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Echocardiographic Findings in Classical and Hypermobile Ehlers–Danlos Syndromes

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Structural cardiovascular alterations in the classical and hypermobile forms of Ehlers–Danlos syndrome(EDS) warrant investigation. We have examined a cohort of 38 patients with hypermobile and classical EDSs using two-dimensional echocardiography. The cohort includes 7 males and 31 females, with an age range from 12–60 years. Altered echocardiographic parameters were seen in the initial cross-sectional data analysis in 24/38 patients. Five of the 38 participants had mildly dilated aortic root (AR) or sinuses of Valsalva (SV), and an additional 7 patients had an abnormal pouching of the SV, although the absolute dimensions did not exceed the normal range. Ten patients had mild mitral, tricuspid, or aortic regurgitation, and only one patient had mitral valve prolapse (MVP). Three patients had low normal systolic function; three had evidence of mildly elevated pulmonary pressures, and two patients had mild concentric left ventricular hypertrophy (LVH). Five patients had evidence of impaired left ventricular relaxation (LVR) based on mitral valve E to A velocity ratio. Interestingly, 26/38 subjects demonstrated a prominent right coronary artery (RCA) easily visualized by trans-thoracic echocardiography, and 10/38 had an elongated cardiac silhouette on the 4-chamber apical views. The "pouching" shape of the SV was more common in hypermobile type than in the classical type of EDS. The study is ongoing and will accrue longitudinal data on 100 subjects with classical and hypermobile EDSs at 2-year intervals. Published 2005 Wiley-Liss, Inc.[†]

Key words: Ehlers–Danlos syndromes; aorta; echocardiography; impaired left ventricular relaxation

INTRODUCTION

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of heritable connective tissue disorders characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. Around 1 in 5,000 individuals are affected [Pyeritz, 2000]. Although more than 10 types of EDSs have been described, a revised nosology [1998] delineates 6 major subtypes, with 90% of the affected individuals falling under the description of hypermobility, classical, or vascular types [Beighton et al., 1998]. Catastrophic arterial rupture is a known complication of the vascular type of EDS [Pepin et al., 2000]. Mild dilatation of the aortic root (AR) as well as mitral valve prolapse (MVP) has been previously described in classical and hypermobile EDS [Tiller et al., 1998; Wenstrup et al., 2002]. In this study, we present echocardiographic data on a cohort of 38 patients with classical and hypermobile EDS.

MATERIALS AND METHODS

Clinical Evaluation

All patients were seen between 2004 and 2005 at the National Institute on Aging, Advanced Studies in Translational Research (NIA-ASTRA) unit under protocol 2003-086 entitled "Clinical and Molecular Manifestations of Heritable Disorders of Connective Tissue." The study was approved by the MedStar

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institutional review board and informed consent was obtained for each subject. The majority of the subjects were diagnosed with EDS by a clinical geneticist prior to participating in the study. In a small number of subjects, the diagnosis was previously suggested by the primary care doctor or a specialist such as an orthopedic surgeon or a rheumatologist. All subjects were evaluated at the NIA-ASTRA unit by a clinical genetics team (NBM, SHS, CAF).

The subjects were classified into classical or hypermobile types according to the Villefranche nosology [Beighton et al., 1998]. The diagnosis of classical type of EDS was made on the basis of joint laxity (Beighton score > 5/9), fragility of the skin with evidence of easy bruising, and the presence of thin atrophic scars. The diagnosis of hypermobile EDS was made on the basis of a history or presence of dislocations, generalized joint laxity, and velvety texture of skin with an absence of abnormal scars. However, some patients had features overlapping with both types of EDS, and classification proved to be difficult in those cases. Since the genetic basis of 50% of classical EDS and the majority of hypermobile EDS is still not known, the diagnoses presented in this study were made on the basis of clinical findings [Beighton et al., 1998]. The inheritance pattern observed in the subjects was consistent with either a new dominant mutation or an autosomal dominant inheritance within the family.

