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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

The Spatial Ventricular Gradient Is an Independent Predictor of Anthracycline-Associated Cardiotoxicity

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ABSTRACT

BACKGROUND Anthracyclines are effective chemotherapies that are limited by cardiotoxicity. The spatial ventricular gradient (SVG) is a marker of electrical heterogeneity linked to adverse cardiovascular outcomes, including sudden cardiac death and heart failure (HF).

OBJECTIVES The purpose of this study was to assess if SVG values before chemotherapy are associated with the risk of anthracycline-associated HF or cardiomyopathy (CM).

METHODS We analyzed 12-lead electrocardiograms obtained within 6 months before initiation of anthracyclines in a retrospective cohort treated for cancer between 1992 and 2019 at a single academic medical center. Incident HF and CM were defined by ICD-9/10 codes and confirmed by chart review. Vectorcardiograms were constructed from baseline electrocardiograms, and the SVG was calculated. The cumulative incidence of anthracycline-associated HF or CM was regressed on SVG vector orientation and magnitude with death as a competing risk.

RESULTS In 889 patients (47% male; mean age 58 $\pm$ 16 years; 71% hematologic malignancies), larger SVG magnitude prechemotherapy was associated with decreased risk of HF or CM after multivariable adjustment, with a subhazard ratio of 0.76 per 1 SD increase (95% CI: 0.59-0.96; $P = 0.024$). SVG vector orientation, specifically a more leftward oriented VGx, was associated with decreased risk of HF or CM with a subhazard ratio of 0.77 per 1 SD increase (95% CI: 0.61-0.96; $P = 0.023$).

CONCLUSIONS Larger SVG magnitude and more leftward SVG orientation were associated with a decreased risk of anthracycline cardiotoxicity in a large retrospective cohort. Improved cardiac risk stratification algorithms incorporating the SVG could personalize both cancer and cardioprotective therapy. (JACC Adv 2023;2:100269) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CM = cardiomyopathy

CI = confidence interval

DM = diabetes mellitus

HF = heart failure

HTN = hypertension

SHR = subhazard ratio

SVG = spatial ventricular gradient

Since the discovery of their antitumor properties, anthracyclines have become essential medications in the treatment of malignancies such as breast cancer, lymphoma, and leukemia.[1,2] Anthracyclines can cause both acute and chronic cardiotoxicity, with over 95% of cardiotoxicity cases in adults expected to occur within the first year after starting treatment.[3] The molecular mechanisms of anthracycline cardiotoxicity have not been well established, although oxidative stress, interaction with topoisomerase 2, and dysfunctional iron metabolism have been suggested as possible contributors.[4]

Risk factors for anthracycline cardiotoxicity include cumulative anthracycline dose, extremes of age, preexisting cardiovascular diseases such as coronary artery disease (CAD), hypertension (HTN), and diabetes mellitus (DM), and the concomitant use of radiotherapy or other cardiotoxic therapies.[5] Pretreatment risk stratification of patients who are planned to receive anthracyclines is needed to identify those who may benefit from cardioprotective strategies and, in some cases, alternative cancer treatments associated with less cardiotoxicity. Echocardiography is the most commonly used technique to assess cardiac function of patients with cancer before and during treatment.[6] However, use of this technology can be limited by poor image quality and interobserver variability in the assessment of cardiac function, which can result in low sensitivity in detecting subtle pre-existing cardiac dysfunction or early cardiotoxicity.[6] Likewise, available data do not support routine use of blood biomarkers such as troponin and NT-pro-BNP (N-terminal pro b-type natriuretic peptide).[7] The utility of obtaining a standard 12-lead electrocardiogram (ECG) during the pretreatment evaluation has not been clearly established, but it is advised by the European Society for Medical Oncology based on expert consensus.[8] Previous work has demonstrated that corrected QT interval (QTc) prolongation and a decrease in QRS amplitude postanthracyclines are associated with left ventricular dysfunction in childhood and adult populations.[9-11] In a small study in adult patients, QTc was significantly prolonged after the last anthracycline dose and 6 months post treatment, compared with baseline values, and was associated with incident left ventricular dysfunction.[11]

Spatial and temporal heterogeneity in electrical depolarization and repolarization are a normal part of myocardial physiology, and this heterogeneity is responsible for the appearance of the normal QRST complex and normal cardiac mechanical function.[12,13] In animal studies, excessive electrical heterogeneity, as manifested by larger than normal spatial and temporal variations in action potential duration, is associated with increased risk of induced and spontaneous ventricular arrhythmias.[14,15] Patients with myocardial infarction and spontaneous ventricular tachycardia and long QT syndrome with prior cardiac arrest also have more electrical heterogeneity compared to patients with structurally normal hearts and no history of ventricular arrhythmias during invasive electrophysiology studies.[16]

Due to electromechanical coupling via the effects of action potential duration and action potential heterogeneity on intracellular calcium cycling,[17] there is also a mechanistic link between electrical heterogeneity and mechanical heterogeneity and cardiac systolic and diastolic function. Furthermore, both animal and human studies have demonstrated that increased electrical heterogeneity is associated with echocardiographic abnormalities, including dyssynchronous contraction and abnormal strain imaging independent of left ventricular ejection fraction (LVEF).[18,19]

