William-Beuren Syndrome patients demonstrate a trend towards increased incidence of diastolic dysfunction: A prospective study

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BACKGROUND

- Williams-Beuren Syndrome (WBS) is a multi-system disease caused by a chromosomal microdeletion (7q11.23) whose cardinal features include intellectual disability and elastin haploinsufficiency leading to cardiovascular disease. Elastin is the main component of the elastic fibers that allow arteries to reversibly expand and relax. Elastin haploinsufficiency leads to changes in the mechanical behavior of these vessels, affecting their cardiovascular mechanics on multiple levels. This is believed to be responsible for WBS patients' characteristic supravalvular aortic stenosis (SVAS), systemic hypertension and coronary abnormalities.
- Although previous studies have characterized the incidence and natural history of great vessel disease seen in WBS, less is known about the long-term consequences of hypertension and vascular stiffness on cardiovascular systolic and diastolic function.
- In this study, we used echocardiogram as a non-invasive, established method to better understand the long-term effects of these systemic processes on the heart mechanics of WBS patients.

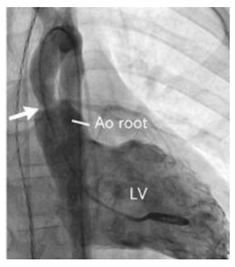

Figure 1: SVAS is present ~70% of WBS patients

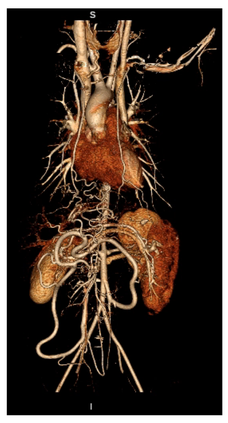

Figure 2: Stenosis of various vessels, including the descending aorta, celiac and superior mesenteric arteries is seen in WBS patients

Pober, Barbara R. "Williams–Beuren Syndrome." *New England Journal of Medicine*, vol. 362, no. 3, 2010, pp. 239–252.,

METHODS

Echocardiographic Evaluation

- A prospective study was done on WBS patients that included 2D and Doppler echocardiographic evaluation. Diastolic function was assessed by mitral inflow Doppler interrogation including both pulsed-wave Doppler and tissue Doppler.
- Echocardiograms were performed on 63 WBS cases and 32 healthy controls **(Table 1)**, including 31 Pediatric WBS cases (mean age 10 years ± 4) and 32 Adult WBS cases (mean age 32 years ± 12). 25 additional pediatric controls were obtained through retrospective chart review from Children's National Medical Center. The following quantitative measures were taken.

- **Indices of left ventricular pump function:** Ejection fraction, defined as (end-diastolic dimension – end-systolic dimension)/end-diastolic dimension calculated using biplanar volume calculations (**figure 3**).
- **Left ventricular mass:** Calculated from M-mode measurements and indexed by height in meters raised to the 2.7 power to minimize differences expected from age and obesity

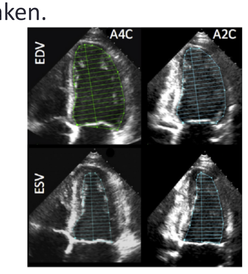

Figure 3: Biplanar disk summation using apical two- and four-chamber views.

- **Chamber dimensions:** Chamber dimensions were measured in the parasternal long-axis view (**figure 4**).

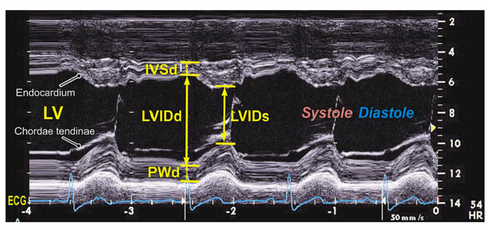

Figure 4: M-mode tracing showing left ventricular internal diameter at diastole (LVIDd) and systole (LVIDs). Internal ventricular septum diameter (IVS) and posterior wall diameter (PWd) are also acquired through this technique

- **Aortic dimensions:** Aortic dimensions: Ascending and aortic root measurement calculated from the parasternal long-axis view at end (**figure 5**)

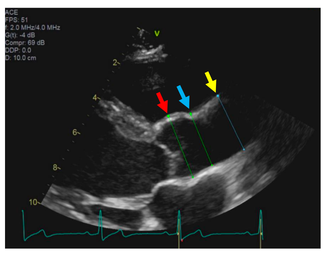

Figure 5: Aortic root measurements showing where aortic root (red), sinotubular junction (blue) and ascending aorta (yellow) measurements are taken on parasternal long axis view.

