Increased Tricuspid Regurgitant Jet Velocity by Doppler Echocardiography in Adult Survivors of Childhood Cancer: A Report From the St Jude Lifetime Cohort Study

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ABSTRACT

Purpose

To determine the prevalence of pulmonary hypertension, a late effect of cancer therapy not previously identified in aging survivors of childhood cancer, and associations with chest-directed radiation therapy (RT) and measures of current cardiac function, lung function, and exercise capacity.

Patients and Methods

Cross-sectional evaluation of 498 survivors at a median age of 38.0 years (range, 20.0 to 59.0 years) and a median of 27.3 years (range, 12.2 to 46.0 years) from primary cancer diagnosis was performed. Abnormal tricuspid regurgitant jet velocity (TRV) was defined as more than 2.8 m/s by Doppler echocardiography.

Results

Increased TRV was identified in 25.2% of survivors who received chest-directed RT and 30.8% of those who received more than 30 Gy. In multivariable models, increased TRV was associated with increasing dose of RT (1 to 19.9 Gy: odds ratio [OR], 2.09; 95% CI, 0.63 to 6.96; 20 to 29.9 Gy: OR, 3.46; 95% CI, 1.59 to 7.54; ≥ 30 Gy: OR, 4.54; 95% CI, 1.77 to 11.64 compared with no RT; *P* for trend $< .001$), body mass index more than 40 kg/m² (OR, 3.89; 95% CI, 1.46 to 10.39), and aortic valve regurgitation (OR, 5.85; 95% CI, 2.05 to 16.74). Survivors with a TRV more than 2.8 m/s had increased odds (OR, 5.20; 95% CI, 2.5 to 11.0) of severe functional limitation on a 6-minute walk compared with survivors with a TRV ≤ 2.8 m/s.

Conclusion

A substantial number of adult survivors of childhood cancer who received chest-directed RT have an increased TRV and may have pulmonary hypertension as a result of both direct lung injury and cardiac dysfunction. Longitudinal follow-up and confirmation by cardiac catheterization are warranted.

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INTRODUCTION

Treatment of children with cancer has become increasingly successful, with more than 80% of patients achieving 5-year survival¹ and the majority surviving into adulthood.² Treatment may include the use of chemotherapeutic agents such as anthracyclines and/or chest-directed radiation therapy (RT) that may adversely impact cardiac or pulmonary function. Impaired left ventricular systolic and diastolic function,³⁻⁵ pericardial thickening, premature coronary artery disease, cardiac valve abnormalities,⁶ decreased lung volumes,⁷⁻⁹ and impaired pulmonary gas exchange^{7,10} have all been described in survivors of childhood cancer. However, pulmonary hypertension

has been described in only a few case reports from the immediate post-treatment period.¹¹⁻¹⁷

Pulmonary hypertension is a progressive condition characterized by increased pulmonary artery pressure that may lead to right ventricular failure, which is associated with increased mortality without treatment.¹⁸ Direct measurement of pulmonary artery pressure by right-heart catheterization is the gold standard for diagnosis of pulmonary hypertension. However, Doppler echocardiography is widely available, noninvasive, and relatively inexpensive, and thus is frequently used to screen for pulmonary hypertension in susceptible or at-risk populations by estimating pulmonary artery pressure via measurement of the tricuspid regurgitant jet velocity

(TRV).¹⁹⁻²² We undertook this study to estimate the prevalence of and risk factors for an increased TRV by echocardiography in adult long-term survivors of childhood cancer who received cancer-related treatment that could adversely affect long-term cardiac or pulmonary function.

PATIENTS AND METHODS

Patients

Patients treated for cancer at St Jude Children's Research Hospital (SJCRH) who were 18 years of age or older and 10 or more years from diagnosis were eligible for the St Jude Lifetime Cohort Study (SJLIFE). Details of eligibility, recruitment methods, and study design have been previously published.²³ Eligible survivors were randomly selected for recruitment to SJLIFE in consecutive blocks of 50 patients. This analysis includes participants recruited to the first 19 blocks (931 eligible; Fig 1). Participation involved completion of questionnaires and risk-based medical screening according to the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers²⁴ developed by the Children's Oncology Group (COG Guidelines). This investigation was approved by the institutional review board at SJCRH.