The ventricular gradient (VG) is a noninvasive assessment of electrical heterogeneity that can be measured on a standard 12-lead ECG. Based on the electrodynamics of ECG signals, measurement of the area under the QRST complex in any 12-lead ECG will result in a value of zero unless there is some degree of spatiotemporal heterogeneity in the direction of the myocardium assessed by that lead.[20] The concept of the VG can be extended into 3 dimensions (3D) (the spatial ventricular gradient [SVG]) to quantify the degree of electrical heterogeneity across the entire 3D myocardium. This can be done by converting a 12-lead ECG into a vectorcardiogram (VCG) which represents the electrical activation of the heart in the 3 orthogonal X, Y, and Z directions, followed by creation of a vector with the X, Y, and Z components equal to the areas under the X (VGx), Y (VGy), and Z (VGz) QRST complexes, respectively. Similar to any 1-dimensional VG, if there is complete uniformity of depolarization and repolarization across the entire 3D structure of the myocardium, the SVG will be a zero vector.[20]

The SVG and other associated measures of myocardial global electrical heterogeneity (GEH) have been associated with adverse clinical outcomes including ventricular arrhythmias, sudden cardiac death, and myocardial mechanical dysfunction in community cohorts.[21-24] In addition to identifying patients at increased risk of ventricular arrhythmias, assessment of the SVG and its link with mechanical heterogeneity may be able to identify patients who

have subclinical mechanical cardiac dysfunction, or those at an increased risk of developing subsequent mechanical dysfunction. The clinical utility of SVG assessment in risk stratification of patients with cancer planned to receive cardiotoxic chemotherapy is not known. We hypothesized that the SVG, as a direct measure of GEH, could identify patients with subclinical myocardial dysfunction that would be associated with the risk of developing anthracycline-associated heart failure (HF) or cardiomyopathy (CM).

METHODS

DATA SOURCE AND STUDY POPULATION. We analyzed existing data from a retrospective cohort study of 2,192 adult cancer patients treated with anthracyclines between 1992 and 2019 at Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, USA. The cohort study collected the following data: date of birth, age at treatment with anthracyclines, date of initiation of anthracycline therapy, type of anthracycline therapy, sex, body mass index, self-reported race/ethnicity, type of malignancy, and date of death. Cardiovascular risk factors such as CAD, diabetes, smoking, and HTN were identified by claims data, and other variables were obtained from the online medical record. Patients with a diagnosis of HF or CM prior to chemotherapy based on ICD-9/10 billing codes and those without a baseline ECG were excluded (n = 1,297). Patients with ECGs of nondiagnostic quality (n = 6) were also excluded.

The primary outcome of incident HF or CM was determined by review of administrative and claims data. The ICD-9/10 codes utilized for HF and CM diagnoses are reported in Supplemental Table 1, and all HF/CM diagnoses were confirmed by manual chart review of electronic medical records. For patients with anthracycline dose data available, the total cumulative dose was obtained using the Oncology Management System at our institution and converted to the equivalent total doxorubicin dose (mg/m^2) based on published dose conversions.[25]

When available, data from prechemotherapy echocardiograms and follow-up echocardiograms were obtained. All follow-up echocardiograms were performed within 12 months after the first anthracycline dose; LVEFs were averaged if reported as a range (ie, 45%-55% would be reported as 50%). If reported as a "greater than" value, 5% points were added to the numerical LVEF value reported (ie, >50% would be considered 55%). "Less than" values were similarly handled by subtracting 5% from the upper range (ie, <40% would be considered 35%). Occurrence of and cause of death were determined by manual review of medical records. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board in conjunction with the BIDMC Cancer Clinical Trials Office.

ECG DATA AND SVG CALCULATION. Baseline 10-second, 12-lead ECGs were obtained within the 6 months prior to each patient's first dose of chemotherapy. Details of ECG processing, VCG construction, and SVG measurement have been previously reported[21] and additional information is available in the Supplemental Methods. In brief, raw digital 10-second, 12-lead ECG signal data were filtered to remove high frequency noise and baseline wander and then transformed into the orthogonal X, Y and Z leads using the Kors transformation.[26] After removing premature ventricular contractions or QRST complexes with severe artifact, the remaining beats were aligned and median X, Y, and Z, QRST complexes were created. We followed previous conventions with the positive X axis oriented pointing toward the left, positive Y-axis pointing toward the feet, and the positive Z-axis pointing posteriorly. The orthogonal (X, Y, Z) leads were baseline corrected so the flattest part of the TP segment was the vectorcardiographic origin and the zero voltage reference point, given that this part of the ECG is isoelectric. The SVG vector components (VGx, VGy, and VGz) were calculated as the area under the X, Y, and Z median QRST complexes between the start of the QRS complex and the end of the T wave, respectively. SVG magnitude was defined as the length of the SVG vector[23] (see Supplemental Methods for additional details).

