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Effects of verapamil on the abnormalities in fatty acid oxidation of myocardium

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Effects of verapamil on the abnormalities in fatty acid oxidation of myocardium. The oxidation of long (LCFA) and short chain fatty acids (SCFA) by myocardial mitochondria is impaired in CRF due to reduced activity of carnitine palmitoyl transferase (CPT) and of enzymes in the β-oxidation sequence in mitochondrial matrix. It was proposed that PTH, through its ability to augment entry of calcium into cells, enhances calcium uptake by the myocardium leading to calcium accumulation which in turn affects mitochondrial function. A calcium channel blocker may therefore correct these derangements. The present study examined the effects of verapamil on LCFA and SCFA oxidation and on CPT activity of myocardial mitochondria and on ^{45}Ca uptake by, and calcium content of, myocardium obtained from CRF rats and rats treated with PTH, with and without administration of verapamil. Both four days of PTH administration and 21 days of CRF produced significant ($P < 0.01$) reduction in the oxidation of LCFA and SCFA by and of CPT activity of myocardial mitochondria and a significant increase in ^{45}Ca uptake by, and content of, the myocardium. Simultaneous administration of verapamil reversed all these derangements. Administration of verapamil alone to normal rats for 4 or 21 days did not cause significant changes in these parameters. The results of our studies are consistent with the notion that the alterations in myocardial oxidation of LCFA and SCFA in CRF or after PTH treatment are related to PTH-induced calcium accumulation in the heart, and could be reversed by a calcium channel blocker. The data could provide a rational therapeutic approach for the management of uremic myocardiopathy.

Oxidation of long and short chain fatty acids by heart mitochondria is impaired in chronic renal failure (CRF) secondary to reduced activity of carnitine palmitoyl transferase (CPT) and to a defect in β-oxidation sequence [1]. Available data indicate that these derangements in fatty acid oxidation are in large part due to secondary hyperparathyroidism of CRF [1].

Since fatty acids are an important energy source for the heart under aerobic conditions [2, 3], a defect in their utilization may contribute to the biochemical derangements underlying the genesis of uremic myocardiopathy. Therefore, agents that may reverse or ameliorate the defects in fatty acid oxidation could provide important therapeutic approach for the management of myocardial disease in CRF.

The mechanisms through which excess blood levels of parathyroid hormone (PTH) exert deleterious effects on fatty acid oxidation by the myocardium are not well delineated. However, it has been suggested that an increase in calcium uptake and/or content of the myocardium [1] induced by the ability of PTH to augment calcium entry into cells [4–6] may be responsible, in large part, for the abnormalities in fatty acid oxidation in CRF. If this is indeed the case, calcium channel blockers should improve or correct those derangements in fatty acid oxidation.

The present study examined the effects of verapamil on ^{45}Ca uptake and calcium content of the myocardium and on long and short chain fatty acid oxidation and CPT activity of myocardial mitochondria in animals treated with PTH and in those with chronic renal failure.

Methods

Male Sprague-Dawley rats weighing 250 to 350 g were used in the study. The animals were fed normal rat chow (Wayne Research Animal Diets, Chicago, Illinois, USA) throughout the study. The diet had 1.4% calcium, 0.97% phosphorus and 4.4 IU/g of vitamin D. Previous studies in our laboratory showed that a clear cut effect of PTH on mitochondrial fatty acid oxidation occurs after four days of treatment with the hormone [1]. Therefore, the present study utilized the four day protocol of PTH treatment. The animals were housed in individual cages.

The rats were given an intraperitoneal injection of 200 U/day of 1-84 PTH (Sigma Chemical Company, St. Louis, Missouri, USA) for four days. The hormone was dissolved in normal saline and half of the daily dose was given in the morning and the other half in the late afternoon hours. The control animals received sham injections containing the vehicle only. A third group of animals were treated for four days with 1-84 PTH (200 U/day) and simultaneously received subcutaneous injections of verapamil (Isoptene, Knoll, Ludwigschafen, FRG) in a dose of 0.1 μg/g body weight twice daily. A fourth group of rats received verapamil only, for four days. Oxidation of α-ketoglutarate, long chain fatty acid (L-CFA), short chain fatty acid (S-CFA), and activity of CTP by mitochondria, and ^{45}Ca uptake and calcium content of the myocardium were examined on the morning of day 5.

