term childhood survivors of therapies with anthracyclines.[21] The same author, later reported on reduced longitudinal function of the RV by STE in a related population.[22] The most comparable study to ours is by Murbraech et al, who found RVSD in 17 (6.2%) by echocardiography in 274 long-term adult survivors of lymphoma treated with anthracyclines and/or radiotherapy prior to autologous-HSCT.[6] In similarity to our findings, they found a strong association between RVSD and LVSD, and identified anthracyclines as a common risk factor.[6] In contrast, our cohort had more reduced LV function, differed in underlying diseases, treatment regimes, stem-cell origin with risk of GVHD, and were treated in their youth. These factors may explain the higher levels of RV systolic impairment and a higher prevalence of RVSD found in our cohort.

Important features of the RV include the thin myocardial wall predominantly consisting of longitudinal orientated fibres, and functioning in the low-resistance pulmonary circuit. The differences in anatomy and physiology between ventricles may lead to varying responses to stress factors such as cardiotoxic therapies. Our study found RV impairment to be milder than the effects on LV function. Disparity in ventricular dysfunction has previously been reported from other cancer survivorship studies.[6 7] Moreover, an experimental study showed daunorubicin to cause greater degrees of cellular damage in the myocardium of the LV as compared with the RV.[8]

The strong correlation between LV and RV function may be explained by common exposure to risk factors (age, cardiotoxic agents, metabolic diseases and GVHD). An alternative explanation is increased RV afterload secondary to LV failure, and/or interdependency with anatomical structures (myocardial fibres and pericardium) shared between the ventricles.[23] Arterial hypertension was found in 40% of our cohort, and can be presumed to reduce LV function by increased afterload, but have minimal direct effects on RV function. Indeed, we have previously identified arterial hypertension as a significant predictor of decreased LV function in this cohort.[5] On the other hand, pulmonary diseases may lead to increased pulmonary vascular resistance and increase RV afterload irrespective of LV function. However, neither pulmonary disease nor arterial hypertension were identified as significant predictors of RV function in this study.

The anatomical position of the RV increases its vulnerability to radiotherapy. In this cohort, very few patients were exposed to radiotherapy, and thus we could not identify radiotherapy as a predictor of cardiac dysfunction. Alkylating agents can potentially instigate cardiac

Table 4 Multivariable linear regression for prediction of right ventricular function

