Left ventricular mass behaviour in hemodialysis patients during 17 years

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Abstract

Introduction: Ventricular hypertrophy is frequent in dialysis patients and is associated with an ominous prognosis. It is not knowledge if this ventricular change is growing or decreasing in hemodialysis patients. **Objective:** To assess left ventricular hypertrophy behaviour during 17 years in patients of a university dialysis center, as well as to verify the possible causes of this behavior. **Methods:** There was performed a retrospective longitudinal study that evaluated the echocardiographic left ventricular mass in hemodialysis patients in our dialysis facility over 17 years. Examinations of 250 patients aged 18 years or more who underwent routine echocardiography were included. **Results:** There was a progressive reduction of ventricular mass over studied period. This reduction was associated with blood pressure reduction. In multivariate analysis, ventricular mass was associated with blood pressure and hemoglobin. **Conclusion:** Left ventricular hypertrophy underwent significant reduction over 17 years in our hemodialysis patients. The factors associated with this reduction that could be identified in the current study were the progressive reduction of blood pressure and hemoglobin increase.

Keywords: echocardiography; hypertension; hypertrophy, left ventricular; renal dialysis; uremia.

Introduction

The prevalence of chronic kidney disease (CKD) is increasing globally.[1] The survival of patients with CKD and individuals in need of dialysis in particular is significantly shorter than that of their healthy peers within the same age range.[2] Cardiovascular disease, the main cause of death in this group of patients,[3,4] is directly associated with left ventricular hypertrophy (LVH), a condition found in 75% of the individuals on dialysis.[5,6] The presence of LVH is a marker for fatal cardiovascular events.[7-11]

Sixty to eighty percent of the individuals on dialysis are diagnosed with high blood pressure (HBP),[12] the leading cause of LVH in patients on dialysis. In addition to its role in the main cause of CKD in Brazil,[2] HBP may affect the prevalence of cardiovascular death of patients with end-stage renal disease, often associated with inadequate blood pressure (BP) control[13,14] and hemodynamic changes secondary to sodium and fluid level increases occurred between dialysis sessions.[6]

The most characteristic morphologic changes seen in the hearts of dialysis patients are the enlargement of the heart cavity and the progressive thickening of the left ventricle walls, which becomes less reversible the longer the patient stays on dialysis.[15] LVH is basically an adaptive remodeling process aimed at minimizing the stresses applied to the ventricular wall.[16] This initially adaptive process, however, may develop into hypertrophy, congestive heart failure, and high rates of morbidity and mortality.

The possibility of reversing LVH in patients on dialysis has been discussed in the literature. Some authors have described such reversals and associated them to reduced cardiovascular risk.[17,18] Therefore, LVH reversal may be considered as an intermediate outcome and a therapeutic goal for patients on dialysis. For that reason, echocardiography has been offered to the patients seen in our center since 1993.

The primary objective of this study was to assess 17 years of data on the progress of left ventricular hypertrophy in the patients seen at a teaching dialysis center. The secondary objective was to look into the possible causes for the patterns observed.

Materials and methods

This longitudinal retrospective study looked into cases of LVH affecting patients on hemodialysis treated at a teaching dialysis center. The study included 250 routine echocardiograms of patients with end-stage renal disease aged 18 years or older.

The echocardiograms were made between dialysis sessions (on Mondays, Wednesdays, and Fridays for patients on dialysis on Tuesdays, Thursdays, and Saturdays, and on Tuesdays and Thursdays for the other patients). The patients were clinically and biochemically stable in their hemodialysis programs and had normal sinus rhythms on their electrocardiograms. Individuals with malignant hypertension, patients presenting exceedingly challenging conditions to have their echocardiograms made, and patients with hemodynamically significant valvular heart disease were excluded. This study complied with the requirements set out in Resolution 169/96 issued by the National Board of Health and was approved by the Research Ethics Committee of the School of Medicine of Botucatu.