Studies were also performed after 21 days of CRF. The animals underwent right partial nephrectomy, and a week later a left nephrectomy was performed. Some of the animals with CRF received subcutaneous injections of verapamil (0.1 μg/g body wt twice daily) for the 21 day period of CRF. A third group of normal rats received only verapamil for 21 days. Studies of

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the oxidation of α-ketoglutarate, L-CFA and S-CFA, and CPT activity in mitochondria, and ^{45}Ca uptake and calcium content of the myocardium were done on the morning of day 22.

After the animals were sacrificed by decapitation, the hearts were removed and washed from blood for the isolation of mitochondria according to the method of Yang, Gieger and Bessman [7]. About 1 g of myocardium was placed in an ice-cold homogenization media containing 180 mM KCl, 10 mM EDTA disodium with pH adjusted to 7.4. The tissue was then cut into small pieces, run through a Harvard tissue press and treated for 30 minutes with trypsin, and then homogenized with a Dounce type homogenizer. A trypsin inhibitor was then added to stop the reaction. The mixture was homogenized again and then centrifuged for 10 minutes, at 400 g, in a Sorvall RC-5 refrigerated centrifuge (DuPont Co., Instrument Produce Division, Newton, Connecticut, USA). The pellet was discarded and the supernatant was centrifuged at 8000 g for 10 minutes, for final isolation of the mitochondria. The mitochondrial pellet was washed several times and suspended in a media containing 180 mM KCl, and 10 mM Tris HCl and centrifuged for 10 minutes at 8000 g. The pellet was then suspended in media containing 180 mM KCl, 10 mM Tris HCl and 0.5% (wt/vol) dialyzed albumin. The pH of the media was 7.4. The protein concentration of the pellet was determined by a modification of the method of Lowry et al [8]. The isolated mitochondria were used for the study of the oxidation of α-ketoglutarate, L-CFA and S-CFA and for the activity of CPT. The consumption with various substrates, respiratory control ratio and ADP:O ratio were determined polarographically by means of a Clark oxygen electrode (Gilson Medical Electronics, Middleton, Wisconsin, USA) fitted to a plexiglass chamber of 2.0 ml capacity as described originally by Chance and Williams [9]. The details for the study of α-ketoglutarate oxidation have been previously reported from our laboratory [10]. The amount of ADP added each time to the oxygraph chamber was 250 μmol. The complete system for fatty acid oxidation contained between 1.0 and 1.5 mg mitochondrial protein added to 2.0 ml of incubation media containing (in mM): 230 mannitol, 10 Tris HCl, 0.02 EDTA disodium, 5 potassium phosphate, 70 sucrose and 1 malate. The final pH was 7.2 and the temperature 28°C. In the studies of the oxidation of S-CFA, the media in the oxygraph chamber contained about 1.0 to 1.5 mg of mitochondrial protein suspended in 120 liters and 50 μl of 40 mM octanoic acid (Sigma Chemical Co., St. Louis, Missouri, USA) giving a final concentration of 1.0 mM of octanoic acid. The studies for the evaluation of the L-CFA oxidation utilized fatty acid palmitoyl CoA (Sigma Chemical Co.). To prepare this fatty acid for use in the study, 1 mg of palmitoyl CoA was added to 1 ml of 96% ethanol and sonicated for 10 to 15 minutes, and then diluted with 9 ml of distilled water. About 1.0 to 1.5 mg mitochondrial protein contained in 120 μl of mitochondrial solution, 50 μl of 2 mM of LD-carnitine, and 30 μl of 0.1 mM palmitoyl CoA were added to the incubation chamber giving a final concentration 0.05 mM of LD-carnitine and 0.0025 mM of palmitoyl CoA. Oxygen consumption was recorded and results were calculated according to Chance and Williams [9] and expressed as nanomoles of oxygen utilized per milligram of protein per minute.

The activity of CPT was measured by the method of Bieber, Abraham and Helmrath [11]. This enzyme activity was determined by the release of free CoA in the presence of exogenous L-carnitine, palmitoyl CoA and 5.5′-dithiobis-(2 nitrobenzoate) (DTNB). The free CoA reduced DTNB giving a yellow color which had a molar absorbance per centimeter of 13.6×10^3 at 412 nm, pH 8.0 and 25°C. To eliminate the effect of endogenous mitochondrial L-carnitine, a parallel assay was run with excess D-carnitine which inhibited the reaction (blank); the activity of the enzyme was then calculated as the difference between results observed in the presence of L- and D-carnitine and expressed as nanomoles of CoA per milligram protein per minute.