- **Indices of LV diastolic function:** Evaluated using both pulsed wave-Doppler recordings of mitral valve inflow pattern and tissue Doppler as described by ASE. Using the apical four-chamber view with color flow imaging, mitral Doppler time velocity curves were obtained by placing the Doppler beam perpendicularly to the plane of the mitral annulus between mitral leaflets tips.

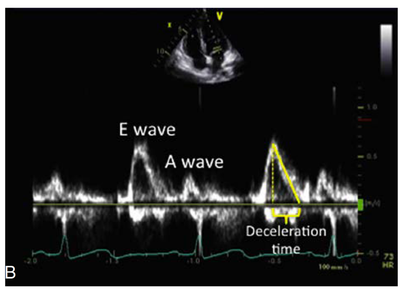

Figure 6: Mitral Doppler time velocity curve was analyzed for peak flow velocities at early (E) and late (A) diastole as well as their ratio (E/A). Deceleration time (DT) was calculated by measuring the time interval from the peak E-wave point at which the descending slope of the E-wave crosses the zero velocity baseline. Isovolumic relaxation time was measured from the time between the closure of the aortic valve to the opening of the mitral valve.

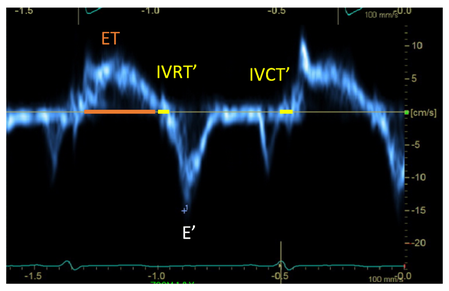

Figure 7: In the apical four chamber view, tissue Doppler of the mitral inflow at the septal and lateral mitral valve tips were used to acquire Septal e' and Lateral e' annular velocities respectively. IVCT' was calculated as time from the end of late diastolic filling to the beginning of systolic ejection. ET was measured as time of LV outflow and IVRT' was measured as time between the end of systolic ejection to the beginning of early diastolic filling. Myocardial performance index (MPI), a measure of overall cardiac function, was calculated as (IVCT'+IVRT')/ET.

Galazka, Patrycja Z., and Amil M. Shah. "Left Ventricular Diastolic Function." *Essential Echocardiography*, Elsevier, 2018.

Orsinelli, David A, et al. "American society of echocardiography recommendation for cardiac chamber quantification in adults", 2015

Solomon, Scott D. and Benard E. Bulwer. "Assessment of left ventricular systolic function", Essential Echocardiography, Elsevier, 2018

RESULTS

Patient Demographics/Characteristics

Table 1: Demographic and Characteristic data for WBS patients and controls. Patients were sub-divided by adult and pediatric subjects. Subject ages ranged from 3 years to 63 years. To determine P-values, Wilcoxon test was used for continuous variables and Fisher's Exact test used for categorical variables

