Cardiac Abnormalities in Patients With Hutchinson-Gilford Progeria Syndrome

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IMPORTANCE Hutchinson-Gilford progeria syndrome (HGPS) is an ultrarare disorder associated with premature death due to cardiovascular events during the second decade of life. However, because of its rarity (107 identified living patients), the natural history of cardiac disease remains uncharacterized. Therefore, meaningful cardiac end points for clinical trials have been difficult to establish.

OBJECTIVE To examine the course of appearance of cardiac abnormalities in patients with HGPS to identify meaningful cardiac end points for use in future clinical trials.

DESIGN, SETTING, AND PARTICIPANTS In this prospective, cross-sectional, observational study, 27 consecutive patients with clinically and genetically confirmed classic HGPS were evaluated at a single center for 1 visit from July 1, 2014, through February 29, 2016, before initiation of treatment.

EXPOSURE Classic HGPS.

MAIN OUTCOMES AND MEASURES Echocardiography was used to assess ventricular and valve function using standard techniques. Diastolic left ventricular (LV) function was assessed using tissue Doppler imaging. Previously published normative data were used to adjust findings to age and body size.

RESULTS This study included 27 patients (median age, 5.6 years; age range, 2-17 years; 15 [56%] male). Among echocardiographic indicators, LV diastolic dysfunction, defined as a tissue Doppler septal or lateral early velocity z score less than −2, was the most prevalent abnormality, seen in 16 patients (59%). Diastolic dysfunction was seen in all age groups, and its prevalence increased with age, mirroring findings seen during normal aging. Indicators of LV diastolic function were more abnormal in older patients. The z scores for lateral and septal early velocities were lower ($r = -0.77$, $P < .001$; and $r = -0.66$, $P < .001$, respectively), whereas those for the ratio of early mitral inflow velocity to early diastolic tissue Doppler myocardial velocity were higher ($r = 0.80$, $P < .001$; and $r = 0.72$, $P < .001$, respectively) in older patients. Other echocardiographic findings, including LV hypertrophy, LV systolic dysfunction, and valve disease, were less prevalent in the first decade and were seen more frequently in the second decade.

CONCLUSIONS AND RELEVANCE In this largest-to-date cohort of patients with HGPS, LV diastolic dysfunction was the most prevalent echocardiographic abnormality and its prevalence increased with aging. Echocardiographic indicators of LV diastolic function may be useful end points in future clinical trials in this patient population.

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Hutchinson-Gilford progeria syndrome (HGPS) is an ultrarare, sporadic, autosomal dominant, segmental, premature aging disease with a prevalence of 1 in 20 million.[1] The disorder occurs because of aberrant splicing of the *LMNA* gene (OMIM 150330) resulting in accumulation of a permanently farnesylated, uncleaved lamin A isoform called *progerin*.[2,3] Accumulation of progerin causes abnormalities in nuclear morphologic features and function as well as cellular stiffening.[4,5] Clinical manifestations include extreme short stature, low body weight, total alopecia, lipodystrophy, sclerodermoid skin, decreased joint mobility, skeletal dysplasia, and strokes.[6] Premature death usually occurs in the second decade of life after premature atherosclerosis leads to myocardial infarction.[6] Cardiovascular findings at autopsy include loss of vascular smooth muscle cells in large and small arteries with replacement by fibrous tissue,[7,8] thickening and calcification of the aortic and mitral valves,[9] and interstitial myocardial fibrosis and infarction.[9] However, because of the rarity of the condition (107 known living patients worldwide), limited information is available regarding the natural history of cardiovascular abnormalities.[10] Therefore, meaningful cardiac end points for clinical trials have been difficult to establish. Echocardiography is a widely available noninvasive technique that can accurately identify anatomical and functional cardiac abnormalities in children.[11,12] We performed a cross-sectional study of the largest-to-date cohort of children with HGPS to examine the prevalence and natural history of cardiac abnormalities to identify indicators that may serve as end points in future clinical trials.

Methods

Patients

Patients with clinically and genetically confirmed c.1824 C>T, p. Gly608Gly classic HGPS who enrolled in a clinical trial at Boston Children's Hospital were evaluated prospectively at a single visit from July 1, 2014, through February 29, 2016. All reported data were obtained at the baseline visit, before initiation of treatment with the protein farnesylation inhibitor lonafarnib. All patients had not previously received treatment at evaluation. Patients with nonclassic forms of progeria were excluded. Written informed consent was obtained from parents, and all data were deidentified. The study was approved by Boston Children's Hospital's Committee on Clinical Investigation.

