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**PhD THESIS**

**INAPPROPRIATE LEFT VENTRICULAR MASS, IN CHILDREN  
WITH PREDYALITIC CHRONIC RENAL INSUFFICIENCY**

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## Abstract

**Background:** Increased left ventricular (LV) mass in children with chronic renal insufficiency (CRI) might represent an adaptive mechanism to compensate for increased workload. We hypothesize that in pre-dialysis CRI children, values of LV mass exceed compensatory value for individual cardiac load. **Methods:** Complete anthropometrics, biochemical profile and echocardiograms were obtained in 33 children with pre-dialysis CRI (age 1-23 yrs, mean 12.2±5.0 yrs; 22 males) and 33 age- and gender-matched healthy controls. LV dimensions and wall thicknesses were measured from the M-mode, LV volume and long-axis dimension from the 2-D, blood pressure from 24-hour ambulatory recordings. Endocardial shortening, ejection fraction, LV mass, LV mass index, relative wall thickness, circumferential wall stress, and excess of LV mass (as ratio of observed LV mass to value predicted from body size, gender, and cardiac workload) were analyzed. **Results:** CRI patients showed higher values of indexed LV chamber diameter and LV mass index, resulting in significantly higher prevalence of LVH (36.3 vs 9%; all p<0.05). In addition CRI patients showed lower LV ejection fraction, lower midwall fractional shortening and lower stress-corrected midwall shortening. The ratio of excess of LV mass was significantly greater in CRI patients than in normal controls (126±19 vs 103±13%; p<0.001). **Conclusions:** In CRI children values of LV mass are higher than those needed to sustain individual cardiac load compared to normal controls, a condition associated with LVH and reduced systolic performance.

## INTRODUCTION

Chronic renal insufficiency (CRI) is associated with the development of cardiac remodelling, premature cardiomyopathy (1, 2, 3, 4) and increased cardiovascular morbidity and mortality. In adult patients with longstanding CRI undergoing dialysis, left ventricular (LV) hypertrophy is common and LV systolic function is often reduced (5). LV hypertrophy is present in more than 30% of patients in the early phases of CRI (6-8) and has been considered to be an adaptation to increased cardiac load (9, 10). Both concentric and eccentric LVH are seen in children with mild to moderate chronic renal failure (8,11), consistent with combined pressure and volume overload present in this condition. Recent data on CRI children undergoing dialysis indicate that despite normal LV chamber function at rest, LV functional reserve during exercise is often decreased (11). We have recently reported depressed resting LV midwall function and contractility, despite normal ejection fraction, in children with mild CRI and concentric LV geometry (12). We have suggested that the combination of concentric LV geometry and midwall dysfunction might represent a cardiac phenotype at higher risk of developing overt cardiovascular disease in children, consistent to what previously reported for adults (13). We have also demonstrated that the combination of concentric geometry with combined systolic and diastolic dysfunction features a cardiovascular phenotype characterized by levels of LV mass that are greater than predicted by individual body size and cardiac workload, a condition called excess of, or inappropriate LV mass (14). This excess of LV

mass is also associated with high cardiovascular risk independent of the presence of clear-cut LVH (15-17).

Also in children with mild to moderate CRI, we found a combination of LV concentric geometry and systolic dysfunction at the midwall level (12), but there is no information on whether this phenotype also correspond to excessive levels of LV mass, similar to what has been found in adults. Accordingly, in the present study we tested the hypothesis that the LV response is excessive in children with mild-to-moderate CRI, referred to individual body size and cardiac workload, and that, similar to adult populations, the excess of LV mass is associated with LV concentric geometry and dysfunction.

