Reduced Systolic Myocardial Function in Children with Chronic Renal Insufficiency

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Increased left ventricular (LV) mass in children with chronic renal insufficiency (CRI) might be adaptive to sustain myocardial performance in the presence of increased loading conditions. It was hypothesized that in children with CRI, LV systolic function is impaired despite increased LV mass (LVM). Standard echocardiograms were obtained in 130 predialysis children who were aged 3 to 18 yr (59% boys) and had stages II through IV chronic kidney disease and in 130 healthy children of similar age, gender distribution, and body build. Systolic function was assessed by measurement of fractional shortening at the endocardial (eS) and midwall (mS) levels and computation of end-systolic stress (myocardial afterload). The patients with CRI exhibited a 6% lower eS (33.1 ± 5.5 *versus* 35.3 ± 6.1%; $P < 0.05$) and 10% lower mS (17.8 ± 3.1 *versus* 19.7 ± 2.7%; $P < 0.001$) than control subjects in the presence of significantly elevated BP, increased LVM, and more concentric LV geometry. Whereas the decreased eS was explained entirely by augmented end-systolic stress, mS remained reduced after correction for myocardial afterload. The prevalence of subclinical systolic dysfunction as defined by impaired mS was more than five-fold higher in patients with CRI compared with control subjects (24.6 *versus* 4.5%; $P < 0.001$). Systolic dysfunction was most common (48%) in patients with concentric hypertrophy and associated with lower hemoglobin levels. CRI in children is associated with impaired intrinsic LV contractility, which parallels increased LVM.

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Alterations of cardiac morphology and function are a common characteristic of ESRD in adult patients and contribute to the higher cardiovascular risk that is associated with this condition (1). Even in the pediatric age, up to 25% of deaths in patients with ESRD are attributable to cardiovascular disease (2). Previous echocardiographic studies indicate that young patients with chronic renal insufficiency (CRI) and ESRD have abnormal left ventricular (LV) geometry and high prevalence of LV hypertrophy (LVH) (3–6). We recently reported that substantial LV remodeling of both concentric and eccentric type occurs also at early stages of CRI in children (7). We found abnormal LV anatomy mainly related to male gender, anemia, and ponderosity but not to BP.

In adults with CRI, LVH is thought to be adaptive initially to improve pump function and lower wall stress in the face of increased afterload (BP) and preload (circulating volume) (8). Consistent with this line of interpretation, normal or even supranormal LV systolic function has been observed in children with CRI, suggesting that increased LV mass (LVM) may represent a compensatory response that balances increased hemodynamic load also in young patients (6,9). In a more recent study in children who were undergoing dialysis, resting LV systolic performance was increased, possibly attributable to the presence of LVH, but LV functional reserve during exercise was decreased, suggesting that LVH actually was maladaptive (10). In the same study, the response to exercise was normal in children with mild to moderate CRI, suggesting that different physiopathologic mechanisms may be operating in LV remodeling in predialysis and dialysis patients.

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In adults, assessment of LV systolic function at the chamber level has been shown to overestimate the real extent of myocardial performance in the presence of concentric LV geometry (11,12). Analysis of LV shortening at the midwall level (midwall shortening [mS]) more accurately reflects the contractile force independent of pathologic changes in LV geometry, which have been demonstrated to preserve LV chamber function when myocardial contractility is depressed (11). At present, there is no information on LV wall mechanics in children with predialysis CRI. Accordingly, our study was designed to assess whether children with mild to moderate CRI have impaired LV systolic wall mechanics at rest, independent of possibly adaptive changes in LV geometry.

Materials and Methods

Patients and Control Subjects

The ongoing Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRI in Pediatric Patients (ESCAPE) trial is a European multicenter study that is evaluating predialysis white children who are being treated for CRI in 33 pediatric nephrology units in 13 European countries (see Acknowledgments); of these, 130 (77 boys and 53 girls) had echocardiographic recordings that were suitable for the analysis of both cardiac geometry and systolic function and comprised the population of this analysis. Children were studied as part of the screening procedure for the ESCAPE trial (13). The study protocol, including echocardiographic examinations, ambulatory BP monitoring, and biochemical assessments, was designed in adherence to the Declaration of Helsinki and approved by the local ethical committees. Written informed consent was given from all parents, and informed consent or assent from the patients was given as appropriate. A group of 130 normotensive white individuals who were studied in Naples, Italy, including a school population and normal volunteers (7,14), formed the normal reference population for our study.

