Published in final edited form as:

Pediatr Blood Cancer. 2015 July ; 62(7): 1228–1231. doi:10.1002/pbc.25456.

Abnormal Circumferential Strain Measured by Echocardiography Is Present in Patients With Shwachman–Diamond Syndrome Despite Normal Shortening Fraction

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Abstract

Background—Shwachman–Diamond Syndrome (SDS) is an autosomal recessive disorder characterized by bone marrow failure and exocrine pancreatic dysfunction. Heart failure has been described in patients with SDS. Circumferential strain (ϵ_{cc}) is a measure of cardiac performance that may identify dysfunction when standard measures are normal.

Procedures—Patients with SDS were identified and the echocardiographic database queried. Cardiac anatomy and function were recorded, and ϵ_{cc} was measured retrospectively

Results—From 1995–2013, 27 patients with biallelic *SBDS* mutations confirming the diagnosis of SDS were identified at our institution: 14 had at least one echocardiogram available; 10 underwent HSCT, with echocardiograms available in nine. Ejection fraction (EF) was normal in all 14 patients evaluated; however, ϵ_{cc} was decreased in 4/12 studies prior to HSCT. In two patients, ϵ_{cc} was abnormal both before and after HSCT, in one, ϵ_{cc} changed from normal to abnormal after HSCT, and in one, ϵ_{cc} was normal after HSCT despite being abnormal prior. Echocardiogram

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Conflict of interest: Nothing to declare.

reports were also available for six patients in the North American SDS registry, all with normal EF.

Conclusions—While EF was normal in all patients with SDS, ϵ_{cc} was abnormal in 33% prior to HSCT and 33% of those who had undergone HSCT. This suggests that SDS is associated with systolic dysfunction. Further studies are needed to define the incidence of dysfunction in this group and the progression to heart failure.

Keywords

Shwachman–Diamond syndrome (SDS); hematopoietic stem cell transplant; cardiomyopathy; heart failure; echocardiography

INTRODUCTION

Shwachman–Diamond Syndrome (SDS) is a rare autosomal recessive condition characterized by bone marrow failure, exocrine pancreatic dysfunction, and predisposition to myelodysplasia and acute myeloid leukemia [1]. SDS is a multi-system disorder, and previous reports have described associations between SDS and cardiac pathology [2–8]. Despite this, it is not currently standard practice to screen patients for cardiac abnormalities.

Echocardiographic measures of systolic function, such as shortening fraction (SF) and ejection fraction (EF), are dependent on geometric assumptions and are operator dependent, and as such susceptible to measurement error. Myocardial strain (ϵ) is an angle-independent measure of ventricular function, noninvasively measured by echocardiogram or cardiac MRI. This technique allows quantification of cardiac motion, or deformation, by tracking selected points within the myocardium on a frame-by-frame basis, and it has been validated against invasively measured hemodynamics and a number of other non-invasive methods [9]. The value ϵ denotes a percentage of deformation in the radial (ϵ_r), longitudinal (ϵ_l), or circumferential (ϵ_{cc}) dimensions of the ventricle. These individual parameters can then be used to describe segmental or global function [10]. The primary applications for ϵ have been in patients with ischemic heart disease, cardiomyopathy, heart transplant, ventricular dyssynchrony, and subclinical cardiac dysfunction [9–11]. Studies on patients at risk for developing ventricular dysfunction, including those exposed to anthracyclines, have shown decreased values of ϵ despite normal SF and EF, and changes in strain may precede eventual changes in EF [12–15].

In the current report, we describe assessment of left ventricular systolic function using standard measures, as well as ϵ in a group of patients with SDS seen over a 17-year period at our institution.

MATERIALS AND METHODS

The study was a retrospective review of medical records and the echocardiographic database at our institution and was approved by the Institutional Review Board. An exploratory query of the medical record and echocardiographic database was performed to identify patients with biallelic *SBDS* mutations confirming the diagnosis of SDS followed at our institution

for the period 1995–2012. Preparative regimen for hematopoietic stem cell transplant (HSCT) included campath, fludarabine, melphalan for all patients; one patient underwent a second HSCT for relapsed acute myeloid leukemia using Busulfan, Fludarabine, ATG. When multiple echocardiograms were present, the most recent was collected. For patients who underwent HSCT, the last echocardiogram prior to transplantation and the most recent were collected.