Echocardiograms from four different years spanning over a total of 17 years were assessed and compared to each other: 23 echocardiograms from 1993, 50 from 2000, 77 from 2006, and 100 from 2010. Data were collected from patient charts. Ten BP measurements made before the start of the hemodialysis sessions prior to the echocardiographic tests were recorded, along with patient weight and height from which the body mass index (BMI) and the mean interdialytic weight gain (IWG) were calculated.

The use of antihypertensive drugs, the number of classes of antihypertensive medications, and the classes of such drugs - angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers (β-blockers), calcium channel blockers (CCB), sympatholytic drugs, and vasodilators - were recorded. The data concerning the type of antihypertensive medication prescribed to the patients seen in 1993 was not available.

The patient charts contained the test results for hemoglobin, calcium, phosphorus, and parathyroid hormone (PTH) levels measured in time periods coinciding with the times at which the echocardiograms were made. Data on PTH levels were not available for the patients seen in 1993.

Trained echocardiographers ran the tests. Echocardiograms were made with the patients in lateral decubitus with the left arm slightly flexed over the head. Images were captured in accordance with the recommendations of the American Society of Echocardiography and recorded on a VCR for further reference. The coefficient of variation between two blinded observers in our laboratory was 2%. The left ventricle (LV) was measured in three to five cycles. Systolic and diastolic function indices were obtained. Echocardiographic tests were performed in accordance with the standard technique[19,20] and the following data were recorded: left ventricle diameter; septum and posterior wall thickness in diastole. These data were used to calculate the left ventricular mass (LVM), which was then indexed to height raised to an exponential power of 2.7 to yield the left ventricular mass index (LVMI).

The data were analyzed on software package Sigma Stat 2.03. Analysis of variance for parametric or non-parametric distributions was used when applicable to compare between continuous variables. Categorical variables were compared through the chi-square test, whereas correlations were assessed using multiple linear regression. The significance level was set at five percent ($p = 0.05$). Data following a parametric distribution were expressed in terms of mean values ± standard deviation; data following a non-parametric distribution were presented in terms of median values (interquartile range).

Results

Table 1 shows the data on patient age, weight, height, BMI, systolic and diastolic BP, LVM, LVMI, use of hypertensive drugs categorized as ACE inhibitors, ARBs, β-blockers, CCB, vasodilators, or sympatholytic drugs, and the number of drug classes prescribed per patient. Table 1 also contains the number of patients on dialysis at each time period and the absolute and relative number of patients with echocardiograms.

Patient mean age increased significantly ($p < 0.001$) over the first three time periods (1993, 2000, 2006), but no statistical difference was observed between 2006 and 2010.

Patient mean height did not change significantly over the years ($p = 0.938$). In general terms, patient weight and BMI increased over time ($p < 0.001$). In 2010, patient mean weight was statistically different from that of previous years. In 1993 and 2000, the mean BMI was lower than in 2010. In 2006 the mean BMI reached an intermediate level, and was not statistically different from the mean BMI observed in the other time periods.

Systolic BP changed significantly over the years ($p < 0.001$), reaching similar values in 2000, 2006, and 2010, and lower levels in 1993. Systolic BP also changed over the years ($p < 0.001$): it was lower in 2010 than in previous years; it did not change between 2000 and 2006, but it was lower than the systolic BP seen in 1993. Therefore, BP generally decreased over the years. Urine output and the number of patients with anuria did not change significantly. Mean IWG decreased significantly.

The echocardiograms showed decreases in LVM and LVMI, which became statistically significant in the most recent time period analyzed ($p < 0.001$). LVM and LVMI were statistically lower in 2010 when compared to previous years, but the difference between the values found in the years prior to 2010 was not significant.

The use of ACE inhibitors ($p = 0.015$), ARBs, and β-blockers ($p < 0.001$) increased over the years. ARBs were prescribed to dialysis patients only in 2010 (11% in 2010 *vs*. 0% in 2006 and 2000) [$p < 0.001$]. In 2010, 41% of the patients were on β-blockers, *versus* 20% in 2006 and 2% in 2000. The use of sympatholytic drugs ($p < 0.001$) and vasodilators ($p = 0.038$) to manage HBP decreased gradually with time. In 2010, sympatholytic drugs were administered to only 12% of the patients, *versus* 39% in 2006 and 36% in 2000 ($p < 0.001$). The number of classes of antihypertensive drugs prescribed to dialysis patients increased in 2010 when compared to 2000 ($p = 0.021$), but not in relation to 2006.