	Pediatric Controls (n= 33)	Pediatric Williams Syndrome Cases (n=31)	*P*	Adult Controls (n= 24)	Adult Williams Syndrome Cases (n=32)	*P*
Age (years)	9 ± 13	10 ± 4	0.528	37 ± 12	32 ± 12	0.107
Male/female	18/15	17/14	0.982	9/15	13/19	0.618
BSA (m^2)	1.12 ± 0.33	1.03 ± 0.28	0.485	1.89 ± 0.26	1.64 ± 0.27	0.001
BMI (kg/m^2)	17.9 ± 3.3	17.6 ± 3.5	0.662	27.3 ± 6.1	24.4 ± 6.2	0.073
HR (beats/min)	83 ± 16	97 ± 17	<0.001	72 ± 10	81 ± 12	0.008
Systolic bp (mmHg)	105 ± 12	121 ± 11	<0.001	116 ± 13	126 ± 13	0.009
Diastolic bp (mmHg)	61 ± 10	70 ± 12	0.004	69 ± 12	71 ± 10	0.550
Hx of HTN	0	16	<0.001	4	17	0.006
Currently on BP Mx	0	7	0.004	3	14	0.049
History of CV Surgery	0	10	<0.001	0	8	0.049

Additional Diastolic Measures

Table 2: Secondary diastolic measures for WBS cases and controls do not show significant differences between case and controls in the pediatric or adult subgroup. Wilcoxon test was used for P-values.

	Pediatric Controls (n= 33)	Pediatric Williams Syndrome Cases (n=31)	*P*	Adult Controls (n= 24)	Adult Williams Syndrome Cases (n=32)	*P*
Deceleration Slope (m/s^2)	5.5 ± 1.6	6.5 ± 2.2	0.186	4.0 ± 1.3	4.8 ± 2.1	0.366
IVRT (ms)	62 ± 28	72 ± 19	0.348	82 ± 19	85 ± 21	0.844
IVRT' (ms)	58 ± 10	63 ± 16	0.566	70 ± 19	73 ± 20	0.549
IVCT' (ms)	60 ± 14	59 ± 17	0.586	66 ± 21	71 ± 19	0.769
Ejection Time (ms)	275 ± 33	273 ± 29	0.918	291 ± 30	289 ± 37	0.719
MPI	0.44 ± 0.33	0.45 ± 0.13	0.751	0.47 ± 0.13	0.51 ± 0.13	0.546
LA Volume Indexed	-	-	-	24 ± 5.9	24 ± 6.7	0.697

Main Diastolic Measures: Pulsed wave Doppler

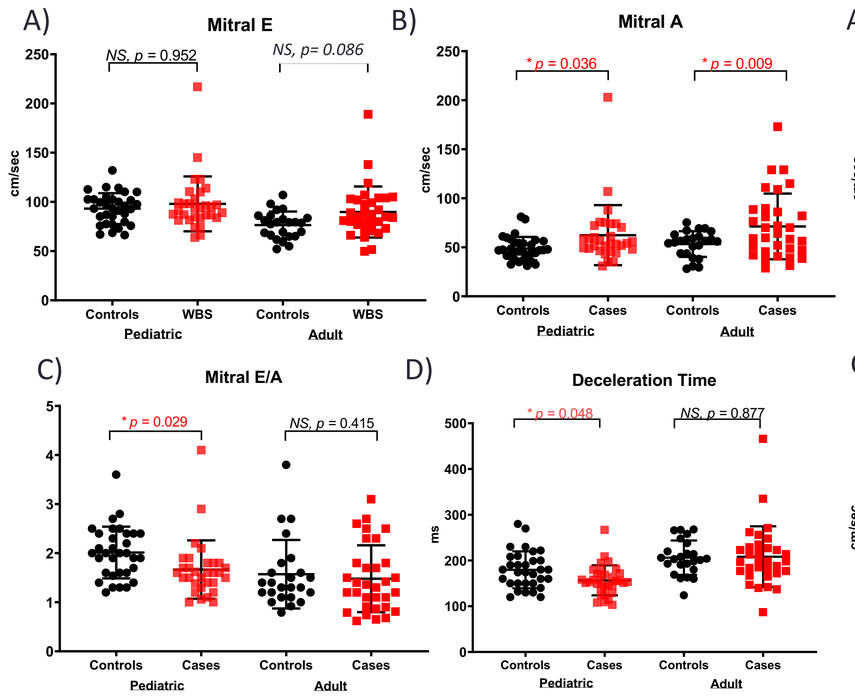

Figure 8: Primary outcome measures for mitral inflow data in pediatric and adult WBS cases. E/A ratio (2.00 ± 0.53 controls vs 1.66 ± 0.59 cases), deceleration time (179 ± 40 controls vs 157 ± 33 cases), and mitral A wave velocity (0.49 ± 0.12 controls vs 0.62 ± 0.31 cases), were all significantly different in the pediatric subgroup. Only mitral A (0.532 ± 0.13 controls vs 0.713 ± 0.33 cases) was significantly different in the adult population. Multivariate analysis was adjusted for age, gender, race, SBP and BMI.