Laboratory Assessments

A full biochemical profile was obtained locally in each center using standard laboratory techniques, as previously reported (7,13).

Echocardiography

Echocardiograms initially were obtained in 179 children, according to local procedures and in the absence of standardization of acquisition methods, using different commercial machines. Videotapes were shipped to the Reading Center, at the Echocardiography Laboratory of the Department of Clinical and Experimental Medicine, "Federico II" University of Naples, for quality check and off-line reading. Quality of two-dimensional echocardiograms for measurements of LV dimensions and systolic function was considered sufficient in 130 individuals (73% of echocardiograms). All echocardiograms were coded and examined off-line by two independent readers according to standard procedures (13,15), as previously reported (7). LVM was obtained according to a necropsy-validated formula (16,17) and normalized for height in meters to the allometric power of 2.7 ($m^{2.7}$, LVM index [LVMI]) (18). LVH was defined as an LVMI >95th percentile of the healthy control subjects (38 $g/m^{2.7}$) for both male and female individuals, as previously suggested (7).

For evaluation of the concentricity of LV geometry, myocardial thickness (wall+septum) was divided by LV minor axis (diameter) to generate a relative wall thickness (RWT), normalized to a mean age of 10 years (19). A value of 0.38 (95th percentile of controls) was used as the cutoff to define concentric LV geometry (7).

Evaluation of LV Systolic Function

LV systolic function was determined by linear measures of shortening of LV minor axis both at the endocardial level (endocardial shortening [eS]) and at the midwall level (mS) (11,12). Systolic dysfunction was categorized as mS <16% (the fifth lowest percentile of normal distribution in the control group of this study).

To account for the effect of myocardial afterload and for the demonstrated influence of age on the stress/shortening relations, we calculated circumferential end-systolic wall stress (σ), a measure of myocardial afterload, assuming a cylindrical geometry (20) and using BP values that were measured in a sitting position during an office visit. Because shortening is a negative function of σ, the derived equation can be used to predict the corresponding value of both eS and mS for a given σ. Thus, age-adjusted, stress-corrected endocardial fractional shortening (eSc) or stress-corrected mS (mSc) were computed as the ratio between observed and predicted values and expressed as a percentage of the predicted value, using the following equations that were derived from our reference population (21):

$$eSc = eS/(90.13 \text{ to } 24.89 \times \log_{10}[\sigma] - 0.32\,[age] - 4.16) \times 100$$

$$mSc = mS/(30.78 \text{ to } 3.98 \times \log_{10}[\sigma] - 0.26\,[age] - 2.75) \times 100$$

Therefore eSc and mSc describe LV chamber and myocardial contractility, respectively.

Statistical Analyses

All results are expressed as means ± SD. Statistical analysis was performed using SPSS 12.0 (SPSS, Chicago, IL). Between-group differences were assessed by ANOVA. The Ryan-Einot-Gabriel-Welsch F *post hoc* test for multiple comparisons was used for more than two groups. χ^2 statistics (with Monte Carlo method to compute exact two-tailed α value, when appropriate) was used to examine categorical variables. When appropriate, analysis of covariance was used to control for potential confounders. Sidak's adjustment of P value was adopted for multiple comparisons in analysis of covariance when needed. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

The baseline clinical characteristics of the patients and control subjects are given in Table 1. Among the 130 patients with CRI, 33% were class II (*i.e.*, GFR 60 to 89 ml/min per 1.73 m^2), 43% class III (GFR 30 to 59 ml/min per 1.73 m^2) and 22% class IV (GFR 15 to 29 ml/min per 1.73 m^2). The underlying renal diseases were renal hypo/dysplasia in 72%, other congenital or hereditary disease in 16%, and glomerulopathies in 12%. Whereas age, gender distribution, and anthropometric measures did not differ between patients and control subjects, casual office BP was significantly higher in patients with CRI than in control subjects ($P < 0.0001$).

