chemotherapy-induced injury caused by any, or all, of these factors.

It is important to determine whether these changes in T_1 mapping persist and whether they predict long-term cardiotoxicity, cardiovascular morbidity, and mortality. Moreover, it will be important to determine whether these surrogate measures of preserved myocardial function associated with exercise training also predict a reduction in long-term clinical events.

The greatest limitation in the interpretation of our data is the nonrandomized nature of the trial. We were unable to randomize the participants because of geographic constraints. It is not possible to exclude the fact that this selection bias may have influenced the observed differences in functional capacity.

In patients with breast cancer, native T_1 times were significantly increased immediately following AC chemotherapy, possibly reflecting myocardial inflammation. A structured exercise program undertaken during chemotherapy was associated with preservation of myocardial function, as opposed to a reduction in GLS in nonexercising patients, but did not influence T_1 times. The significance of these changes on long-term cardiac function and heart failure is yet to be determined.

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Biventricular Dysfunction in Patients After Bone Marrow Transplant

Cardiovascular events are a significant cause of morbidity and mortality in cancer survivors in the long-term. Anthracyclines (AC) are powerful cytotoxic agents, used to treat a wide spectrum of hematologic malignancies and solid tumors. However, 5% to 23% of patients develop late-onset heart failure secondary to AC-induced cardiotoxicity (1).

Bone marrow transplantation (BMT) is considered the treatment of choice for most hematologic malignancies. Heart failure rates are quoted at 5% at 5 years after BMT, increasing to 10% at 10 years (2). Therefore, contemporary management of patients with hematologic malignancies treated with both AC-based chemotherapy and BMT should include careful consideration of potential cardiotoxicity.

The aim of our study was to comprehensively evaluate biventricular function using traditional echocardiographic parameters and 2-dimensional (2D) speckle tracking strain parameters in patients with prior BMT.

TABLE 1 Clinical and Echocardiographic Characteristics

	BMT Only (n = 16)	BMT + AC (n = 50)	Control Patients (n = 50)	p Value
Age, yrs	53 ± 13 57 [47 to 63]	54 ± 13 56 [45 to 66]	48 ± 16 51 [33 to 61]	0.113
Male	69	66	50	0.194
Time between BMT to TTE, yrs	9 ± 5 9 [5 to 14]	7 ± 6 6 [3 to 11]		0.204
Follow up post TTE, yrs	1.6 ± 0.6	1.7 ± 0.8		
Baseline LVEF, %	62 ± 6 63 [58 to 66]	59 ± 7 58 [56 to 65]		0.249
Smoking status				0.420
Never	84	63		
Prior	8	22		
Current	8	15		
Hypertension	21	40		0.205
Hypercholesterolemia	36	47		0.471
Diabetes	20	20		0.970
LV parameters, n	16	50	50	
LVEF, %	62 ± 6 61 [57 to 67]	58 ± 6 58 [53 to 63]	63 ± 6 61 [58 to 66]	0.001
GLS, mid-myocardial, %	−19.9 ± 2.4 −19.5 [−18.8 to −22.5]	−17.8 ± 3.1 −18.2 [−15.6 to −20.2]	−20.5 ± 2.2 −20.3 [−18.8 to −21.6]	0.001
GCS, mid-myocardial, %	−18.2 ± 3.3 −16.9 [−11.1 to −18.4]	−15.0 ± 4.4 −15.4 [−12.4 to −18.2]	−19.3 ± 4.0 −18.6 [−16.6 to −21.6]	0.001
Radial strain, %	44.6 ± 16.5 51.4 [33.1 to 54.4]	38.9 ± 15.9 37.6 [28.1 to 49.1]	45.0 ± 13.4 45.4 [35.8 to 53.6]	0.148
RV parameters, n		46	30	
FAC, %		39 ± 5 40 [35 to 43]	44 ± 5 43 [40 to 46]	0.001
RV FWS, %		−23.2 ± 4.0 −23.4 [−20.6 to −26.3]	−27.9 ± 2.7 −28.4 [−25.7 to −29.4]	0.001
TAPSE, cm		21 ± 4 21 [18 to 24]	25 ± 4 23 [22 to 26]	0.016
RV s′, cm/s		10 ± 2 10 [9 to 11]	11 ± 3 11 [10 to 13]	0.004

Values are mean ± SD, median [interquartile range], or %, except as noted. The Kruskal-Wallis test was used to compare continuous variables among 2 or more groups. Categorical variables were compared using the chi-square test.