Table 2 shows hemoglobin, calcium, phosphorus, and PTH serum levels. In 2010, hemoglobin levels were higher than in 1993 ($p < 0.001$). No significant difference was seen in the calcium and phosphorus levels over the years ($p > 0.05$). PTH levels increased gradually in 2000, 2006, and 2010 ($p < 0.001$).

Table 3 shows a multiple regression looking into the factors associated with LVH. Pre-dialysis systolic BP ($p < 0.001$) was independently associated with LVMI.

Figure 1 shows the correlation between diastolic and systolic BP in the studied time periods. In 1993, only 22% of the patients had BP below 140/90 mm Hg. In 2000, the number grew to 34% and was kept at a similar level in 2006, at 35%. In 2010, another increase was observed in the number of patients with properly managed BP, taking it to 44%.

Figure 2 shows a positive correlation between mean systolic BP values in each year studied and their respective LVMI. Progressive decreases in systolic BP were accompanied by proportional decreases in LVMI over the years.

Table 1 Secular trends of the parameters related to high blood pressure management in patients on hemodialysis

Year	1993	2000	2006	2010	*p*
Patients on HD (n)	32	69	115	115	
Assessed patients (%)	23 (72%)	50 (72%)	77 (67%)	100 (87%)	
Age (years)	36 ± 15[a]	47 ± 14[b]	54 ± 14[c]	59 ± 14[c]	< 0.001
Height (cm)	162 ± 10.3	161 ± 8.7	161 ± 9.1	162 ± 9.4	0.938
Weight (Kg)	58 ± 11.7[a]	58 ± 10.6[a]	62 ± 13.0[a]	67 ± 14.4[b]	< 0.001
BMI (m/Kg^2)	22 (19-24)[a]	22 (20-24)[a]	23 (21-25)[ab]	24 (22-29)[b]	< 0.001
SBP (mm Hg)	163 (156-172)[a]	150 (135-163)[b]	146 (137-154)[b]	142 (128-153)[b]	< 0.001
DBP (mm Hg)	105 (100-109)[a]	88 (83-105)[b]	89 (82-93)[b]	80 (74-90)[c]	< 0.001
Anuria (n)	-	28/50	37/77	45/100	0.424
Urine output (mL)	-	60 (0-440)	190 (0-915)	200(0-800)	0.313
Mean IWG (L)	-	2.9 ± 0.80[a]	2.7 ± 1.29[ab]	2.4 ± 0.90[b]	0.006
LVM g	303 (243-411)[a]	272 (234-391)[a]	262 (227-318)[a]	234 (193-266)[b]	< 0.001
LVMI g/m^{2,7}	85 (67-102)[a]	80 (66-102)[a]	74 (63-86)[a]	63 (52-76)[b]	< 0.001
Antihypertensive drugs					
ACE inhibitors (%)	-	22	44	45	0.015
ARBs (%)	-	0	0	11	< 0.001
ACEi/ARB (%)	-	22	44	55	< 0.001
β-blockers (%)	-	2	20	41	< 0.001
CCB (%)	-	26	29	38	0.236
Sympatholytic drugs (%)	-	36	39	12	< 0.001
Vasodilators (%)	-	10	6	1	0.038
Number of classes	-	1 (0-2)[a]	1 (0-2)[ab]	2 (1-2)[b]	0.021

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; IWG: interdialytic weight gain; LVM: left ventricular mass; LVMI: left ventricular mass index; ACEi: angiotensin-converting-enzyme inhibitors; ARB: angiotensin II receptor blockers; β-blockers: beta blockers; CCB: calcium channel blockers; abc equal letters indicate statistical similarity; data expressed as mean ± standard deviation; median (interquartile range) or percent rate (%).

