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## Myocardial Fat Overgrowth in Proteus Syndrome

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### Abstract

Proteus syndrome is a rare, mosaic disorder with asymmetric and distorting overgrowth of the skeletal system, skin, and adipose tissues. Cardiac abnormalities are rare in this syndrome and only two prior cases have been reported. Many patients with PS followed at our institution underwent transthoracic echocardiograms for preoperative evaluation or as work-up for associated pulmonary disease. Some were noted to have prominent, focal echodense areas in the myocardium. We further investigated cardiac findings in a cohort of children and adult patients with PS. Patients with abnormal echocardiograms were referred for cardiac magnetic resonance imaging, Holter monitoring, and exercise treadmill testing. Twenty children and adults with PS, age 24 months to 50 years old, underwent transthoracic echocardiograms. Seven patients (35%) had focal bright echodense areas within the myocardium suggesting fatty infiltration. The majority of patients had significant involvement of the interventricular septum. The cardiac characteristics of all patients with fatty infiltration on transthoracic echocardiograms were compared to Proteus patients without these findings. There were no significant differences in chamber sizes, mass, systolic or diastolic function. No increased risk of conduction defects or arrhythmias was found. This study shows that abnormal fat overgrowth is a common finding in the myocardium in patients with Proteus syndrome; however, it is not associated with functional derangements or arrhythmias. Further evaluation of a larger number of Proteus patients is needed in order to determine the frequency and prognosis of cardiac involvement.

### Keywords

Proteus syndrome; cardiac; myocardial fatty infiltration; interventricular septum

## INTRODUCTION

Proteus syndrome (PS) is a rare syndrome characterized by segmental, postnatal overgrowth of diverse tissues originating from all germ layers. The onset of overgrowth typically occurs in infancy and the skin, bones, and adipose tissue are most commonly affected [Biesecker,

2006; Cohen, 2013b]. Proteus syndrome is thought to affect only a few hundred patients in the US and Western Europe [Biesecker et al., 1998]. Since there is a significant degree of variation in the severity of disease and extent of tissue involvement, stringent diagnostic criteria have been proposed to differentiate PS from other overgrowth syndromes [Biesecker et al., 1999; Turner et al., 2004]. Other syndromes in the differential diagnosis include Klippel-Trenaunay syndrome, CLOVES syndrome, PTEN hamartoma tumor syndrome, Neurofibromatosis type 1, and isolated hemihyperplasia. For a clinical diagnosis of PS, the presence of general and specific criteria is required. A mosaic, activating mutation of the *AKT1* gene causes PS, and is found in affected tissues from the majority of patients meeting diagnostic criteria for PS [Lindhurst et al., 2011].

While PS typically affects the skeleton, skin, and vascular systems, a hallmark of the disorder is dysregulation of fatty tissue and this usually presents as overgrowth of adipose tissue, sometimes termed lipomas, in the abdomen and pelvis that may lead to secondary gastrointestinal complications. This localized overgrowth of fatty tissue usually occurs in areas of normal fat deposition and is distinct from the encapsulated lipomas seen normally in older patients. Paradoxically, the adipose tissue dysregulation may also present as fatty hypoplasia in other parts of the body. There have been only two prior case reports [Mayatepek et al., 1989; Shaw et al., 1993] that described cardiac abnormalities in patients with PS, and one report described a cardiac mass in a patient with a non-Proteus overgrowth syndrome [Nishimura and Nishimura, 1997].

Patients with Proteus syndrome enrolled in the clinical research protocol at the National Institutes of Health (NIH) typically undergo an echocardiogram as part of a pre-operative evaluation or as part of the evaluation for associated pulmonary disease. Several of these patients were found to have prominent, focal, echodense areas of the myocardium. Based upon this distinctive cardiac finding, a prospective comprehensive cardiac evaluation of a series of patients with PS seen at the NIH was initiated. We present a summary of the cardiac findings in this cohort of patients with PS.

## MATERIALS AND METHODS

All patients were enrolled in a protocol approved by the Institutional Review Board of the National Human Genome Research Institute (94-HG-0132). All patients were initially evaluated by geneticists at the NIH, who confirmed the clinical diagnosis of PS according to the diagnostic criteria [Biesecker, 2006; Biesecker et al., 1999]. All patients had a detectable *AKT1* c.49G→A (p.Glu17Lys) mutation in their affected tissue(s).