LV Morphology and Function

As previously reported (7), children with CRI had increased LV diameter, LVM, and RWT compared with healthy control subjects (Table 2). eS was slightly lower in children with CRI than in control subjects ($P < 0.05$). Correction for end-systolic stress yielded completely normal eS values, suggesting that the apparent decrease in eS was due entirely to increased myocardial afterload. In contrast, mS was reduced markedly ($P < 0.001$; Table 2), and this reduction was independent of myocardial afterload as shown by a persistent difference in stress-

Table 1. Anthropometric and BP characteristics of 130 patients with CRI and 130 healthy control subjects[a]

Characteristic	Patients with CRI	Control Subjects	*P*
Gender (% boys)	59	53	NS
Age (yr)	11.3 ± 4.1	10.6 ± 3.6	NS
Height (cm)	139 ± 20	142 ± 23	NS
Weight (kg)	39.6 ± 16.9	36.9 ± 16.4	NS
BMI (kg/m^2)	18.3 ± 3.1	18.0 ± 3.6	NS
Casual systolic BP (mmHg)	118 ± 13	106 ± 9	<0.001
Casual diastolic BP (mmHg)	73 ± 11	62 ± 9	<0.001
Heart rate (beats/min)	83 ± 19	81 ± 15	NS
Duration of CRI (yr)	6.3 ± 4.4	—	
CKD class II/III/IV (%)	33/43/22	—	
GFR (ml/min per 1.73 m^2)	50 ± 19	—	
Urinary protein excretion (mg/m^2 per d)	735 ± 1338	—	
Blood hemoglobin (g/dl)	12.1 ± 1.6	—	

[a]Data are means ± SD. BMI, body mass index; CKD, chronic kidney disease; CRI, chronic renal insufficiency.

Table 2. LV morphology and systolic function in 130 patients with CRI and 130 healthy control subjects[a]

Parameter	Patients with CRI	Control Subjects	*P*
LV end-diastolic diameter indexed for height (cm/m)	3.01 ± 0.36	2.91 ± 0.29	<0.005
LV mass index (g/m$^{2.7}$)	36.4 ± 13.2	26.5 ± 6.2	<0.001
Relative wall thickness (%)	0.34 ± 0.05	0.30 ± 0.06	<0.05
eS (%)	33.1 ± 5.5	35.3 ± 6.1	<0.05
mS (%)	17.8 ± 3.1	19.7 ± 2.7	<0.001
End-systolic stress (kdynes/cm^2)	144 ± 38	126 ± 31	<0.002
Age and stress-corrected eS (% predicted)	100.9 ± 12.1	100.4 ± 13.0	NS
Age and stress-corrected mS (% predicted)	91.1 ± 15.6	101.5 ± 13.9	<0.001
Reduced systolic function (%)	24.6	4.5	<0.01

[a]eS, endocardial shortening; mS, midwall shortening.

corrected mS ($P < 0.001$). As illustrated in Figure 1, mS was lower in children with CRI compared with healthy control subjects at any given value of fractional shortening measured at the chamber level ($P < 0.001$). The overall prevalence of systolic dysfunction was increased five-fold in the CRI group ($P < 0.01$). Systolic dysfunction was significantly more prevalent in patients with concentric LV geometry (48% of patients) than in patients with either normal LV geometry or eccentric LVH ($P < 0.0001$; Figure 2).

Characteristics of Children with Systolic Dysfunction

LV mS, expressed either as raw value or corrected for end-systolic stress, was positively associated with GFR ($r = 0.20$ and 0.21 respectively; each $P < 0.05$) and negatively with RWT ($r = -0.42$ and -0.52 respectively; each $P < 0.0001$). Children with normal or impaired systolic function did not differ with respect to LVMI (36.4 ± 13.5 *versus* 36.2 ± 12.6 g/m$^{2.7}$), but those with systolic dysfunction at the midwall level exhibited greater RWT (0.36 ± 0.07 *versus* 0.33 ± 0.05; $P < 0.005$). LV systolic function was not correlated with any of the BP measures (casual or 24-h ambulatory BP). Children with reduced systolic function had lower hemoglobin levels than patients with normal mS (11.8 ± 1 *versus* 12.4 ± 1.5 g/dl). Notably, in the patients with subnormal systolic function, mS was inversely correlated with the current rate of GFR loss ($r = 0.55$, $P < 0.005$).

