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EFFECTS OF SECONDARY HYPERPARATHYROIDISM ON CARDIAC FUNCTION IN PEDIATRIC PATIENTS ON HEMODIALYSIS*

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Cardiovascular complications are an important cause of morbidity and mortality in chronic hemodialysis patients. In order to examine the effect of parathyroid hormone (PTH) and vitamin D on left ventricular functions, 11 patients between the ages of 13 and 18 years on regular hemodialysis were investigated using M-mode echocardiography and systolic time intervals. The ratio of the pre-ejection period to the left ventricular ejection time was found to be 0.38 ± 0.02 (range 0.25 ± 0.50) and was elevated above normal in five of the 11 patients examined. Four of these patients had hypertension and one had severe anemia. The left ventricular ejection fraction was 55 ± 2.54% and fractional fiber shortening was 31.55 ± 2.26%, both of which were within normal limits for age. Although the velocity of circumferential fiber shortening was within normal limits in the majority of cases, the mean value was 1.437 ± 0.11 circ/s, which is above normal for this age period. PTH levels were between one and 4.70 ng/ml. All of the hemodialysis patients had been receiving 1α hydroxy-cholecalciferol and had normal calcium levels. Although they had high PTH levels, most of these patients displayed normal myocardial contractility. No significant correlation was obtained between increment in PTH levels and myocardial function indices. These results imply that PTH is not the only factor affecting myocardial functions. Since all of these patients have received vitamin D therapy for long periods, we suggest that vitamin D may have prevented the deleterious effect of PTH on myocardial function. *Key words: hemodialysis, cardiac function, hyperparathyroidism, children.*

Cardiovascular complications are the leading cause of mortality in patients on maintenance hemodialysis[1]. Some experimental studies have shown that uremic toxins are capable of depressing myocardial function[2]. In addition, parathyroid hormone (PTH) may be a potent uremic toxin which in experimental conditions has several adverse effects on myocardial cell function and metabolism[3-5]. Controversy exists concerning the impact of secondary hyperparathyroidism

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(SHPT) in end-stage renal disease (ESRD) on the development of left ventricular (LV) hypertrophy and systolic dysfunctions[6,7]. It is not clear whether PTH has a direct effect or the changes are due to the lack of 1.25-dihydroxycholecalciferol (HCC)[6]. Administration of vitamin D_3 has been proven to improve LV function in hemodialysis patients, and amelioration of echocardiographic disturbances in chronic renal failure patients has been reported after 1α-hydroxycholecalciferol [1α (OH) D_3] treatment[8].

In this study we evaluated LV function in patients on maintenance hemodialysis by M-mode echocardiography, and assessed the effect of PTH on these function.

Material and Methods

Eleven uremic patients (eight girls and three boys) on maintenance hemodialysis were included in the study. The age range was 13-18 years. The patients had been on dialysis for four to 40 months (mean 19 months). All patients had arteriovenous fistulas, and the duration of dialysis was 14-18 weeks. None received digitalis and none had any signs of heart failure. Four of 11 had severe hypertension. They were all receiving diets low in protein and phosphate binders along with 0.5-1 μg/day 1α (OH) D_3.

Serum creatinine, BUN, sodium, potassium, calcium, phosphorus, uric acid, hemoglobin, PTH with X-ray and ECG were obtained before dialysis. Echocardiographic examinations were performed with a Smith-Kline Echoline 20 diagnostic ultrasonoscope combined with an Echoline 21 recorder. A 2.75-MHz transducer was used. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness (IVST), left ventricular ejection time (LVET), left ventricular pre-ejection period (LVEP), left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV), cardiac output and stroke volume were assessed. These parameters were the mean of at least three strokes. Percentiles were calculated according to the standard values for LVEDD determined by Gutgesell and Paquest[9].

Left ventricular ejection fraction (LVEF) for the LV end-systolic (ES) and end-diastolic (ED) minor diameters were obtained by the following equation:

$$EF = \frac{ES}{ED}$$

The normal rage for EF was 53-77 percent[10].

Fractional shortening (FS) was calculated by the formula:

$$\frac{LVEDD\text{-}LVESD}{LVEDD} \times 100$$

The normal range was 28-44 percent[10].

The mean velocity of circumferential fiber shortening (Vcf) was obtained by the following formula:

$$(Vcf) = \frac{LVEDD/\,LVES\,/\,IVEDD}{EF}$$

The normal range was 1.34 ± 0.03 circ/s.

The mean value for the ratio of pre-ejection period (PEP) to LVET (PEP/LVET) was 0.35 (range 0.30-0.39)[10].

Results

The mean hemoglobin value in our patients was 6.25 ± 0.38 with a range of 4.20 9.0 g/dl. Serum creatinine and BUN levels before dialysis were 7.8 ± 0.5 mg/dl (5.2 ± 9.8 mg/dl) and 75 ± 5.5 mg/dl (54 ± 120 mg/dl), respectively. The mean values for electrolytes were as follows: sodium 133 ± 1.60 mEq/L, potassium 4.8 ± 0.28 mEq/L, calcium 8.9 ± 0.2 mg/dl and phosphorus 4.5 ± 0.25 mg/dl. The C-terminal PTH levels in our cases were between 1 and 4.7 ng/ml which was well above the normal range.

X-ray and ECG findings of the patients were evaluated before dialysis. Four patients with abnormal ECG findings were noted to have hypertension and one had severe anemia.

