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Cardiovascular risk assessment in children and adolescents with congenital solitary kidneys

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Abstract

Patients with solitary kidneys (SKs) are at risk of hypertension (HT) and associated end-organ damage. The authors aimed to evaluate whether children with congenital SKs (CSKs) have higher office, ambulatory, or central blood pressure (BP), increased arterial stiffness or left ventricular mass index, or any risk for arrhythmia. With this purpose, patients with CSK and healthy controls being followed up between January 2018 and June 2019 were enrolled in the study. Demographic, biochemical, and office blood pressure (BP) data were recorded. Then, ambulatory blood pressure monitoring (ABPM) and measurements of central BP (cBP), pulse wave velocity (PWV), and augmentation index (AIx@75) were obtained. Ventricular repolarization parameters were acquired by 12-lead electrocardiography. Left ventricular mass index (LVMI) and abdominal aortic stiffness parameters including strain, pressure strain elastic modulus (Ep), and normalized Ep (Ep*) were calculated with echocardiographic measurements. Finally, 36 children with CSK and 36 healthy controls were included. Serum creatinine, uric acid, total cholesterol levels, ABPM parameters, cBP levels, and PWV values were significantly higher, and eGFR levels were significantly lower in the CSK group. VR parameters, abdominal aortic stiffness indices, and LVMI were similar between the groups. CSK increased the risk of HT in ABPM (HT_{ABPM}) by 6 times. PWV was significantly correlated with Ep and Ep* in cases with CSK. Determination of cBP and PWV along with 24-hour ABPM would be a useful tool in children with CSK.

1 | INTRODUCTION

It is well known that patients with solitary kidneys (SKs) are at risk of hypertension (HT), proteinuria, and glomerulosclerosis due to their low number of nephrons.[1-4] They tend to have higher levels of HT-associated end-organ damage markers, such as left ventricular mass index (LVMI) and microalbuminuria.[5] Congenital SKs (CSKs) or acquired SKs (ASKs) have different effects on glomerular filtration rate (GFR) and blood pressure (BP).[1-3] Patients with CSK maintained better GFR levels by developing better adaptation mechanisms [5]; however, HT risk was higher or similar to those with ASK in different studies.[2,5,6]

The risk of ambulatory or masked HT (AHT and MHT, respectively) is increased in cases with CSK (4). Arterial stiffness, which shows subclinical end-organ damage, is increased in cases with AHT and MHT, and may lead to increased central BP (cBP).[7] Central BP is suggested to be more valuable in predicting the severity of cardiovascular events than peripheral BP and has become the gold standard for diagnosis and classification of HT in adults.[8,9,10] Over the last few years, cBP has been recommended to be assessed in children with HT, even in the early childhood period.[8,9] Besides, arrhythmia risk determined by elongation in ventricular repolarization indices has been increased in patients with hypertension.[11,12,13]

We have hypothesized that patients with CSK might be at risk for all of the abovementioned cardiovascular risks since they are more prone to HT. To the best of our knowledge, no study on vascular stiffness, cBP, or ventricular repolarization parameters has been conducted in children with a unilateral functioning kidney. In this study, we have aimed to investigate pBP profile, cBP, arterial stiffness determined by both oscillometric and echocardiographic indices, arrhythmia risk, and end-organ damage in a homogenous group including only children with CSKs.

2 | PATIENTS AND METHODS

The study protocol was approved by the local ethics committee (14.12.2017/128). Written informed consent was obtained from all guardians, and participants were informed about the purpose of the study, based on their age.

Patients with CSK being followed up in our clinic between January 2018 and June 2019 were recruited for this prospective cohort study. Those with unilateral renal agenesis (URA) or multicystic dysplastic kidneys (MCDK) were included in the study. Patients with any uptake defect or confirmed renal scarring in $Tc^{99\,m}$ dimercaptosuccinic acid scan ($Tc^{99\,m}$-DMSA); estimated glomerular filtration rates (eGFRs) ≤60 ml/min/1.73 m^2; vesicoureteral reflux, ureteropelvic junction obstruction, duplex system, megaureter, posterior urethral valve, or neurogenic bladder; those with type 1 or type 2 diabetes mellitus, or those under anti-hypertensive medication were excluded.