Main Diastolic Measures: Tissue Doppler

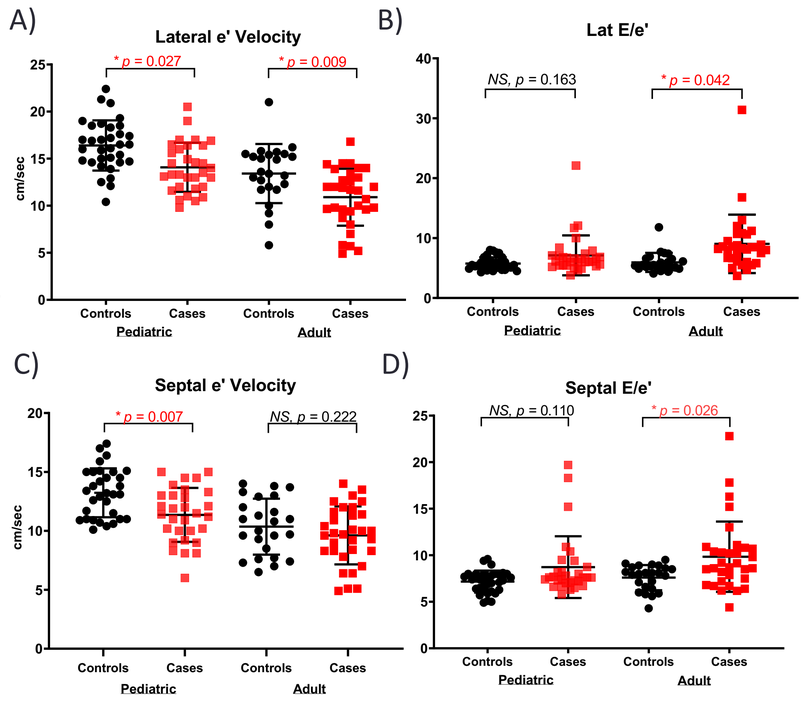

Figure 9: Primary outcome measures for tissue Doppler analysis in pediatric and adult WBS cases. Lateral e' velocity (0.16 ± 0.03 controls vs 0.14 ± 0.03 cases) and Septal e' velocity (0.13 ± 0.02 controls vs 0.11 ± 0.02 cases) were significantly different in the pediatric subgroup. Lateral e' velocity (0.13 ± 0.03 controls vs 0.11 ± 0.03 cases), Lateral E/e' (6.0 ± 1.6 controls vs 9.0 ± 4.9 cases) and Septal E/e' (7.7 ± 1.3 controls vs 9.8 ± 3.8 cases) were significantly different in the adult population. Multivariate analysis was adjusted for age, gender, race, SBP and BMI.