The LV myocardial contractility indices and volume functions were assessed by M-mode echocardiography before hemodialysis. The cardiac investigations in our patients are summarized in Table I. The mean PEP/LVET ratio, which is a good index of LV function in our patients, was 0.38 ± 0.02 with a range of 0.25 ± 0.50. In the four patients with intractable hypertension and in one patient with severe anemia, this ratio was above normal. The mean LVET was 55 ± 2.54 percent (range 41.50-71.80%). The mean FS was 31.55 ± 2.26% and this was within normal limits. Vcf was 1.47 ± 0.11 circ/s (Table II), which was above the normal range for this age group (1.34 ± 0.03 circ/s).

When relations were sought between the PEP/LVET ratio, EF, FS and Vcf (which are the indices of LV contractibility functions) and Hb, serum creatinine, BUN, calcium and PTH levels, no significant correlations were found. There was a linear relationship between the stroke volume (mean 89.95 ± 12.57 ml) and cardiac output (10.0 ± 1.4 ml/min) and the serum PTH levels. A significant correlation was also found between Hb levels and stroke volumes.

Table I: Results of Cardiac Investigations in Dialysis Patients

	$\bar{X} \pm SD$	Range
LVEDD, mm	53.82 ± 2.99	37-71
LVESD, mm	31.54 ± 2.28	26-45
IVST, mm	9.54 ± 0.58	8-13
PEP ms	218.18 ± 7.84	180-260
LVESV, ml	74.53 ± 9.18	60-112
LVEDV ml	164.83 ± 20.57	66.20-308.20
Stroke volume, ml	89.95 ± 12.57	24.90-162.40
Cardiac output, 1/min	10 ± 1.4	6-14
Cardiothoracic ratio	1.18 ± 0.04	0.95-1.43

Table II: LV Function Results of Hemodialysis Patients

	$\bar{X} \pm SD$	Range	Normal Values
EF, %	55 ± 2.54	41.50-71.80	53-77
FS, %	31.55 ± 2.26	26-45	28-44
Vcf, circ/s	1.47 ± 0.11	1.09 ± 2.15	1.34-0.03
PEP/LET	0.38 ± 0.02	0.25-0.50	0.30-0.39

Discussion

Controversy exists concerning the impact of SHPT in ESRD on development of left ventricular hypertrophy and systolic dysfunction. Drüeke et al.[7] reported that myocardial contractility was reduced in dialysis patients with SHPT, which improved after parathyroidectomy. This idea has been supported by the experimental myocardial changes induced by PTH[4,5]. Gater et al.[11] assessed the LV function in chronic renal failure patients and showed that excess PTH had only a minor effect on myocardial performance and that there was no improvement even long after parathyroidectomy. Hüting et al.[12] did not show any influence of the amount of SHPT on LV function and suggested that LV ejection phase indices were not related to PTH activities in ESRD patients.

Although the C-terminal PTH levels were above normal in our study group, EF and FS values were within normal limits. The PEP/LVET ratio was normal in our cases except for the five with severe hypertension and anemia. The abnormal X-ray and ECG findings in these five patients were explained by their hypertension and anemia. Blanchard et al.[13] reported that although there were slight increases, the PEP/LVET ratio was generally within normal limits. In our patients without cardiac failure, the mean PEP/LVET was 0.38 ± 0.02, which is at the upper limit of normal. This is in accordance with the literature. In our study the mean Vcf before hemodialysis was 1.47 ± 0.11 circ/s and this was above normal for age.

It has been previously reported that maintenance hemodialysis increases Vcf significantly[14, 15]. No significant correlation was found between the PTH levels and the parameters reflecting left ventricular function ($p > 0.05$).

In another study[16], the effects of PTH and vitamin D on LV function in uremic patients on maintenance hemodialysis were examined. When the patients were given 1 µg/day 1α (OH) D_3 for six weeks, the plasma PTH levels decreased along with an increase in FS from 34.6 to 37.6 percent and an increase in Vcf from 1.25 to 1.32 circ/s. In the same study in the parathyroidectomized patients, the FS and Vcf increased from 34.9 to 36.3 percent and from 1.22 to 1.38 circ/s, respectively. The authors did not conclude whether myocardial dysfunction was due to PTH increment or the lack of 1.25 $(OH)_2$ D_3[16]. The effects of vitamin D may be related to modifications in serum Ca^{2+} levels. More direct effects on the myocardium can be deduced from experimental vitamin D3 depletion studies; this induces cardiac hypertrophy related to interstitial edema, increased collagen and decreased myofibrillar area.

All of our cases received 1α (OH) D_3 at a dose of 0.5-1 µg/day, and all had normal serum calcium levels. Since LV contractibility functions were normal in spite of increased serum PTH levels and since no significant correlation was found between the high levels of PTH and other parameters, we suggest that PTH alone is not responsible for myocardial dysfunction. The active vitamin D therapy might have prevented the myocardial dysfunction by a direct effect. The increase in cardiac output, which is due to a variety of causes in uremia, decreases after parathyroidectomy and this is related to heart rate rather than stroke volume[11].

In this study, the positive correlation between serum PTH and cardiac output and stroke volume, which are the indices of LV volume functions, imply that PTH affects these parameters. It is known that anemia is an important contributor to cardiac output and stroke volume. Anemia is inevitable in ESRD. PTH also contributes to anemia, but we were unable to demonstrate a statistical relationship between PTH level and anemia. A correlation was documented, however, between the Hb level and stroke volume.

These results imply that PTH is not the only factor affecting myocardial functions. Since all of these patients had received 1α (OH) D_3 therapy for long periods, we suggest that vitamin D may have prevented the abnormalities in myocardial function.

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