The uptake of ^{45}Ca by the myocardium was determined by a modification of the method of Fleckenstein et al [12]. On the day of the study, the animals received 20 μCi of ^{45}Ca per kg body weight, intraperitoneally at 6 a.m. Six hours later the animals were sacrificed by decapitation, blood was collected and myocardial samples were obtained, and the wet weight was determined. The myocardial tissue was dissolved in soluene X-100 (Packard Instrument Corp., Downers Grove, Illinois, USA); 1 ml of soluene was used per 1 mg wet weight. ^{45}Ca in blood and myocardium was determined with a Beckman liquid scintillation counter model L 5700 (Beckman Instruments, Irvine, California, USA). The myocardial uptake of ^{45}Ca was expressed as percentage uptake in 1 g wet tissue relative to the counts in 100 ml of blood.

Myocardial calcium content was also determined. After sacrifice by decapitation, myocardial samples were obtained, washed with saline, and the wet weight was determined. The samples were then dried in an oven for 24 hours at 105°C. Dry weight was determined. The tissue samples were then ashed at 400°C for four to six hours. The ash was dissolved in 3 N nitric acid and calcium concentration was measured with atomic absorption spectrophotometer (Model 505, Perkin Elmer Corporation, Norwalk, Connecticut, USA).

In all studies, blood samples were obtained for the measurements of calcium with atomic absorption spectrophotometer, and for inorganic phosphorus and creatinine with an autoanalyzer (Technicon Corp., Tarrytown, New York, USA). Data are expressed as mean ± SE and statistical significance was evaluated by parametric *t*-test.

Results

Table 1 presents the biochemical and mitochondrial data in the various groups of animals. The plasma levels of creatinine, calcium and phosphorus were not different among the normal rats and those treated with PTH alone, PTH and verapamil, and verapamil alone, except for plasma phosphorus in the PTH treated rats. In these animals plasma phosphorus (6.5 ± 0.35 mg/dl) was significantly lower than normal. The plasma creatinine was significantly ($P < 0.01$) higher in the rats with CRF produced by 5/6 nephrectomy than in normal rats. There were no significant differences between the plasma levels of calcium and phosphorus in normal rats and in those with CRF with and without treatment with verapamil.

The respiratory control ratios of the myocardial mitochondria in the various groups of rats and for the three substrates studied were within the range of intact mitochondria.

The administration of 1-84 PTH for four days was associated with marked and significant ($P < 0.01$) reduction in mitochondrial oxidation of α-ketoglutarate, the S-CFA octanoic acid and the L-CFA palmitoyl CoA (Fig. 1 and Table 1). Treatment with

Table 1. Effects of 1-84 PTH treatment and chronic renal failure with and without verapamil and of verapamil alone