STATISTICAL ANALYSES. Continuous variables were compared using 2-sample *t*-tests. Categorical variables were compared using Pearson's chi-squared test. Competing risks models were constructed to estimate the associations between SVG components and magnitude with the primary outcome of time to onset of HF or CM within 5 years of starting anthracycline treatment, accounting for the competing risk of death from any cause. Models were adjusted for clinical characteristics previously associated with the SVG and/or anthracycline cardiotoxicity, including age, sex, CAD, HTN, DM, total cumulative anthracycline dose or equivalent, and variables with $P < 0.10$ in univariable testing (QRS duration and QTc).[5] For patients without HF or CM events, censoring occurred at the date of the last clinical visit, date of death, or at a maximum of 5 years after the initiation of chemotherapy. As the total cumulative anthracycline dose

TABLE 1 Baseline Clinical Characteristics of the Patient Cohort (N = 889)

Demographics	
Age at first anthracycline dose (y)	58.1 ± 15.7
Age >50 y	635 (71.4)
Male	422 (47.4)
White	670 (75.3)
Cardiovascular risk factors	
Hypertension	319 (35.8)
Coronary artery disease	101 (11.3)
Diabetes mellitus	148 (16.6)
Smoking, past or current	55 (6.2)
Total anthracycline dosage in doxorubicin equivalents (mg/m^2)[a]	170 ± 103
Malignancies	
Breast cancer	108 (12.1)
Hematological	627 (70.5)
AML	193 (21.2)
ALL	38 (4.5)
CML	4 (0.5)
CLL	15 (1.7)
Non-Hodgkin lymphoma	313 (35.2)
Hodgkin lymphoma	51 (5.7)
Multiple myeloma	13 (1.5)
Other	154 (17.3)
ECG parameters	
Heart rate (beats/min)	84 ± 19
QTc interval (ms)	405 ± 29
QRS duration (ms)	90 ± 15
SVG magnitude (mV.ms)	42.4 ± 19.5
VGx (mV.ms)	33.9 ± 18.2
VGy (mV.ms)	18 ± 13.9
VGz (mV.ms)	1.6 ± 13.2

Values are mean ± SD or n (%). [a]Anthracycline dose in doxorubicin equivalents was available in 579 patients (65.1% of the cohort).

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; QTc = corrected QT interval; SVG = spatial ventricular gradient.

or equivalent was not available for all patients, we performed models with and without inclusion of this variable. To assess the possibility of selection bias, we compared patients without a baseline preanthracycline ECG (who were excluded from the current analysis) to patients with a baseline ECG included in the analysis. Adjusted Cox proportional hazards models for the outcome of all-cause death were also constructed. The proportional hazards assumption was validated for all models using Schoenfeld residuals. All statistical analyses were performed with STATA/BE 17.0 software (StataCorp LLC).

RESULTS

The final cohort included 889 patients; demographic characteristics are summarized in **Table 1**. The mean age was 58 ± 16 years, 47% of patients were male and 75% of patients were White. The most prevalent malignancies were hematological, followed by breast cancer. Anthracycline dose data were available for 579 (65%) patients; patients without dose data available had similar characteristics, with the exception of a lower proportion of male patients (41.9% vs 50.4%; $P = 0.016$) and a lower prevalence of smoking (3.9% vs 7.4%; $P = 0.036$) (Supplemental Table 2). In general, participants without a baseline ECG who were excluded from the study were older and more likely to have breast cancer, and they had a higher prevalence of preexisting CAD (20% vs 11%; $P < 0.0001$), DM (22% vs 17%; $P = 0.030$), and HTN (60% vs 36%, $P < 0.0001$) relative to those with a baseline ECG who were included in the analysis (Supplemental Table 3).

Within 5 years of the first dose of anthracyclines, 95 patients developed incident HF/CM. Characteristics of patients with and without incident HF/CM are shown in Supplemental Table 4. Diagnoses of HF/CM were made by cardiologists in 70% of cases and by other physicians in 30% of cases. Of the 613 patients with a baseline echocardiogram, 27% had a follow-up echocardiogram at a median of 4.7 (IQR: 1.6-12.9) months after the first anthracycline dose. Patients who developed HF/CM after anthracycline treatment had a lower LVEF at follow-up compared with patients who did not develop HF/CM, as summarized in Supplemental Table 5. Of the final cohort, 365 (41%) patients died; 73% had hematological malignancies, 8% had breast cancer, and 19% had other malignancies. The cause of death was clearly stated in the chart in 204 patients (56%). The most common causes of death were progression of malignancy (57%) and infection (34%). Ventricular arrhythmias and sudden cardiac death were not identified as a cause of death in any patients in the cohort. Of the 204 patients with cause of death available, acute decompensated HF was the cause of death in <1%.

Table 2 reports the univariable competing-risks regression results for developing incident HF/CM during follow-up. Consistent with prior reports, patients with CAD had a higher risk of incident HF/CM (subhazard ratio [SHR]: 2.27, 95% CI: 1.39-3.72; $P = 0.001$). Wider baseline QRS duration (SHR: 1.27 per 1 SD increase, 95% CI: 1.09-1.47; $P = 0.0017$) and larger VGz (SHR: 1.27 per 1 SD increase, 95% CI: 1.02-1.59; $P = 0.031$) were associated with an increased risk of developing incident HF/CM. Larger SVG magnitude (SHR: 0.80 per 1 SD increase, 95% CI: 0.65-0.97; $P = 0.023$) and larger VGx and VGy (SHR: 0.76 per 1 SD increase, 95% CI: 0.63-0.93; $P = 0.007$ and SHR 0.78 per 1 SD increase, 95% CI: 0.65-0.94; $P = 0.010$, respectively) were associated with a decreased risk of incident HF/CM.