Discussion

Our study reports on the largest population sample of children who have CRI and in whom LV function has been assessed, including intrinsic wall contractility as assessed by computation of echocardiographic parameters that match LV chamber function and wall mechanics with a reliable measure of myocardial afterload. This study shows that despite normal LV chamber function, myocardial dysfunction can be identified at the midwall level in children and adolescents with mild to moderate CRI. Similar to adults with arterial hypertension (22), this pathology is more pronounced in the presence of concentric LV geometry.

In children with CRI, a single report by Colan *et al.* (23) found a significantly reduced ejection fraction in children who were undergoing dialysis, whereas most other previous studies of children with predialysis or dialysis-dependent CRI showed a normal or even supranormal ejection fraction at rest (6,9,10,24).

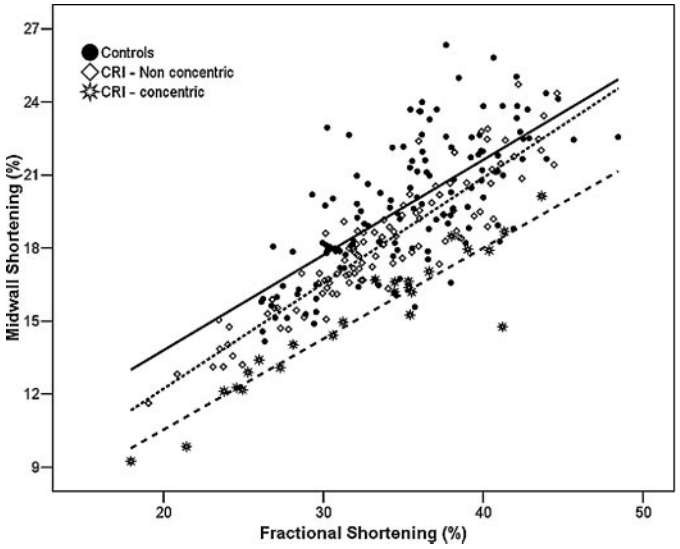

Figure 1. Relationship between fractional shortening (FS%) and midwall shortening (mS%) in normal control subjects (●, solid line) and children with chronic renal insufficiency (CRI) and nonconcentric (◇, dotted line) or concentric (stars, dashed line) left ventricular (LV) geometry.

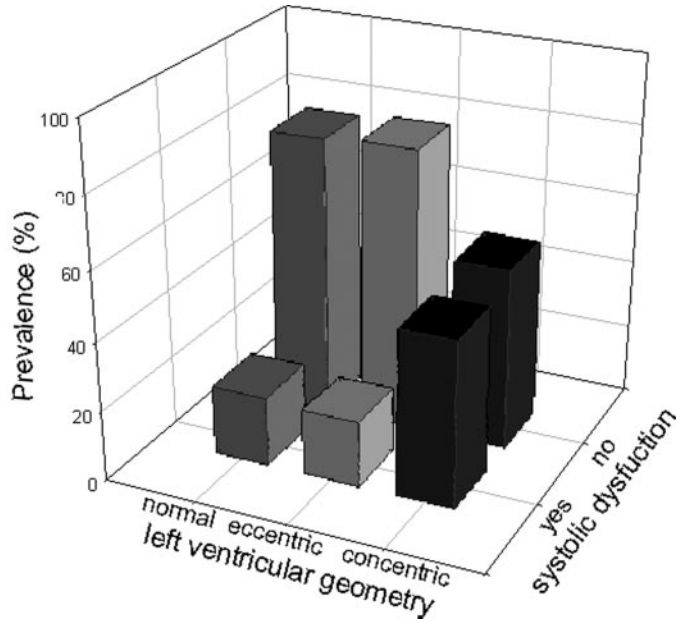

Figure 2. Percentage of patients with impaired systolic function according to LV geometry (concentric *versus* eccentric *versus* normal geometry) in children with CRI ($n = 130$).