Table 2 Secular trends of hematologic and biochemical parameters of patients on hemodialysis

Year	1993	2000	2006	2010	*p*
Patients (n)	32	69	115	115	-
Assessed patients (%)	23 (72%)	50 (72%)	77 (67%)	100 (87%)	-
Hemoglobin (g/dL)	7.3 (6.7-8.2)[a]	10.1 (9.2-11.3)[b]	10.7 (9.5-11.8)[b]	11.6 (10.6-12.7)[c]	< 0.001
Calcium (mg/dL)	9.0 (8.6-9.6)	9.0 (8.5-9.4)	9.1 (8.3-9.7)	8.9 (8.6-9.4)	0.863
Phosphorus (mg/dL)	5.5 (4.6-6.3)	5.2 (3.9-6.7)	5.6 (4.2-7.8)	5.2 (4.3-6.2)	0.507
Parathyroid hormone (pg/dL)	-	84 (49-245)[a]	201 (99-494)[b]	477 (250-810)[c]	< 0.001
Residual renal urea clearance (mL/min)	-	0.28 (0-1.1)	0.33 (0-1.9)	0.42 (0-2.0)	0.337

[a,b,c] equal letters indicate statistical similarity; data expressed as median (interquartile range).

Discussion

LVH is a common finding and a marker of poor prognosis in patients with CKD. Reversing LVH may be one of the goals of the treatment offered to patients with CKD. In recent years, our service saw an increase in the intensity with which the BP of patients on dialysis is managed and in the use of drugs acting on the renin angiotensin aldosterone system (RAAS). The impact of these measures upon patient cardiac hypertrophy is unknown. Thus, this study aimed to analyze the secular trends of the LVMI of dialysis patients seen at our center.

This study revealed a progressive decrease in the LVM of the dialysis patients seen at our center, accompanied by a gradual decrease of BP levels, an increase in the use of drugs acting on

Table 3 Predictors for left ventricular mass index in patients with chronic kidney disease seen in 1993, 2000, 2006, and 2010

	Beta	*p*
Age (years)	-0.053	0.500
BMI (Kg/m²)	0.084	0.273
SBP (mm Hg)	0.271	< 0.001
Using ACEi or ARBs	0.017	0.820
PTH (pg/mL)	-0.067	0.380
Hemoglobin (g/dL)	-0.105	0.181
Mean IWG (L)	0.083	0.271

BMI: body mass index; SBP: pre-dialysis systolic blood pressure; ACEi: angiotensin-converting-enzyme inhibitors; ARB: angiotensin II receptor blockers; PTH: parathyroid hormone; IWG: interdialytic weight gain.

the RAAS, and a decrease in the use of direct vasodilators over the years.

Experimental and clinical evidence suggest that reversing LVH is an attainable therapeutic goal for patients with CKD. In recent years, LVH reversal has become a hot topic and a desirable intermediate endpoint, particularly due to the possible improvements it may bring to hypertensive individuals and patients with CKD.[17] Interest has revolved around the role antihypertensive agents in protecting the vascular and myocardial structures.

The factors connected to the pathogenesis of LVH in patients with CKD relate to preload and afterload alterations. In preload, the related factors include intravascular volume expansion (salt and fluid) and anemia. In this study, a negative correlation was observed between hemoglobin levels and LVMI. Similar results have been reported for individuals with CKD off dialysis.[21] However, multiple linear regression revealed that hemoglobin level was not an independent predictor for decreased LVH.

Afterload is determined by aortic impedance, which is basically constituted by two elements: artery compliance and peripheral vascular resistance, the latter a determinant of blood pressure. Previous studies found a strong correlation between elevated systemic BP and development of LVH in pre-dialysis CKD patients.[21,22] In this study, decreases in systolic and diastolic BP were found over the years. Consequently, significant decreases were observed in afterload and LVM. Interestingly, a direct correlation was verified between decreases in systemic BP and LMVI.

Vasodilators are a class of antihypertensive drugs that decrease blood pressure mostly without interfering with ventricular hypertrophy, although Minoxidil may increase it. The prescription of these drugs in the patients included in the study gradually decreased over the years, at the same rate as the prescription of drugs that affect disease mechanisms common to elevated BP and myocardial growth increased.