TABLE 2 Univariable Competing Risk Regression Model

	SHR	95% CI	*P* Value
SVG magnitude (mV*ms)	0.80	0.65-0.97	0.023
VG_X (mV*ms)	0.76	0.63-0.93	0.007
VG_Y (mV*ms)	0.78	0.65-0.94	0.010
VG_Z (mV*ms)	1.27	1.02-1.59	0.031
Age (y)	1.22	0.98-1.52	0.073
Male	1.19	0.80-1.78	0.40
Coronary artery disease	2.27	1.39-3.72	0.001
Diabetes	1.17	0.70-1.94	0.56
Hypertension	0.81	0.53-1.25	0.34
Smoking	0.71	0.26-1.93	0.50
Cumulative doxorubicin equivalent dose	1.22	0.99-1.51	0.067
QTc (ms)	1.19	0.98-1.44	0.084
QRS duration (ms)	1.27	1.09-1.47	0.002

Results for continuous variables are presented as SHR per 1 SD change in value.
QTc = corrected QT interval; SHR =subhazard ratio; SVG = spatial ventricular gradient.

TABLE 3 Multivariable Competing Risk Regression Models for SVG

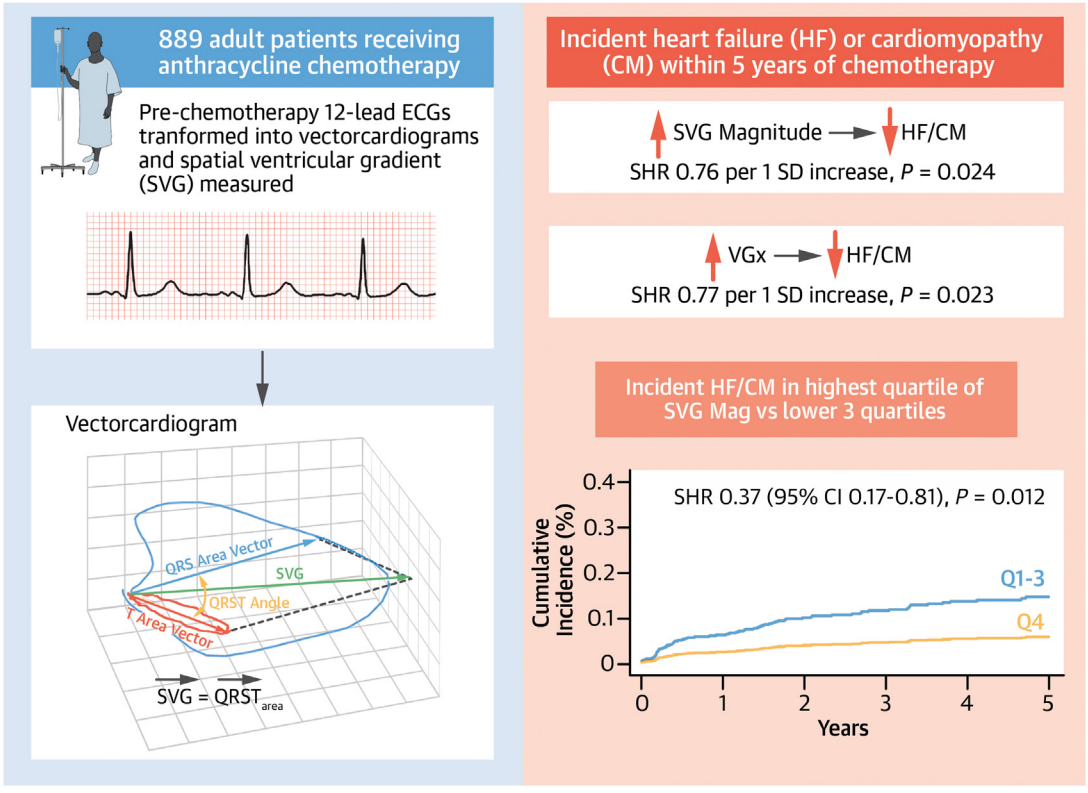
	SHR	95% CI	*P* Value
SVG magnitude (mV*ms)	**0.76**	**0.59-0.96**	**0.024**
Age (y)	1.07	0.78-1.46	0.69
Male	1.25	0.79-1.99	0.34
Coronary artery disease	2.00	0.94-4.26	0.072
Diabetes	1.18	0.60-2.31	0.63
Hypertension	0.52	0.28-0.97	0.039
Smoking	0.38	0.09-1.58	0.19
Cumulative doxorubicin equivalent dose	1.25	1.01-1.55	0.036
QTc (ms)	1.07	0.87-1.32	0.54
QRS duration (ms)	1.15	0.95-1.39	0.15
VG_X (mV*ms)	0.77	0.61-0.96	0.023
Age (y)	1.08	0.79-1.48	0.63
Male	1.32	0.83-2.10	0.25
Coronary artery disease	2.00	0.94-4.25	0.071
Diabetes	1.17	0.60-2.29	0.64
Hypertension	0.52	0.28-0.98	0.043
Smoking	0.39	0.10-1.62	0.20
Cumulative doxorubicin equivalent dose	1.26	1.02-1.56	0.029
QTc	1.06	0.86-1.30	0.61
QRS duration (ms)	1.12	0.93-1.36	0.23
VG_Y (mV*ms)	0.91	0.71-1.17	0.47
Age (y)	1.07	0.798-1.48	0.66
Male	1.22	0.77-1.95	0.40
Coronary artery disease	2.02	0.95-4.30	0.068
Diabetes	1.14	0.58-2.24	0.69
Hypertension	0.52	0.28-0.96	0.038
Smoking	0.40	0.10-1.63	0.20
Cumulative doxorubicin equivalent dose	1.25	1.01-1.55	0.043
QTc	1.05	0.84-1.31	0.68
QRS duration (ms)	1.16	0.93-1.45	0.18
VG_Z (mV*ms)	1.27	0.99-1.64	0.063
Age (y)	1.07	0.78-1.47	0.67
Male	1.44	0.88-2.37	0.15
Coronary artery disease	2.06	0.95-4.45	0.066
Diabetes	1.16	0.59-2.28	0.66
Hypertension	0.52	0.28-0.97	0.040
Smoking	0.41	0.10-1.70	0.22
Cumulative doxorubicin equivalent dose	1.24	1.01-1.53	0.041
QTc	1.03	0.83-1.28	0.79
QRS duration (ms)	1.18	0.96-1.44	0.12