Echocardiography

Trans-thoracic echocardiograms were performed by an experienced sonographer (BLG) according to the recommendations of American Society for Echocardiography [ASE Guidelines, 2005] using a Philips Sonos 5500 machine with an Xcelera reviewing station. All patients had measurements obtained of the left ventricular outflow track (LVOT), AR, and sinus of Valsalva (SV) performed at end-systole. Ascending aorta was also measured in some patients when technically feasible. The echocardiograms were interpreted by cardiologists (SAM, SSN).

RESULTS

Demographics

The demographic and diagnostic distribution for the 38 subjects included in the study is shown in Table I. There was a significant overrepresentation of female patients in both classical and hypermobile types, consistent with the prior observation that despite theoretically affecting both sexes equally, there is preponderance of females who are more severely affected with EDS and therefore, come to medical attention (Levy, 2004). Ten of our subjects were under the age of 18, and the average age of the cohort was 36. Nineteen subjects had hypermobile EDS, and 16 had classical EDS. Three of the patients, all children from the same family, were not clearly classified due to the possibility of compound heterozygosity.

TABLE I. Demographic and Diagnostic Classification of Study Subjects

Diagnosis	Classical EDS	Hypermobile EDS	Possible compound heterozygote	Total
Age 12–39	5	8	3	16
Age 40–60	11	11	0	22
Female	15	14	2	31
Male	1	5	1	7

In this family of five affected members included in our study, the parents were both affected with different forms of EDS. The father was found to be affected with hypermobile EDS, while the mother fit best under the description of classical type. These individuals were non-consanguineous and there was a history of a dominant inheritance pattern in their respective families. The couple had a reproductive history of five live births and three spontaneous early abortions. Since there is no molecular confirmation available, a reasonable possibility exists that some of their children are compound heterozygotes. All these children had impressive joint hypermobility, however, only one, a 15-year-old boy, had a significant finding in his echocardiogram, with mild to moderate aortic regurgitation with eccentric jet directed against the anterior mitral leaflet, thickened aortic valve (AV), and dilated proximal aorta to 3.1 cm in end-systole (Fig. 1). His father had a dilated SV of 3.9 cm.

The height, weight, body surface area, and echocardiographic findings in the study subjects are shown in Table II. The height and the weight of the study subjects were within population norms for age.

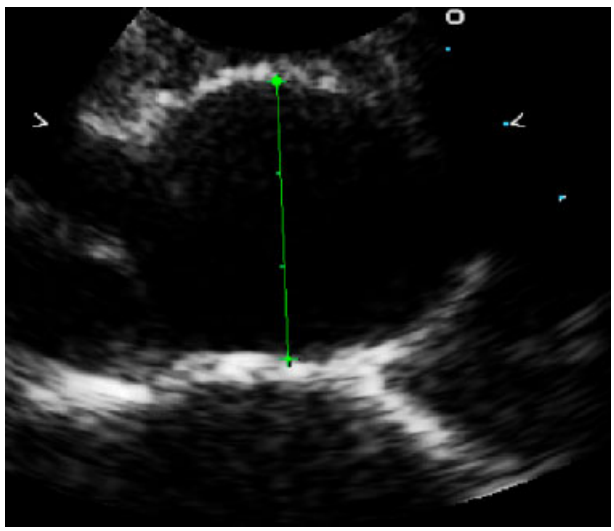

FIG. 1. Dilated proximal aorta with a measured diameter of 3.1 cm in a 15-year-old boy with EDS, as seen in a left parasternal long axis view.