The control group consisted of age- and gender-matched otherwise healthy children who were evaluated in the pediatric cardiology clinic for cardiac murmur and found to have physiological murmur without any underlying cardiac pathology.

Bodyweight, height, and office systolic BP (SBP) and diastolic BP (DBP) were measured in all participants. Body mass index (BMI) was calculated as a ratio of body weight (kg) per square body height (m^2). Standard deviation scores (SDSs) of BMI, and office SBP and DBP were determined via the Child Metrics program according to published normal values.[14-16] Laboratory blood and urine tests were estimated in all patients with standard methods. Estimated glomerular filtration rates were calculated due to the original Schwartz formula.[17]

In addition, PWA, ambulatory blood pressure monitoring (ABPM), electrocardiographic, and echocardiographic evaluations were performed in all cases. Patients were evaluated with an automated oscillometric PWA-ABPM device (Mobil-O-Graph; IEM, Stolberg, Germany) validated for office and ambulatory pBP and cBP measurements according to the British Hypertension Society and the European Society of Hypertension recommendations.[18] The device has shown good accuracy for cBP when compared with invasive measurements in children.[19] By using this device, cSBP and cDBP, aortic pulse wave velocity (PWV), validated by referring to tonometric devices and/or invasive methods, and augmentation index normalized for an HR of 75 bpm (AIx@75) can be assessed.[20] The cuff of the device is placed in the non-dominant arm. Brachial SBP, DBP, pulse pressure, and waveforms are obtained using an algorithm (ARC Solver algorithm).[21] The BP measures were converted into SDSs via Child Metrics using the published reference LMS data (a measure of skewness [L], median [M], the coefficient of variation [S] for transforming the data to normality) for healthy children established by Wühl et al.[14,22]

With PWA and wave separation analysis, PWV and AIx@75 were calculated.[21] AIx@75 represents increased wave reflection and/or early return of the reflected wave due to increased arterial stiffness presented by PWV.[23] As a result, PWV is considered as a direct indicator of vascular stiffness, while AIx@75 is an indirect measure.[24]

With the combination of office and ABPM measurements, study patients were designated into four classical phenotypes: "Normotension (NT)" was defined as having normotensive BP measurements on both office and ABPM measurements; "masked HT (MHT)" was defined as having normotensive office BP measurements with hypertensive ABPM measures; "white coat HT (WCHT)" was defined as having hypertensive office BP measurements with normotensive ABPM measures; and "ambulatory (sustained) HT (AHT)" was defined as having hypertensive BP measurements on both office and ABPM measurements.[8] In addition, we grouped patients with any abnormalities on ABPM irrespective of the office BP measurements, as HT according to ABPM (HT_{ABPM}) including hypertensive ABPM measures and/or high BP loads (≥25%).

2.1 | Electrocardiographic assessment

A 12-lead digital ECG was performed in all patients and healthy volunteers. The standard 12-lead ECG (Cardiofax GEM, Model 9022 K; Nihon Kohden) was recorded at a speed of 25 mm/sec and an amplitude of 1 mV/cm. QT dispersion (QTd), corrected QT dispersion (QTcd), Tpeak to Tend (Tp-e) interval, Tp-e dispersion (Tp-ed), and Tp-e/QT and Tp-e/QTc ratios were calculated to evaluate ventricular and repolarization periods. For QTd, we measured the QT interval from the beginning of the QRS complex to the end of the T wave. The QTd was calculated as the difference between the maximum and minimum of QT interval. QTc interval was calculated according to the Bazett formula [QTc = QT/ √RR (ms)].[25] QTcd was calculated as the difference between the maximum and

the minimum QTc intervals.[26] Tp-e was measured from the highest point to the endpoint of T wave. If reverse T waves were present, the measurement was taken from the lowest point to the endpoint of the T wave. Tp-ed was the difference between the maximum and minimum Tp-e values.[27]