Results for continuous variables are presented as SHR per 1 SD change in value.
CAD = coronary artery disease; CI = confidence interval; QTc = corrected QT interval; SHR = subhazard ratio; SVG = spatial ventricular gradient.

Table 3 shows results for separate competing-risks regressions for SVG magnitude, VGx, VGy, and VGz assessed individually after multivariable adjustment for age, sex, CAD, QTc, QRS duration, HTN, DM, and total cumulative doxorubicin equivalent dose. After adjustment, larger SVG magnitude remained associated with a decreased risk of developing HF or CM (SHR: 0.76 per 1 SD increase, 95% CI: 0.59-0.96; $P = 0.024$). More leftward orientation of the SVG (larger VGx) was also associated with reduced risk of HF or CM, with a SHR of 0.77 per 1 SD increase (95% CI: 0.61-0.96; $P = 0.023$). As expected, higher cumulative doxorubicin dose was associated with an increased risk of developing HF or CM[5] in all models for SVG magnitude, VGx, VGy, and VGz. Surprisingly, all of the models also found that HTN was associated with a reduced risk of HF/CM, even though this association was not significant in the univariable analysis. Given that all patients did not have cumulative doxorubicin equivalent dose data, we also performed the same competing risks regressions without adjustment for anthracycline dose (Supplemental Table 6). A larger SVG magnitude was no longer associated with a decreased risk of HF or CM (SHR: 0.83 per 1 SD increase, 95% CI: 0.68-1.01; $P = 0.069$), and VGz was associated with an increased risk of HF or CM (SHR: 1.27 per 1 SD increase, 95% CI: 1.03-1.56; $P = 0.025$).

We then compared patients in the highest quartile of SVG magnitude to those in the remaining 3 lower quartiles. After multivariable adjustment, patients in the highest quartile of SVG magnitude had a lower risk of incident HF or CM compared to the remaining patients with a SHR of 0.37 (95% CI: 0.17-0.81; $P = 0.012$). The **Central Illustration** shows the adjusted cumulative incidence of HF/CM for patients in the highest quartile compared to the lower 3 quartiles of SVG magnitude over the study period. **Figure 1** shows the analogous Kaplan-Meier plots for the hazard of incident HF/CM for patients who had the highest

CENTRAL ILLUSTRATION **The Spatial Ventricular Gradient and its Association With Anthracycline Cardiotoxicity**



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Patients treated with anthracyclines were identified retrospectively, and 12-lead electrocardiograms were obtained within 6 months prior to initiation of cancer therapy. Vectorcardiograms were constructed from baseline electrocardiograms. The spatial ventricular gradient (SVG) was defined as the QRST area vector. Competing-risks models were constructed to estimate the associations between SVG components and magnitude with the primary outcome of time to onset of heart failure (HF) or cardiomyopathy (CM) within 5 years of starting anthracycline treatment. Larger SVG magnitude prechemotherapy was associated with a decreased risk of incident HF or CM after multivariable adjustment for age, sex, CAD, corrected QT interval, QRS duration and total cumulative anthracycline dose. CM = cardiomyopathy; HF = heart failure; SHR = subhazard ratio; SVG Mag = spatial ventricular gradient magnitude.

quartile of SVG magnitude compared to the remaining 3 lower quartiles. Similar to the competing risks models, patients in the highest quartile of SVG magnitude had improved HF/CM-free survival when analyzed with Cox proportional hazards modeling (P log rank = 0.013, HR: 0.50 per 1 SD increase, 95% CI: 0.29-0.87; P = 0.015) (**Figure 1**).

Cox proportional hazards models for the outcome of all-cause death adjusted for age, sex, CAD, QTc, QRS duration, HTN, DM, type of malignancy, and cumulative doxorubicin equivalent dose are shown in Supplemental Table 7. Associations between SVG parameters and all-cause mortality were weaker than for the outcome of HF/CM, with only VGz having a borderline significant association (HR: 1.18 per 1 SD increase, 95% CI: 1.01-1.38; P = 0.042). Increasing age and male gender were associated with increased risk of death. Supplemental Figure 1 shows Kaplan-Meier curves for the hazard of incident all-cause mortality.