TABLE II. Summary of Characteristics and Echocardiographic Parameters in the Study Cohort

Age	Sex	Type of EDS	Height (cm)	Weight (kg)	BSA (m^2)	Findings	LVOT (cm)	Sinus of Valsalva (cm)	Aortic root(cm)	Ascending aorta(cm)	RCA	Cardiac shape
49	F	Hypermobile	160	55	1.6	Mild AR, AV sclerosis, trace TR, SV pouch	1.9	2.9	2.7	2.5	Visible	Normal
15	F	Hypermobile	160	47	1.5	Low normal EF, SV pouch	1.6	2.7	2.4	2.4	Visible	Normal
12	F	Hypermobile	142	31	1.1	SV pouch	1.7	2.2	1.6		Visible	Normal
46	F	Hypermobile	161	50	1.5	Impaired LVR	2.0	2.5	2.4		Visible	Normal
29	M	Hypermobile	165	75	1.8	None	3.0	3.0	3.5		Visible	Normal
42	F	Hypermobile	175	74	1.9	Mild septal hypokinesis, SV pouch	2.2	3.2	2.2	2.8	Visible	Normal
46	M	Hypermobile	188	95	2.2	Mildly dilated AR and SV	2.9	4.1	3.6		Visible	Normal
46	F	Classical	163	70	1.8	Trace MR and TR	2.2	3.0	3.1	2.9	Visible	Normal
42	F	Hypermobile	169	74	1.9	Trace MR, SV pouching	1.9	2.8	2.8	2.8	Not visible	Normal
51	F	Classical	156	84	1.8	Impaired LVR	1.5	3.1	2.9		Not visible	Normal
53	F	Classical	167	81	1.9	MVP (posterior leaflet) moderate MR, mild AR, thickening of the aortic cusp	2.4	3.0	2.6	2.8	Visible	Elongated
17	M	Classical	185	86	2.1	Trace MR	2.2	3.1	3.1	2.7	Visible	Elongated
44	F	Classical	164	61	1.7	Mod TR, RVSP 30mm, trace MR, AR, PR	2.1	2.6	2.6		Visible	Normal
18	F	? Compound heterozy-gote	168	69	1.8	Trace MR and TR	2.0	2.9	2.5		Visible	Elongated
46	M	Hypermobile	182	100	2.2	Mildly dilated SV, trace TR, MR	2.2	3.9	3.4		Not visible	Normal
13	F	Classical	155	52	1.5	None	2.0	2.3	2.5	2.1	Visible	Normal
12	F	?Compound heterozy-gote	147	31	1.1	None	1.7	2.3	2.2		Visible	Normal
15	M	?Compound heterozy-gote	169	56	1.6	Mod AR with eccentric jet, thickened AV, dilated proximal aorta	2.1	2.6	2.2	3.1	Visible	Normal
24	F	Classical	160	60	1.6	None	2.0	2.2	2.2		Visible	Elongated
60	F	Classical	166	130	2.3	Impaired LVR	2.1	3.0	2.8		Not visible	Normal
30	F	Hypermobile	174	81	2.0	None	2.1	2.8	2.5		Not visible	Elongated
54	F	Hypermobile	161	64	1.7	Mild MR and TR, trace AR	1.9	2.5	2.4		Visible	Normal
40	F	Classical	160	50	1.5	Mild AR with central jet, trace MR	2.0	2.6	2.3	2.7	Visible	Normal
51	F	Hypermobile	163	49	1.5	Trace MR and TR	2.0	3.0	2.7		Visible	Normal
33	F	Hypermobile	164	57	1.6	Trace MR and TR, SV pouch	1.9	3.0	2.7		Visible	Normal
56	F	Classical	159	78	1.8	Mild MR,TR,RVSP 40–45 mm Hg	2.0	2.7	2.3	2.8	Not visible	Normal
17	F	Hypermobile	180	54	1.7	Mild TR, RSVP 35–40 mm Hg	2.2	2.6	2.7		Visible	Normal
50	F	Classical	170	128	2.3	Trace MR, trivial pericardial effusion	1.9	2.4	2.5	2.2	Visible	Normal
15	F	Classical	158	61	1.6	trace TR	1.9	2.5	2.2	1.9	Visible	Normal
47	M	Hypermobile	181	80	2	Mild concentric LVH, impaired LVR, SV pouch	2.0	3.1	2.6		Not visible	Elongated
51	F	Hypermobile	159	91	1.9	Trace MR	2.0	2.7	2.2	2.7	Not visible	Normal
54	F	Hypermobile	161	59	1.6	Mild AR, Mild TV, MV, and AV sclerosis, impaired LVR, mildly dilated SV and ascending aorta	2.0	3.6	3.6	3.6	Not visible	Normal