Twenty patients, ages 24 months to 50 years, who were seen at the NIH Clinical Center in Bethesda, MD underwent clinically indicated electrocardiograms (ECGs) and transthoracic echocardiograms using commercially available systems. Standard echocardiographic views were obtained with patients in the left lateral recumbent position and images were stored digitally. Patients with abnormal echocardiograms were referred for cardiac magnetic resonance (CMR) imaging. Some of the patients also underwent Holter monitoring and exercise treadmill testing. One patient had an echocardiogram at another institution and was

found to have a septal mass. She was referred for CMR and those images were reviewed here.

Cardiac magnetic resonance studies were performed on either a 1.5T or 3T scanner (Siemens, Erlangen, Germany). Cine magnetic resonance imaging (MRI) was performed to assess cardiac anatomy and systolic function. Myocardial fat water separation images were acquired with modified Dixon methods [Dixon, 1984] optimized for the heart [Hernando et al., 2010; Kellman et al., 2009]. Typical image parameters used for our cardiac fat water separation acquisitions were recently reviewed [Kellman et al., 2010].

Statistical analysis was done using SPSS version 17 (Chicago Inc.). Continuous variables are presented as mean  $\pm$  standard deviation (SD). Unpaired Student's *t* tests were used to compare continuous data between patients with and without fat infiltration and from the subgroup patients with the most cardiac involvement and the cohort of cases without fatty infiltration.

## RESULTS

Between December, 2001 and January, 2014, 20 children and adults with PS ranging in age from 24 months to 50 years old underwent transthoracic echocardiograms. Seven patients (35%) had focal echodense areas within the myocardium suggesting fatty infiltration. No discrete masses were seen within any cardiac chambers. The cardiac characteristics of the patients with fatty infiltration on echocardiogram were compared to PS patients without these findings in Table I. Both groups had normal chamber sizes by standards recommended for chamber quantification [Lang et al., 2005], in addition to preserved left ventricular function. The presence of fat did not result in an overall increase in mass or abnormal diastolic function. One patient with no evidence of fatty infiltration on echo had a dilated right heart consistent with a known history of pulmonary emboli. He died of cardiopulmonary compromise secondary to a pulmonary embolus nine months after the echocardiogram, and although the autopsy showed no evidence of abnormal fat in the myocardium, there were numerous areas of lipomas in the mediastinum and periaortic region.

The cardiac testing results of the seven patients with fatty infiltration on echocardiogram are shown in Table II. The majority of patients had significant involvement of the interventricular septum with a bright echodense area noted on the echocardiograms (Fig 1). The CMR on these patients showed a diffuse patchy involvement of the mid-myocardial and subendocardial layers of the left ventricular (LV) wall in numerous scattered wall segments (Fig 1). The LV papillary muscles were often involved with fatty infiltration as were the right ventricular free wall and trabeculae. Since the fatty deposition on CMR was suggestive of that seen in arrhythmogenic right ventricular cardiomyopathy (ARVC), these patients underwent comprehensive cardiac evaluation. Some patients had exercise testing and Holter monitoring for risk stratification. The results of these studies did not show significant arrhythmias; one patient developed oxygen desaturation during exercise but was known to have significant pulmonary disease.

The clinical characteristics of the patients are shown in Table III. All patients met the published criteria for PS. The patients with abnormal cardiac findings had no significant differences in age, gender, or BSA compared with those with normal echocardiograms. An informal severity score was calculated by summing points for increasing severity of skeletal involvement and overgrowth of other organ systems. Up to 5 points were assigned for asymmetric, disproportionate overgrowth of the skeletal system. Up to 6 points were assigned for overgrowth in the CNS, eye, spleen, liver, tonsils/adenoids, and testes. One point each was assigned for the presence of lung cysts or lipomas. Vascular malformations were assigned one point if superficial and one point if deep, visceral. The severity scores ranged from 2 to a maximum of 15. There were no significant differences between the two groups in terms of severity of dermatologic findings, lipomatous overgrowth/lipoatrophy, vascular malformations, and skeletal overgrowth. Of note, the fasting glucose level was slightly lower in the group with myocardial fatty infiltration. Because these statistical analyses were not corrected for multiple hypothesis testing, this single finding is not significant and should be replicated in a larger cohort. Among the group with no fatty infiltration, eight patients underwent ECG; one of these patients met criteria for LV hypertrophy, which was not seen on the echocardiogram, and one had a junctional escape rhythm. One patient out of five with an ECG in the fatty infiltration group had poor R wave progression in the septal leads. Overall, electrocardiograms did not appear to be a sensitive marker of cardiac abnormalities in patients with fatty infiltration.