DISCUSSION

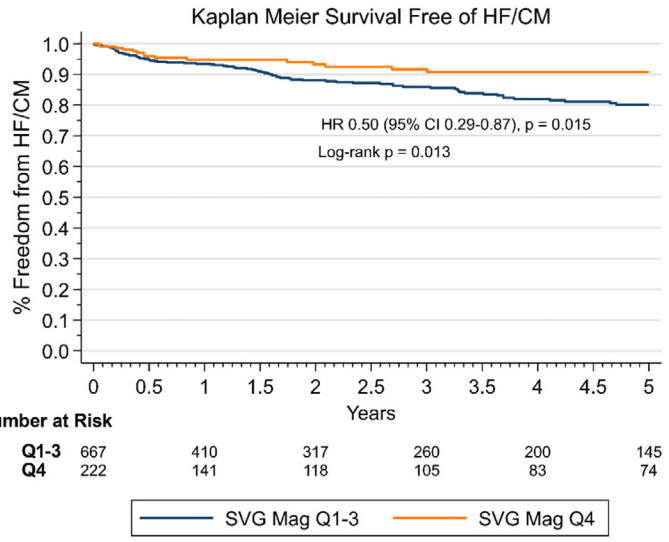
We found that vectorcardiographic measurements of baseline GEH, and specifically the SVG, were independently associated with incident HF or CM after anthracycline chemotherapy. This is a novel avenue for HF/CM risk stratification, as GEH has not been studied before in the context of anthracyclines and subsequent cardiotoxicity. As expected, we found

that cumulative anthracycline dose was associated with an increased risk of developing HF/CM in our cohort.[5] An unexpected finding of our analyses was that HTN was associated with a reduced risk of HF/CM after multivariable adjustment. However, in a survival analysis with the outcome of all-cause mortality, there was a trend toward HTN being associated with higher mortality which may partially explain this result. Deaths occurring early after chemotherapy initiation (leading to an incomplete course of chemotherapy) may account for the observed association between higher total anthracycline dose and lower mortality, highlighting the challenges of assessing competing risks of cancer vs cardiovascular disease in observational studies. We also found that higher baseline SVG magnitude and more leftward SVG orientation were independently associated with a decreased risk of developing HF/CM after anthracycline treatment after adjustment for various other factors known to be associated with anthracycline cardiotoxicity.

There are clear mechanistic links between electrical and mechanical heterogeneity, likely due to the way in which myocardial calcium handling influences action potential morphology and duration, inotropy, and lusitropy.[17] Human and animal studies have also shown an association between action potential heterogeneity, myocardial mechanical heterogeneity, and diastolic dysfunction.[18,19] Directionality of the SVG is likely important because the normal SVG tends to point in the same direction as the main axis of the left ventricle.[27] Deviations from this direction are caused by accumulation of electrical or mechanical abnormalities. The exact reasons for more leftward oriented SVG (as opposed to other directions) and larger SVG magnitude being associated with improved outcomes in this cohort require further study. It should be noted that variations in the transverse plane, which is spanned by the X and Z axes, have been found to be predictive of poor cardiovascular outcomes in numerous previous studies.[21-24]

Compared with traditional ECG measures such as QTc and QRS duration, the SVG provides a more complete representation of electrical heterogeneity. Notably, in our results, QT interval and QRS duration were not associated with the development of HF/CM after multivariable adjustment. In general, the SVG is a more robust measure of electrical heterogeneity as it accounts for the interplay between depolarization and repolarization which is not captured with static measures like QRS duration or QT interval. Additionally, QT interval, although often associated with adverse cardiovascular outcomes, reflects total repolarization time and is not a robust measurement of electrical heterogeneity.

FIGURE 1 Kaplan Meier Event Curves by Quartiles of SVG Magnitude



Patients in the highest quartile of spatial ventricular gradient (SVG) magnitude (fourth quartile) had a decreased risk of developing heart failure/cardiomyopathy during a 5-year period. CI = confidence interval; CM = cardiomyopathy; HF = heart failure; HR = hazard ratio.

Previous work on GEH and the SVG has focused primarily on risk stratification for sudden death and ventricular arrhythmias and the relationship between GEH and cardiac structure and function.[22-24] In a prospectively enrolled community-based cohort, baseline values of SVG orientation differed between patients who developed LV dysfunction compared with patients who maintained normal systolic function.[22] Similarly, the SVG magnitude and other GEH markers have been associated with an increased risk of sudden cardiac death after adjusting for demographic characteristics, prevalent cardiovascular diseases, and traditional cardiovascular risk factors.[23] Consistent with previous work, in this study we found that GEH parameters at baseline differed between patients who did or did not develop HF or CM.

We selected a follow-up period of 5 years based on prior observations that 98% of anthracycline cardiotoxicity can be detected within the first year[3] and to decrease the likelihood that patients would develop new comorbidities (eg, HTN or ischemic heart disease) that could lead to HF independent of anthracycline exposure. The high mortality seen in our cohort is similar to that observed in populations

with active cancer.[28] In those patients where cause of death was available (n = 204), most of the patients who died had hematological malignancies, and <1% of patients died of a cardiovascular cause such as myocardial infarction or acute HF. Notably, previous studies of GEH and the SVG have shown that GEH is more specific for sudden cardiac death over other modes of death.[22] Our finding of a weak association between SVG and total mortality is, therefore, not surprising, given that the majority of patients in this study died due to their malignancy.