Echocardiography

Transthoracic echocardiography was performed using commercial scanners (iE33, Philips Healthcare) and standard imaging techniques recommended by the American Society of Echocardiography.[13,14] Left ventricular (LV) volumes and mass were quantified using the area-length method as recommended by the American Society of Echocardiography.[13] Body surface area (BSA) was calculated using the Haycock formula,[15] and LV volume and mass were adjusted to the BSA by calculating z scores using previously published normative data from the echocardiography laboratory at Boston Children's Hospital.[16,17]

Key Points

Question What is the natural history of cardiac disease in children with Hutchinson-Gilford progeria syndrome, an ultrarare premature aging disorder?

Findings In this case-series study of 27 patients with Hutchinson-Gilford progeria syndrome, diastolic dysfunction was the most prevalent cardiac abnormality, appearing early in life with age-related decline, a finding mirroring those seen with normal aging. Other abnormalities, such as valve dysfunction and left ventricular hypertrophy, were less prevalent and appeared during the second decade of life.

Meaning Diastolic dysfunction was the most prevalent cardiac abnormality in patients with Hutchinson-Gilford progeria syndrome and may be a potential end point in future clinical trials.

Diastolic Function

Mitral valve inflow velocity during early (E) and late (A) diastole were measured using pulsed wave Doppler imaging, and the E/A velocity ratio was calculated. Pulsed wave tissue Doppler evaluation of LV diastolic function was performed by measuring the lateral and septal early (E′) and late (A′) diastolic myocardial velocities. The E:E′ and E′:A′ velocity ratios were calculated using standard guidelines[13,18] and were adjusted for age by using published normative data from our echocardiography laboratory to calculate z scores for each value.[16,17] Patients with a septal or lateral E′ velocity z score less than −2 were classified as having LV diastolic dysfunction.

Valve Abnormalities

The mitral valve and aortic valves were assessed from apical 4-chamber and parasternal long- and short-axis views using standard techniques.[14] A qualitative assessment for valve calcification was performed based on increased echogenicity visible from multiple imaging planes. Mitral and aortic regurgitation were graded semiquantitatively as mild, moderate, or severe, as previously described.[14,19] Patients with a mitral valve mean inflow pressure gradient greater than 3 mm Hg measured using continuous wave Doppler imaging were classified as having mitral stenosis. Aortic stenosis was defined as a maximum instantaneous pressure gradient greater than 15 mm Hg measured using continuous wave Doppler imaging.

Electrocardiography

Twelve-lead electrocardiography was performed using a standard technique. Heart rate z scores were calculated using normative data from our laboratory.[17] Electrocardiographic intervals were corrected for heart rate using the Bazett formula.[20]

Blood Pressure and Carotid-Femoral Pulse Wave Velocity Measurement

Blood pressure (BP) was recorded in both arms after 5 minutes of rest with the patient seated with feet flat on the floor using a standard auscultation technique and size-appropriate cuffs.[21] The BP measurements were taken twice in the arm, with the higher initial systolic BP reading and the

Table 1. Characteristics of the Study Patients

Characteristic	Finding[a]
Age, y	5.6 (2.1 to 17.5)
Male, No. (%)	15 (56)
Weight, kg	10.9 (7.2 to 22.7)
Weight-for-age z score	−7.8 (−43.7 to −1.7)
Height, cm	93.6 (70.6 to 133)
Height-for-age z score	−4.7 (−9.3 to −1.5)
BSA, m^2	0.5 (0.4 to 0.9)
BMI	12.8 (9.4 to 18.7)
Weight-for-height z score	−4 (−18.7 to 1)
Ideal body weight, kg	14 (8.6 to 21.2)
BSA using ideal body weight, m^2	0.6 (0.4 to 0.9)
Heart rate, /min	106 (85 to 174)
SBP, mm Hg	101 (62 to 124)
SBP percentile[b]	90.5 (14.9 to 99.9)
DBP, mm Hg	66 (43 to 85)
DBP percentile[b]	88.5 (8 to 99.8)
Hypertension, No. (%) (n = 26)[c]	13 (50)
Continent of origin, No. (%) (n = 27)	
Asia	10 (37)
South America	7 (26)
North America	6 (22)
Africa	2 (7)
Europe	1 (4)
Australia	1 (4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] Data are presented as median (range) unless otherwise indicated.

[b] The SBP and DBP percentiles were calculated using height-age instead of chronological age as previously described.[22]

[c] Accurate data were not available for 1 of the patients.