Since a progressive increase in extra-cardiac (intra-thoracic and abdominal) fatty lesions has been noted in some patients with PS, we looked for evidence of disease progression in the cardiac lesions. This cohort included five patients with follow-up echocardiograms and one with a follow-up CMR. In the group with normal echocardiograms, one patient with no fatty infiltration on his initial echo at age 31 years had repeat exams 9 and 11 years later, which showed no evidence of new fatty deposits. The second patient had a normal echocardiogram at age 11 years, and a repeat study 4 years later was also normal. In the group with evidence of fatty infiltration on echocardiogram, one patient with a focal echodense area in the mid-anterior septum at age 19 years had a repeat echocardiogram 10 years later and this showed a larger area of fatty infiltration in the septum extending into the right ventricle and moderator band and other smaller lesions in the LV apex and mid-inferolateral wall segments. The second patient with numerous areas of fatty infiltration including the mid-anterior septum, inferolateral wall and papillary muscle at age 50 years had no significant change in these lesions on repeat echocardiogram and CMR after four years. The third patient had evidence of fat infiltration in the interventricular septum at age 5 years, and repeat echo one year later showed no change.

## DISCUSSION

This study presents cardiac abnormalities in a cohort of patients with Proteus Syndrome. The characteristic pattern of cardiac findings includes extensive, patchy regions of intramyocardial fat in a mid-myocardial and subendocardial diffuse pattern involving the interventricular septum, the inferolateral wall, papillary muscles, right ventricular free wall, and trabeculae. However, based upon our cardiac evaluations, there were no functional

derangements due to this process, nor did it appear to be associated with significant arrhythmias.

Dysregulation of fatty tissue is a known feature of PS and it can present as lipomatous overgrowth or regional hypoplasia of fatty tissues. The fatty overgrowth has been noted to develop in areas of normal fat deposition and has generally been seen in the abdomen, pelvis, and subcutaneous tissue in patients with PS. Lipomatous infiltration in the heart has rarely been reported. Only two prior case reports have included cardiac involvement and one report of a patient with an overgrowth syndrome not meeting Proteus criteria describes a cardiac mass. Shaw et al. [1993] described a 20 year old man with a thickened echogenic septum, RBBB on ECG, and a mass in the apex of his right ventricle. The pattern of cardiac overgrowth described in this patient appears to be very similar to that seen in the patients in our series. Mayatepek et al. [1989] reported on a boy with PS who developed heart failure at 5 months and cardiac catheterization showed a dilated left ventricle, abnormal aortic valve, coarctation of the descending aorta, and a patent ductus arteriosus. Autopsy at 16 months also showed dilation of both atria and marked dilation and thickening of the aorta and arch vessels. On histology of the aorta and right common carotid artery, he was found to have cystic degeneration of the media. This report described only congenital cardiac anomalies and their associated complications with no suggestion of fatty infiltration in the myocardium. One patient in our series was a 5-year-old boy with a history of a septal defect that subsequently closed. On our evaluation, no shunts were detected, although he did have evidence of bright echodense areas in his septum and at the point of RV insertion into the left ventricle. The third report described a hamartomatous syndrome in a girl found on echocardiogram to have an hyperechoic mass arising anteriorly from the right ventricular free wall [Nishimura and Nishimura 1997]. The diagnosis of Proteus syndrome was suggested among others; however, this patient did not appear to meet strict clinical diagnostic criteria for PS, and she had an atypical finding for PS of isolated multi-sutural cranial hyperostosis. Her cardiac mass appeared unchanged upon repeat imaging at age 6 years, and on CMR it had characteristics of a lipomatous lesion. Although this patient did not have PS, the lipomatous mass in the right ventricle is similar to the abnormalities seen in the patients reported here.