Twelve-lead electrocardiography is an accessible tool worldwide that is straightforward to perform in patients who are planned to receive anthracycline treatment. If validated prospectively in larger populations, GEH/SVG measurement could serve as a pretreatment cardiac risk stratification tool in patients with cancer. Measurement of myocardial GEH/SVG at baseline might identify patients at low (or high) risk of developing cardiotoxicity. Patients at lower risk of developing HF/CM might benefit from the use of higher and more effective doses of anthracyclines or less intensive cardiac surveillance. Conversely, alternative cancer therapies might be considered if the risk of developing HF/CM is particularly elevated. It is also possible that the benefit of higher doses of anthracyclines could outweigh the risk in specific patient populations with a favorable GEH profile; for instance, in patients with secondary malignancies where a high cumulative anthracycline dose over the patient's lifetime is necessary to achieve the best cancer outcomes, or in aggressive malignancies such as sarcomas,[29] where higher doses of anthracyclines are commonly used with curative intent. Further prospective study will be needed to validate this approach before it can be adopted into clinical practice.

Future investigations into associations between GEH and cardiotoxicity will focus on the utility of assessing longitudinal changes in GEH parameters in patients receiving anthracyclines and the relationship of GEH parameters with changes in left ventricular function as assessed by imaging. Large prospective studies will ultimately be needed to evaluate the role of GEH parameters in the risk stratification of anthracycline cardiotoxicity.

STUDY LIMITATIONS. Limitations of our study include the use of ICD 9/10 billing codes for diagnosis of HF and CM, although charts were reviewed to confirm the diagnosis. Due to its retrospective nature, we are unable to determine if some HF/CM cases were primarily due to anthracyclines or other etiologies. Patients who had baseline ECGs included in the present analysis were younger, had less cardiovascular comorbidities, a higher prevalence of hematological malignancies, and received lower cumulative mean doses of doxorubicin equivalents. Patients without baseline ECGs were more likely to have breast cancer, compared to patients with baseline ECGs who were more likely to have hematologic malignancies. Patients with breast cancer are generally less acutely ill compared to patients with hematologic malignancies, which may explain the decreased utilization of baseline ECGs for risk stratification. Some patients had a baseline ECG but it was obtained >6 months before starting chemotherapy. It is also possible that an ECG was performed before starting treatment but that it was not uploaded in the medical records or it was performed outside our institution. Data on use of concomitant cardiotoxic treatments, such as HER-2 (human epidermal growth factor receptor-2) targeted therapies, were not available, and only 65% of patients had anthracycline dose available. Our results need to be addressed prospectively in a higher risk population.

Limitations of using SVG measurement in this context include intraindividual variation and the effects of various medications on SVG measurement, factors which are currently being investigated. As of now, calculation of the SVG also requires specialized software, although all modern ECG acquisition systems have the ability to create VCGs from standard 12-lead ECGs. It would be straightforward to calculate the SVG using existing hardware with minimal software modification and without the need for any human ECG annotation or overreading. Our group is also planning to release open-source software for calculation of the SVG and other related parameters in the near future. With appropriate software, automated measurement of the SVG should not take longer than a few seconds.

CONCLUSIONS

Prechemotherapy SVG as measured on a standard 12-lead ECG predicted the risk of developing HF or CM after treatment with anthracyclines. The SVG and other parameters that assess GEH may help with risk stratification in cardio-oncology patients exposed to other cardiotoxic agents as well.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The SVG is a vectorcardiographic measure of myocardial electrical heterogeneity that is associated with ventricular arrhythmias and cardiac mechanical dysfunction. SVG magnitude and direction prechemotherapy are associated with the risk of developing HF or CM after treatment with anthracyclines even after adjusting for potential confounders such as CAD, gender, and age.

TRANSLATIONAL OUTLOOK: Our findings highlight that standard ECGs obtained prechemotherapy can be used to assess risk of incident cardiotoxicity via measuring the SVG. Future prospective studies are needed to assess the role of the SVG in a cardio-oncology population with a higher prevalence of cardiovascular risk factors and to define its association with changes in left ventricular function.

REFERENCES

1. Arcamone F, Cassinelli G, Fantini G, et al. Adriamycin, 14-hydroxydaunomycin, a new antitumor antibiotic from S. peucetius var. caesius. Reprinted from Biotechnology and Bioengineering, Vol. XI, Issue 6, Pages 1101-1110 (1969). *Biotechnol Bioeng*. 2000;67(6):704-713. https://doi.org/10.1002/(SICI)1097-0290(20000320)67:6<704::AID-BIT8>3.0.CO;2-L

2. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer*. 2010;10:337. https://doi.org/10.1186/1471-2407-10-337

3. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131(22):1981-1988. https://doi.org/10.1161/CIRCULATIONAHA.114.013777

4. Raber I, Asnani A. Cardioprotection in cancer therapy: novel insights with anthracyclines. *Cardiovasc Res*. 2019;115(5):915-921. https://doi.org/10.1093/cvr/cvz023

5. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. 2020;7:26. https://doi.org/10.3389/fcvm.2020.00026

6. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27(9):911-939. https://doi.org/10.1016/j.echo.2014.07.012