Table 2. Left Ventricular Size, Systolic Function, and Mass[a]

Variable	Median (Range)	P Value vs Normative Data
EDV/BSA ratio	63.4 (43.6 to 79.8)	NA
EDV z score	0.6 (−1.1 to 2.5)	.009
EDV z score using ideal body weight	−0.5 (−2.5 to 2.7)	.04
ESV:BSA ratio	19.2 (13.8 to 28.5)	NA
ESV z score	0.5 (−2.1 to 2.3)	.02
ESV z score using ideal body weight	−0.4 (−1.9 to 2.1)	.20
Ejection fraction, %	0.7 (0.6 to 0.8)	NA
Mass:BSA ratio	54.9 (40.6 to 98.9)	NA
Mass z score	0.8 (−0.5 to 3.6)	<.001
Mass z score using ideal body weight	−0.2 (−1.2 to 2.6)	.57
Mass to volume ratio	0.9 (0.7 to 1.6)	NA

Abbreviations: BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; NA, not applicable.

[a] The z scores were calculated using previously published normative data from the echocardiography laboratory at Boston Children's Hospital.[16,17] The P values were calculated by comparing median z scores against the expected population mean value of 0.

mean of the 3 measurements in this arm used for final analysis. To account for the severe growth restriction in this patient population, height-age was substituted for chronologic age while calculating age- and sex-specific BP percentiles.[22] As previously described, height-age was determined by calculating the median age in the general population of a child with the height of each patient with HGPS using the US Centers for Disease Control and Prevention sex-specific pediatric growth charts (http://www.cdc.gov/growthcharts/cdc_charts.htm).[22] Similar to a prior report[23] of patients with HGPS, for height-age calculations, segmental whole-body length was used instead of standing height, because joint contractures inherent to HGPS can result in an underestimation of true height. Patients who satisfied standard pediatric criteria (for patients <18 years of age, systolic and/or diastolic BP≥95th percentile for age, sex, and height-age) were classified as being hypertensive.[21] Carotid-femoral pulse wave velocity (CFPWV) was determined using a previously described ultrasound technique.[22,24]

Statistical Analysis

The statistical significance of differences between continuously distributed indicators was assessed using the Wilcoxon rank sum test. Associations between outcome and indicator variables were examined using simple linear regression and multivariable linear regression to adjust for potential confounders. The statistical significance level was set at P < .05 (2-sided). Statistical analysis was performed using SAS software, version 9.4 or higher (SAS Institute Inc).

Results

Study Patients

Characteristics of the 27 study patients (median age, 5.6 years; age range, 2-17 years; 15 [56%] male) are given in **Table 1**. Patients were evaluated before entry into an open-label drug trial of protein farnesylation inhibitors. Of 29 screened patients, 2 were excluded: one was ineligible for therapy because of liver dysfunction, and the other was excluded because of technical reasons. As previously reported,[25] patients demonstrated severe growth failure with severe reduction in weight-for-age, height-for-age, and weight-for-height z scores and a reduced body mass index (BMI), findings suggesting that their body composition included a higher proportion of lean body mass compared with healthy individuals. Systemic hypertension was common, as previously reported.[22] With use of height-age to calculate BP percentiles, 13 of 26 patients (50%) were hypertensive.

Metabolic profiles were similar to those in a prior report.[22] As seen in the eTable in the Supplement, 13 patients (48%) had hyperinsulinemia, and 9 (33%) were insulin resistant. Lipid abnormalities were notable for abnormally low high-density lipoprotein cholesterol level in 17 (63%).

LV Size, Systolic Function, and Mass

Echocardiographic indicators of LV size, function, and mass are summarized in **Table 2**. Compared with normative data

from our laboratory, *z* scores for LV end-diastolic volume, end-systolic volume, mass, mass to volume ratio, and ejection fraction were elevated. Because of the unusual body habitus, characterized by low BMI and weight-for-height *z* scores, we repeated these analyses using ideal body weight instead of actual body weight to calculate the BSA. We found that these adjusted *z* scores for LV size and mass were closer to normal values. Systolic dysfunction, defined as an LV ejection fraction less than 55%, was not seen in any patient. Left ventricular hypertrophy (LVH), defined as both LV mass and LV mass-to-volume *z* scores greater than 2, was present in 7 patients (25%). The presence of LVH was associated with older age at evaluation but not with sex, systemic hypertension, or CFPWV.