This analysis was limited to patients who underwent a screening echocardiogram according to the COG Guidelines because of their prior exposure to cardiotoxic therapy (ie, anthracyclines, chest-directed RT). Of the first 931 survivors recruited to SJLIFE, 737 were exposed to cardiotoxic therapy and

were eligible for echocardiography (Fig 1). One patient with congenital heart disease was excluded from evaluation of TRV. Five hundred five patients (68.5% of eligible) completed echocardiography. Participants were similar to nonparticipants in all categories except for sex ($P = .02$). Ultimately, 498 patients undergoing echocardiography had an evaluable TRV, and seven were inevaluable for TRV.

Outcome Measures

Echocardiograms were performed by using a VIVID-7 cardiovascular ultrasound system ($n = 435$; General Electric, Milwaukee, WI) or an iE33 echocardiography system ($n = 70$; Phillips, Andover, MA). Complete two-dimensional echocardiograms with Doppler ultrasound were performed following the American Society of Echocardiography (ASE) guidelines.²⁵ Diastolic assessment was limited to peak mitral flow velocity of the early rapid filling wave (E), early diastolic velocity of the mitral annulus (E') and their ratio (E/E').²⁶ Increased TRV was defined on the basis of Evian criteria as a TRV more than 2.8 m/s on Doppler ultrasound.²⁷ Moderate or severe valvular regurgitation was determined according to ASE Guidelines.²⁸ Patients who received therapies associated with lung injury, per COG Guidelines, also underwent pulmonary function testing (PFTs). Subsequently, study procedures were changed to expand screening beyond COG Guideline recommendations to include PFTs in survivors treated with spinal-field RT. PFTs were performed on 187 survivors in a single laboratory according to the guidelines of the American Thoracic Society/European Respiratory Society task force.²⁹ PFTs included spirometry, lung volume measurements, and single-breath carbon monoxide diffusing capacity (DL_{CO}). Spirometry was performed with a pneumotachograph, and lung volumes were determined with a plethysmograph

Fig 1. Diagram of recruitment of eligible St Jude Lifetime Cohort Study (SJLIFE) cohort participants for evaluation of pulmonary hypertension. RT, radiation therapy; SJCRH, St Jude Children's Research Hospital.

Table 1. Characteristics of Patients Who Were Eligible for Echocardiographic Assessment and Had Echocardiography With an Evaluable TRV

Characteristic*	Eligible for Evaluation (n = 737)		Evaluable for TRV (n = 498)	
	No.	%	No.	%
Sex				
Male	369	50.1	232	46.6
Female	368	49.9	266	53.4
Race/ethnicity				
Non-Hispanic white	661	89.7	444	89.2
Others	76	10.3	54	10.8
Age at diagnosis, years				
0-4	261	35.5	170	34.1
5-9	164	22.3	112	22.5
10-14	151	20.5	99	19.9
15-19	152	20.7	111	22.3
20-24	8	1.1	6	1.2
Diagnosis				
Acute lymphoblastic leukemia	288	39.1	196	39.4
Acute myelogenous leukemia	31	4.2	19	3.8
Chronic myelogenous leukemia	2	0.3	2	0.4
Carcinoma	2	0.3	1	0.2
CNS tumor	6	0.8	3	0.6
Ewing sarcoma family of tumors	49	6.7	32	6.4
Germ cell tumor	3	0.4	3	0.6
Hodgkin lymphoma	198	26.9	134	26.9
Non-Hodgkin lymphoma	24	3.3	18	3.6
Neuroblastoma	36	4.9	22	4.4
Osteosarcoma	58	7.9	40	8.0
Rhabdomyosarcoma	18	2.4	11	2.2
Soft tissue sarcoma	3	0.4	2	0.4
Wilms tumor	19	2.6	15	3.0
Chest-directed RT dose, Gy				
None	388	52.7	264	53.0
> 0 to < 20	59	8.1	38	7.6
20 to 29.9	127	17.2	89	17.9
≥ 30	163	22.1	107	21.5
Anthracycline exposure				
Yes	558	75.7	377	75.7
No	179	24.3	121	24.3
Anthracycline cumulative dose, mg/m ²				
> 350	156	21.5	108	21.8
> 150 to 350	137	18.8	98	19.8
0 to 150	255	35.1	169	34.1
None	179	24.6	121	24.4
Bleomycin, mg/m ²				
Yes	63	8.6	43	8.6
No	674	91.5	455	91.4
Median	109.5		116	
Range	32-237		34-237	
Education level				
0: No high school	—	—	54	11.1
1: High school or some college	—	—	253	52.0
2: Bachelor's degree or higher	—	—	180	37.0
Age at questionnaire, years				
16-25	—	—	71	14.3
26-35	—	—	137	27.6
36-45	—	—	220	44.3
46-55	—	—	66	13.3
> 55	—	—	3	0.6