Transthoracic echocardiograms were performed on one of three ultrasound systems used at our institution during the study period: Vivid 7 (General Electric Healthcare, Milwaukee, WI), iE33 (Phillips Medical Systems, Best, The Netherlands), or Sequoia 512 (Acuson, Oceanside, CA). Offline quantification of echocardiographic data for ϵ was performed as described previously [16]. Briefly, Digital Imaging and Communications in Medicine (DICOM) data were analyzed using vendor-independent clinical echocardiographic software (Image Arena, TomTec Imaging Systems, Munich, Germany) for myocardial circumferential ϵ according to American Society of Echocardiography 16-segment model for chamber quantification at the mid-papillary level [17]. Values for the six mid-papillary segments were averaged for a single value, heretofore referred to as “ ϵ_{cc} .” Of note ϵ_{cc} is negative; therefore, values that are less negative represent abnormal function. One user performed all analyses (J.J.S), with a comparison read by a second user (M.D.T). Images were read by a third user (T.D.R) and the original value in closest agreement was recorded for values that varied between readers by more than 10%, or if there was disagreement on normal versus abnormal. We have previously published low inter- and intra-observer variability for ϵ_{cc} measurements in our laboratory [16]. All ϵ_{cc} values were compared to normal values for age and determined to be normal [$\leq$ reference value – 2(standard deviation)] or abnormal [$>$ reference value – 2 (standard deviation)] [18]. Values of longitudinal ϵ were not measured due to an inconsistent inclusion of complete apical 4-chamber views. Radial ϵ as measurements from the parasternal short axis and apical views did not correlate well with each other and were therefore excluded as an unreliable measurement in our dataset.

In addition to patients seen at our institution, echocardiographic data on another six patients were available from the North American Shwachman–Diamond Syndrome Registry (NASDSR) in the form of written reports. DICOM data were not available for ϵ_{cc} analysis for these patients.

RESULTS

During the study period 1995–2012, 27 patients with biallelic SBDS mutations confirming the diagnosis of SDS were seen at our institution (Table I). Of those patients, 14 had at least one echocardiogram performed; the echocardiogram for one patient was performed prior to digital storage of studies and another was of insufficient quality for analysis. A total of 10 patients underwent HSCT, with at least one echocardiogram of sufficient quality for ϵ_{cc} analysis performed post-HSCT available in nine. In one patient, the most recent post-HSCT echocardiogram was unable to be analyzed reliably and instead the next most recent study was used.

Patients studied showed a wide range of ages, from 0.8–29.2 years in the group defined as SDS with no HSCT to 5–31.2 years in the post-HSCT group (Table II). Both groups were slightly male dominated. As would be expected for groups with a large age range, there was a great amount of variability in height, weight, and BSA.

SF and EF were normal in all SDS patients studied, whether in SDS alone or in SDS–HSCT (Table III). While these standard measures of systolic function were normal in all patients, ϵ_{cc} was abnormal in 4/12 (33%) at baseline and 3/9 (33%) after HSCT. In two patients, ϵ_{cc} was abnormal before and after HSCT, while one patient had normal ϵ_{cc} before HSCT and abnormal after. A single patient showed change from abnormal ϵ_{cc} prior to HSCT to normal ϵ_{cc} after.

Other abnormal structural findings were noted in 4/14 (29%) studies. Left ventricular chamber dilation was recorded in a patient with abnormal ϵ_{cc} prior to HSCT, both of which resolved post-HSCT although left atrial dilation persisted. Another patient developed a pericardial effusion and tamponade physiology post-HSCT, although ϵ_{cc} remained normal. In one patient, there was bicuspid aortic valve and in another mild aortic stenosis, and two others had dilation of the aorta. Finally, there was a clinically insignificant valvar disease, including trivial aortic insufficiency and trivial mitral regurgitation.

For the six patients from the NASDSR, SF and EF were normal for all studies compared to age-based norms. In a single patient, there was a small patent foramen ovale noted, but this is a normal finding in approximately one-quarter of the general population.

Discussion

Although SDS is rare, several previous studies have shown an association with cardiovascular pathology. The first reports described myocardial fibrosis and necrosis on autopsy, and in some cases, a description of clinical heart failure [2–4]. Follow-up reports have shown decreased myocardial reserve, as measured by echocardiography and cardiac MRI, in response to stress, but normal systolic function at baseline and no symptoms of heart failure [6]. Most recently, a case report and a French national survey have documented patients with SDS and symptomatic dilated cardiomyopathy, in some cases requiring inotropic support [7,8].