LV Diastolic Function

As indicated in **Table 3**, all echocardiographic indicators of diastolic LV function were abnormal compared with normative values from the echocardiography laboratory at Boston Children's Hospital. Left ventricular diastolic function indicators are insensitive to body composition; therefore, these *z* scores were not recalculated using ideal body weight.[17] Left ventricular diastolic dysfunction, defined as a tissue Doppler septal or lateral E' velocity *z* score less than 2, was present in 16 patients (59%), and its prevalence steadily increased with age (**Table 4**). As seen in the **Figure**, LV diastolic function indicators were worse in older patients. Specifically, *z* scores for lateral and septal E' velocities were lower ($r = -0.77$, $P < .001$; and $r = -0.66$, $P < .001$, respectively), whereas those for the E:E' ratio were higher in older patients ($r = 0.80$, $P < .001$; and $r = 0.72$, $P < .001$, respectively). Diastolic indicators were not significantly different between hypertensive and normotensive patients.

Mitral Valve Abnormalities

As indicated in Table 4, the most common mitral valve abnormalities were annular and chordal calcification, occurring in roughly one-fourth of patients. Significant mitral stenosis and regurgitation were less common. As indicated in Table 4, the prevalence of mitral valve abnormalities was higher in older patients.

Aortic Valve Abnormalities

As indicated in Table 4, annular calcification was the most common abnormality, occurring in more than one-third of patients. Valvar aortic stenosis and regurgitation were less common. As seen in Table 4, the prevalence of aortic valve abnormalities was higher in older patients.

Aortic Root Wall Brightness

Assessed qualitatively, an unusually increased echo brightness of the aortic root wall was noted in 19 of the 27 patients (70%). Patients with an abnormally bright aortic root had lower lateral and septal E' velocity *z* scores and higher lateral and septal E:E' velocity *z* scores. Aortic root brightness was not associated with age.

Electrocardiography

The results of 12-lead electrocardiography were normal in 25 patients (93%). One 12-year-old patient's electrocardiogram

Table 3. Left Ventricular Diastolic Function Indicators[a]

Indicator	Median (Range)	P Value vs Normative Data
Mitral inflow velocities		
E:A ratio	1.2 (0.7 to 2.7)	NA
E:A ratio z score	−1.4 (−2 to 1.2)	<.001
Tissue Doppler velocities		
Septal E', cm/s	9.3 (6.0 to 13.3)	NA
Septal E' z score	−1.8 (−3.6 to 1.3)	<.001
E:septal E' ratio	9.1 (6.5 to 17.4)	NA
E:septal E' z score	1 (−1 to 6.3)	<.001
Septal E':A' ratio	1.2 (0.8 to 3.5)	NA
Septal E':A' z score	−1.6 (−2.5 to 1.9)	<.001
Lateral E', cm/s	9.9 (5.6 to 17)	NA
Lateral E' z score	−2.4 (−4.4 to 0.8)	<.001
E:lateral E' ratio	8.7 (4.9 to 16.1)	NA
E:lateral E' z score	2.1 (−0.8 to 7.3)	<.001
Lateral E':A' ratio	1.4 (0.6 to 4.6)	NA
Lateral E':A' z score	−1.7 (−2.5 to 2.4)	<.001

Abbreviations: A', mitral late diastolic tissue Doppler myocardial velocity; E, mitral early diastolic Doppler inflow velocity; E', mitral early diastolic tissue Doppler myocardial velocity; NA, not applicable.

[a] The *z* scores were calculated using previously published normative data from the echocardiography laboratory at Boston Children's Hospital.[16,17] The *P* values were calculated by comparing median *z* scores against the expected population mean value of 0.

showed LVH, biatrial enlargement, and right axis deviation. Echocardiography revealed aortic and mitral stenosis and LVH. A 16-year-old patient's electrocardiogram showed LVH with strain. Echocardiography showed LVH.

Among electrocardiographic measurements, heart rate was elevated for age (median *z* score, 1.8; range, 0.17-3.07), but the *z* score did not vary with age. The PR, QRS, and QT intervals (all corrected for heart rate) did not vary with age.

Carotid-Femoral Pulse Wave Velocity

As reported previously,[22,26] CFPWV was elevated compared with prior published normative values in children (median, 9.1 m/s; range, 7.3-13.0 m/s). A higher CFPWV was associated with a lower lateral E' *z* score ($r = -0.41$, $P = .05$). No associations were found between CFPWV and other indicators of diastolic LV function or with LVH.