(continued on following page)

Table 1. Characteristics of Patients Who Were Eligible for Echocardiographic Assessment and Had Echocardiography With an Evaluable TRV (continued)

Characteristic*	Eligible for Evaluation (n = 737)		Evaluable for TRV (n = 498)	
	No.	%	No.	%
Body mass index, kg/m ²				
Normal or underweight (< 25)	—	—	175	35.1
Overweight (25-29)	—	—	148	29.7
Obese I (30-34)	—	—	96	19.3
Obese II (35-39)	—	—	44	8.8
Obese III (≥ 40)	—	—	35	7.0
Splenectomy				
Yes	—	—	87	17.5
No	—	—	411	82.5
Hypertension (BP > 140/90 mmHg)				
Yes	—	—	115	23.1
No	—	—	383	76.9
Systolic function (EF), %				
≥ 50	—	—	433	90.4
< 50	—	—	47	9.6
Aortic valve regurgitation†				
Yes	—	—	19	3.8
No	—	—	479	96.2
Coronary artery disease				
Yes	—	—	21	4.2
No	—	—	477	95.8
Pulmonary function				
Normal (≥ 60% predicted)	—	—	126	25.3
Abnormal (< 60% predicted)	—	—	61	12.3
Not screened	—	—	311	62.5
Left atrial pressure (E/E')				
< 9	—	—	339	70.2
≥ 9 to < 13	—	—	94	19.5
≥ 13	—	—	50	10.4

Abbreviations: BP, blood pressure; E/E', ratio of early rapid filling wave and early diastolic velocity of the mitral annulus; EF, ejection fraction; RT, radiotherapy; TRV, tricuspid regurgitant jet velocity.

*Percentages provided for total number of participants for whom data were available for a given characteristic.

†Aortic valve regurgitation limited to moderate and severe regurgitation as defined by the American Society of Echocardiography Guidelines.

(Medical Graphics Platinum Elite, St Paul, MN). DL_{CO} was measured by using the single-breath technique and was corrected for hemoglobin concentration to yield the DL_{CO-corr}. The observed values of each patient for forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), total lung capacity (TLC), and DL_{CO-corr} were reported as a percentage of predicted values based on the patient's age, race, sex, and height by using reference equations.^{30,31} The 6-minute walk was performed indoors, according to the guidelines established by the American Thoracic Society.³² Participants who walked less than 300 meters were categorized as having a severe functional limitation.³³

Demographic and Exposure Variables

Exposures to chemotherapy (anthracycline, carmustine, lomustine, bleomycin, busulfan, and cyclophosphamide) and chest-directed RT (maximum dose to the chest) were abstracted from each patient's medical record. Additional variables included age at diagnosis, age at evaluation, sex, race/ethnicity, education, primary cancer diagnosis, body mass index (BMI), and splenectomy (Table 1). Hypertension was defined as blood pressure of more than 140/90 mmHg in participants seated upright in a chair with both feet on the floor for 5 minutes. Coronary artery disease was defined as a history of

Fig 2. Distribution of tricuspid regurgitant jet velocity (TRV; median and 95% CIs) by (A) primary cancer diagnosis and (B) dose of chest-directed radiation therapy received. Horizontal line at 2.8 m/s represents the cutoff for an abnormal TRV.

myocardial infarction (n = 9) or detection of coronary disease on research-based screening evaluation (n = 12).