2D Echocardiographic Data: Chamber wall and thickness

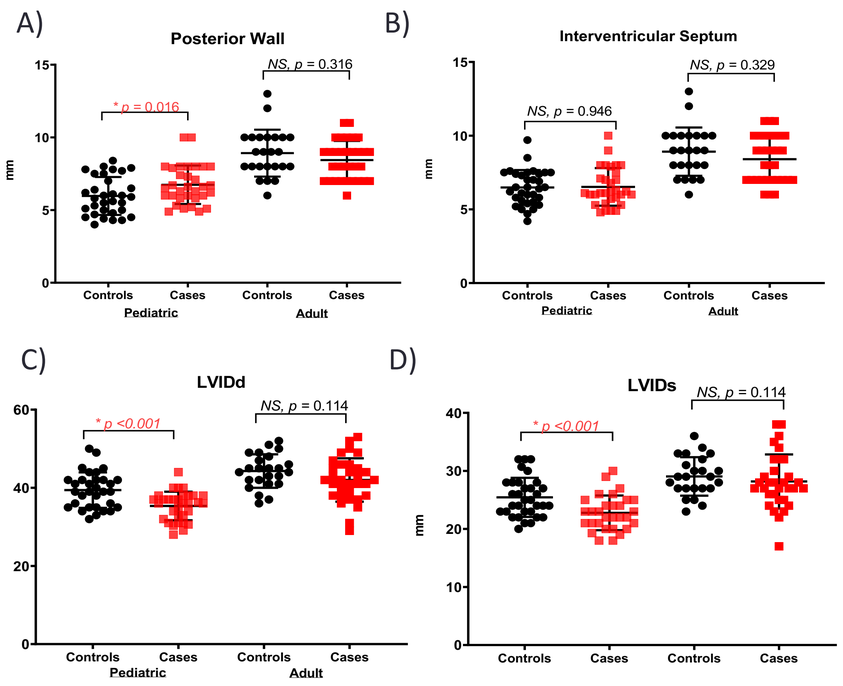

Figure 10: Left ventricular chamber dimensions and wall thickness show significant differences in the size of LVIDd, LVIDs and Posterior wall in the pediatric subgroup. P values calculated using Wilcoxon test. LVIDd: left ventricular internal diameter at diastole. LVIDs: left ventricular internal diameter at diastole.

2D Echocardiographic Data: Systolic Function and LV mass

Table 3: Measures of systolic function and LV mass show no significant difference between cases and controls in either the adult or pediatric subgroups.

	Pediatric Controls (n= 33)	Pediatric Williams Syndrome Cases (n=31)	*P*	Adult Controls (n= 24)	Adult Williams Syndrome Cases (n=32)	*P*
Ejection Fraction (%)	64 ± 5	63 ± 4	0.420	63 ± 5	62 ± 5	0.470
Fractional Shortening (%)	35 ± 4	36 ± 4	0.445	34 ± 3	33 ± 5	0.172
LV mass/BSA (g/m^2)	61 ± 13	59 ± 10	0.496	68 ± 12	68 ± 19	0.966

2D Echocardiographic Data: Aortic measurements

Table 4: Aortic root measurements show significant differences in aortic size between controls and WBS cases in both the adult and pediatric populations

	Pediatric Controls (n= 33)	Pediatric Williams Syndrome Cases (n=31)	*P*	Adult Controls (n= 24)	Adult Williams Syndrome Cases (n=32)	*P*
Aortic root (mm)	21 ± 4	20 ± 3	0.133	30 ± 3	28 ± 3	0.025
Aorta StJ (mm)	18 ± 3	15 ± 3	0.001	25 ± 3	22± 3	0.018
Ascending aorta (mm)	18 ± 3	17 ± 3	0.100	30 ± 5	24 ± 4	<0.001

CONCLUSIONS

- Our cohort of William-Beuren Syndrome patients showed normal values for left ventricular systolic indices and no left ventricular hypertrophy relative to our control population.
- Our pediatric cases had significantly larger internal chamber diameters and thicker posterior wall compared to controls.
- As expected, proximal aortic measurements were smaller in the Williams cases compared to controls, which was more pronounced in the adult cohort
- Significant differences were seen in several measures of diastolic function in both the adult and pediatric WBS cases. In the pediatric group, measures of E/A ratio, lateral e' and septal e' velocities were significantly decreased. In the adult populations, measures of Septal E/e', Lateral E/e' were significantly increased and lateral E' was significantly decreased compared to the control group. These findings suggests possible increased incidence of diastolic dysfunction in the WBS population.

FUTURE DIRECTIONS

- Further work will seek to determine the underlying cause of the trends we have observed in this study by investigating the effect of blood pressure, age, and arterial stiffness on the measures of diastolic function.
- We also aim to obtain strain and strain rate (SR) in our patients to continue our investigation of global and regional deformation of the myocardium.