AC = anthracyclines; BMT = bone marrow transplant; FAC = fractional area change; FWS = free wall strain; GCS = global circumferential strain; GLS = global longitudinal strain; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TTE = transthoracic echocardiography.

A total of 66 BMT patients who underwent routine surveillance transthoracic echocardiogram (November 2016 to October 2017) were recruited from the Hematology Late Effects BMT Clinic. Sixteen patients were AC naive (BMT), whereas 50 received AC and underwent BMT (BMT + AC group). BMT and BMT + AC patients were compared with 50 control patients from our departmental database. Major adverse cardiovascular events (MACE) were defined as acute coronary syndrome, coronary revascularization, cerebrovascular accident, atrial fibrillation, and heart failure (as defined by a clinically significant reduction in left ventricular ejection fraction [LVEF] requiring initiation of heart failure therapy). MACE were collected from time of BMT to the date of the last transthoracic echocardiogram or clinical follow-up, which may have occurred after the echocardiogram.

A comprehensive 2D transthoracic echocardiogram was performed using Vivid E9 or E95 ultrasound systems (GE Vingmed, Horten, Norway). Left ventricular (LV) systolic function was evaluated by Simpson's biplane LVEF, and LVEF <53% was considered abnormal. Right ventricular (RV) function was assessed using fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) using M-mode and tissue Doppler tricuspid lateral annular systolic velocity (RV s′ velocity). RV-focused, apical 4-chamber views were used for all measurements. FAC was considered abnormal if <35%, per the American Society of Echocardiography guidelines (3).

LV- and RV-focused images were obtained at high frame rates (>55 frames/s) for offline strain analysis. LV apical 4-, 2-, and 3-chamber views were used for LV longitudinal strain analysis using semiautomated tissue tracking where the endocardial border was

traced and the region of interest manually adjusted if required. If more than 2 segments could not be tracked in a single view, the global longitudinal strain (GLS) was excluded. Multilayer LV strain analysis was performed with offline measurements of endocardial, mid-myocardial, and epicardial layer longitudinal strain. Parasternal short-axis image, at the papillary muscle level, was used for circumferential and radial strain analysis. RV longitudinal free wall strain (RV FWS) was measured from RV-focused apical views by tracing 6 segments including both free wall and septum, and calculated as the arithmetic mean of the 3 free wall segments. Measurements were repeated over 3 cardiac cycles, and an average of 3 measurements was used in the final analysis. Strain analysis was performed using offline software (GE EchoPAC, version 201; GE Healthcare, Horten, Norway). Ethics approval was provided by the Western Sydney Local Health District ethics committee (HREC No. 180413-5582).

In 10 randomly selected patients, strain measurements were performed by a second operator blinded to previous measurements, and by the same observer at least 4 weeks later, to determine intraobserver variability for measurements. The intraobserver intraclass correlation coefficient estimates and their 95% confidence intervals were 0.92 (0.72 to 0.98; $p = 0.001$) for GLS, 0.91 (0.61 to 0.98; $p = 0.001$) for global circumferential strain (GCS), and 0.95 (0.79 to 0.99; $p = 0.001$) for RV FWS.

Statistical analysis was performed using SPSS software version 24 (IBM Corporation, Armonk, New York). Continuous data were analyzed for mean, SD, median, 25th percentile, and 75th percentile. Categorical data were analyzed for counts with percentages. The Kruskal-Wallis test was used to compare continuous variables among 2 or more groups. Categorical variables were compared using the chi-square test. A p value <0.05 was considered statistically significant.

There were no significant differences in the cardiovascular risk factor profile between the 2 BMT groups or control patients (**Table 1**). All but 2 BMT + AC patients received AC doses below the recommended cumulative lifetime thresholds set by the European Society of Medical Oncology (4). The follow-up time for the groups was variable, as noted in **Table 1**.

MACE occurred in 9 patients, all in the BMT + AC group: 1 with a cerebrovascular accident, 2 with atrial fibrillation/flutter, 2 with ischemic heart disease, and 4 with heart failure. Seven of 9 MACE events occurred within the period after BMT, but before the echocardiogram, whereas 2 of 9 occurred after the echocardiogram.