Statistical Methods

Univariate logistic regression was used to evaluate the relationship between increased TRV and demographic and treatment variables. Covariates with *P* values less than .1 in the univariate analysis were included in the multiple logistic regression models. The multivariable model used for evaluating the association between increased TRV and prior chest-directed RT and anthracycline exposure was adjusted for race, sex, BMI, education level, and age at the time of echocardiography. All of these factors were significant in the univariate model except for sex, education level, and current age, which were forced into the model. To further explore the potential pathway between RT exposure and increased TRV, we evaluated the impact of organ injury (cardiac left atrial pressure [E/E'] ν pulmonary function, defined as < 60% of predicted function on at least one PFT), systolic dysfunction (ejection fraction [EF] < 50%), and cardiac injury pathways (coronary artery disease, aortic valve regurgitation, hypertension) on increased TRV in multivariable models. All models were adjusted for race, sex, BMI, education level, and age at the time of echocardiography. In addition, associations between increased TRV and individual pulmonary function tests were examined by the Cochran-Armitage test for trend. All analyses were performed by using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

The characteristics of the study population are provided in Table 1. Evaluable participants were most commonly treated for acute lymphoblastic leukemia or Hodgkin lymphoma (HL), had a median current age of 38.0 years (range, 20.0 to 59.0 years), and were a median of 27.3 years (range, 12.2 to 46.0 years) from cancer treatment. Cardiotoxic exposures included anthracycline without chest-directed RT (n = 264; 53.0%), chest-directed RT without anthracyclines (n = 121; 24.3%), and anthracyclines plus chest-directed RT (n = 113; 22.7%). The mean EF was 60.7% (standard deviation, 9.94%).

Prevalence of Increased TRV

The mean TRV was 2.50 m/s $\pm$ 0.34 m/s standard deviation, and 75 (15.1%) of 498 survivors had a TRV more than 2.8 m/s. Patients treated for HL had a prevalence of increased TRV of 27.6% (Fig 2A). Among patients who received chest-directed RT, the prevalence was 25.2% (Table 2). Prevalence increased with increasing dose of chest-directed RT (Fig 2B). Lower levels of pulmonary function (decreased FVC, FEV₁, TLC, and DL_{CO-corr}) were statistically significantly associated with increasing TRV (*P* for trend < .01; Appendix Fig A1, online only).

Diagnosis and Treatment-Related Risk Factors

In univariate analysis, diagnosis of HL (OR, 4.20; 95% CI, 2.16 to 8.16), but not acute lymphoblastic leukemia (OR, 1.53; 95% CI, 0.77

Table 2. Distribution of TRVs

TRV (m/s)	No. of Patients	%	Median TRV (m/s)*	Range (m/s)
Total population (N = 498)				
≤ 2.8	423	85.0	2.4	0.9-2.8
> 2.8-3.4	69	13.9	3.0	2.8-3.4
> 3.4	6	1.2	3.6	3.4-4.0
Survivors with any chest-directed RT (n = 234)				
≤ 2.8	175	74.8	2.5	1.8-2.8
> 2.8-3.4	54	23.1	3.0	2.8-3.4
> 3.4	5	2.1	3.5	3.4-4.0
Survivors with chest-directed RT ≥ 30 Gy (n = 107)				
≤ 2.8	74	69.2	2.5	1.8-2.8
> 2.8-3.4	28	26.2	3.0	2.8-3.4
> 3.4	5	4.7	3.5	3.4-4.0

Abbreviations: RT, radiotherapy; TRV, tricuspid regurgitant jet velocity.