Cardiac History and Symptoms

As indicated in Table 4, all patients were asymptomatic, and none had documented cardiac arrhythmia, congestive heart failure, or myocardial infarction.

Discussion

In this cohort of patients with HGPS, representing approximately 25% of the world's population with HGPS, we found that LV diastolic dysfunction was the most prevalent echocardiographic abnormality, seen in all age groups, but its prevalence increased with age. Other cardiac abnormalities, includ-

Table 4. Prevalence of Cardiac Abnormalities by Age

Abnormality	No. (%) of Patients by Age Quartiles, y			
	2.1-3.6 (n = 6)	3.7-5.9 (n = 7)	6.0-9.2 (n = 7)	>9.2 (n = 7)
LV abnormalities				
Diastolic dysfunction[a]	1 (17)	3 (43)	6 (86)	6 (86)
Systolic dysfunction (LVEF<55%)	0	0	0	0
LVH (mass and mass/volume z scores >2)	0	0	1 (14)	6 (86)
Mitral valve abnormalities				
Stenosis (mean gradient >3 mm Hg)	0	0	0 (10)	2 (29)
Regurgitation (more than mild)	0	0	0	0
Annular or chordal calcification	0	0	3 (43)	5 (71)
Aortic valve abnormalities				
Stenosis (MIG>15 mm Hg)	0	0	0	1 (14)
Regurgitation (more than mild)	0	0	0	0
Annular calcification	0	0	1 (14)	3 (43)
ECG abnormalities	0	0	0	2 (29)
Cardiac history and symptoms				
Congestive heart failure	0	0	0	0
Dyspnea	0	0	0	0
Chest pain	0	0	0	0
Cardiac arrhythmias	0	0	0	0
Myocardial infarction	0	0	0	0

Abbreviations: ECG, electrocardiogram; EF, ejection fraction; LV, left ventricle; LVH, left ventricular hypertrophy; MIG, maximum Doppler instantaneous gradient.

[a] Left ventricular diastolic dysfunction was defined as septal or lateral E' velocity z score less than −2.

ing mitral and aortic valve stenosis or regurgitation and LVH, were less common and seen only during the second decade of life.

Although cardiovascular disease is the most frequent cause of death in patients with HGPS, studying the course of cardiac abnormalities in HGPS has been difficult because of the rarity of the syndrome (prevalence of 1 in 20 million living individuals).[1] Until recently, description of the phenotype has relied on the review of isolated case reports.[6,9] A more recent prospective report included 15 patients, most during the first decade of life, but did not include assessment of diastolic LV function.[10] Our study includes the largest-to-date cohort that underwent comprehensive echocardiographic evaluation to assess for abnormalities in LV systolic and diastolic function, LVH, and LV valve abnormalities.

LV Size, Systolic Function, and Mass

The BSA-adjusted end-diastolic and end-systolic LV volumes were elevated in patients with HGPS compared with normative data from our laboratory. Left ventricular volume measurements in patients with HGPS have not been previously reported. It has been previously reported that cardiac output and LV volumes in healthy children are linearly related to BSA.[16] These associations assume a normal body composition and BMI. Patients with HGPS have a markedly abnormal body composition, with reduced subcutaneous and visceral fat and low BMI values. As a result, the proportion of lean body mass to less metabolically active fatty tissue in patients with HGPS is higher compared with that in healthy children. Therefore, it may be expected that BSA-corrected cardiac output would be higher in patients with HGPS and could be responsible for the higher than normal LV volume z scores in our study. The confounding effect of body composition is supported by our find-

ing that when ideal body weight was used to calculate BSA, LV volume z scores were similar to normative values. However, LV mass z scores remained significantly higher than normative values despite this correction, suggesting that elevated LV mass observed in patients with HGPS is independent of body composition abnormalities.

No patients had LV systolic dysfunction. The LV ejection fraction was on average higher than normal in our cohort, consistent with a prior report.[10]

LV Diastolic Function

In contrast to normal systolic function in most patients, LV diastolic dysfunction was highly prevalent, with a higher prevalence in older patients. Although this finding is not surprising in the context of a premature aging disorder, it had not been previously reported; therefore, the course and severity of abnormalities were not known. The largest previous report[10] of patients with HGPS did not include assessment of diastolic function. The inverse association between age and diastolic tissue Doppler velocities observed in our cohort mirrors the changes seen during the normal process of aging.[27,28] However, the pathogenesis of LV diastolic dysfunction in HGPS remains unknown. Systemic hypertension is known to be associated with diastolic LV dysfunction. In our cohort, although hypertension and diastolic dysfunction were common, they were not significantly associated. It could be speculated that diffuse myocardial fibrosis, endocardial fibrosis, or subclinical coronary ischemia may play a role in the pathogenesis of cardiac disease in HGPS. Prior pathologic case reports found myocardial interstitial fibrosis[6] and endocardial thickening,[8] both of which could contribute to diastolic dysfunction. In the future, quantification of myocardial extracellular volume fraction by cardiac magnetic resonance may help evaluate the role