However, systolic dysfunction is well established in adult patients who have longstanding CRI and are undergoing dialysis (25), and mild systolic dysfunction also has been observed in dialyzed children during exercise testing (4). Therefore, it has been suggested that the observation of normal (or even supranormal) systolic function in pediatric patients with CRI represents an adaptive mechanism to increase cardiac output and improve renal perfusion. However, no previous pediatric study has analyzed LV function at both the endocardial and the midwall levels, related LV mechanics to myocardial afterload, and examined the relationship between systolic function and LV geometry.

In the two previous studies that assessed LV geometry in children, concentric LVH was frequent in predialysis CRI, at a prevalence that might explain the seemingly normal LV function at the chamber level (6,7). In fact, concentric LV geometry has been demonstrated to preserve LV chamber function even when myocardial contractility is depressed (11). We found a slight reduction of average systolic function at the LV chamber level; however, this was readily explained by the increased myocardial afterload (end-systolic stress, as seen in Table 2) despite increased myocardial wall thickness, suggesting that the compensatory increase in myocardial thickness was not sufficient to offset the elevated end-systolic stress. We recently demonstrated that the hemodynamic pattern of children with CRI is characterized by a combined pressure and volume overload (7). This condition might offset at least in part the effect of wall thickness (Laplace principle) (26). When endocardial fractional shortening was adjusted for end-systolic stress, LV chamber function in fact was completely normal, providing evidence that the slight decrease of uncorrected endocardial fractional shortening was due to an "afterload mismatch" (*i.e.*, the reduction of net LV chamber performance resulting from increased afterload that is not fully compensated by an adequate increase in—albeit normal—endocardial function).

In contrast, mS, a more direct measure of wall mechanics, was decreased substantially. The reduction remained evident also after correction for the level of myocardial afterload, highlighting a decrease in intrinsic myocardial contractility. Although midwall systolic function was globally correlated with GFR, we were unable to associate any specific sequelae of CRI with the impaired myocardial function in this pediatric population with mild to moderate chronic kidney disease. The observed slightly lower hemoglobin level in the patients with systolic dysfunction may indicate a subclinical effect of suboptimal myocardial oxygenation in early renal anemia.

Our finding of a significant prevalence of subclinical systolic dysfunction in children with mild to moderate CRI may be of clinical relevance, because in hypertensive adults with normal LV chamber function, reduced midwall function is associated with an unfavorable cardiovascular prognosis (27). Remarkably, in patients who exhibited systolic dysfunction, we also noted a close quantitative relationship between mS and the current CRI progression rate. It is tempting to speculate about a putative common mechanism underlying both cardiac dysfunction and progressive loss of renal function, which might include sympathetic hyperactivation and/or overstimulation of the renin-angiotensin system at the tissue levels.

Conclusion

LV systolic function measured at the midwall level is decreased significantly in children with predialysis CRI. This impairment is independent of increased myocardial afterload and BP but linked to concentric LV geometry. In view of similar observations in adults, the combination of concentric LV geom-

etry with midwall dysfunction might represent a cardiac phenotype designating an increased risk for development of overt cardiovascular disease.

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Disclosures

None.