*Median and range do not include patients for whom Doppler echocardiography was fully evaluable but TRV was not measurable.

to 3.07), compared with all other cancer diagnoses was associated with development of a TRV more than 2.8 m/s. Treatment with any dose of chest-directed RT (1 to 19.9 Gy: OR, 3.00; 95% CI, 1.09 to 8.24; 20 to 29.9 Gy: OR, 4.43; 95% CI, 2.18 to 9.00; ≥ 30 Gy: OR, 6.91; 95% CI, 3.60 to 13.25, compared with no RT), BMI ≥ 40 kg/m² (OR, 2.40; 95% CI, 1.03 to 5.60, compared with BMI < 25 kg/m²), splenectomy (OR, 3.15; 95% CI, 1.82 to 5.44), older current age (OR, 1.07; 95% CI, 1.04 to 1.11), left atrial pressure ($E/E' \geq 13$ v < 9 : OR, 9.27; 95% CI, 4.79 to 17.95), systolic cardiac dysfunction ($EF < 50\%$ v $\geq 50\%$: OR, 2.11; 95% CI, 1.04 to 4.28), hypertension (OR, 1.85; 95% CI, 1.09 to 3.15), aortic valve regurgitation (OR, 7.08; 95% CI, 2.77 to 18.08), coronary artery disease (OR, 3.01; 95% CI, 1.17 to 7.72), and pulmonary dysfunction defined as pulmonary function less than 60% of predicted value (FVC: OR, 3.97; 95% CI, 1.89 to 8.36; FEV₁: OR, 2.95; 95% CI, 1.42 to 6.13; TLC: OR, 3.35; 95% CI, 1.36 to 8.25; DL_{CO-corr}: OR, 2.29; 95% CI, 1.07 to 4.86) were significantly associated with an increased risk for a TRV more than 2.8 m/s. Anthracycline exposure (yes/no) was associated with a significantly reduced risk (OR, 0.25; 95% CI, 0.15 to 0.42).

Multivariable regression identified chest-directed RT as an independent risk factor for increased TRV in a dose-dependent fashion (P for trend $< .001$; Table 3). BMI more than 40 kg/m² remained significantly associated with increased TRV in the multivariable analysis, but anthracycline exposure was no longer identified as a statistically significant protective factor ($P = .50$).

Because both abnormal pulmonary and cardiac function were significant in univariate analysis, we hypothesized that, although the primary inciting event in the causal pathway for increased TRV was radiation exposure, the causal pathway for increased TRV could be mediated through either a pulmonary or cardiac injury pathway or both (Fig 3). To clarify the causal pathway, additional multivariable models that excluded treatment factors (chest-directed RT, anthracycline) demonstrated that increased left atrial pressure and aortic valve regurgitation were independently and statistically significantly associated with the development of a TRV more than 2.8 m/s (Table 3) and were associated with chest-directed RT (Appendix Table A1, online only).

Functional Assessment

Of the 498 survivors with an evaluable TRV, 485 (98%) completed the 6-minute walk evaluation. Of 73 survivors with a TRV value more than 2.8 m/s who completed the 6-minute walk, 14 (19.4%) walked less than 300 meters, 12 of whom could not complete the first 50 meters of the test because of dyspnea, tachycardia, or increased blood pressure requiring early termination of the assessment. None of these participants had either a lower extremity amputation or a limb-sparing surgical procedure for their primary cancer that would interfere with walking performance. Six survivors had a BMI more than 30 kg/m². By comparison, only 18 survivors (4.4%) in the group with a TRV ≤ 2.8 m/s walked less than 300 m on the 6-minute walk test. Adjusting for height, weight, and age, the mean difference between the two groups on the 6-minute walk test was 63.1 m (SE 13.2 m; $P = .02$). Increased TRV was associated with an increased risk for functional limitation on the 6-minute walk (OR, 5.20; 95% CI, 2.5 to 11.0).

Table 3. ORs in Multivariable Models for Association Between Increased TRV and Primary Treatment Exposures, Cardiac and Lung Injury, Systolic Function, and Mechanisms of Cardiac Injury*