The detection of fatty overgrowth in the heart is a challenge for non-invasive imaging techniques because it must be differentiated from normal fat deposition. Myocardial fat can be seen in normal hearts and is identified by its characteristic location and appearance. Epicardial fat can be measured with transthoracic echocardiography and has been associated with insulin resistance, metabolic syndrome, and coronary artery disease [Iacobellis and Willens, 2009]. Lipomatous hypertrophy of the interatrial septum (LHIS) is a common finding on echocardiograms and is usually described as a thickening of the septum in a typical dumbbell shape with sparing of the fossa ovalis. LHIS has been associated with increasing age, obesity, and atrial arrhythmias [Heyer et al., 2003; Roberts, 1997]. Although it is regarded as an incidental finding, only a few patients with obstructive physiology or intractable arrhythmias requiring surgery have been reported [Christiansen et al., 2000; Zeebregts et al., 1997]. Histologically, LHIS is made up of mature fat cells interspersed with hypertrophic cardiomyocytes [Cale et al., 2009; Sheikh et al., 2012]. Physiologic myocardial fat has also been seen during CT scans of asymptomatic subjects, most commonly along the

right ventricular outflow tract and free wall, and on histology, it is typically seen in perivascular areas [Kimura and others 2010].

Pathologic conditions with myocardial fat involvement include ARVC, healed myocardial infarctions, cardiomyopathies, and cardiac lipomas. In ARVC, fibrofatty infiltration of the RV is a hallmark of the disease process and imaging generally shows regional right ventricular akinesia or dyskinesia with possible involvement of the left ventricle [Marcus et al., 2010]. Histology studies of excised hearts in patients undergoing transplant have shown that lipomatous metaplasia is extensive in ischemic heart disease and is commonly seen in areas of myocardial scar [Baroldi et al., 1997; Su et al., 2004]. Cardiac magnetic resonance studies demonstrate fibrofatty infiltration in areas of chronic infarcts and these are generally subendocardial and follow a coronary distribution [Kellman et al., 2010]. Fat deposition is seen often in dilated cardiomyopathy by CMR and is associated with fibrosis and left ventricular dysfunction [Lu et al., 2013]. Solitary infiltration of fat can be seen in the left ventricle in patients with arrhythmias [Coelho-Filho et al., 2009; Sen-Chowdhry et al., 2008]. Cardiac lipomas consist of an encapsulated mass of mature adipocytes within the pericardium or any cardiac chamber, but they are generally considered benign neoplasms.

Segmental overgrowth disorders have been shown to be caused by mosaic activating mutations of the phosphatidylinositol 3-kinase (*PI3K*)-*AKT* signaling pathway [Kucrek et al., 2012; Lee et al., 2012; Lindhurst et al., 2012; Lindhurst et al., 2011; Poduri et al., 2012; Rios et al., 2013; Riviere et al., 2012; Shirley et al., 2013]. This pathway plays a critical role in cellular growth and metabolism and activating mutations in this pathway are commonly found in solid tumors [Yuan et al., 2008]. The *AKT* family of oncogenes includes three isoforms that have diverse effects on cells. *AKT1* is important in cardiac development, *AKT2* plays a role in diabetes and is found more often in tumors, and *AKT3* is associated with neurologic conditions [Cohen 2013a]. *AKT2* is found in muscle tissue and adipocytes and is felt to play a critical role in glucose metabolism and the development or maintenance of adipose tissue [Garofalo et al., 2003]. A heterozygous mutation in *AKT1* has been found in tissues from patients with PS and constitutive activation of the encoded protein is felt to be responsible for the overgrowth and tumor susceptibility in these patients [Lindhurst et al., 2011]. The mechanism for myocardial fatty tissue deposition in individuals with somatic *AKT1* mutations in Proteus syndrome is not known at this time. In reviewing the literature regarding those mouse models of cardiac-specific Akt overexpression, resulting in increases cardiomyocyte cell size and concentric left ventricular hypertrophy, the particular transgenic mice were generated using E40K mutants of Akt [Condorelli et al., 2002; Kim et al., 2003]. This particular Akt mutation, E40K is different from the mutation causing Proteus syndrome, which is E17K. Therefore, it is possible that the different mutation in Akt may account for absence of the cardiac findings in humans that are described in the mouse models in the literature. It is possible that *AKT1* E17K is not expressed in the cardiac myocytes at a level to cause cardiac muscle hypertrophy or that it is more predominantly expressed in the interventricular wall (since these patients have primarily interventricular fatty infiltration).

