Introduction

Cardiovascular diseases are common in patients with chronic renal failure (CRF) and represent the leading cause of death in this population, besides being an important cause of morbidity, motivating 1/3 of hospitalizations of patients on dialysis. It was believed that such changes would happen due to hypertension (increased afterload), hypervolemia (increased preload) or anemia. Heart disease of uremic patients can relate to common changes in this condition, such as dyslipidemia, prothrombotic states, hyperhomocysteinemia, hemodynamic overload, anemia, oxidative stress, hypoalbuminemia, inflammatory abnormalities and bivalent ions. The high prevalence of traditional cardiac risk factors – hypertension, diabetes mellitus, hyperlipidemia, smoking, hypercoagulability and physical inactivity – predisposes patients with CRF to heart disease. The factors act alone or synergistically and...
cause cardiac abnormalities in this population\textsuperscript{1,12}.

One of the factors involved in the origin of cardiovascular changes in uremic patients is secondary hyperparathyroidism (SHPT). This is the metabolic disorder most often described in patients with CRF, even in the early stages of this condition. The pathophysiology involves changes in the balance between substances such as calcium, phosphorus, calcitriol and parathyroid hormone (PTH)\textsuperscript{1,13}. Therefore, the main pathogenetic factors of SHT are hypocalcemia, hyperphosphoremia and deficit of calcitriol. Other factors are increased bone strength to the action of PTH, acidosis, and reduction in vitamin D receptors and calcium receptors on parathyroid hormones\textsuperscript{1,13}.

Mortality from cardiovascular causes interfere with the survival of patients with CRF and the current focus is on the specific cardiovascular changes in uremia. There is interest in identifying the echocardiographic changes and their prevalence in relation to PTH levels.

The purpose of this study was to evaluate the prevalence of echocardiographic abnormalities in chronic kidney disease patients with SHPT, comparing the changes in the different levels of circulating PTH.

**Methods**

A retrospective study at the Nephrology Service of Universidade Estadual de Ciências da Saúde de Alagoas, Maceió, AL, with data taken from medical records from 2005 to 2007, which included 150 patients, of both sexes, with chronic kidney disease on a regular dialysis program.

The study was approved by the Research Ethics Committee of the institution under n° CEP Uncisal 049639/2013 and was conducted according to the CNS Resolution 466/12.

The following exclusion criteria were adopted: diabetic patients; patients under 18; with data suggesting coronary or valvular disease; cardiovascular functional group different from group I; uncontrolled blood pressure (BP); patients undergoing parathyroidectomy.

The study population consisted of 52 patients of both sexes stratified into three groups based on plasma levels of PTH: Group I \(\leq 299\) pg/mL (n=10); Group II 300-499 pg/mL (n=21); and Group III \(\geq 500\) pg/mL (n=21).

We evaluated the following echocardiographic parameters: aortic root, left atrial and ventricular diameter; septal and posterior wall thickness; ejection fraction; end diastolic and systolic volumes. The echocardiographic findings were correlated with calcium levels, phosphoremia, calcium-phosphorus product (Ca \(\times\) P), hematocrit and hemoglobin levels, and systolic and diastolic blood pressure.

Blood pressure data were taken from dialysis prescriptions:

- Predialysis BP: pre-dialysis average systolic blood pressure (SBP) and diastolic blood pressure (DBP) values of the first and final week of the 12 months preceding echocardiography were considered.
- Post-dialysis BP: average post-dialysis SBP and DBP of the first and last week of the 12 months preceding echocardiography were considered. That corresponded to 72 checks to obtain the mean and calculation of standard deviation of both pre-dialysis and post-dialysis blood pressures.

Calcium (Ca) and phosphorus (P) dosages were taken using the colorimetric method in Cobas\textsuperscript{®} 6000 equipment (Roche Diagnostics International Ltd CH-6343 Rotkreuz, Switzerland) and the mean values of the 12 months preceding echocardiography were calculated. Ca — reference value: 8.5-10.5 mg/dL; P — reference value: 3.5-5.5 mg/dL.