		4 Days			21 Days		
	Normal	PTH	PTH-VER	VER	CRF	CRF-VER	VER
Weight *g*	310 ± 8.6	294 ± 3.3	315 ± 3.4	301 ± 12.9	301 ± 9.3	302 ± 8.6	307 ± 13.9
Serum creatinine *mg/dl*	0.44 ± 0.03	0.46 ± 0.03	0.48 ± 0.04	0.50 ± 0.04	1.67 ± 0.17	1.45 ± 0.25	0.46 ± 0.03
Serum calcium *mg/dl*	10.6 ± 0.3	10.6 ± 0.3	10.7 ± 0.2	10.0 ± 0.4	10.2 ± 0.3	10.0 ± 0.3	9.9 ± 0.4
Serum phosphorus *mg/dl*	8.7 ± 0.10	6.5 ± 0.35[a]	7.9 ± 0.22	8.2 ± 0.36	8.3 ± 0.36	8.0 ± 0.50	8.3 ± 0.35
α-Ketoglutarate							
RC ratio	16.2 ± 2.00	12.0 ± 0.60	13.5 ± 0.80	15.4 ± 0.74	15.4 ± 0.57	11.1 ± 0.76	14.9 ± 0.71
ADP:O	2.8 ± 0.05	2.9 ± 0.02	2.6 ± 0.06	2.9 ± 0.08	2.9 ± 0.04	2.8 ± 0.09	2.8 ± 0.04
Oxygen consumption *nmol/mg protein/min*	196 ± 2.4	148 ± 4.0[a]	195 ± 2.7	197 ± 2.7	158 ± 1.9[b]	193 ± 5.2	202 ± 2.2
Octanoic acid							
RC ratio	13.6 ± 1.40	10.1 ± 0.45	8.3 ± 1.10	8.8 ± 0.32	11.7 ± 1.08	9.4 ± 0.93	11.6 ± 1.11
ADP:O	2.5 ± 0.04	2.6 ± 0.04	2.4 ± 0.03	2.5 ± 0.05	2.5 ± 0.03	2.4 ± 0.06	2.6 ± 0.04
Oxygen consumption *nmol/mg protein/min*	169 ± 2.4	132 ± 1.7[a]	173 ± 2.9	168 ± 4.3	149 ± 4.9[b]	174 ± 5.6	166 ± 1.6
Palmitoyl CoA							
RC ratio	5.5 ± 0.64	4.6 ± 0.44	5.7 ± 0.62	6.4 ± 0.19	4.9 ± 0.41	5.2 ± 0.14	5.6 ± 0.47
ADP:O	2.7 ± 0.06	2.8 ± 0.09	2.8 ± 0.09	2.9 ± 0.13	2.8 ± 0.05	2.7 ± 0.06	2.8 ± 0.05
Oxygen consumption *nmol/mg protein/min*	64 ± 1.1	54 ± 1.8[a]	68 ± 1.8	66 ± 1.3	49 ± 1.6[b]	65 ± 1.6	67 ± 1.0
Carnitine palmitoyl transferase *nmol/mg protein/min*	17.3 ± 0.64	12.7 ± 0.47[a]	19.6 ± 1.28	17.5 ± 0.67	13.5 ± 0.60[b]	17.6 ± 0.84	17.5 ± 0.62
^{45}Ca uptake %	40 ± 1.9	54 ± 1.5[a]	41 ± 1.7	42 ± 1.9	56 ± 1.8[b]	42 ± 1.3	43 ± 2.2
Calcium content *μg/g dry weight*	17 ± 1.2	24 ± 1.8[a]	16 ± 1.8	17 ± 1.4	25 ± 1.3[b]	16 ± 1.7	18 ± 1.6

Abbreviations are: RC, respiratory control; VER, verapamil. The number of animals in normal is 10, in PTH is 13, in PTH-VER is 13, in VER 4 days is 14, in CRF is 10, in CRF-VER is 10, and in VER 21 days is 10. The studies of ^{45}Ca and calcium content were done in 10 rats in each group. The *N* in studies with octanoic acid in PTH, PTH-VER and VER 4 days groups is 6.

[a] $P < 0.01$ compared to normal, to PTH-VER or VER 4 days

[b] $P < 0.01$ compared to normal, CRF-VER and VER 21 days.

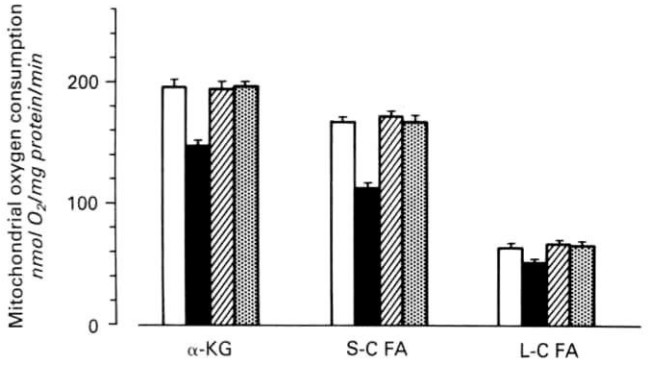

Fig. 1. *Effects of administration of 1-84 PTH with and without treatment with verapamil and of verapamil (VER) alone on oxidation of α-ketoglutarate (α-KG), long chain fatty acid (L-CFA) and short chain fatty acid (S-CFA) by myocardial mitochondria.* Each column represents the mean value and brackets denote 1 SE. Symbols are: (□) normal; (■) 4 days PTH; (▨) 4 days PTH + verapamil; (▣) 4 days verapamil.