The clinical cardiac findings described in these patients with Proteus syndrome, identified by echocardiogram and cardiac MRI scan, include primarily enlarged interventricular wall

characterized by imaging as fatty infiltrate. However, the histopathology of these abnormalities has not been done yet. Since we do not know the actual type of adipose tissue involved in this fatty infiltrate, one hypothesis is that it may be composed of brown adipose tissue rather than white, which is derived from a common precursor cell to muscle and is more metabolically active than white cells. There is evidence that there is a common precursor cell of muscle and brown fat, that when activated by BMP7 can induce PRDM16, a transcription factor that will direct the cells in to the pathway to develop into brown fat cells [Seale et al., 2008; Cannon and Needergaard, 2008]. The presence of brown adipose cells in place of muscle (rather than white) may explain why there is no obvious functional effect on the heart in these patients with Proteus syndrome. Further study of the cardiac findings in specific Akt E17K mouse models will help address some of these hypotheses.

Those disorders caused by mutations in genes in the AKT/PI3K signaling pathway that may have cardiac findings including intramyocardial fat include: Tuberous sclerosis complex, and CLOVES syndrome. Tuberous Sclerosis (TSC), caused by mutations in *TSC1* and *TSC2*, which are in the AKT/PI3K gene pathway, involves abnormalities of the skin, brain, kidney and lungs. However, rhabdomyomas are the most common cardiac finding (present in 47-67% of individuals with TSC [Dabora et al., 2001; Jones et al., 1999; Sancak et al., 2005] and focal areas of intramyocardial fat involving the septum and lateral wall have also been seen [Adriaensen et al., 2009; Friesen et al., 2013]. These tumors have been documented to regress with time and eventually disappear. The cardiac rhabdomyomas are often largest during the neonatal period. CLOVES (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal Nevus, Skeletal/ Spinal) syndrome has overlapping clinical findings with Proteus syndrome and is caused by somatic mutations in *PIK3CA* gene, which is in the same signaling pathway as *AKT1* gene causing PS. Cardiac involvement has not been studied in this group of patients.

Further, in the differential diagnosis of individuals presenting with a combination of cardiac findings (cardiomyopathy and cardiac tumors) and overgrowth (generalized and/or segmental), there are syndromes including the RASopathies [Tidyman & Rauen, 2009], namely Cardio-Facio-Cutaneous (CFC) syndrome [Rauen 2008], Noonan syndrome [Noonan, 2005], Costello syndrome [Gripp and Lin, 2006] and Neurofibromatosis, type 1 (NF1) [Friedman, 1998], Beckwith-Wiedemann syndrome (BWS) [Shuman et al., 2010], Simpson-Golabi-Behmel (SGB) syndrome [Lin et al., 1999] and Sotos syndrome [Martinez et al., 2011]. Their cardiac findings are distinguished from those in these patients with Proteus syndrome. The RASopathies, caused by gene mutations in the RAS-RAF-MEK-ERK signaling pathway may have overlapping findings with Proteus syndrome including: cardiac, skin and musculoskeletal abnormalities, benign tumors and increased cancer risk. The cardiac abnormalities in Costello syndrome, CFC syndrome, and Noonan syndrome are similar [Gripp et al., 2006; Lin et al., 2011] with at least one of the three main types of cardiac abnormality (pulmonic stenosis, hypertrophic cardiomyopathy, and/or atrial tachycardia) occurring in 75% to 95% of individuals. Hypertrophic cardiomyopathy occurs in 20-40% of individuals may be present at birth or appear in infancy or childhood, and may be progressive. Non-reentrant tachycardia (chaotic atrial rhythm/multifocal tachycardia) is most distinctive for (though not unique to) Costello syndrome. As in Proteus syndrome, in

Noonan syndrome, varied coagulation defects and lymphatic dysplasia are frequently observed. Neurofibromatosis I is characterized by development of multiple subcutaneous benign fibromas, but can have hemihyperplasia or segmental overgrowth. Beckwith-Wiedemann syndrome is a disorder of growth, where individuals may have cardiac findings of neonatal hypertrophic cardiomyopathy and hemihyperplasia among other characteristic features. Intraventricular myocardial fat infiltration has not been reported in these overgrowth syndromes.