(*Continued*)

TABLE II. (*Continued*)

Age	Sex	Type of EDS	Height (cm)	Weight (kg)	BSA (m^2)	Findings	LVOT (cm)	Sinus of Valsalva (cm)	Aortic root(cm)	Ascending aorta(cm)	RCA	Cardiac shape
46	F	Classical	164	70	1.8	Mild concentric LVH, EF 40%, mild MV and AV sclerosis, mild MR, mildly dilated AR, SV.	2.1	3.9	3.7		Not visible	Normal
36	M	Hypermobile	182	82	2	Trace MR and TR, mildly dilated SV	2.5	3.4	2.8		Not visible	Normal
49	F	Classical	166	84	1.9	Mildly dilated Right Ventricle	2.1	2.7	2.4		Visible	Elongated
16	F	Classical	158	63	1.7	Trace TR	2.0	2.3	2.1	2.2	Visible	Elongated
41	F	Classical	168	53	1.6	Low normal EF, mildly thickened MV	1.8	2.9	2.4	2.4	Visible	Elongated
16	F	Hypermobile	170	72	1.9	None	2.2	2.7	2.4	2.6	Not visible	Elongated

BSA, body surface area; LVOT, left ventricular outflow tract; RCA, center coronary artery; AR, aortic regurgitation; AV, aortic valve; TR, tricuspid regurgitation; SV, sinus of valsalva; EF, ejection fraction; LVR, left ventricular relaxation; MV, mitral valve; TV, tricuspid valve; MVP, mitral valve prolapse; MR, mitral regurgitation; RSVP, center ventricular systolic pressure; LVH, left ventricular hypertrophy.

Aortic Dilatation

A significant dilatation (>95% centile of population norms) of the SV, AR, or proximal aorta was noted in 5/38 (13%) of subjects (Table II). Two of these patients were from the family already described, and of the remaining three, two had hypermobile EDS. An unusual pear-shaped "pouching" shape, especially the sinuses, as shown in Figure 2, was seen in additional seven (18%) subjects; all seven of these patients were diagnosed with hypermobile EDS. The overall two-dimensional measurement of the sinus did not reach an abnormal size in these seven patients.

Valvular Abnormalities

Despite reports of a frequent finding of MVP and mitral regurgitation in the EDS population [Leier et al., 1980; Jaffe et al., 1981; Handler et al., 1985], there was only one subject in our study population, diagnosed as classical EDS, who met current criteria for MVP (Table II). This patient also had mild aortic regurgitation in addition to moderate mitral regurgitation. Including this patient, a total of four subjects had significant (classified as at least mild) mitral regurgitation. Three subjects, one with hypermobile and two with classical EDS had mild or above tricuspid regurgitation (TR). The right ventricular systolic pressure (RVSP) was mildly elevated to a range above 30 mm Hg as calculated by TR Doppler velocity [McQuillan et al., 2001] in two of these patients, implying the presence of mild pulmonary hypertension. Mild aortic regurgitation was present

FIG. 2. The left parasternal long axis view demonstrates pear-shaped "pouching" of the sinus of Valsalva in a 41-year-old woman with hypermobile EDS.

in a total of four patients. Two of these patients had hypermobile EDS, one had classical EDS, and the fourth one was the 15-year-old adolescent boy with possibility of compound heterozygosity. Trace regurgitation across different valves was present in a high number of patients as can be seen in Table II, and is not considered to be a notable finding unless accompanied by other echocardiographic abnormalities. There was no predilection for the presence of "leaky" valves in classical versus hypermobile type of EDS.