In the current report, we detail the experience at a single institution over a 17-year period by measuring left ventricular systolic function, including retrospective ϵ_{cc} analysis, in a group of patients with SDS. While none of the patients were reported to have symptomatic heart failure and all had normal function by SF and EF, 33% had evidence for abnormal left ventricular systolic function as measured by ϵ_{cc} , which is known to predict eventual changes in SF and EF in adult and pediatric populations of patients with treated malignancy [12–15]. There was no appreciable effect of HSCT on this finding, with 33% of patients showing abnormal ϵ_{cc} after treatment. This may be, in part, reflective of the reduced intensity preparative regimen of campath, fludarabine and melphalan, none of which are generally considered among the main cardiotoxic medications [19]. The regimen also avoided more cardiotoxic agents, such as cyclophosphamide. A prior case report documented fatal cyclophosphamide-induced pancarditis in a patient undergoing HSCT for SDS; however, the

cardiac function at baseline was unknown [5]. In addition to evidence for dysfunction, we also found that 29% of our patients had abnormal structural findings, such as dilation of the aorta or bicuspid aortic valve. These findings were relatively mild and would not be expected to have any effect on myocardial function.

The link between SDS and cardiac dysfunction is unknown. The reported findings of fibrosis on autopsy suggest a possible pathologic mechanism, as replacement of myocardium with scar can lead to dysfunction. A study on patients exposed to anthracycline demonstrated the relationship between myocardial fibrosis and decreased myocardial performance [20], which could account for the decreased cardiac reserve during exercise stress previously documented in SDS [6]. The presence of chronic anemia can lead to dilated cardiomyopathy and dysfunction; however, with the exception of one patient in our cohort, there was no evidence for left ventricular dilation. Patients with SDS may have more comorbid conditions in general, and in particular after HSCT. The available records on our patients do not suggest any patients had significant illness or abnormal vital signs signifying concomitant risk factors for cardiac dysfunction. One patient developed cardiac tamponade after HSCT that was present at time of the most recent echocardiogram; however, the function by SF, EF, and e was normal.

It is unknown whether decreases in ϵ_{cc} correlate with the development of symptomatic heart failure. However, according to the American Heart Association/American College of Cardiology grading system, once evidence of dysfunction is evident by standard modes of imaging the patient is at a minimum Stage B heart failure (Table IV) and warrants follow up for the development of cardiovascular disease [21]. The guidelines were not prepared with ϵ as part of the algorithm, and how it fits in is not entirely clear, but there may be a role for inclusion of ϵ in future versions [22]. An important question is whether all patients with SDS should be considered Stage A, and therefore at high risk for developing heart failure; a similar sentiment has been expressed for patients with anthracycline exposure [23]. Multi-institutional prospective studies are needed to define the incidence of dysfunction in this group, and the progression to symptomatic heart failure. These should include analysis of imaging parameters to describe standard measures of ventricular function, markers of myocardial fibrosis, and measurement of subclinical dysfunction by ϵ . Inclusion of serum biomarkers of cardiac dysfunction may also give insight into the pathologic processes involved in linking SDS and cardiomyopathy. Work is also underway to determine the effects of HSCT on ventricular function, as measured by ϵ , in patients with SDS and other diagnoses.

This study has some important limitations. The work was retrospective in nature, and thus only captured half of the patients seen by our institution. Because of the rarity of SDS, the patient group studied was small, and findings should be interpreted accordingly. Further, the echocardiograms available were not performed with ϵ analysis in mind, and at times, did not include adequate apical 4-chamber images to allow for measurement of longitudinal ϵ . The study would have been strengthened if longitudinal ϵ had been found abnormal as well because it is thought to be a more reliable measure of function in pediatric patients [24]. Finally, although radial ϵ , as measured by tissue Doppler imaging, has been shown to be

abnormal in other populations at risk for myocardial dysfunction, we found this to be unreliable when measured by speckle tracking, similar to previous evaluations [24,25].