## **METHODS**

### *Patients and control subjects*

Thirty-three children with established CRI from the Nephrology Unit of Bambino Gesù Children's Hospital and a group of 33 sex and gender-matched healthy, non-obese children were enrolled in the study. Patients and controls underwent complete echocardiographic examination with simultaneous office blood pressure (BP) measurement. Ambulatory blood pressure monitoring (ABPM) and biochemical assessments were obtained in CRI patients. Data from a series of 130 normal children from previous studies (8, 18) were also analyzed to generate normal gradients of echocardiographic variables with age. The study protocol was designed in adherence to the declaration of Helsinki and approved by the Bambino Gesù Children's Hospital Ethical Committee. Written informed consent was obtained from all parents and informed consent or assent from the patients when appropriate.

### *BP Monitoring*

ABPM was performed only in CRI patients with a Spacelabs 90207 automatic cuff-oscillometric device (Issaquah, WA). The cuff size was adjusted to the individual upper arm circumference. ABPM measurements were performed according to previously described standardized protocol (19). ABPM measurements were performed every 15 minutes during daytime and every 20-30 minutes at night. All ABPM profiles were analyzed centrally. ABPM profiles were divided into daytime (8:00 a.m. to 8:00 p.m.) and nighttime periods (12:00 p.m. to 6:00 a.m.). Mean values of 24-h, systolic, and diastolic BP were calculated

and compared with reference data from healthy children (20) and presented as standard deviations from normal mean. Office BP measurements were obtained in patients and controls at the time of echocardiography after sitting for 5 min in a relaxed position, using oscillometric devices.

#### Laboratory assessments

A full biochemical profile was obtained only in CRI patients using standard laboratory techniques. In addition, serum and urinary sodium, creatinine, C-reactive protein (CRP, ultrasensitive assay), intact parathyroid hormone (Immulite Intact PTH, Medical Systems, Los Angeles) were measured. GFR was estimated from serum creatinine and height using the pediatric equations of Schwartz et al (21).

#### Echocardiography

Echocardiograms were performed in all participants using commercially available machines and standardized procedures and recorded onto videotapes. Videotapes were shipped to the Echocardiography Laboratory of the Department of Clinical and Experimental Medicine “Federico II” University of Naples, Italy, for quality control and off-line reading. Echocardiograms were digitally acquired and electronically read using specifically designed work stations (MediMatic S.r.l., Genoa, Italy) according to standard procedures as previously reported (8). Measurements were made from either parasternal short-axis M-mode or parasternal long-axis two-dimensional images accordingly to the recommendations of the American Society of Echocardiography (22,23).

#### Echocardiographic derived variables

LV mass was obtained according to a necropsy validated formula (24, 25) and normalized for height in meters to the allometric power of 2.7 (LVMI), to account for differences in body growth (26). LV hypertrophy (H) was defined when LVMI was greater than  $38 \text{ g/m}^{2.7}$ , as previously reported (8). To evaluate the concentricity of LV geometry, myocardial thickness (posterior wall + septum) was divided by LV minor axis (diameter) to generate a relative wall thickness (RWT). LV diastolic diameter was normalized by height.

Stroke work was estimated by systolic blood pressure times stroke volume, calculated by the Teichholz formula (Teichholz, AJC) and converted to grams/beat by multiplying by 0.014 (27). To establish whether the LVM was consistent with the increase in cardiac workload we calculated the individual predicted ideal value of LVM (LVM<sub>p</sub>) using the following equation generated in a reference normotensive, normal-weight population of children and adolescents (27) by stroke work, gender (male gender=1, female gender=2) and height in meters to the 2.7 power:

$$LVM_p = 1.59 + 17.81 \times \text{height}^{2.7} + 0.36 \times \text{stroke work} - 3.88 \times \text{gender}.$$

The value of LVM measured from echocardiograms was divided by LVM<sub>p</sub> and expressed as % of predicted value ( $\Delta\%LVM$ ). Values of  $\Delta\%LVM > 95^{\text{th}}$  percentile of reference population (138%) were considered inappropriately high, indicating clear-cut excess of LVM relative to the value that would compensate and sustain the individual cardiac workload.