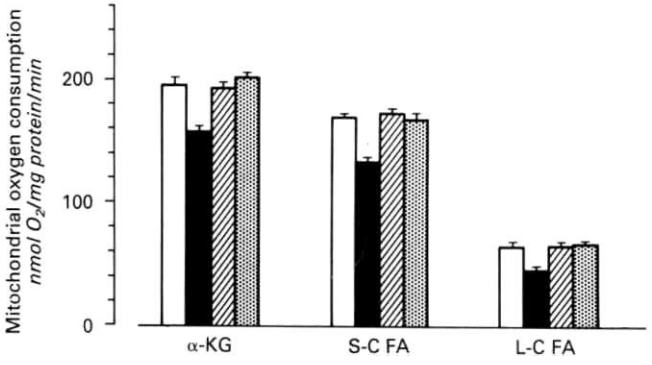

Fig. 2. *Oxygen consumption by myocardial mitochondria from normal rats (□), animals with chronic renal failure (■), CRF rats treated with verapamil (▨) and normal animals given only verapamil (▣).* Each column represents mean value and brackets denote 1 SE.

verapamil reversed these abnormalities. The mitochondrial oxidation of the three substrates in rats treated with PTH and verapamil were significantly ($P < 0.01$) higher than those observed in rats treated with PTH alone and were not different from those seen in normal rats (Fig. 1, Table 1). Treatment of normal rats with verapamil alone did not produce significant changes in mitochondrial oxidation of α-ketoglutarate, octanoic acid and palmitoyl CoA.

Twenty-one days of CRF was also associated with significant ($P < 0.01$) and marked decrements in mitochondrial oxidation of α-ketoglutarate, octanoic acid and palmitoyl CoA. These abnormalities were corrected by the treatment with verapamil. Further, treatment of normal rats for 21 days with verapamil had no significant effect on mitochondrial oxidation of these substrates (Fig. 2, Table 1).

Both treatment of normal rats for four days with 1-84 PTH and 21 days of CRF was associated with significant reduction in the activity of CPT (Figs. 3 and 4). The impairment in the activity of this enzyme was prevented by the administration of verapamil to the PTH-treated rats or to the CRF animals.

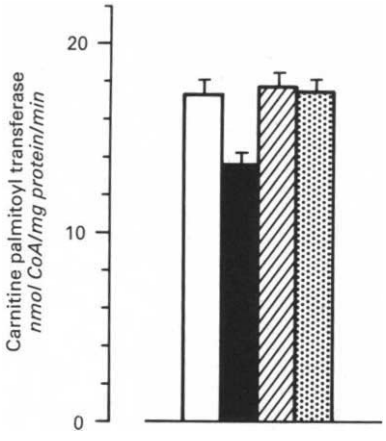

Fig. 3. *Carnitine palmitoyl transferase activity of myocardial mitochondria from normal rats (□), animals treated with 4 days of 1-84 PTH (■), those treated simultaneously for 4 days with PTH and verapamil (▨), and rats which received 4 days of verapamil alone (▣).* Each column represents the mean value and the brackets denote 1 SE.

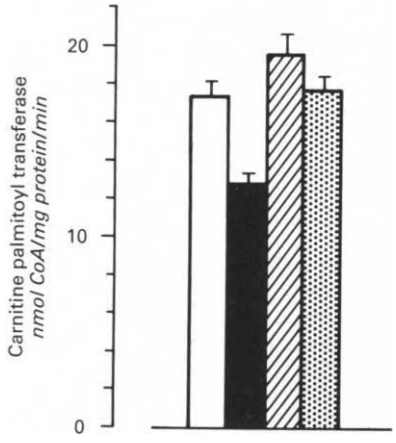

Fig. 4. *Carnitine palmitoyl transferase activity of myocardial mitochondria from normal rats (□), animals with 21 days of chronic renal failure (■), CRF rats treated with verapamil (▨), and normal rats given only verapamil (▣).* Each column represents mean value and brackets denote 1 SE.

Verapamil given to normal rats for 21 days had no effect on the activity of CPT.

Treatment for four days with PTH produced a significant ($P < 0.01$) increment in ^{45}Ca uptake by and in calcium content of the myocardium. These changes were corrected by the simultaneous administration of verapamil (Table 1). This drug given to normal rats, however, did not cause significant changes in myocardial uptake of ^{45}Ca or in myocardial calcium content (Table 1). Similarly CRF was associated with significant ($P < 0.01$) augmentation in ^{45}Ca uptake by and in calcium content of the myocardium. These derangements were reversed by the treatment of the CRF animals with verapamil (Table 1).