Impaired Left Ventricular Relaxation (LVR)

Five patients, one man and a woman with hypermobile EDS, and three women with classical EDS, had evidence of impaired LVR based on mitral valve E to A velocity ratio (Fig. 3) [Palmieri et al., 1999b]. All of these patients were over 45 years of age, representing 5/17 (30%) of patients in the above 45 age group in our cohort. One of these patients, a 46-year-old man, also had mild concentric LV hypertrophy. A 46-year-old woman with classical EDS also had mild concentric LVH, as well as mildly reduced ejection fraction and mild dilatation of the AR. This person was reported as having impaired LV relaxation in an echocardiogram performed at another facility several weeks earlier, however, this finding was not seen in our study.

Low normal measurements of left ventricular systolic function were seen in two asymptomatic subjects; a 41-year-old woman with classical EDS who also had a Chiari I malformation and recurrent pneumothorax, and a 15-year-old girl with hypermobile EDS with "pouching" of the sinuses. One patient, a 42-year-old woman with hypermobile EDS and a history of myocardial infarction related to coronary vasospasm, had evidence of mild septal hypokinesis.

Elongated Cardiac Silhouette and Prominent Right Coronary Artery (RCA)

One of the unexpected findings in our study was the observation of an elongated shape to the heart observed in apical four-chamber views in 10/38 subjects. Seven of the 10 had a diagnosis of classical EDS. None of these patients were unusually tall. Although we did not find objective criteria to assess a "normal" length for the heart, the unusual elongation disproportionate to the size of the thorax of these patients was apparent to the experienced eye (Fig. 4). An additional interesting observation was an easily visualized RCA in 26/38 subjects during routine trans-thoracic echocardiography (Fig. 5). The vessels did not appear to be significantly dilated. Although the two-dimensional measurement of the vessels of small caliber is not expected to be accurate, many appeared to be in the range of 0.2–0.5 cm in two-dimensional measurements when a measurement was possible. This observation was made in both types of EDS and in all age groups and both sexes. The elongated shape of the heart and the prominence of the RCA are not known to have pathological significance.

DISCUSSION

Echocardiographic evaluation of subjects with classical and hypermobile EDS confirmed previous

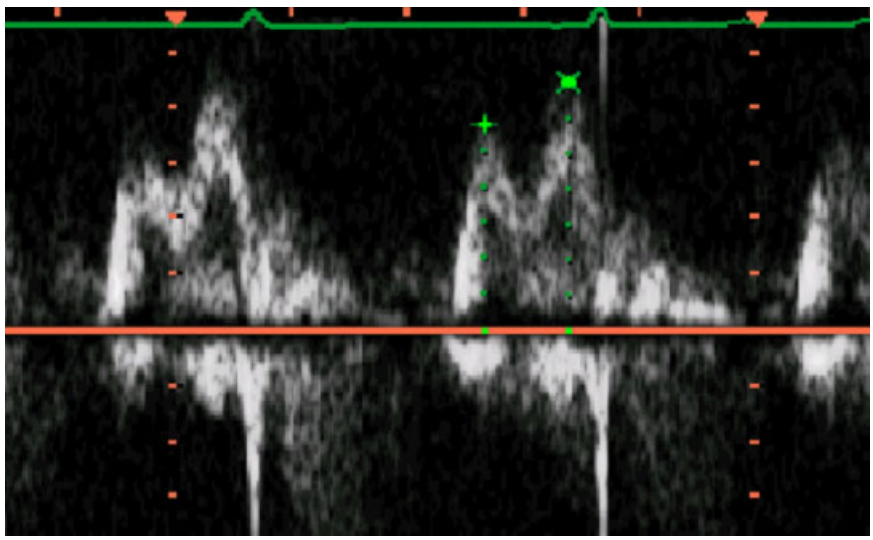

FIG. 3. Evidence of impaired left ventricular relaxation as measured by the mitral valve E to A ratio in a 47-year-old woman with hypermobile EDS.