Variable	OR	95% CI	P
Primary treatment exposure model			
Race/ethnicity			
Other	2.52	1.21 to 5.23	.01
Non-Hispanic white	1.00		
Body mass index, kg/m ²			
Obese III (≥ 40)	3.89	1.46 to 10.39	$< .01$
Obese II (35-39)	1.14	0.38 to 3.42	.81
Obese I (30-34)	1.19	0.53 to 2.65	.67
Overweight (25-29)	0.91	0.46 to 1.82	.79
Normal (< 25)	1.00		
Chest-directed RT dose, Gy			
≥ 30	4.54	1.77 to 11.64	$< .01$
20-29.9	3.46	1.59 to 7.54	$< .01$
1-19.9	2.09	0.63 to 6.96	.23
None	1.00		
Anthracycline			
Yes	0.77	0.35 to 1.65	.50
No	1.00		
Organ injury model			
Pulmonary function			
Abnormal ($< 60\%$ predicted)	1.73	0.76 to 3.92	.19
Not screened	0.59	0.29 to 1.21	.15
Normal ($\geq 60\%$ predicted)	1.00		
Left atrial pressure (E/E')			
Moderate/severe dysfunction (≥ 13)	4.55	2.04 to 10.13	$< .01$
Mild dysfunction (9-13)	0.95	0.44 to 2.05	.90
Normal (< 9)	1.00		
Cardiac function model			
EF, %			
< 50	2.05	0.94 to 4.45	.07
≥ 50	1.00		
Cardiac injury model			
Hypertension			
Yes	0.97	0.51 to 1.85	.94
No	1.00		
Aortic valve regurgitation			
Yes	5.85	2.05 to 16.74	$< .01$
No	1.00		
Coronary artery disease			
Yes	2.38	0.80 to 7.07	.12
No	1.00		

Abbreviations: E/E', ratio of early rapid filling wave and early diastolic velocity of the mitral annulus; EF, ejection fraction; OR, odds ratio; TRV, tricuspid regurgitant jet velocity.

*All models adjusted for sex, race/ethnicity, education level, current age, and body mass index.

DISCUSSION

Adult survivors of childhood cancer are at risk for several cardiopulmonary late effects due to cancer and its treatment. Pulmonary hypertension has not previously been investigated or reported in this population. Through the unique resource of the SJLIFE population, we identified a TRV more than 2.8 m/s by Doppler echocardiography in 15.1% of adult survivors (75 of 498) exposed to cardiotoxic therapy and in 25.2% of those who received chest-directed RT. This risk was associated with chest-directed RT in a dose-dependent manner,

Fig 3. Model of radiation therapy (RT)-induced lung and cardiac injury and resultant pulmonary hypertension.

reaching a prevalence of 30.8% among those who received more than 30 Gy. Although previous echocardiographic evaluations of cardiac structure and function in survivors have been reported, these studies, largely evaluating younger populations of survivors, have not commented on pulmonary hypertension as defined by an increased TRV.^{3-6,34,35} Thus, to the best of our knowledge, this is the first report addressing the risk of pulmonary hypertension as a late sequela of chest-directed RT among long-term survivors of childhood cancer.

A definitive diagnosis of pulmonary hypertension should be based on right-heart catheterization.²⁷ However, Doppler echocardiography is often used to screen for possible pulmonary hypertension since it is widely available, noninvasive, and relatively inexpensive.¹⁹⁻²² Although Doppler echocardiography parameters for pulmonary hypertension are established,^{27,36} and echocardiographic detection of pulmonary hypertension (TRV > 2.8 m/s) is associated with a higher risk for mortality in other noncancer populations,^{22,37} echocardiography may result in both over- and underestimation of the pulmonary artery pressure measured at catheterization.³⁸ A recent meta-analysis of 29 studies demonstrated that estimations of systolic pulmonary artery pressure based on TRV have modest diagnostic accuracy (sensitivity 83%, specificity 72%) and modest correlation ($r = 0.70$) with pulmonary artery pressures from catheterization.³⁹ Thus, Doppler echocardiography as an initial screening tool is warranted, but definitive diagnosis of pulmonary hypertension and follow-up of hemodynamic assessments should be based on right-heart catheterization.⁴⁰

In this study, increased left atrial pressure was associated with an increased risk for increased TRV on multivariable analysis. Cardiac injury is a well-established complication of chest-directed RT that may be manifested as valvular incompetence or stenosis, pericarditis, and/or early onset coronary artery disease. In addition, both RT and anthracycline exposure can cause cardiomyopathy resulting in systolic dysfunction.^{4,41} Our findings suggest that RT-related aortic valve regurgitation, coronary artery disease, and subsequent increased left atrial pressure may ultimately lead to an increase in pulmonary venous pressure (Fig 3). Furthermore, systemic hypertension, although not significantly associated with TRV on multivariate analysis, remains an important potential etiology of pulmonary hypertension, because it is a modifiable risk factor and a potential target for risk reduction.⁴² In

the general population, pulmonary hypertension resulting from left-heart failure can lead to right-heart failure, which is associated with poor survival; however, the natural history of pulmonary hypertension after chest-directed RT is unknown.