	TAPSE (cm)						RV-s' (cm/s)						RVFWS (%)					
	Univariable			Multivariable (n=99, r²=0.36)			Univariable			Multivariable (n=98, r²=0.36)			Univariable			Multivariable (n=93, r²=0.30)		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Gender (reference=female)	0.37	-0.01 to 0.76	0.056	0.50	0.14 to 0.85	**0.007**	0.73	0.36 to 1.11	**<0.001**	0.73	0.38 to 1.08	**<0.001**	0.32	-0.06 to 0.71	0.101	0.31	-0.04 to 0.66	0.084
Age at examination (years)	0.14	-0.06 to 0.34	0.161	0.08	-0.12 to 0.27	0.447	-0.00	-0.20 to 0.20	0.984	-0.17	-0.37 to 0.02	0.079	0.06	-0.14 to 0.25	0.567	0.19	-0.00 to 0.38	0.053
Body mass index (kg/m²)	0.19	-0.01 to 0.38	0.056	0.14	-0.8 to 0.35	0.208	0.25	0.06 to 0.44	**0.011**	0.21	0.00 to 0.43	**0.048**	-0.10	-0.32 to 0.12	0.383	-0.28	-0.50 to -0.05	**0.017**
Heart rate (bpm)	-0.25	-0.44 to -0.06	**0.011**	-0.09	-0.28 to 0.10	0.335	0.03	-0.17 to 0.23	0.782	0.14	-0.05 to 0.32	0.143	0.15	-0.04 to 0.34	0.121	0.01	-0.17 to 0.20	0.885
Anthracyclines dosage (mg/m²)	-0.11	-0.30 to 0.09	0.270	0.07	-0.12 to 0.26	0.451	-0.23	-0.42 to -0.03	**0.022**	-0.02	-0.20 to 0.16	0.857	-0.14	-0.33 to 0.05	0.149	0.05	-0.14 to 0.23	0.620
Hypertension	-0.07	-0.41 to 0.39	0.974	–	–	–	0.10	-0.30 to 0.51	0.610	–	–	–	0.12	-0.28 to 0.52	0.556	–	–	–
Hypercholesterolaemia	-0.32	-0.88 to 0.23	0.250	–	–	–	-0.19	-0.74 to 0.37	0.503	–	–	–	0.20	-0.38 to 0.78	0.501	–	–	–
GVHD (including BOS)	-0.36	-0.76 to 0.05	0.081	-0.34	-0.72 to 0.05	0.085	-0.25	-0.66 to 0.16	0.222	-0.28	-0.65 to 0.10	0.147	-0.03	-0.44 to 0.38	0.900	-0.15	-0.54 to 0.23	0.430
GLS (%)	-0.44	-0.62 to -0.26	**<0.001**	-0.48	-0.67 to -0.29	**<0.001**	-0.27	-0.45 to -0.08	**0.006**	-0.43	-0.62 to -0.24	**<0.001**	0.45	0.27 to 0.62	**<0.001**	0.41	0.23 to 0.60	**<0.001**
2D-LVEF (%)	0.32	0.13 to 0.50	**0.001**	–	–	–	0.28	0.09 to 0.47	**0.004**	–	–	–	-0.24	-0.42 to -0.05	**0.011**	–	–	–
E/e'	0.08	-0.12 to 0.27	0.431	–	–	–	0.14	-0.06 to 0.34	0.158	0.19	0.00 to 0.38	**0.048**	-0.12	-0.33 to 0.08	0.232	–	–	–
PASP (mm Hg)	0.15	-0.05 to 0.34	0.133	0.18	-0.05 to 0.29	0.177	0.13	-0.07 to 0.32	0.191	0.04	-0.13 to 0.21	0.659	-0.04	-0.23 to 0.15	0.675	–	–	–

All continuous variables are standardised. GLS and RVFW are entered as negative values. Statistically significant values in boldface (p<0.05).
BOS, bronchiolitis obliterans syndrome; 2D, two dimensions; E/e', ratio of early-diastolic velocity to mean early-diastolic myocardial velocity; GLS, global longitudinal strain; GVHD, graft-versus-host disease; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure; RV-e', RV early-diastolic velocity; RVFWS, RV-free-wall strain; RV-s', RV-peak systolic velocity; TAPSE, tricuspid annular plane systolic excursion.

dysfunction. In this cohort, the conditioning regimes were standardised and the effects of alkylating agents are unknown. Anthracyclines are well known to cause myocyte degradation and were administered in first-line therapies to approximately half of the survivors in this cohort. Therapies with anthracyclines are reported to increase the risk of late-onset heart failure by a fivefold in survivors treated in their youth.[24] We observed a dose-related relationship between anthracyclines and level of RV impairment as illustrated in table 3. However, in regression analyses, a significant effect from anthracyclines was absent, possibly due to the main effects being confined to the 22 survivors receiving the highest doses, and possibly due to modification by LV function in the multivariable analyses. It seems that anthracyclines (particular at higher dosages) are a catalyst for pathways leading to progressive bi-ventricular dysfunction. The disparity in ventricle dysfunction implies RV affection in survivors of allo-HSCT is not solely dependent on anthracyclines.

The main contributor to systolic function in the RV is foreshortening of the longitudinal fibres in the free-wall.[23] However, RV performance is also reliant on traction (pulling) forces generated by LV myocardium and function of the pericardium.[23] This cohort had a high percentage (approximately 45%) of mild to moderate LVSD (by LVEF or GLS). Echocardiographical parameters of right and left ventricular function showed consistent linear relationships, and GLS remained a strong predictor of reduced RV function when controlled for risk factors. Elevated LV filling pressures was found in approximately 21% of the patients, and in almost 48% of the individuals with LVSD, despite frequent use of antihypertensive and/or cardioprotective medication. E/e' was significantly higher in survivors than in controls, and there was significant correlation between E/e' and TRP; both reflecting increased RV afterload, and likely involved in the observed RV impairment.[23]