2.2 | Echocardiographic assessment

All of the participants underwent echocardiographic examination performed by the same pediatric cardiologist with the same echocardiography device and appropriate transducer. Ejection fraction (EF) and fractional shortening (FS) were evaluated for each patient by M-mode and color Doppler echocardiography. LVMI was calculated according to the LVM calculated via Devereux formula = LVM (gram): $0.8 \times 1.04\ [(\text{LVEDD} + \text{IVST} + \text{PWT})^3 - (\text{LVEDD})^3] + 0.6$ [LVEDD: left ventricular end-diastolic diameter, IVST: interventricular septum thickness, PWT: posterior wall thickness] and indexed to height $(\text{m})^{2.7}$.[28,29] An LVMI exceeding the 95th percentile for sex and age in normal children and adolescents was used to define LVH.[29]

Abdominal aortic stiffness was evaluated with "strain" that showed the elasticity or distensibility and "pressure strain elastic modulus (Ep)" that represents the stiffness of the aortic wall. To calculate these parameters, minimum diastolic and maximum systolic aortic diameters were measured in the subxiphoid long axis. The systolic aortic diameter was recorded during the maximum anterior movement of the aorta, and the diastolic diameter was recorded as the aortic diameter measured during the QRS peak, according to simultaneous ECG. The values measured from 10 consecutive heartbeats were averaged. Accordingly, strain, Ep, and normalized Ep were calculated according to the following formulas [24,30]: Strain = [(systolic aortic diameter − diastolic aortic diameter)/diastolic aortic diameter]; Pressure strain elastic modulus (Ep) = [(SBP-DBP)/strain]; and Normalized Ep (Ep*) = (Ep/DBP).

2.3 | Statistical analysis

The SPSS 24.0 (SPSS Inc.) package program was used for statistical analysis. The Kolmogorov- test was used to evaluate the normal distribution of continuous variables between groups. Normally distributed continuous variables were presented as mean ± standard deviation and compared by Student's *t* test, whereas parameters not distributed normally were presented as median (interquartile range, IQR) and compared by the Mann-Whitney *U* test. The chi-square test was used to compare categorical variables between groups, which were expressed as frequency. Depending on the distribution type of the variables, Pearson's or Spearman's correlation analysis was performed. Factors affecting specific parameters adjusted for age, gender, and BMI were assessed by linear regression analysis. Logistic regression analysis was used to determine the odds ratio for probability to have HT_{ABPM}. A *p*-value <.05 was considered statistically significant for all statistical evaluations.

3 | RESULTS

A total of 36 children with CSK and 36 healthy age- and gender-matched controls were enrolled in the study. We had excluded one patient with severe hydroureteronephrosis and vesicoureteral reflux, and two cases with heterogeneous Tc99m DMSA uptake in renal scan advised to be followed up for scarring although they had no reflux. Of the patients with CSK, 25 (69%) had MCDK, and 11 (31%) had URA. Single functioning kidneys were on the right side in 20 (56%) and on the left side in 16 (44%) of the patients with CSK. Eight (22%) of the patients had a prenatal diagnosis. The rest of the patients were found to have URA or MCDK by chance upon abdominal ultrasounds performed for abdominal complaints. One of the cases with URA had a history of maternal URA. None of the patients were active smokers.

3.1 | Laboratory findings

Serum creatinine, uric acid, and total cholesterol levels were significantly higher, while eGFR levels were significantly lower in patients with CSK (Table 1). In patients with CSK, only one patient had an eGFR < 90 ml/min/1.73 m^2, which was 82.5 ml/min/1.73 m^2 and all other eGFR values were ≥ 90 ml/min/1.73 m^2.