Abbreviations

HSCT	hematopoietic stem cell transplant
EF	ejection fraction
ϵ	strain (myocardial)
ϵ_{cc}	circumferential strain (myocardial)
SDS	Shwachman–Diamond Syndrome
SF	shortening fraction

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TABLE I

Shwachman–Diamond Syndrome Patient Mutations

Patients (n = 27)	SBDS mutations
19	258 + 2T>C and 183_184TA>CT
3	258 + 2T>C (homozygous)
2	258 + 2T>C and 258 + 1 G>C
1	258 + 2T>C (homozygous) and 1VS1–3 A>G
1	258 + 2T>C and 183_184 TA>CT and 201 A>G and 635 T>C
1	258 + 2T>C and 120delG

TABLE II

Demographic Information for Patients With Shwachman-Diamond Syndrome at the Time of Echocardiography Evaluation

	SDS	HSC T
Number of patients with studies	13	9
Age at time of study (years)	10.1 (0.8-29.2)	13.6 (5.0-31.2)
Female	5 (36%)	4 (44%)
Height (cm) ^a	121.5 (91.5-148)	124.7 (86.9-164.9)
Weight (kg)	30.3 (5.2-90)	31.7 (11.3-53)
Body Surface Area (m ²)	1.0 (0.3-1.97)	1.0 (0.5-1.5)
Heart rate (beats per minute)	93 (52-122)	99 (66-155)
Systolic blood pressure (mmHg) ^b	107 (71-138)	109 (92-124)
Diastolic blood pressure (mmHg) ^b	64 (40-77)	64 (55-77)
Hemoglobin at time of study (g/dl) ^c	11.6 (8.2-13.2)	14.1 (9.9-15.0)

Average and range for various parameters at the time of the most recent echocardiography evaluation or last study prior to hematopoietic stem cell transplantation ("SDS" group) or the most recent study since hematopoietic stem cell transplantation ("HSC T" group).

^aData available in (12) SDS and (8) HSC T patients.

^bdata available in (10) SDS and (8) HSC T patients.

^cdata available in (7) SDA and (8) HSC T patients.

TABLE III

Assessment of Left Ventricular Systolic Function in Patients With Shwachman-Diamond Syndrome

Patient	Age	SF (%)	EF (%)	ϵ_{cc} (%)	Age	SF (%)	EF (%)	ϵ_{cc} (%)	Other
1	0.8 years	46	55-60	-20.1	5.0 years	39	60-65	-19.2 ^a	
2	19.3 years	37	55-60	-18.2					
3	7.4 years	33	55-60	-19.6	9.7 years	34	55-60	-13.2	
4	4.4 years	41	55-60	-15.8	6.6 years	31	55-60	-26.4	LV and LA dilation pre-HSCT LA and Ao dilation post-HSCT
5	9.1 years	37	60-65	-22.1					History of Kawasaki, normal coronaries
6	21.4 years	37	55-60	-22.1	21.7 years	32	n/a	-23.7	Pericardial effusion, tamponade
7	10.6 years	38	55-60	-17.9	15.4 years	35	55-60	-19.1	Trivial AI
8	2.0 months	39	n/a	n/a					
9	6.9 years	34	55-60	-21.5	12.3 years	37	60-65	-20.0	Trivial MR pre-HSCT Mild Ao root and ascending Ao dilation post-HSCT
10	9.4 years	32	55-60	-21.5					
11	3.3 years	35	60-65	-25.9	5.4 years	32	60-65	-18.1	BAV, trivial AI
12	13.0 years	39	60-65	-24.4	14.9 years	35	60-65	-23.6	Trivial AI post-HSCT
13	29.2 years	36	55-60	-24.8	31.2 years	36	55-60	-22.1	Mild AS
14	4.1 years	34	55-60	n/a					

Shortening fraction, ejection fraction, and global circumferential strain (ϵ_{cc}) at the time of the most recent echocardiography evaluation or last study prior to hematopoietic stem cell transplantation ("SDS" group) or the most recent study since hematopoietic stem cell transplantation ("HSCT" group). Values for ϵ_{cc} less negative than reference values [16], i.e., abnormal, are underlined. Preparative regimen for HSCT is given in the text. AI = aortic insufficiency; AS = aortic stenosis; BAV = bicuspid aortic valve; EF = ejection fraction; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; n/a = not analyzed due to unavailability of sufficient DICOM data or poor image quality; PFO = patent foramen ovale; SF = shortening fraction.

^aImage quality poor in most recent study, next most recent study used.

TABLE IV**ACC/AHA Stages in the Development of Heart Failure**

ACC/AHA Stage	Description
A	At high risk for heart failure, but without structural heart disease or symptoms.
B	Structural heart disease but without signs or symptoms of heart failure.
C	Structural heart disease with prior or current symptoms of heart failure.
D	Refractory heart failure requiring specialized interventions.

Adapted from Hunt et al. [21]. ACC, American College of Cardiology; AHA, American Heart Association.