Figure. Association Between Tissue Doppler Indicators of Diastolic Left Ventricular Function and Age
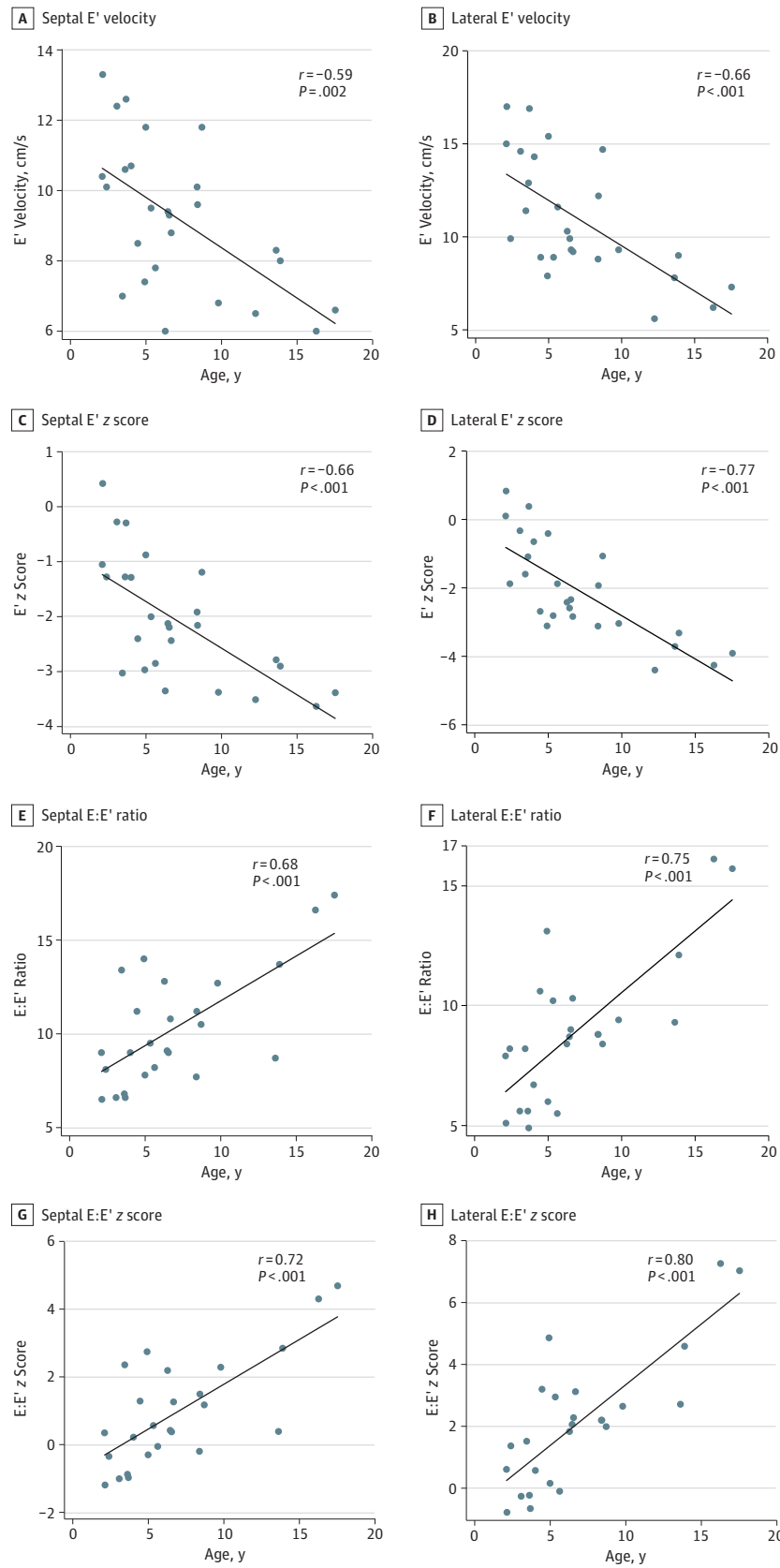
In this cross-sectional analysis, each data point represents a unique patient. E indicates early mitral inflow velocity; E', early diastolic tissue Doppler myocardial velocity.

of diffuse fibrosis in the etiology of diastolic dysfunction.[29-31] The identification of LV diastolic dysfunction as an early abnormality in patients with HGPS raises the possibility of its use as an noninvasive marker to assess progression of disease and response to therapy in future studies.