As detailed in **Table 1**, LV GLS was reduced in the BMT + AC group compared with BMT alone and control patients. Additionally, circumferential and radial strain were significantly worse in the BMT + AC group as compared with the BMT alone and control groups. However, there were no significant differences in longitudinal or circumferential strain in the BMT alone group as compared with control patients. Four BMT + AC patients and 20 control patients were excluded due to inadequate RV-focused views. Thus, 46 BMT + AC and 30 control patients had RV analysis performed. RV FWS was reduced, as defined by a FWS >25%, in the BMT + AC group compared with control patients.

We also determined the number of patients in the BMT + AC group who met criteria for cardiac dysfunction, on the basis of an LVEF <53% (5) or an abnormal LV GLS >−17% (indicative of worse function) (3). All patients with an LVEF <53% had abnormal GLS and GCS. However, GLS was significantly reduced even when LVEF was preserved (i.e., LVEF >53%). In the 40 BMT + AC patients with an LVEF >53%, 11 patients (28%) had abnormal GLS. Similarly, 52% of BMT + AC patients had subclinical RV dysfunction, defined as a preserved FAC >35% and an abnormal RV FWS >−25%.

To our knowledge, this study is one of the first to evaluate biventricular cardiac dysfunction, years after BMT, using 2D speckle tracking echocardiography. We observed that 20% of BMT + AC patients had an asymptomatic, but significant, reduction in LVEF, whereas of those with a normal LVEF, 28% demonstrated a reduction in LV GLS (subclinical LV dysfunction). Although the majority of our patients had a LVEF >53%, they still had a significant worsening of LV GLS and GCS as compared with control patients. We also found that in those with an LVEF below 53%, all strain measurements were reduced, suggesting that identification of subclinical dysfunction may potentially warrant closer follow-up for further deterioration. Nine of our 50 BMT + AC patients also experienced MACE. Additionally, RV FWS was significantly altered in 52% of patients, despite preserved RV FAC. These results highlight that there is a significant proportion of patients, exposed to AC therapy, that develop subclinical biventricular dysfunction.

LVEF measurement is subject to interobserver variability of up to 10%, which is similar to the thresholds used to define cardiotoxicity (6). LV GLS using 2D echocardiography is a well-validated, semi-automated, reproducible technique for measurement of LV dysfunction that is sensitive to functional changes in the myocardium (7). LV GLS has demonstrated prognostic value in noncancer populations;

reduction in LV GLS was an independent predictor of cardiac mortality and MACE, with prognostic value superior to that of LVEF (8).

We additionally evaluated subclinical RV dysfunction (defined as RV FWS >−25% with preserved FAC >35%), which was present in 52% of BMT + AC patients. There was a higher incidence of subclinical RV dysfunction than LV dysfunction. The RV is composed predominantly of longitudinal muscle fibers, hence, RV longitudinal strain analysis may improve sensitivity in screening protocols for cardiotoxicity (9). Moreover, the thin-walled RV, working upstream from a relatively low pressure pulmonary circulation, may have less compensatory reserve than the LV. RV dysfunction was also demonstrated using conventional parameters (TAPSE and FAC), as well as RV FWS, supporting results obtained from previous studies demonstrating that AC toxicity affects both ventricles (10). As with LV strain, RV strain was altered in a subgroup of patients in whom traditional measures (FAC and TAPSE) were preserved. There remains a paucity of data with respect to RV involvement in BMT + AC-treated patients.

Limitations of this study are its cross-sectional nature; thus, serial measurements were not available to evaluate changes within individual patients. In the group of patients studied, biomarker data were not available. Additionally, the sample size was relatively small, albeit in a specialized group of patients, from a single center. Nevertheless, it does provide insights into the use of echocardiographic speckle tracking strain in the detection of subclinical cardiac dysfunction that might occur in patients late after BMT. The follow-up time was also variable; standardized, longitudinal follow-up is needed to better understand clinical and subclinical cardiac dysfunction over time and the relationship to MACE. The specific effect of cardiovascular risk factors, concomitant medication, and the effect of therapy with BMT + AC cannot be ascertained. Future studies are needed to evaluate the potential impact of cardioprotective medical therapy in those with subclinical RV and LV dysfunction.

In conclusion, traditional echocardiographic functional measurements of LVEF and RV FAC appear to be less sensitive than biventricular strain analysis (LV GLS and RV FWS) for evaluation of cardiac dysfunction in BMT patients. 2D strain offers an opportunity to improve sensitivity of screening protocols by evaluation of LV GLS, LV GCS, and RV FWS. Future studies are needed to determine the utility of incorporating these measures in the monitoring of BMT patients, and if cardioprotective therapy is beneficial in the setting of subclinical dysfunction.

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