7. Vohra A, Asnani A. Biomarker discovery in cardio-oncology. *Curr Cardiol Rep*. 2018;20(7):52. https://doi.org/10.1007/s11886-018-1002-y

8. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. *Ann Oncol*. 2012;23 Suppl 7:vii155-vii166. https://doi.org/10.1093/annonc/mds293

9. Desai L, Balmert L, Reichek J, Hauck A, Gambetta K, Webster G. Electrocardiograms for cardiomyopathy risk stratification in children with anthracycline exposure. *Cardiooncology*. 2019;5:10. https://doi.org/10.1186/s40959-019-0045-6

10. Markman TM, Ruble K, Loeb D, et al. Electrophysiological effects of anthracyclines in adult survivors of pediatric malignancy. *Pediatr Blood Cancer*. 2017;64(11). https://doi.org/10.1002/pbc.26556

11. Horacek JM, Jakl M, Horackova J, Pudil R, Jebavy L, Maly J. Assessment of anthracycline-induced cardiotoxicity with electrocardiography. *Exp Oncol*. 2009;31(2):115-117.

12. Boukens BJ, Walton R, Meijborg VM, Coronel R. Transmural electrophysiological heterogeneity, the T-wave and ventricular arrhythmias. *Prog Biophys Mol Biol*. 2016;122(3):202-214. https://doi.org/10.1016/j.pbiomolbio.2016.05.009

13. Antzelevitch C, Dumaine R. Electrical heterogeneity in the heart: physiological, pharmacological and clinical implications. In: *Comprehensive Physiology*. Wiley; 2002:654-692.

14. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation*. 1983;67(6):1356-1367. https://doi.org/10.1161/01.CIR.67.6.1356

15. Thomsen MB, Verduyn SC, Stengl M, et al. Increased short-term variability of repolarization predicts d-sotalol-induced torsades de pointes in dogs. *Circulation*. 2004;110(16):2453-2459. https://doi.org/10.1161/01.CIR.0000145162.64183.C8

16. Vassallo JA, Cassidy DM, Kindwall KE, Marchlinski FE, Josephson ME. Nonuniform recovery of excitability in the left ventricle. *Circulation*. 1988;78(6):1365-1372. https://doi.org/10.1161/01.CIR.78.6.1365

17. Prenner SB, Shah SJ, Goldberger JJ, Sauer AJ. Repolarization heterogeneity: beyond the QT interval. *J Am Heart Assoc*. 2016;5(5):e003607. https://doi.org/10.1161/JAHA.116.003607

18. Odening KE, Jung BA, Lang CN, et al. Spatial correlation of action potential duration and diastolic dysfunction in transgenic and drug-induced LQT2 rabbits. *Heart Rhythm*. 2013;10(10):1533-1541. https://doi.org/10.1016/j.hrthm.2013.07.038

19. Haugaa KH, Amlie JP, Berge KE, Leren TP, Smiseth OA, Edvardsen T. Transmural differences in myocardial contraction in long-QT syndrome: mechanical consequences of ion channel dysfunction. *Circulation*. 2010;122(14):1355-1363. https://doi.org/10.1161/CIRCULATIONAHA.110.960377

20. Waks JW, Tereshchenko LG. Global electrical heterogeneity: a review of the spatial ventricular gradient. *J Electrocardiol*. 2016;49(6):824-830. https://doi.org/10.1016/j.jelectrocard.2016.07.025

21. Stabenau HF, Shen C, Zimetbaum P, Buxton AE, Tereshchenko LG, Waks JW. Global electrical heterogeneity associated with drug-induced torsades de pointes. *Heart Rhythm*. 2021;18(1):57-62. https://doi.org/10.1016/j.hrthm.2020.07.038

22. Biering-Sørensen T, Kabir M, Waks JW, et al. Global ECG measures and cardiac structure and function: the ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol*. 2018;11(3):e005961. https://doi.org/10.1161/CIRCEP.117.005961

23. Waks JW, Sitlani CM, Soliman EZ, et al. Global electric heterogeneity risk score for prediction of

sudden cardiac death in the general population: the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation*. 2016;133(23):2222–2234. https://doi.org/10.1161/CIRCULATIONAHA.116.021306

24. Waks JW, Haq KT, Tompkins C, et al. Competing risks in patients with primary prevention implantable cardioverter-defibrillators: global electrical heterogeneity and clinical outcomes study. *Heart Rhythm*. 2021;18(6):977–986. https://doi.org/10.1016/j.hrthm.2021.03.006

25. Dodos F, Halbsguth T, Erdmann E, Hoppe UC. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. *Clin Res Cardiol*. 2008;97(5):318–326. https://doi.org/10.1007/s00392-007-0633-6

26. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. *Eur Heart J*. 1990;11(12):1083–1092. https://doi.org/10.1093/oxfordjournals.eurheartj.a059647

27. Scherptong RWC, Henkens IR, Man SC, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. *J Electrocardiol*. 2008;41(6):648–655. https://doi.org/10.1016/j.jelectrocard.2008.07.006

28. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. https://doi.org/10.3322/caac.21660

29. Le Cesne A. Making the best of available options for optimal sarcoma treatment. *Oncology*. 2018;95(Suppl 1):11–20. https://doi.org/10.1159/000494861

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APPENDIX **For supplemental methods, tables, and figures, please see the online version of this paper.**