Mitral and Aortic Valve Abnormalities

The most common valve abnormalities were calcification involving the mitral valve annulus and chords and the aortic valve annulus. These findings were most prevalent in the second decade of life. Similarly, valve dysfunction, including stenosis or regurgitation, was late and seen only in the second decade of life. These findings are similar to those reported by Merideth et al[10] in a smaller cohort.

Electrocardiography

Electrocardiographic abnormalities were rare in our cohort and were seen only during the second decade of life. In contrast to a prior report,[32] we did not find significant repolarization abnormalities. In the prior report,[32] several patients with repolarization abnormalities had T-wave inversion in the right precordial leads, which is a normal finding in children. Misclassification of this normal finding likely led to an overestimation of abnormalities. It is also possible that some of the older patients in the prior report[32] with ST-T-wave abnormalities had hemodynamically significant valve disease, resulting in pressure and/or volume overload of the left ventricle, contributing to the echocardiographic abnormalities. In our cohort, the prevalence of hemodynamically significant valve disease was low. Furthermore, in contrast to the bradycardia and PR, QRS, and QTc prolongation reported in progeroid mice, the patients in our cohort had higher than average heart rates, normal electrocardiographic intervals, and no documented arrhythmia. Given the discrepancy between preclinical and clinical data, this area deserves further investigation.

Cardiac History and Symptoms

Despite a high prevalence of diastolic dysfunction and a small but significant number of patients with mitral and/or aortic valve abnormalities, no patients reported cardiac symptoms, congestive heart failure, documented arrhythmias, or myocardial infarction. However, further longitudinal research is needed to determine whether some patients develop symptoms with further progression of valve disease or with development of coronary artery disease.

Other Cardiac Abnormalities

We subjectively found an unusually high level of echo brightness of the aortic root wall in a subset of patients with HGPS compared with pediatric and adult patients without HGPS. In our cohort, patients with HGPS with increased wall bright-ness were more likely to have features of diastolic LV dysfunction. The significance of this observation is unclear but may relate to pathologic findings that describe prominent thickening of the aortic adventitial layer.[8] Increased carotid artery echo brightness demonstrated by ultrasonography in HGPS also suggests a more diffuse vascular pathologic finding.[22] Future studies that use quantitative methods to assess aortic root wall brightness and correlation with pathologic observations may provide greater insight into the significance of this finding.

As previously shown, aortic stiffness assessed using CFPWV measurements was increased in this HGPS cohort. We found an association between higher CFPWV and lateral E' velocity z score but not with other indicators of diastolic LV function. Although the association is relatively weak, it is consistent with a previously reported association between progressive ventricular and arterial stiffening during the process of normal aging.[33] This association requires further investigation during longitudinal follow-up of these patients.

Limitations

Several limitations of the current study are worth considering. Although we report data on the largest-to-date cohort of patients with HGPS (representing approximately 25% of the world's population with HGPS), our analyses remain limited by the small sample size inherent in the rarity of this condition. However, because of the small number of patients worldwide, larger studies may not be feasible to conduct. The cross-sectional study design has inherent limitations. In the future, we plan to report longitudinal data from these patients to address these limitations. Because of radiation and procedural risks, our study did not include cardiac catheterization to assess coronary artery stenosis or calcification. The assessment of diastolic dysfunction was based on tissue Doppler techniques, and invasive confirmation of abnormal diastolic compliance was not possible because of ethical considerations. However, the use of tissue Doppler echocardiography for assessment of LV diastolic function is well established. We did not measure other indicators of diastolic function, such as strain and left atrial size, because of the lack of adequate normative data.

Conclusions

In this largest-to-date cohort of patients with HGPS, LV diastolic function was the most prevalent cardiac abnormality, appearing early and affecting almost all patients older than 6 years. Other cardiac abnormalities, including valve abnormalities, were less common and appeared during the second decade of life. Echocardiographic indicators of LV diastolic dysfunction may be useful end points in future clinical trials.