End-systolic wall stress was estimated using a cylindrical model as previously reported (28)

$$cESS = \frac{SBP(\frac{1}{2}LVID_s)^2 [1 + \frac{(\frac{1}{2}LVID_s + PWT_s)^2}{(\frac{1}{2}LVID_s + \frac{1}{2}PWT_s)^2}]}{(\frac{1}{2}LVID_s + PWT_s)^2 - (\frac{1}{2}LVID_s)^2}$$

where SBP is systolic pressure in mmHg, LVIDs is end-systolic diameter in cm, PWTs is end-diastolic posterior wall thickness in cm.

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) (29-30). To account for the effect of myocardial afterload and for the demonstrated influence of age on the stress/shortening relations, both eS and mS were also expressed as the ratio between the observed values and the values predicted from individual age and circumferential end-systolic wall stress ( $\sigma$ ), using equations developed in a 4-to-17 year-old reference normal population of children and adolescents (31):

$$\begin{aligned} eS &= 90.13 - 24.89 * \log_{10}[\sigma] - 0.32 \text{ [years]} \\ mS &= 30.78 - 3.98 * \log_{10}[\sigma] - 0.26 \text{ [years]} \end{aligned}$$

LV diastolic function was assessed by transmitral pulsed Doppler, recorded in apical 4-chamber view according to standard procedures. Peak early (E) and late, or atrial (A), velocities were recorded and their ratio calculated.

### Statistical Analysis

Statistical analyses was performed using SPSS 15.0.0 (SPSS Inc., Chicago, Illinois) software. Data are presented as mean $\pm$ SD for continuous variables and as proportions for categorical variables. Chi-square statistics were used to determine



differences for categorical variables (with Monte Carlo method to compute exact two-tailed alpha value, when appropriate). One-way analysis of variance and analysis of variance were used to compare continuous variables both in cases and controls and in subgroup-analysis, always including controls. When needed, Ryan-Einot-Gabriel-Welsch F post-hoc test was used, or main effects were compared by Sidak's adjustment of p value. The p values were shown for post-hoc tests. Two-tailed  $p < 0.05$  was considered statistically significant.

## RESULTS

### Patient characteristics

The baseline clinical characteristics of patients and control subjects are given in Table 1 and 2. Among the 33 CRI patients, 15 (45.5%) were CKD class II (i.e. GFR 60-89 mL/min/1.73 m<sup>2</sup>), 3 (9%) class III (GFR 30-59 mL/min/1.73 m<sup>2</sup>) and 15 (45.5%) class IV (GFR 15-29 mL/min/1.73 m<sup>2</sup>). The underlying renal diseases were renal hypo/dysplasia in 63%, other congenital or hereditary disease in 30% and glomerulopathies in 7%. CRI patients and controls showed similar values of BMI, casual systolic/diastolic blood pressure and heart rate (all p=NS). 24-h BP in CRI patients was 0.6 SDS relative to reference populations (20).

### Cardiac Geometry and Function (table 2).

CRI patients showed higher values of indexed LV chamber diameter (3.12±0.28 vs 2.90±0.27 cm/m) and LV mass index (35.9±11.2 vs 27.7±7.2), resulting in markedly higher prevalence of LVH. Relative wall thickness tended to be greater in CRI patients than in normals, but the difference did not achieve statistical significance (table 2). CRI patients also exhibited lower endocardial and midwall shortening than normal controls, only partially consistent with significantly increased end-systolic stress. In fact, stress-corrected midwall shortening was also significantly lower in CRI patients than in normal controls, indicating reduced myocardial contractility (Table 2). Transmitral Doppler velocities and their ratio did not show differences between groups (table 2).

### Inappropriate LV mass.

Although stroke work tended to be greater in CRI patients, it was not statistically distinguishable from normal controls (table 2 ). Nevertheless, for the given workload and body size the amount of observed/predicted LV mass in CRI patients was largely exceeding the needs imposed by workload. Figure 1 shows the distribution of observed/predicted LV mass in controls and in CRI patients, using the 95 percentile of the normal distribution. Ten CRI patients (30%) fell over the 95<sup>th</sup> percentile of the normal distribution. Table 3 shows comparison between CRI patients with or without inappropriate LV mass. Inappropriate LV mass was associated with concentric LV geometry and substantially reduced midwall shortening and stress-corrected midwall shortening, without differences in diastolic parameters.