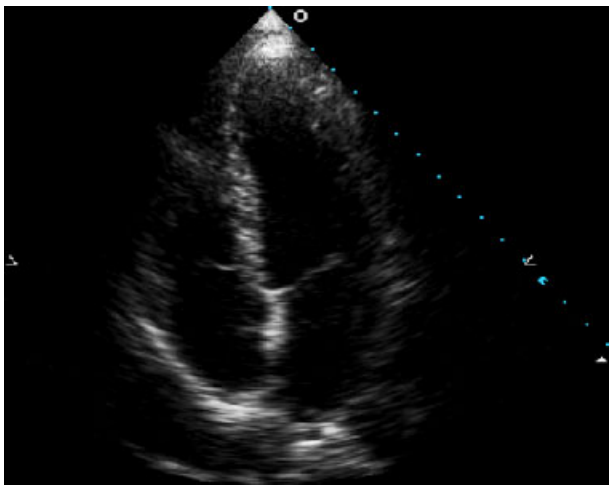

FIG. 4. Elongated cardiac silhouette in a 41-year-old woman with classical EDS as seen in a four chambered apical view.

observations that mild dilation of the AR is fairly common in EDS. An earlier study found an incidence of AR dilation in 33% of classical and 17% of hypermobile EDS patients [Wenstrup et al., 2002]. This study had a smaller number of patients in the older age group with a mean age of 20.6 as compared to the mean age of 36 in our group, and it was noted that younger age was associated with a higher incidence of dilatation. A possible explanation for this is the higher distensibility of the aorta in the younger patients, as well as the impact of small errors of measurement in aortic dimensions in patients with smaller body surface area. A new finding in our study was the observation of a "pouching" shape of the sinuses without frank dilation in hypermobile EDS.

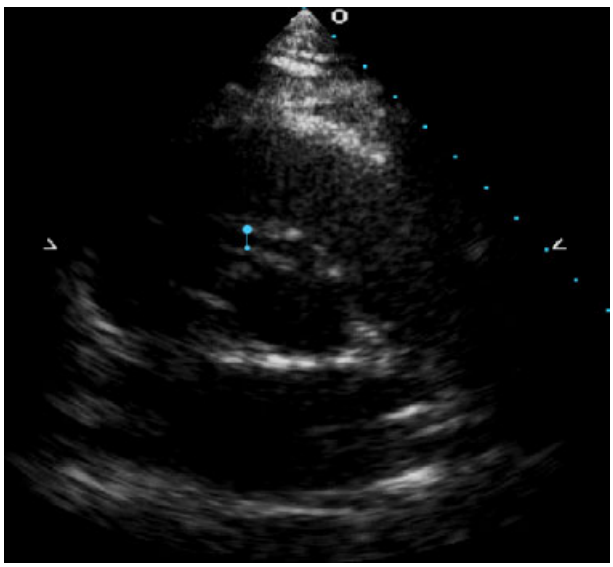

FIG. 5. Prominent right coronary artery (marked) in a 51-year-old woman with hypermobile EDS.

An association with MVP has been previously reported for EDS [Leier et al., 1980; Jaffe et al., 1981; Handler et al., 1985], with a more modest association reported since the revision of the criteria for MVP [Mishra et al., 1996; Dolan et al., 1997]. In our cohort, there was only one patient with classical EDS who met diagnostic criteria for MVP. Mild regurgitation of mitral, tricuspid, or aortic valves was seen in 21% of the subjects, as well as mild thickening or sclerosis involving these valves (16%) without a predilection for classical versus hypermobile EDS. An unexpected observation was the incidence of mildly elevated pulmonary artery pressure in three subjects. One 44-year-old woman with classical EDS had a RVSP of 30 mm Hg, where as a 17-year-old adolescent girl with hypermobile EDS and a 56-year-old woman with classical EDS who had a recent bout of pneumonia had RVSP measurements above 35 mm Hg. None of these patients had a complaint of dyspnea on their review of systems. Pulmonary hypertension, either primary or secondary, has not been previously reported in association with EDS, and the natural history of this finding warrants further investigation.