3.2 | BP measurements

Although office SBP and DBP levels were similar between the groups, most of the ABPM parameters, as well as cBP parameters, were significantly higher in patients with CSK (Table 2, Figure 1A-E). In ABPM, almost all SBP-related parameters including 24-hour SBP SDS, daytime SBP SDS, nighttime SBP SDS, 24-hour central SBP, daytime central SBP, nighttime central SBP, and daytime systolic load were higher in patients with CSK. Besides, 24-hour DBP SDS, daytime DBP SDS, 24-hour central DBP, daytime central DBP, 24-hour MAP SDS, daytime MAP SDS, and nighttime MAP SDS were also significantly higher in patients with CSK ($p < .05$, Table 2).

When we compared the BP phenotypes between the groups, the rate of patients with NT, MHT, WCHT, or AHT was similar between the groups ($p > .05$), while patients with HT_{ABPM} were significantly higher in the CSK group ($p = .001$, Table 3). The probability of HT_{ABPM} significantly increased with having CSK (OR: 6.00, 95% confidence interval: 2.15-16.71, $p = .001$).

3.3 | Ventricular repolarization indices

Electrocardiographic ventricular repolarization parameters, namely QTd, QTcd, Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc, and Tp-e/QTcd, were all similar between the groups ($p > .05$).

TABLE 1 Comparison of demographic and laboratory values

	CSK group (*n* = 36)	Control group (*n* = 36)	*p*
Age (year)	11 (4.75)	10.5 (3.75)	.298
Gender (male)	53%	53%	1.000
BMI	20.27 ± 3.64	19.50 ± 3.63	.389
BMI SDS	0.24 (2.11)	0.43 (1.72)	.963
Urea (mg/dl)	24.69 ± 5.88	23.98 ± 6.32	.628
Serum creatinine (mg/dl)	0.7 (0.2)	0.6 (0.2)	**.006**
eGFR (ml/min/1.73 m^2)	127.30 ± 19.85	138.8 ± 20.35	**.021**
Uric acid (mg/dl)	4.7 (2.4)	3.85 (2.30)	**.025**
Na (mmol/L)	139.5 (4)	140 (2)	.194
K (mmol/L)	4.33 (0.50)	4.36 (0.53)	.641
Triglyceride (mg/dl)	94 (61.75)	87.5 (53.5)	.326
Total cholesterol (mg/dl)	161.78 ± 30.91	146.50 ± 25.5	**.044**
ALT (IU/L)	13.5 (7.25)	13 (8.25)	.237
Microalbumin/creatinine (mg/g)	7 (9.40)	7.02 (12.89)	.860

Note: Data were defined as median (interquartile range) or mean ± standard deviation.

Abbreviations: BMI SDS, body mass index standard deviation score; BMI, body mass index; CSK, congenital solitary kidney; eGFR, estimated glomerular filtration rate.

3.4 | Arterial stiffness parameters

Abdominal arterial stiffness was assessed with PWV and AIx@75 by the oscillometric method and with strain, elastic modulus, and normalized elastic modulus (Ep and Ep*, respectively) calculated based on echocardiographic measurements. Although PWVs were significantly higher in patients with CSK (Figure 1E), AIx@75 values were similar between patients with CSK and healthy controls (Table 4). Strain, Ep, and Ep* were similar between the groups (Table 4). Since strain represents the "elasticity," and Ep and Ep* represent the "stiffness" of the arteries, we expected a negative correlation between PWV and strain and positive correlations between PWV and Ep and Ep*. However, a correlation in the reverse direction than expected was observed in the control group between 24-hour PWV and strain and between 24-hour PWV and Ep. When adjusted for age, gender, and BMI SDS, the significance only remained between 24-hour PWV and strain. In patients with CSK, 24-hour PWV tended to correlate with strain negatively and it was positively and significantly correlated with Ep and Ep*, which remained significant after adjustment for age, gender, and BMI SDS (Table 5).