Chest-directed RT can also result in pulmonary injury characterized by pulmonary fibrosis.⁴³ Chest-directed RT can secondarily affect lung function through impairment of chest wall and respiratory muscle growth. However, the failure of pulmonary function testing to achieve statistical significance in multivariable models suggests that RT-related cardiac injury may play a greater role in the development of pulmonary hypertension than direct lung injury does. Furthermore, in this analysis, obesity was associated with increased TRV in survivors. Although this might be expected, because obesity is an established risk factor for pulmonary hypertension in the general population,⁴⁴ female survivors who received cranial RT have increased rates of obesity and represent a population at increased risk for obstructive sleep apnea.⁴⁵ Future evaluations for pulmonary hypertension should include assessment for sleep-disordered breathing in this high-risk population.

There are several limitations that must be considered when interpreting our findings. First, although TRV was increased in many survivors, most fell within a range of only modest increase (> 2.8 to 3.4 m/s). However, on functional assessment, survivors with an increased TRV demonstrated significantly reduced exercise capacity compared with those with normal TRV, strengthening the suggestion that underlying pulmonary hypertension may exist. Future evaluations should include stress echocardiography, formal assessment of maximal aerobic exercise capacity, and catheterization for a definitive diagnosis of pulmonary hypertension.⁴⁶ Second, the cross-sectional nature of this investigation did not allow us to determine whether the natural history of increased TRV after chest-directed RT is progressive. Third, because the COG guidelines prescribe screening echocardiography only for survivors exposed to cardiotoxic therapies, we did not have a control population of nonexposed survivors. Similarly, only patients exposed to pulmonary-toxic therapies received screening pulmonary function testing. Fortunately, however, survivors with no such exposure (and thus not undergoing formal pulmonary function assessment) were less likely to develop increased TRV when

compared with survivors with normal pulmonary function who were exposed to pulmonary-toxic agents. Finally, future assessment of this population may benefit from echocardiographic evaluation that includes comprehensive diastolic assessment, based on recent guidelines from the ASE.²⁶ In addition to E/E', assessment of left atrial volume may more adequately reflect chronically increased left atrial pressure. Likewise, more precise cardiac dosimetry may allow for more specificity in the dose-response relationship between cardiac RT exposure and increased TRV.

In conclusion, we identified an increased prevalence of TRV more than 2.8 m/s, which may indicate pulmonary hypertension, in a large, well-characterized population of childhood cancer survivors. Increased risk was associated with chest-directed RT exposure, potentially mediated through both cardiac and pulmonary dysfunction. Current guidelines for screening and early detection of cardiomyopathy, developed by the COG, recommend transthoracic two-dimensional echocardiography for evaluation of systolic function for all survivors exposed to cardiotoxic therapy.²⁴ Although subsequent studies should validate the prevalence of pulmonary hypertension by catheterization, our current findings suggest that inclusion of TRV in screening echocardiography should be considered. Fortunately, the design of the SJLIFE study will allow for continued investigation of these survivors. Future investigation of this population will include longitudinal follow-up by echocardiography with recommended confirmation of pulmonary hypertension by right-heart catheterization in survivors with functional deficits. Other mechanisms, such as sleep-disordered breathing among obese survivors, will be explored as a

possible etiology. Finally, on the basis of the considerable prevalence of this finding among survivors exposed to chest-directed RT and the known progressive nature of pulmonary hypertension, compliance with the COG screening guidelines for echocardiography after chest-directed RT should be emphasized. Evaluation of TRV should be part of the routine screening echocardiogram, although ongoing studies seek to further define the significance and natural history of an increased TRV in this population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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