## CONCLUSION

We have identified myocardial fat deposition as a common manifestation in Proteus syndrome. To date, we have not identified an association of this finding with arrhythmias, conduction defects, or hemodynamic abnormalities but this requires further study and longitudinal investigation. The marked heterogeneity in the presentation and organ involvement in PS suggests that cardiac involvement may not be predicted by involvement and progression in other organ systems. Our data on follow-up of these lesions suggests that the myocardial fatty deposition is an indolent process. The relatively specific location of this abnormal fat deposition in the myocardium suggests that it may have a different origin than intra-abdominal and intra-thoracic fat deposits. The possibility of a common precursor for the muscle and fat cells has important implications for future studies.

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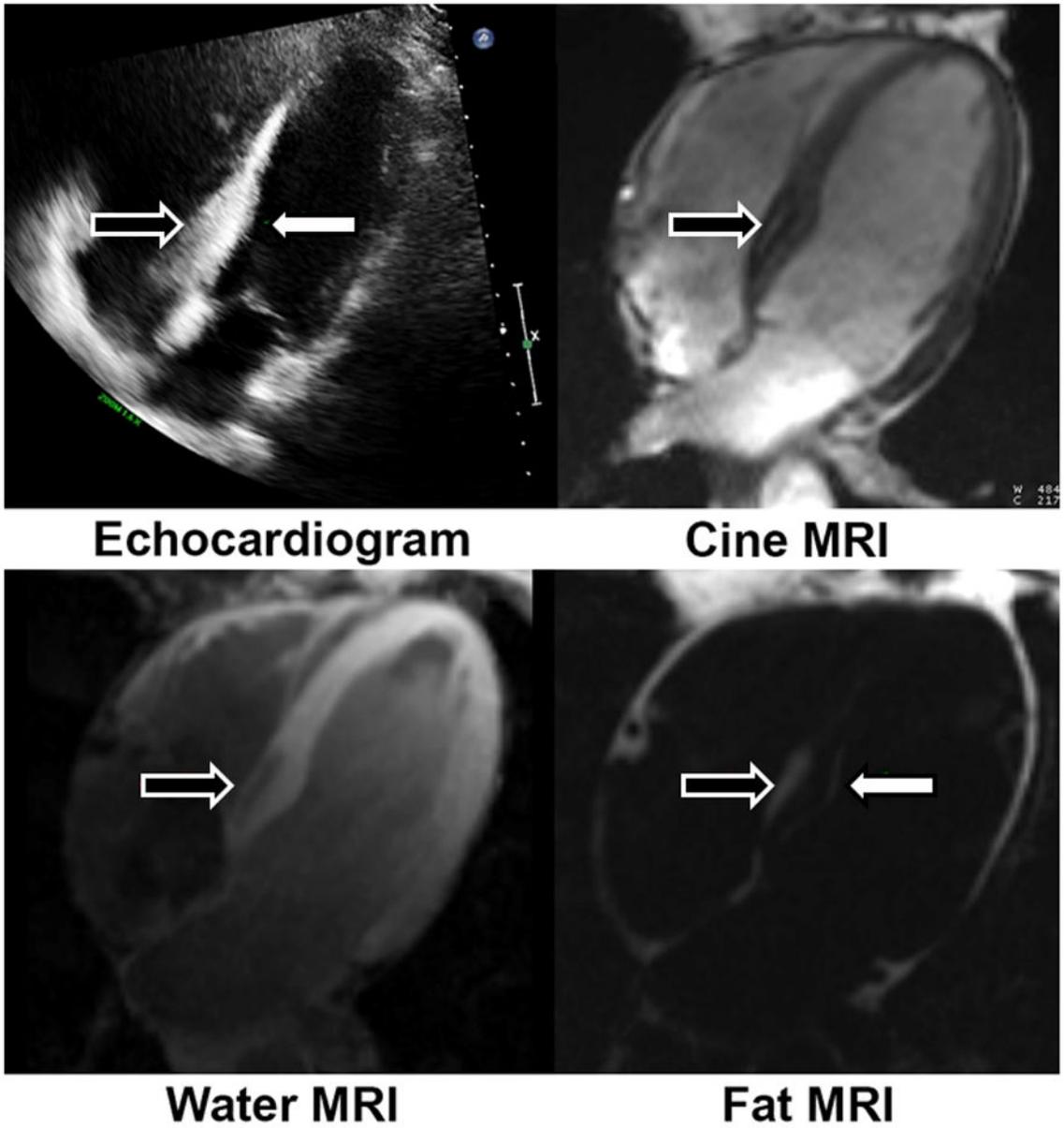


Figure 1.