4 | DISCUSSION

In our study, we have found that children with CSK have higher serum creatinine, uric acid, and total cholesterol levels with lower eGFR values, higher ABPM, and cBP measures despite similar office BP measurements and ventricular repolarization parameters; higher arterial stiffness determined by oscillometric PWA despite similar abdominal aortic stiffness parameters calculated concerning echocardiographic measurements; and similar LVMI values when compared to the healthy controls. PWV was significantly correlated with Ep and Ep* in cases with CSK.

The functional SKs try to compensate for the increased glomerular blood flow and the loss of function by increasing the workload leading to hyperfiltration, which increases the risk of HT, microalbuminuria, and impaired renal functions.[2,31,32] It has been shown that one out of every five cases with functional SK may have HT, and HT

TABLE 2 Comparison of office BP and ABPM parameters between the groups

Blood pressure parameters	CSK group	Control group	*p*
Office SBP SDS	0.69 ± 1.09	0.79 ± 0.96	.662
Office DBP SDS	0.72 ± 0.92	0.49 ± 0.74	.260
24-hour SBP SDS	−0.10 ± 0.92	−0.93 ± 0.71	**<.001**
24-hour DBP SDS	−0.47 ± 0.96	−1.01 ± 0.86	**.015**
24-hour MAP SDS	0.79 ± 0.74	0.06 ± 0.67	**<.001**
24-hour central SBP	98.79 ± 4.39	93.47 ± 6.20	**<.001**
24-hour central DBP	65.94 ± 5.41	62.18 ± 5.27	**.005**
24-hour central PP	44 (7.75)	42.5 (6.25)	.069
Daytime SBP SDS	−0.46 ± 0.82	−1.21 ± 0.75	**<.001**
Daytime DBP SDS	−0.78 ± 0.86	−1.24 ± 0.81	**.022**
Daytime MAP SDS	0.32 ± 0.71	−0.31 ± 0.66	**<.001**
Daytime central SBP	98.82 ± 5.69	93.74 ± 5.95	**.001**
Daytime central DBP	70 (6)	65.5 (8.25)	**.003**
Daytime central PP	44 (7.75)	42 (8)	.116
Daytime systolic load (%)	9 (17.5)	4 (7.75)	**.009**
Daytime diastolic load (%)	10.5 (12.75)	6 (14)	.275
Nighttime SBP SDS	0.63 ± 1.05	0.08 ± 0.76	**.014**
Nighttime DBP SDS	0.44 ± 0.93	0.18 ± 0.87	.226
Nighttime MAP SDS	1.43 ± 0.69	1.01 ± 0.78	**.018**
Nighttime central SBP	98.18 ± 5.85	92.85 ± 8.34	**.004**
Nighttime central DBP	59.42 ± 4.55	57.38 ± 5.82	.115
Nighttime central PP	46.5 (10.75)	44 (7)	.086
Nighttime systolic load (%)	22.5 (40)	8.5 (18.75)	.072
Nighttime diastolic load (%)	17.5 (29.25)	7 (17)	.107
Systolic dip (%)	5.85 ± 5.38	5.59 ± 5.32	.840
Diastolic dip (%)	13.1 ± 7.13	11.74 ± 8.30	.458

Note: Data were defined as median (interquartile range) or mean ± standard deviation.

Abbreviations: CSK, congenital solitary kidney, DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; SDS, standard deviation score.