Based on average of calcium and phosphorus values in the 12 months before echocardiography, the mean calcium \(\times\) phosphorus product was calculated: Ca \(\times\) P — reference value: 20-55 mg\(^2\)/dL. It was figured out how many times, over the 12-month study, the multiplication of calcium level by phosphorus level was \(\geq 55\) mg\(^2\)/dL.
Parathyroid hormone levels were determined by radioimmunoassay at Instituto H. Pardini, Belo Horizonte, MG, using kit CIS Bio International S.A. (Gif-sur-Yvette, Essonne, France) and the mean values of the 12 months preceding echocardiography were considered. PTH — reference value: 4–67 pg/mL.

All patients underwent two-dimensional echocardiograms with color Doppler using a GE Vivid 3 device (GE Medical Systems Israel, Ultrasound, Ltd. Tirat Hacarmel, Israel) with 2.5 Mhz transducer, to assess the following parameters: 1) Structural aspects: LV end-diastolic diameter (normal value = 35-56 mm); LV end-systolic diameter (normal value = 25-40 mm); septal thickness (normal value = 7-11 mm); posterior wall thickness (normal value = 7-11 mm); septal/wall ratio (normal value = <1.3); aorta diameter (Ao) (normal value = 20-30 mm); left atrial diameter (LA) (normal value = 20-40 mm); right ventricular diameter (RV) (normal value = 7-26 mm); 2) Functional aspects: left ventricular end-diastolic volume (normal value = 73-156 mL); LV end-systolic volume (normal value = 18-57 mL); ejection fraction (normal value => 58%); 3) Valvular changes; and 4) Pericardial changes.

Statistical treatment

Considering the assumption and the number of variables, the minimum number calculated to establish statistical power was 10 patients in different study groups. Data were expressed as mean and standard deviation.

Calcium, phosphorus, calcium and phosphorus product, hematocrit and hemoglobin reflect the annual average of 12 measurements. Systolic and diastolic blood pressure reflects the arithmetic mean of 72 annual inspections.

The Student t test was used to establish comparisons of unpaired data among the groups; and the Spearman correlation to detect possible correlations between variables. Statistical significance assigned to p<0.005. Besides the significance of the variables in the three groups, pairs of groups were compared (group I with group II, group I with group III and group II with group III) applying the Tukey test to determine the population groups presenting statistical significance.

Results

These include the clinical, laboratory and echocardiographic findings of 52 patients.

Regarding the study population, the results were: mean age 43.9±11.9 years. Clinical data: Pre-hemodialysis systolic BP 139.5±14.0 mmHg; pre-dialysis diastolic BP 79.3±5.5 mmHg; post-dialysis systolic BP 137.8±17.0 mmHg; post-dialysis diastolic BP 77.9±5.7 mmHg; hematocrit 32.6±4.2%; hemoglobin 10.56±1.3 g/dL; calcium 9.1±0.4 mg/dL; phosphorus 5.6±1.1 mg/dL; Ca x P 52.6±10.7 mg²/dL; number of times Ca x P >55 mg²/dL: 5.1±3.2; PTH 590±364.8 pg/mL.

Group I presented the following results: mean age 39.1±8.3 years. Clinical data: Pre-hemodialysis systolic BP 130.5±19.8 mmHg; pre-dialysis diastolic BP of 74.1±11.62 mmHg; post-dialysis systolic BP 128.2±24.92 mmHg; post-dialysis diastolic BP 76±9.74 mmHg; hematocrit 32.3±4.7%; hemoglobin 10.8±1.2 g/dL; calcium 9.2±0.6 mg/dL; phosphorus 4.7±1.04 mg/dL; Ca x P 45.5±11.4 mg²/dL; number of times Ca x P> 55 mg²/dL 3.2±2.8; PTH 72.4±46.0 pg/mL.

Group II showed the following results: mean age 44.2±15.8 years. Clinical data: Pre-dialysis systolic BP 141.5±14.7 mmHg; pre-dialysis diastolic BP 79.7±3.35 mmHg; post-dialysis systolic BP 139.1±17.1 mmHg; post-dialysis diastolic BP 78.0±4.94 mmHg; hematocrit 31.5±3.8%; hemoglobin 10.3±1.4 g/dL; calcium 9.1±0.3 mg/dL; phosphorus 45.6±1.2 mg/dL; Ca x P 51.8±11.8 mg²/dL; number of times Ca x P > 55 mg²/dL 4.8±3.4; PTH 274.2±74.4 pg/mL.