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Invited Commentary

Left Ventricular Diastolic Dysfunction in Hutchinson-Gilford Progeria Syndrome

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Hutchinson-Gilford progeria syndrome (HGPS) is a premature aging disorder that affects approximately 1 in 4 to 8 million newborn infants.[1,2] Affected individuals present with failure to thrive and a progeroid appearance, with progressive manifestation of short stature, bone and joint abnormalities, and subcutaneous fat loss.[1,2] This disorder is invariably fatal in the midteenage years owing to myocardial infarction or stroke associated with severe accelerated atherosclerosis. Because of the extreme rarity of HGPS, relatively little is known about the full spectrum and outcomes of cardiovascular complications. In this issue of *JAMA Cardiology*, Prakash et al[3] report the results of echocardiographic analyses undertaken in 27 patients with HGPS who were aged 2 to 17 years. The presence of left ventricular (LV) diastolic dysfunction in nearly two-thirds of the participants was a novel and surprising finding.

Cases of HGPS are caused by variants in the *LMNA* gene that result in abnormal processing of prelamin A and accumulation of a mutant protein termed *progerin* at the periphery of cell nuclei.[1,2] Progerin accumulation has been associated with a wide range of intranuclear and extranuclear defects in the context of HGPS, including dysregulated gene expression, impaired DNA repair, telomere shortening, genomic instability, epigenetic changes, mitochondrial dysfunction, oxidative stress, metabolic defects, autophagy, impaired proteolysis, cell senescence, and reduced stem cell regenerative capacity.[4,5] These changes have been predominantly described in proliferating cells, and they mirror those seen with normal aging.[6] Interestingly, prelamin A has been shown to accumulate with age in vascular smooth muscle cells of healthy individuals and also in atherosclerotic plaques.[7] Although mechanisms of atherosclerosis have been frequently studied in HGPS, to my knowledge, cardiomyocyte properties and causes of LV diastolic dysfunction remain relatively unexplored.

A number of factors at the whole-organ level are known to affect LV diastolic function in the aging heart by promoting LV hypertrophy, ischemia, and fibrosis, all of which have subsequent associations with active relaxation and compliance.[8,9] This includes increased LV afterload owing to central arterial stiffness, coronary macrovessel and microvessel dysfunction, and expansion and increased stiffness of the myocardial extracellular matrix.[8,9] These changes are exacerbated by commonly occurring comorbidities, such as hypertension, diabetes, and obesity.[9] Although many of these factors can be expected to be relevant to HGPS, it is noteworthy that diastolic dysfunction preceded hypertrophy or occurred in the absence of hypertrophy in the cohort studied by Prakash et al.[3] Moreover, despite a high prevalence of systemic hypertension (13/26; 50%) and hyperinsulinemia (13/27; 48%) in the study cohort, neither of these conditions showed significant statistical association with diastolic dysfunction.[3] In addition, patients with HGPS were severely underweight rather than obese.[3]

Additional abnormalities at the cellular level that prolong active relaxation and reduce compliance of cardiac muscle have been associated with age-related cardiac dysfunction.[8,9] Changes in cardiomyocyte calcium handling associated with ion channel remodeling, calcium leak, and reduced uptake by the sarcoplasmic reticulum can increase diastolic calcium concentration and actin-myosin crossbridge activation.[8,9] These effects are exacerbated by increases in heart rate or by the presence of reactive oxygen species. Ventricular diastole is energy-requiring, and age-related mitochondrial dysfunction can both reduce adenosine triphosphate reserves and increase production of reactive oxygen species.[9] These defects in myocardial energetics compromise efficient ventricular relaxation and are augmented under hypoxic conditions.[9] Passive stiffness of cardiomyocytes is increased in patients with diastolic heart failure and this is in part because of changes in the titin isoform composition and titin posttranslational modification. Numerous factors regulate these titin characteristics, including activity of RNA splicing factors (such as RNA binding motif protein 20) and levels of β-adrenergic stimulation, nitric oxide, endothelin-1, natriuretic peptides, and angiotensin-II.[9]

Collectively, these data provide food for thought for HGPS-related diastolic dysfunction. Given that the fundamental issue is nuclear progerin accumulation, elucidation of cardiomyocyte nuclear structure and function appears to be a compelling starting point. Changes in nuclear architecture and chromatin organization would be expected to have a myriad of potential effects on cardiomyocyte function, including changes in gene expression, RNA processing, cell signaling, and mechanotransduction. The cardiomyocyte nucleus is a central component of a structural scaffolding linking the surface