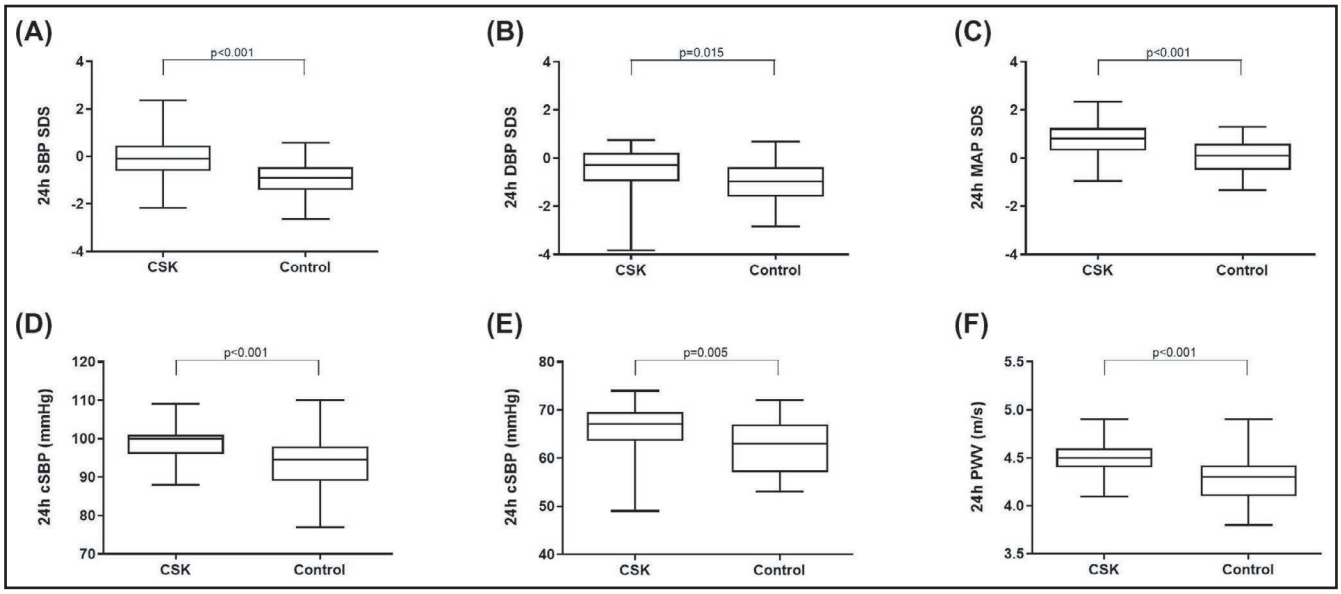

FIGURE 1 Box-whisker graphs of 24-hour SBP SDS (A), 24-hour DBP SDS (B), 24-hour MAP SDS (C), 24-hour central SPB (D), 24-hour central DPB (E), and 24-hour PWV (F) levels among the groups. (The horizontal lines within the boxes indicate the median, boundaries of the boxes indicate the 25th and 75th percentiles, and the whiskers indicate the minimum and maximum values of the results.). DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; SDS, standard deviation score

TABLE 3 Distribution of BP phenotypes between the groups

	CSK group (*n*, %)	Control group (*n*, %)	*p*
NT	20 (56)	23 (64)	.631
MHT	5 (14)	4 (11)	1.000
WCHT	8 (22)	9 (25)	1.000
AHT	2 (6)	0 (0)	.493
HT_{ABPM}	27 (75)	12 (33)	**.001**

Abbreviations: AHT, ambulatory hypertension; CSK, congenital solitary kidney; HT_{ABPM}, HT according to ABPM; MHT, masked hypertension; NT, normotension; WCHT, white coat hypertension.

TABLE 4 Comparison of stiffness indexes and LVMI findings between the groups

	CSK group	Control group	*p*
24-hour PWV (m/s)	4.50 (0.20)	4.30 (0.33)	**<.001**
24-hour AIx@75 (%)	21.20 (7.95)	18.65 (9.93)	.915
Daytime PWV (m/s)	4.50 (0.20)	4.30 (0.40)	**.001**
Daytime AIx@75 (%)	22.11 ± 6.41	21.96 ± 7.40	.928
Nighttime PWV (m/s)	4.49 ± 0.24	4.28 ± 0.31	**.004**
Nighttime AIx@75 (%)	13.73 ± 6.24	16.44 ± 6.92	.097
Strain[a]	0.13 ± 0.05	0.13 ± 0.07	.735
Ep (N/m^2; force/unit area)	315.38 (277.14)	337.39 (252.32)	.605
Ep* [a]	4.40 (4.27)	5.11 (4.13)	.899
LVMI ($g/m^{2.7}$)	31.27 ± 7.11	34.49 ± 6.99	.057

Note: Data were defined as median (interquartile range) or mean ± standard deviation.