Group III showed the following results: mean age 44.6±9.8 years. Clinical data: Pre-dialysis systolic BP 141.9±10.4 mmHg; Pre-dialysis diastolic BP 81.5±4.6 mmHg; post-dialysis systolic BP 141.5±13 mmHg; post-dialysis diastolic BP 78.0±4.5 mmHg; hematocrit 33.8±5.3%; hemoglobin 10.6±1.3 g/dL; calcium 9.1±0.3 mg/dL; phosphorus 6.2±1.0 mg/dL; Ca x P 56.8±9.2 mg²/dL; number of times Ca x P > 55 mg²/dL 6.3±3.3; PTH 1164.5±814.6 pg/mL.

Table 1 shows the echocardiographic data of patients among the three groups. The only variable that was statistically significant was the diastolic posterior wall thickness.
Table 1
Echocardiographic data of the sample population and by study groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sample population (n=52)</th>
<th>GI (n=10) PTH &lt;299 pg/mL</th>
<th>GII (n=21) PTH 300-499 pg/mL</th>
<th>GIII (n=21) PTH ≥500 pg/mL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic root (mm)</td>
<td>32.6±3.56</td>
<td>31.3±4.0</td>
<td>31.7±3.3</td>
<td>34.2±3.5</td>
<td>ns</td>
</tr>
<tr>
<td>Left atrium (mm)</td>
<td>40.4±5.15</td>
<td>38.6±5.2</td>
<td>40±5.5</td>
<td>41.7±4.7</td>
<td>ns</td>
</tr>
<tr>
<td>RV diameter (mm)</td>
<td>21.5±4.3</td>
<td>22.7±5.1</td>
<td>21.1±3.9</td>
<td>21.3±4.2</td>
<td>ns</td>
</tr>
<tr>
<td>LV diastolic diameter (mm)</td>
<td>51.1±7.8</td>
<td>48.4±8.1</td>
<td>50.3±7.9</td>
<td>53.1±7.5</td>
<td>ns</td>
</tr>
<tr>
<td>LV systolic diameter (mm)</td>
<td>33.4±7.2</td>
<td>31.3±8.1</td>
<td>31.7±6.4</td>
<td>36.3±7.5</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic septal thickness (mm)</td>
<td>13.0±2.7</td>
<td>11.1±2.2</td>
<td>13.6±3.3</td>
<td>13.5±2.3</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic posterior wall thickness (mm)</td>
<td>12.1±2.4</td>
<td>10.4±2.1</td>
<td>12.5±2.6</td>
<td>12.6±2.3</td>
<td>0.009</td>
</tr>
<tr>
<td>Septal x posterior wall ratio</td>
<td>1.0±0.08</td>
<td>1.0±0.07</td>
<td>1.0±0.09</td>
<td>1.0±0.07</td>
<td>ns</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.6±0.09</td>
<td>0.6±0.08</td>
<td>0.6±0.07</td>
<td>0.5±0.1</td>
<td>ns</td>
</tr>
<tr>
<td>End diastolic volume (mL)</td>
<td>129.5±45.9</td>
<td>116.9±44.0</td>
<td>124.2±44.6</td>
<td>141.1±48</td>
<td>ns</td>
</tr>
<tr>
<td>End systolic volume (mL)</td>
<td>50.7±26.9</td>
<td>42.3±26.3</td>
<td>44.6±23.9</td>
<td>61.0±30.2</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data expressed as mean±standard deviation
PTH – parathyroid hormone; RV – right ventricle; LV – left ventricle; ns – no statistical significance

Discussion

CRF produces changes in various organs and systems and the relationship between cardiac alterations and uremia is often described. In 1827, Richard Bright reported cardiac hypertrophy as a common finding in this condition14; in 1872, Mahomed described major changes in large arteries in patients with chronic kidney disease15. In 1944, Raab suggested that substances in the blood of patients with uremia could cause specific heart disease of this condition16. In 1981, Drueke et al.17 described congestive cardiomyopathy in seven of 21 patients undergoing dialysis; all of them had normal coronary arteries and no other cause of cardiomyopathy17.