## DISCUSSION

This study presents the first evidence that the reported high LV mass in children with CRI is not matched with consistent cardiac workload. Similar to adults (14) this excess of LV mass is associated with left ventricle concentric geometry and with substantial fall of systolic function (endocardial shortening and midwall shortening (32)), but preservation of LV performance (stroke work). The fall in systolic function is not related to the increased myocardial afterload (end-systolic stress), which is in fact reduced when LV mass is inappropriate, while it is substantially associated with a depressed wall mechanics indicating reduced myocardial contractility. These findings substantially parallel findings in adults (14), and suggest that CRI-related cardiac modifications occur independently of the age of exposition to the disease.

Also, interestingly, the excess of LV mass and the tendency to concentric LV geometry not completely offset myocardial afterload that appears to identical to normals confirming findings in adults where normal-low end-systolic stress was associated with a high-risk cardiovascular phenotype

Our findings also indicate differences of CRI from other conditions altering LV geometry in children. For example, infants with coarctation of the aorta develop concentric LVH before surgical repair. In many patients some degree of LV hypertrophy persists even after adequate surgical repair. In these children, however, LV systolic function and contractility, evaluated with different methods are usually increased (33-34). Although more recent data suggest that hyperdynamic function might originate from artifacts (35), contractility is at least

normal in these patients with concentric hypertrophy, differently from what is found in children with CRI. Unfortunately, there is no information on the appropriateness of LV mass in other conditions of increased loading conditions in children.

Moreover, severe LV hypertrophy and abnormal LV geometry are relatively prevalent in young patients with essential hypertension (36) with LV regional systolic function not showing a difference according to the LV geometric pattern (37).

Pathophysiologic differences might account for the different phenotypes found in aortic coarctation, hypertension and CRI, including age of exposure of myocardium to increase in loading conditions and non-hemodynamic factors (38). In aortic coarctation, loading conditions are already abnormal at the birth and hypertrophic process begins to take place at a time when cardiomyocytes still replicate, whereas in both hypertension and CRI the abnormality is delayed. In addition, and perhaps even more important, in aortic coarctation the kidneys are not exposed to high blood pressure.

Taken together our findings suggests that the development of LV mass in children with CRI might not be entirely due to needs to compensate hemodynamic load, but also to other non-hemodynamic factors affect LV growth, possibly related with kidney disease.

We know that the adrenergic overdrive exerts a number of adverse effects on the cardiovascular system, by favoring the genesis of cardiac hypertrophy, vascular hypertrophy, arterial remodeling and endothelial dysfunction (39)

Furthermore, the renin-angiotensin system (RAS) and inflammation may play a decisive role in hypertensive end organ damage (EOD) including left ventricular (LV) hypertrophy and vascular remodeling. It seems to be the tissue RAS, rather the circulating RAS and inflammatory factors, that contributed to hypertensive cardiovascular hypertrophy (40,41)

Also pregnancy is associated with physiological cardiac hypertrophy, but with a progressive decline in LV contractility through the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. There is rapid reversal of hypertrophy in the postpartum period while recovery of cardiac function is delayed, possibly related to postpartum upregulation of JNK (42).

The possible implications of our findings can be surrogated from findings in adults. Increasing levels of excess LV mass significantly increase risk for cardiovascular morbidity and mortality in hypertensive adults (13) and portend a high risk of congestive heart failure in general population, independently of prevalent and incident myocardial infarction (43). Although we cannot prove the same prognostic effect in children with CRI, there are evident similarity between adults and children.

This study is not designed as a prospective survey and we cannot derive prognostic conclusions. However, the emerging phenotype of children with excess LV mass is very similar to what is reported in adults, with a cluster of adverse cardiovascular modifications including concentric LV geometry, and systolic dysfunction (14). These children might require very close cardiovascular monitoring.