When compared to conventional therapies, survivors of HSCT have greater risk of heart disease, partially due to higher frequencies of cardiovascular risk factors and GVHD.[25] [26] Traditional cardiovascular risk factors were common in this cohort and comparable to previous HSCT studies.[2–4 6] However, in this study, none of the cardiovascular risk factors were associated with RV function. This may indicate higher tolerance in the RV to effects from cardiovascular risk factors and partially explain the disparity in ventricle dysfunction. GVHD may affect cardiac function by processes of inflammation, indirectly by respiratory complications (BOS) or modification of risk factors. Neither GVHD nor BOS were identified as predictors of RV function. GVHD was associated with pericardial abnormalities that potentially can alter RV function by effects on preload and ventricular interdependency. However, repeated statistical comparisons after exclusion of cases with pericardial disease did not alter the significance of the results.

Echocardiography of the RV is technically challenging due to its position in the thorax, complex anatomy and its sensitivity to changes in load. While our definition of RVSD was highly specific it remains limited by potential inaccuracies with use of cut-off values. We observed gender differences that were not accounted by with the recommended cut-offs. Also, it is plausible that techniques for the detection of RVSD are not as accurate as those for the detection of LVSD. TAPSE and RV-s' have excellent repeatability, although are angle dependent and measure myocardial shortening in only one dimension. We found the reduction in FAC to be less significant than the drop in parameters reflecting longitudinal shortening. This is possibly due to FAC representing a composite measure of myocardial contractions in all dimensions, more analogous to 2D-LVEF, and is also influenced by the interactions between ventricles through the septum. Whereas, strain is angle independent and can measure the longitudinal myocardial fibres that constitute the majority of RV myocardium. Longitudinal shortening in the LV measured by GLS is a sensitive marker of cardiotoxicity, while LVEF drops later and represent more progressive dysfunction.[27] Similarly, RV strain has been shown to be superior in detecting subtle changes in RV function.[28 29]

Our findings showed reduced RV function to be strongly associated with progressive LVSD and elevated NT-pro-BNP. This finding is in consensus with statements that proclaim reduced RV function as a good prognostic marker.[9 10] Therefore, allo-HSCT survivors identified with reduced RV function may profit from frequent surveillance and assertive cardioprotective interventions. However, due to the infrequency and subclinical severity of RV impairments, dedicated echocardiography of the RV is most beneficial in survivors with LV dysfunction, pre-existing structural cardiac disease, respiratory complications or arrhythmias.

CONCLUSION
Long-term survivors of allo-HSCT who were treated in their youth had significantly reduced RV function as compared with a control group. This was associated with progressive left ventricle systolic dysfunction. The occurrence of RVSD was less frequent and was milder than coexisting LVSD in this cohort.

Limitations
This cross-sectional study can only describe associations. Reasons for death in individuals deceased prior to study inclusion are not available. Registry data on non-participants was restricted. The controls were recruited without known cardiovascular disease, introducing potential selection bias. Larger prospective studies are required to determine the prognostic effects in survivors with RV impairment.

Author affiliations
[1]Cardiology, Oslo University Hospital, Oslo, Norway
[2]Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[3]Pediatric Research, Division of Pediatric and Adolescent Medicine, University of Oslo, Oslo, Norway
[4]Hematology, Oslo University Hospital, Oslo, Norway
[5]Department of Circulation and Medical Imaging, Norges teknisk-naturvitenskapelige universitet, Trondheim, Norway

[6]Clinic of Cardiology, St Olavs Hospital Universitetssykehuset i Trondheim, Trondheim, Norway

[7]KG Jebsen Center for Cardiac Research at University of Oslo, and Center for Heart Failure Research, Oslo University Hospital, Oslo, Norway

[8]Hematology and Oncology, Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

ORCID iDs
Richard John Massey http://orcid.org/0000-0002-6609-0569
Anette Borger Kvaslerud http://orcid.org/0000-0001-9923-2685
Lars Gullestad http://orcid.org/0000-0002-5932-6641
Ellen Ruud http://orcid.org/0000-0002-6956-5005

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