Another significant finding concerned the use of ARBs in recent years. Antihypertensive drugs do not reverse LVH by merely decreasing patient BP.[23] Peripheral vascular resistance, an indicator of afterload, is decreased when the renin angiotensin aldosterone system is inhibited, thus significantly affecting LVM. RAAS inhibition also affects the myocardium directly and independently from the impact it has in decreasing BP. However, multiple linear regression analysis revealed that ACE inhibitors and ARBs were not associated with LVMI independently from BP, thus indicating that the impact these drugs had on heart remodeling was chiefly mediated by their antihypertensive effects.

Improved pre-dialysis care may have affected the magnitude of LVH observed in this study. Patients submitted to care by a nephrologist prior to starting dialysis are known to have the alterations associated with kidney disease (hypertension, anemia, and mineral and bone disorders) treated more effectively and to, consequently, present less LVH.[24]

Echocardiograms were supposed to have been made within more regular time periods (seven years from the first to the second time period, six from the third to the fourth, and four on the fourth). There is an agreement between the Nephrology and Cardiology services in our institution that has been in effect for two decades, which dictates that

Figure 1. Scatter diagrams for diastolic blood pressure (DBP) and systolic blood pressure (SBP) of hemodialysis patients at different times between 1993 and 2010.

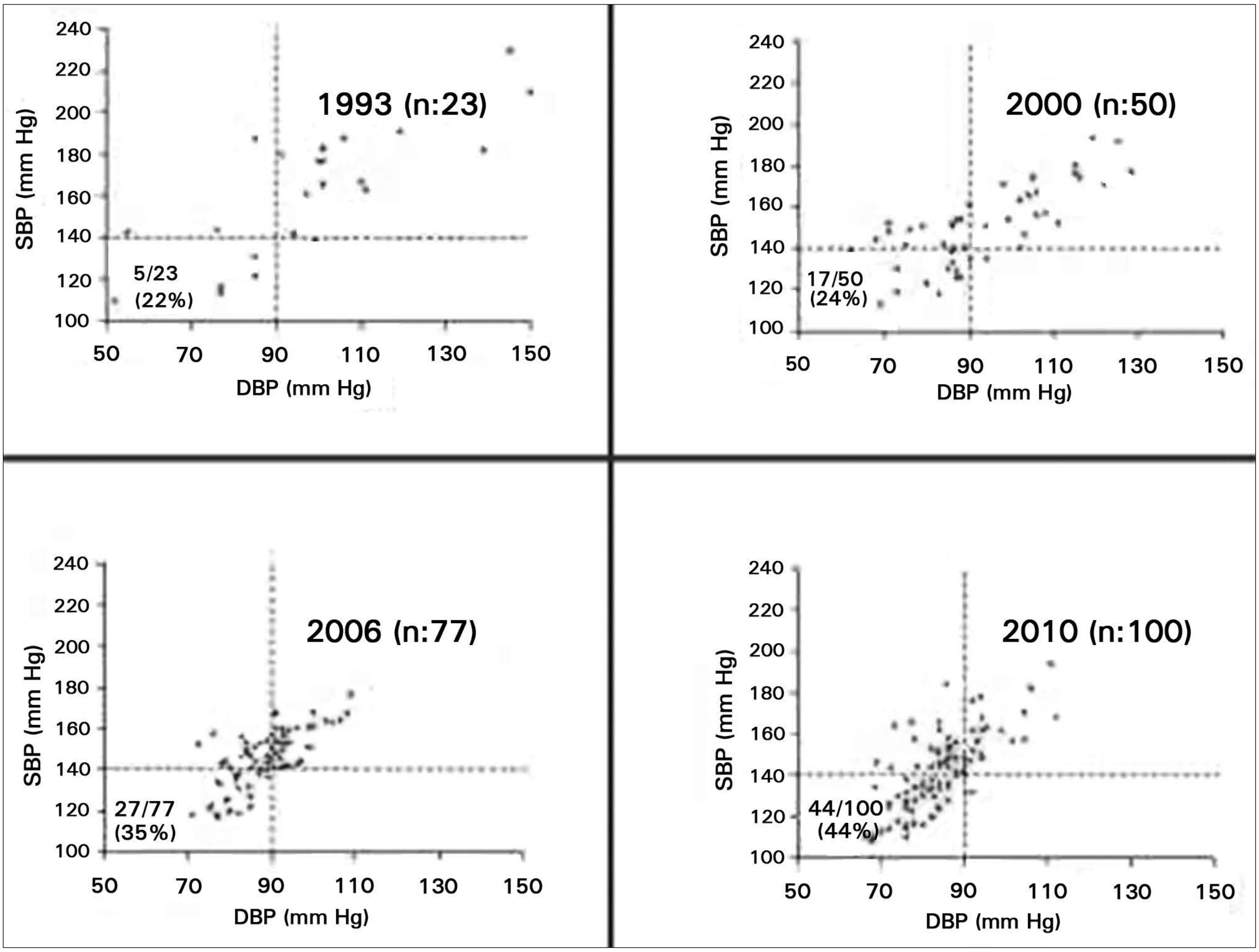
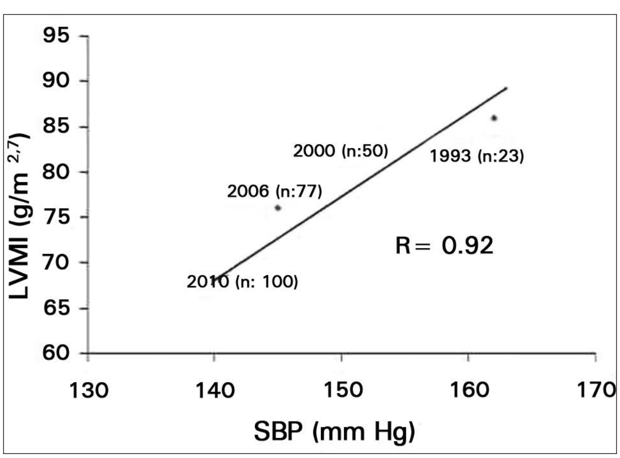