One of the common forms of cardiovascular disease in CRF is ischemic heart disease. End-stage renal failure is also associated with structural and functional cardiac changes, such as left ventricular hypertrophy (LVH), coronary artery disease, valvular disease and pericarditis18.

The role of calcium in cardiac metabolism is very important, influencing the contraction and relaxation of the heart19-21. In severe hypocalcemia, segmental echocardiographic changes may be observed in contractility; however, cases of hypocalcemic cardiomyopathy or heart failure are very rarely reported in these patients19-21.

Serum calcium is physiologically regulated by the action of PTH. Under normal conditions, its secretion is increased when hypocalcemia occurs, promoting rapid release of calcium stored in the bone tissue resting cells, a phenomenon that partly tends to fix calcium levels; in the kidney, PTH promotes greater tubular reabsorption of calcium and decreases phosphate reabsorption19-21. In
CRF, hypocalcemia is due to decreased intestinal absorption of calcium secondary to calcitriol deficit and also to a poor intake of this ion\(^1\).

Phosphorus retention contributes to hypocalcemia through a physical-chemical mechanism; another cause is the increased bone resistance to PTH\(^2\). Hyperphosphoremia has a dramatic effect on the development of SHPT in patients with advanced CRF, as it interferes with the secretion of parathyroid glands, in gene expression and cell proliferation of these glands; besides causing hyperplasia, there is PTH hypersecretion through direct and indirect mechanisms.

The kidneys are the main organs involved in the production of calcitriol; therefore, the deficit of renal function decreases in the production of this substance, affecting the metabolism of calcium, phosphorus and bone tissue. Calcitriol, the active form of vitamin D, is directly involved in calcium homeostasis by promoting intestinal absorption. Hypocalcemia by absorptive deficit is a major mechanism of increased secretion of PTH in calcitriol deficiency\(^13\).

The clinical picture of SHPT is characterized by bone pain, usually diffuse and progressive, with difficulty walking and even immobility, proximal myopathy, muscle weakness, severe itching, vascular calcifications of soft tissues and skin, arthralgia and tendon rupture. More rarely, spontaneous fractures occur with collapsed vertebrae and impact on posture and mobility.

In 2005, Randon et al.\(^12\) reported a significant number of patients who started dialysis treatment and had cardiac abnormalities, especially LVH; besides, about 70% of patients on chronic hemodialysis had HVE\(^12\). PTH has been recently identified as an important cardiotoxin in CRF and high serum levels of this hormone in uremic patients can have deleterious effects on metabolism and myocardial function\(^23\). There is a direct and independent relationship of high PTH levels (>280 pg/mL) with the development of LVH in patients undergoing chronic hemodialysis, and SHPT contributes to the high cardiovascular morbidity associated with HVE\(^17\).

PTH is an independent LVH factor in men older than 59 and women under 60; this effect can occur with very high levels of PTH that change cardiac function\(^24\). Nagashima et al.\(^25\) reported significant improvement in left ventricular function after parathyroidectomy in patients subjected to 12 years of dialysis presenting SHPT associated with left ventricular dysfunction. There was a decrease in PTH levels after surgery, suggesting an important role of PTH in ventricular dysfunction\(^25\).

SHPT can cause LVH through several mechanisms, including direct trophic effects on myocytes and interstitial fibroblasts; and indirect effects such as increased blood pressure, hypercalcemia, anemia and alterations in small and large vessels. LVH partly results from myocardial fibrosis that is independent of hypertension and can significantly contribute to diastolic dysfunction and arrhythmias in patients with end-stage renal disease\(^18\).

**Conclusion**

Echocardiography is useful in the evaluation of cardiovascular disease in cases of uremia.

Patients with chronic renal failure with secondary hyperparathyroidism may present echocardiographic abnormalities, some of which correlate with circulating levels of parathyroid hormone.

Although with the limitations typical of retrospective studies, these findings suggest the need to conduct prospective studies that include a bigger number of patients in the different groups.

**Potential Conflicts of Interest**

This study has no relevant conflicts of interest.

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**Academic Association**

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