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Table 1. Anthropometric and blood pressure characteristics of 33 patients with CRI and 33 healthy controls.

Variable	Units	Patients		Controls		p
		<i>mean±SD</i> <i>median (range)</i> count (%)	n	<i>mean±SD</i> <i>median (range)</i> count (%)	n	
Gender	male	22 (67)	33	22 (67)	33	ns
Age	years	12.2±5.0	33	11.6±5.0	33	ns
Weight	Kg	43.2±21.4	33	42.0±18.1	33	ns
Height	cm	143±26	33	145±25	33	ns
Weight	SDS	0.45±1.47	33	0.66±1.31	33	ns
Height	SDS	-0.40±1.53	33	0.4±1.2	33	<0.05
BMI	SDS	0.61±1.3	33	0.97±1.6	33	ns
HR	b/min	75±15	33	78±12	33	ns
SBP	mmHg	108±15	33	103±13	33	ns
DBP	mmHg	60±16	33	56±9	33	ns
SBP	SDS	0.17±1.32	33	-0.24±1.32	33	ns
DBP	SDS	-0.20±1.49	33	-0.46±1.04	33	ns
24-h BP	SDS	0.60±1.27	24	N/A		N/A
Duration of CRI	years	12±5	33	N/A		N/A
GFR	ml/min/1.73 m <sup>2</sup>	46 (7-100)	33	N/A		N/A
Serum creatinine	mg/dl	2 (1-7)	33	N/A		N/A
Serum CRP	mg/L	0.3±0.5	27	N/A		N/A
Serum PTH	pmol/L	88.2±87.3	26	N/A		N/A

Values are mean ± SD; CKD, chronic kidney disease; NA, not applicable.



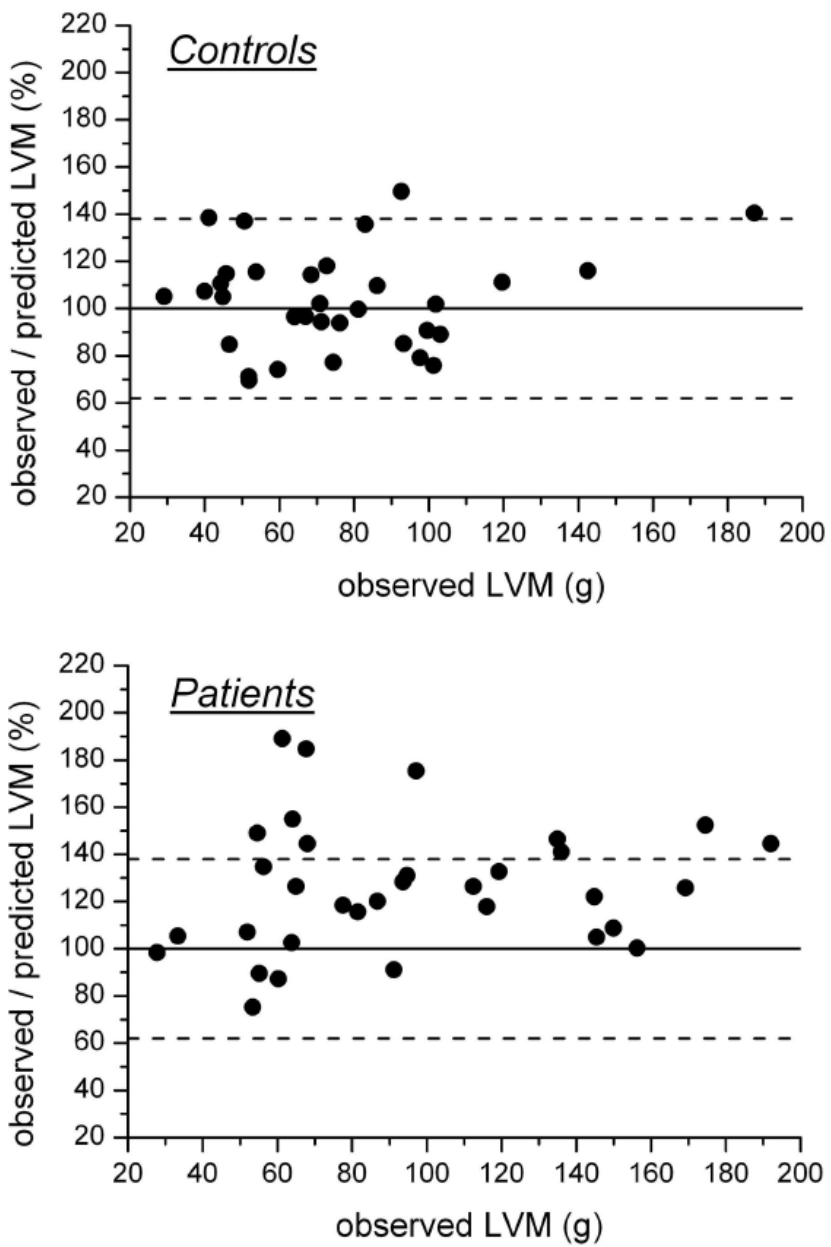
Table 2. LV geometry and systolic function in 33 CRI patients and 33 healthy controls.