Abbreviations: AIx@75, augmentation index corrected for heart rate; BMI, body mass index; CSK, congenital solitary kidney; Ep*, normalized Ep; Ep, pressure strain elastic modulus; LVMI, left ventricular mass index; PWV, pulse wave velocity.

[a]Strain and normalized Ep* are dimensionless ratios.

and/or microalbuminuria may be present in approximately half of the cases with CSK, especially in those with subtle dysplastic changes.[2,3] In addition, patients with SKs, including both CSK and ASK, have also been found to have lower eGFR levels, higher risk of HT, and MHT when evaluated with ABPM compared to healthy children.[1,32] Therefore, ABPM has been advised to be applied to all cases with SKs.[2] However, other studies stated that the risk of HT and levels of microalbuminuria and eGFR might be similar to those of healthy children in patients with unilateral SKs, in the event the SK was completely healthy or in cases who had a prenatal diagnosis and early postnatal follow-up.[5,33,34] Since subtle dysplastic anomalies may accompany CSK, we preferred to include only patients without any uptake defect or confirmed renal scarring in Tc^{99m}-DMSA.

In studies comparing cases with CSK and ASK, the results were much more conflicting. In one study, GFR was better in patients with CSK, which was thought to be associated with functional adaptation, while HT and microalbuminuria were similar.[35] In other studies, HT and/or ABPM parameters were significantly increased in patients with CSK,[2] while HT risk was increased in Wilms tumor survivors with ASK, eGFR values were similar to each other, and tubular

TABLE 5 Correlation of 24-hour PWV and other stiffness parameters and correlation coefficients when adjusted for age, gender, and BMI SDS

	All patients				CSK group				Control group			
	r	*p*	*β*[a]	*p*[a]	*r*	*p*	*β*[a]	*p*[a]	*r*	*p*	*β*[a]	*p*[a]
Strain	.140	.271	.074	.496	−.234	.197	−.272	.138	0,491	**.004**	.266	**.041**
Ep	−.138	.281	−.099	.366	.413	**.019**	.455	**.011**	−.478	**.006**	−.165	.222
Ep*	−.129	.301	−.094	.380	.361	**.042**	.385	**.036**	−.338	.055	−.130	.319

Abbreviations: Ep*, normalized Ep; Ep, pressure strain elastic modulus.

[a]When adjusted for age, gender, and BMI SDS.

damage was more common in patients with CSK.[6] In our study, we only included cases with CSK to avoid confusion. We found that most of the ABPM parameters were significantly higher in patients with CSK compared to the control group. It was an interesting finding that children with CSK in our study had 24-hour and daytime mean SBP and DBP values below the mean of the healthy children according to Wühl et al and control cases had even lower BP values. Besides, eGFR levels were significantly lower in cases with CSK, while the rate of microalbuminuria was similar among the groups in our study.

Central BP, which is considered to represent BP in the aortic root, is calculated from the pulse wave measured from the peripheral arteries via the transfer function and is generally lower than the value measured from the brachial artery.[9] In recent years, cBP measurement is superior in determining cardiovascular risk especially in young adults.[36] Since the middle-sized arteries such as the brachial artery are more elastic in children than in adults, the accumulation of pulse waves by the brachial artery results in higher brachial BP measurements in children although cBPs are within normal ranges.[37] Thus, measuring cBPs may prevent the overestimation of hypertension determined by peripheral ABPM measurements in children and young adults. The number of studies in childhood is scarce. In a recent study, children with primary hypertension had normal cBP values even in those with severe AHT, and cBP measures had at least the same or higher power as ABPM in predicting end-organ damage.[37] No studies have encountered cBP in children with CSK. In our study, cBP values were higher in patients with CSK and peripheral ABPM measurements confirming a real increase in BP. Also, we have demonstrated that having CSK increased the risk of HT_{ABPM} sixfold. Thus far, we may conclude that ABPM should be performed in cases with CSK.