**Table I**

Echo Characteristics of Patients with PS with and Without Cardiac Fat Infiltration

Parameter	No fat(n=13)	Fatty infiltration(n=6)	p value
Septal thickness (mm)	7.7 ± 1.9	7.7 ± 2.5	0.983
Posterior wall thickness (mm)	7.5 ± 1.8	6.0±2.1	0.653
Left ventricular end diastolic diameter (mm)	40.9 ± 5.5	37.8 ± 5.3	0.272
Left ventricular end systolic diameter (mm)	27.2 ± 3.9	24.0 ± 3.7	0.111
Left ventricular mass index (g/m <sup>2</sup> )	56.8 ± 9.2	57.0 ± 6.4	0.807
Left atrial volume index (ml/m <sup>2</sup> )	19.4 ± 6.7	22.5 ± 3.8	0.307
Left ventricular ejection fraction (%) <sup>*</sup>	63.2 ± 4.1	67.8 ± 5.3	0.99
E/A ratio <sup>†</sup>	2.0 ± 1.0	2.3 ± 1.2	0.637
Lateral E/e' ratio <sup>α</sup>	6.2 ± 2.7	7.0 ± 1.2	0.519

Data are expressed as mean ± SD

<sup>\*</sup> Normal ejection fraction is reported as 55%<sup>†</sup> Early to late mitral filling velocity ratio<sup>α</sup> Early mitral to lateral wall tissue Doppler mitral diastolic velocity ratio

Table II

## Results of Cardiac Testing in Patients With PS with Fat Infiltration

Patient #	Age	ECG Findings	Echo Findings	CMR Findings	Cardiac Testing
4	29	sinus bradycardia with sinus arrhythmia	bright focal echodense area mid anterior septum, smaller lesion LV apex	Extensive patchy regions of intramyocardial fat in the LV myocardium, papillary muscle and RV	Holter-NSR with rare ventricular ectopics; ETT-no ischemia or arrhythmia
7	50	poor R wave prog in V1-V2	bright focal echodensities in mid-anterior septum and inferolateral wall	Mild interventricular septal hypertrophy, extensive mid-myocardial and subendocardial fatty involvement of the LV and regions of the RA and RV free wall.	Holter-unremarkable; ETT-no ischemia or arrhythmia
11	5	sinus arrhythmia	bright septum; RV insertion bright	Extensive patchy regions of intramyocardial fat in the LV and RV	Holter-unremarkable
12	2	-----	bright septum; RV insertion bright		
15	7	sinus arrhythmia	possible basal and mid lateral bright	Few small focuses suspicious for fat in basal-mid RV free wall	
16	28	sinus bradycardia	bright echodensity in septum	Extensive patchy regions of intramyocardial fat in the LV and RV	Holter-unremarkable; submaximal ETT-O2 desaturation, no ischemia or arrhythmia
19	7	-----	intraseptal mass	Diffuse lipomatous infiltration of entire length of septum, normal septal thickening, EF53%, dilated left atrium	

**Table III**

Clinical Characteristics of Patients with PS with and Without Cardiac Fat Infiltration

Parameter	No fat (n=13)	Fatty infiltration(n=7)	p value
Age at time of first echo (yr)	18 ± 8	17 ± 17	0.91
Gender-female (%)	30.8	28.6	0.66
Body surface area (n)	1.6 ± 0.42 (11)	1.5 ± 0.67 (5)	0.94
Fasting glucose (n)	90.4 ± 9.3 (12)	80.0 ± 8.5 (6)	0.03
Severity Score *	7.2 ± 3.9	8.1 ± 2.9	0.56

\* see text for details