References

1. Parfrey PS, Foley RN: The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 10: 1606–1615, 1999
2. Parekh RS, Caroll CE, Wolfe RA, Port FK: Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr* 141: 191–197, 2002
3. Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF: Severe left ventricular hypertrophy in pediatric dialysis: Prevalence and predictors. *Pediatr Nephrol* 14: 898–902, 2000
4. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 47: 186–192, 1995
5. Levin A, Singer J, Thompson CR, Ross H, Lewis M: Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. *Am J Kidney Dis* 27: 347–354, 1996
6. Johnstone LM, Jones CL, Grigg LE, Wilkinson JL, Walker RG, Powell HR: Left ventricular abnormalities in children, adolescents and young adults with renal disease. *Kidney Int* 50: 998–1006, 1996
7. Matteucci MC, Wuhl E, Picca S, Mastrostefano A, Rinelli G, Romano C, Rizzoni G, Mehls O, de Simone G, Schaefer F; ESCAPE Trial Group: Left ventricular geometry in children with mild to moderate chronic renal insufficiency. *J Am Soc Nephrol* 17: 218–226, 2006
8. Dahan M, Siohan P, Viron B, Michel C, Paillole C, Gourgon R, Mignon F: Relationship between left ventricular hypertrophy, myocardial contractility, and load conditions in hemodialysis patients: An echocardiographic study. *Am J Kidney Dis* 30: 780–785, 1997
9. Palcoux JB, Palcoux MC, Jouan JP, Gourgand JM, Cassagnes J, Malpuech G: Echocardiographic pattern in infants and children with chronic renal failure. *Int J Pediatr Nephrol* 3: 311–314, 1982
10. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR: Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. *Circulation* 107: 864–868, 2003
11. de Simone G, Devereux RB, Celentano A, Roman MJ: Left ventricular chamber and wall mechanics in the presence of concentric geometry. *J Hypertens* 17: 1001–1006, 1999
12. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, Laragh JH: Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. *J Am Coll Cardiol* 23: 1444–1451, 1994
13. Sahn DJ, DeMaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: Results of a survey of echocardiographic measurements. *Circulation* 58: 1072–1083, 1978
14. de Simone G, Mureddu G, Greco R, Scalfi L, Del Puente AE, Franzese A, Contaldo F, Devereux RB: Relations of left ventricular geometry and function to body composition in children with high casual blood pressure. *Hypertension* 30: 377–382, 1997
15. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux RB, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, Silverman NH, Tajik AJ: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2: 358–367, 1989
16. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 57: 450–458, 1986
17. Daniels SR, Meyer RA, Liang YC, Bove KE: Echocardiographically determined left ventricular mass index in normal children, adolescents and young adults. *J Am Coll Cardiol* 12: 703–708, 1988
18. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 20: 1251–1260, 1992
19. de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M, Galderisi M, Devereux RB: Evaluation of concentric left ventricular geometry in humans: Evidence for age-related systematic underestimation. *Hypertension* 45: 64–68, 2005
20. Shimizu G, Hirota Y, Kita Y, Kawamura K, Saito T, Gaasch WH: Left ventricular midwall mechanics in systemic arterial hypertension. Myocardial function is depressed in pressure-overload hypertrophy. *Circulation* 83: 1676–1684, 1991
21. de Simone G, Kimball TR, Roman MJ, Daniels SR, Celentano A, Witt SA, Devereux RB: Relation of left ventricular

chamber and midwall function to age in normal children, adolescents and adults. *Ital Heart J* 1: 295–300, 2000
22. Mureddu GF, Pasanisi F, Palmieri V, Celentano A, Contaldo F, de Simone G: Appropriate or inappropriate left ventricular mass in the presence or absence of prognostically adverse left ventricular hypertrophy. *J Hypertens* 19: 1113–1119, 2001
23. Colan A, Sanders SP, Ingelfinger JR, Harmon W: Left ventricular mechanics and contractile state in children and adolescents with end-stage renal disease: Effect of dialysis and renal transplantation. *J Am Coll Cardiol* 10: 1085–1094, 1987
24. Valsangiacomo E, Neuhaus TJ, Goetschel P, Bauersfeld U: Cardiac rhythm disturbances in children on hemodialysis. *Pediatr Nephrol* 17: 837–841, 2002
25. Perfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE: Outcome and risk factors for left ventricular disorders in chronic uremia. *Nephrol Dial Transplant* 11: 1328–1331, 1996
26. de Simone G: Left ventricular geometry and hypotension in end-stage renal disease: A mechanical perspective. *J Am Soc Nephrol* 14: 2421–2427, 2003
27. de Simone G, Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH: Midwall left ventricular mechanics. An independent predictor of cardiovascular risk in arterial hypertension. *Circulation* 93: 259–265, 1996