Arterial stiffness can be evaluated by pulse wave analysis (PWA) or echocardiographic methods. The gold standard for PWA measurement is tonometry; however, this technique is operator-dependent and may be challenging in childhood and obesity.[19,24] Thus, the oscillometric method has been increasingly preferred as an easier way to assess PWA in recent years.[24,30] A pulse wave is generated when the left ventricle contracts. When a vessel wall hardens, its elasticity decreases, leading to early wave reflection and increased PWV. PWV is considered as a direct measure of vascular stiffness, whereas AIx@75 is considered as an indirect measure.[24] Increased PWV was reported to be closely associated with the risk of cardiovascular mortality and morbidity.[27] In our study, cBP, PWV, and AIx@75 were measured using an oscillometric device for PWA along with ABPM.[19] No studies have been conducted on vascular stiffness in patients with SKs. To fill this gap, one of our aims was to assess the risk of increased PWV in children with CSK. In our study, arterial stiffness determined by PWA was higher in patients with CSK, although abdominal aortic strain representing elasticity of the aorta, and Ep and Ep* representing stiffness of the aortic wall determined by echocardiography [38] were similar between the groups. Although they were stiffness parameters determined by different methods, PWV was only significantly correlated with Ep and Ep* in patients with CSK, who were the risky group for arterial stiffness. In a previous study,[39] brachial PWV measurements with a tonometer were correlated with strain, distensibility, and elastic modulus determined by echocardiographic measurements mainly in NT patients. In our healthy patients, echocardiographic elasticity and stiffness determinations were correlated with PWV but in the reverse direction than expected. This finding should be checked in larger series. On the other hand, we may consider that PWV determined along with ABPM by the same device may be beneficial in children with CSK.

Stiffening of arteries leads to increased cBP, which indicates increased LVH and associated comorbidities such as arrhythmias.[7,11,37,40] Despite increased PWV and cBP levels in patients with CSK, we did not observe any increase in LVMI or tendency for ventricular arrhythmia or sudden cardiac death. To the best of our knowledge, this is the first study assessing the ventricular repolarization parameters in patients with CSK.

Our study has some limitations. The patients were not being followed up from the prenatal or early postnatal period, which might have changed the outcomes. We have tried to evaluate all cardiovascular parameters that we could, and this might make it difficult to follow the manuscript. Since L, M, and S levels needed to calculate SDS levels for 24-hour oscillometric cBP and PWV were not available, we could only use raw measurements of 24-hour cBP and PWVs instead of their SDS values. The lack of patients with ASK in our study would be considered as another limitation; however, we thought that including only patients with CSK would provide a homogenous study group.

In conclusion, we have found that children with CSK have lower GFR levels, as shown in several previous studies. For the first time in the literature, we have shown that cBP and PWV values are higher in children with CSK compared to healthy controls; however, they have

no increased tendency for ventricular arrhythmia. Since we have additionally found that CSK increased the risk of HT_{ABPM}, determining cBP and PWV along with 24-hour ABPM would be a useful tool to detect children with CSK at risk for HT and cardiovascular events. Further studies seem to be needed to define the most efficient parameter of the PWA-ABPM device for defining and predicting cardiovascular problems in children with CSK.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Belde Kasap-Demir served as the principle investigator and involved in all aspects of the study, including study concept, study design, recruitment of patients, data analysis, and manuscript preparation. Eren Soyaltın and Seçil Arslansoyu-Çamlar involved in the recruitment of patients, data analysis, and manuscript preparation. Caner Alparslan involved in data acquisition. Demet Alaygut and Önder Yavaşcan involved in study design. Tülay Demircan performed echocardiographic evaluation. Fatma Mutlubaş involved in data interpretation. Cem Karadeniz involved in electrocardiographic data evaluation and manuscript preparation.

INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study and their parents or legal guardians.

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