Figure 2. Left ventricular mass indexed to height raised to the power of[2,7] *versus* systolic blood pressure (SBP) of hemodialysis patients at different times between 1993 and 2010.



echocardiograms should be made regularly for patients on dialysis. However, despite the goodwill of both services, once there are fewer echocardiographers in Cardiology than orders for echocardiograms, tests were run only when possible.

Pre and post dialysis volume variations were significant and had a decisive impact on the results.[25] The tests presented herein do not reflect the pre or immediate post-dialysis reality. Echocardiograms were made on days in which the patients were not on dialysis. There might be minor volume variations from the first to the second or third day between dialysis sessions, but these variations were certainly much smaller than the ones seen between the pre and post-dialysis periods.

IWG, independently associated with BP by other authors,[25] decreased gradually, as shown in multiple linear regression analysis. Nonetheless, this risk factor was no longer statistically significant after adjustment for other variables, BP in particular.

This study had some limitations. First, there was no information on the drugs prescribed in the first time period. The echocardiograms included in the study were produced in different echocardiography systems over the years, but the medical staff responsible for analyzing and interpreting the tests was never changed. The decrease in LVM could have been explained from the standpoint of survival, i.e., the patients who survived over the years were the ones with lower LVM. However, after excluding repeat patients, the decrease in LVM was still statistically significant (p = 0.001; data not presented), thus excluding the occurrence of survival bias. Some of the data from 1993 were incomplete. Other factors not included in our analysis - new technologies and improved diet therapy - may not have their roles in LVM improvement ruled out.

To sum up with, left ventricular hypertrophy decreased significantly within the last 17 years in our center. The factors associated with this decrease identified by the present study were the gradual decrease in blood pressure and the increase in hemoglobin levels. The effects from the more frequent use of medications acting on the renin angiotensin aldosterone system upon left ventricular hypertrophy reversal seems to have been mediated by the decrease in BP.

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