Discussion

We have previously shown that excess blood levels of PTH, whether produced by exogenous administration of the hormone or by increased endogenous release of PTH as in CRF, are associated with marked abnormalities in fatty acid oxidation by myocardial mitochondria [1]. These derangements were attributed to reduced activity of CPT, a key enzyme for the transfer of L-CFA to mitochondrial matrix and to impairment in the β-oxidation sequence [1].

However, the mechanisms responsible for the PTH-induced derangement in the enzymatic steps involved in the oxidation of the L-CFA and S-CFA were not elucidated. It was suggested that these effects of PTH may be related to its ability to enhance entry of calcium into cells [4–6]. Such an effect may result in an enhanced and prolonged calcium uptake by the myocardium, resulting in increased calcium content with consequent adverse effects on the function of myocardial mitochondria. Such a postulate was based on previous observations that PTH given to normal rats [10] and CRF in rats [13] were associated with increased myocardial ^{45}Ca uptake and calcium content and with impaired oxidation of α-ketoglutarate. These effects were reversed by treatment with a calcium channel blocker or by parathyroidectomy in CRF rats.

The results of the present study are consistent with this sequence of events. PTH administration to normal rats or CRF with its attendent secondary hyperparathyroidism were associated with increased myocardial calcium uptake and content, reduced activity of CPT and impaired mitochondrial oxidation of L-CFA and S-CFA. The treatment with verapamil, a calcium channel blocker, prevented the rise in myocardial calcium uptake and content, and reversed the derangement in fatty acid oxidation in both the normal rats treated with PTH and in the CRF animals.

Similar observations were also reported in skeletal muscle treated with PTH or in CRF rats [14, 15]. These maneuvers were also associated with increased skeletal calcium uptake and impaired CPT activity and L-CFA oxidation. Prevention of the augmented calcium uptake by a calcium channel blocker was associated with normalization of the activity of CPT and L-CFA oxidation.

The results of the present study and those previously reported [1, 10, 13–16] clearly demonstrate that states associated with excess PTH independent of the presence or absence of CRF caused marked derangement in myocardial and skeletal mitochondrial function manifested by impaired mitochondrial utilization of various substrates, including fatty acids for energy production. These derangements in mitochondrial oxidation appear to be related to calcium elevation of the myocardium and the skeletal muscle.

The derangements in mitochondrial function observed in our study may play an important role in the myocardiopathy of CRF. Renal insufficiency is associated with secondary hyperparathyroidism in man [17–19], rats [20] and dogs [21]. Although the blood levels of PTH in our animals were not measured, it is reasonable to assume that a state of secondary hyperparathyroidism did develop in the rats with CRF and intact parathyroid glands. The results of the present study in rats with CRF and those treated with PTH, and our previous report demonstrating that parathyroidectomy of CRF rats reversed the increased ^{45}Ca uptake and calcium content of myocardium [13] and prevented the abnormalities in fatty acid oxidation [1], indicate that excess PTH is the culprit; since we know of no data suggesting that verapamil may inhibit PTH secretion and since verapamil corrected the calcium overload of the myocardium and the abnormalities in fatty acid oxidation,

we conclude that the beneficial effect of verapamil must have been mediated by antagonizing the ionophoric property of PTH.

Several lines of evidence indicate that the myocardium is indeed a target organ for PTH [1, 10, 13, 22–26] and that excess of PTH in patients with chronic renal failure [25, 26] and in patients with parathyroid adenoma and normal renal function [27] display myocardial dysfunction. Thus, therapeutic approaches are needed to ameliorate these deleterious effects of PTH. The results of our study provide a potential rational approach for counter balancing the harmful effects of excess PTH on myocardial function. Indeed, Eren et al [28] treated six dialysis patients with 250 mg/day of "slow release verapamil" for three months and found a significant decrease in left ventricular wall thickness, suggesting a reduction in left ventricular hypertrophy. These changes occurred without a significant effect on blood pressure.

Such a potential therapeutic effect of verapamil in the management of the myocardiopathy of CRF provides another example of the therapeutic benefits of calcium channel blockers in the management of disturbances in the cardiovascular system, such as hypertension, ischemic heart disease and arrhythmias [29]. These actions have also been attributed to the blocking of calcium entry in the arterial wall or the myocardium [30].

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