Another finding in our study was the incidence of impaired LVR in patients with both hypermobile and classical EDS in the age group of over 45 years. This finding is regarded as a harbinger of diastolic dysfunction, and the 30% incidence of this in our cohort is much higher than has been observed in healthy subjects, and even higher than would be expected in hypertensive subjects in this age category [Vasan et al., 1996; Palmieri et al., 1999a,b; Simone et al., 2005]. Patients with EDS often have autonomic dysfunction [Rowe et al., 1999], and may experience alternating high and low systolic pressures in the course of a day, making the diagnosis and treatment of hypertension difficult. Only one individual in this sub-group, which included males and females as well as classical and hypermobile EDS, had been diagnosed and was on treatment for hypertension. It is also possible that the etiology of impaired LV relaxation in the setting of EDS may be related to factors other than hypertension, such as the presence of concentric LV hypertrophy, or increased stiffness with age due to higher levels of remodeling activity. Also of concern was the observation of low normal ejection fraction in three relatively young (15–44) females with no apparent cause. The natural history of these findings will be followed in our study; however, the affected patients were advised to have follow-up evaluations on clinical grounds.

Two non-pathological, but interesting structural observations emerged from our study in reference to patients affected with EDS. The first one, the

visualization of the RCA on routine trans-thoracic echocardiography was initially noted by the sonographer performing the studies and brought to attention as an unusual phenomenon. There has been little reported on the measurement of the RCA in normal subjects since the observation of this vessel in adults by echocardiography is technically difficult and error prone unless special techniques are used, due to the relatively small size of the vessel [Douglas et al., 1988; Krzanowski et al., 2003]. A prominent RCA may be seen in children and young adults; however, it was readily seen in many of the older adults in our cohort, including many (13/22) in the over 40 age group. Although there is no evidence from our study to speak to a pathological nature of this finding, it is curious to note that the coronary arteries originate from the SV embryologically, where mild dilation and pouching is observed in our cohort. We would like to proceed with assessment of the size of the RCA in these patients using a three dimensional technique such as cardiac Magnetic Resonance Imaging (MRI). Plans are also underway to compare an age matched control cohort for the visibility of the RCA using the same equipment operated by the same sonographer. One of the patients in our cohort had a coronary angiogram during an evaluation for chest pain subsequent to her participation in our study; however, the coronary measurements from her angiogram were not useful as a correlation since a prominent RCA was not observed on her echocardiogram.

The second interesting but non-pathological observation was the disproportionately "elongated" heart seen in 26% of our cohort. There are no established criteria for an appropriate "length" for the heart in the apical four-chamber view. In our experience, it is not unusual to see this elongated cardiac silhouette in patients with Marfan syndrome who have tall stature or pectus deformity; however, this finding was unexpected in our cohort of EDS patients who did not have abnormalities of body habitus.

Our study reinforces the need for an initial echocardiographic study when a diagnosis of EDS is made, given that 13% of the patients in this small cohort had a significant dilatation of the SV or the AR. Repeat evaluations on a periodic basis even when no pathology is identified in the initial evaluation are justified especially in light of the findings of the increased pulmonary pressures and the impaired LV relaxation in a sub-group of patients.

The diagnosis of EDS remains elusive in many cases since identification of physical findings requires an experienced observer who is searching for a cluster of clinical signs such as cigarette paper scars, joint hyperextension, stretchy or soft skin, and piezogenic papules that do not lead to a complaint on the part of the patient, in the absence of overt signs such as dislocations, severe bruising or bleeding, and impaired post-surgical wound healing. The elucidation of other non-pathological but unusual findings, such as the prominent RCA or the elongated cardiac silhouette on routine transthoracic echocardiography, may ultimately help in the diagnosis and classification of EDS in such patients.

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