Variable	Units	Patients		Controls		p
		<i>mean±SD</i> <i>median (range)</i> count (%)	n	<i>mean±SD</i> <i>median (range)</i> count (%)	n	
LVM/height <sup>2.7</sup>	g/m <sup>2.7</sup>	35.9± 11.3	33	27.7± 7.3	33	<0.05
LVH	%	36.3	33	9	33	<0.05
RWT		0.30±0.05	33	0.29±0.04	33	ns
eS	%	31.7± 3.8	33	35.5±6.1	33	<0.05
mS	%	17.7±1.9	33	19.6±2.8	33	<0.05
cESS	g /cm <sup>2</sup>	154± 34	33	136.4± 32	33	<0.05
σ-corrected mS	%	93.7±12.3	33	101.5±13.3	33	<0.02
LVEDD/height	cm/m	3.12±0.28	33	2.90±0.27	33	<0.002
Stroke work	gmtr/beat	86.9±39.9	33	76.63±28.13	33	ns
Obs/pred LVM	%	126±27	33	103±21	33	<0.001
E peak	cm/sec	102±20	30	102±14	17	ns
A peak	cm/sec	56±15	30	56±12	17	ns
E/A ratio		1,92±0,57	30	1,90±0,39	17	ns
DTE	msec	140±26	30	130±20	17	ns

Table 3. Appropriateness of LV mass in 33 CRI patients

<i>Variable</i>	<i>Units</i>	<i>Inappropriate LVM pts</i>		<i>Appropriate LVM pts</i>		<i>p</i>
		<i>mean±SD median (range) count (%)</i>	<i>n</i>	<i>mean±SD median (range) count (%)</i>	<i>n</i>	
LVM/height <sup>2.7</sup>	g/m <sup>2.7</sup>	48.9±10.3	10	30.3±5.6	23	<0.001
LVH	%	90	10	13	23	<0.001
RWT		0.34±0.04	10	0.29±0.04	23	<0.001
eS	%	32±5	10	31.5±3.3	23	ns
mS	%	16.8±2	10	18±1.7	23	ns
σ-corrected mS	%	87±9	10	99±12	23	<0.001
cESS	g /cm <sup>2</sup>	134±36	10	163±29	23	<0.05
Stroke work	gmtr/beat	82.8±46.2	10	88.7±37.8	23	ns
E peak	cm/sec	99±17	10	104±21	20	ns
A peak	cm/sec	53±12	10	58±17	20	ns
E/A ratio		1.90±0.5	10	1.92±0.7	20	ns

Figure 1



Distribution of observed/predicted LVM ratio in CRI patients and controls using 95 th percentile of the normal distribution