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«HIPERTENSIÓN Y ENFERMEDAD CARDIOVASCULAR EN PACIENTES CON INSUFICIENCIA RENAL CRÓNICA»

Effects of hyperparathyroidism in the pathogenesis of hypertension, left ventricular hypertrophy and cardiovascular disease in CRF patients

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PTH has been shown to influence cardiac and vascular function and growth, as shown experimentally in *in vitro* and *in vivo* etudies, and alco-in-human subjects with normal renal function. Because of the increased prevalence of hyperparathyroidism in chronic renal failure (CRF), these alterations have long been felt to contribute to the increased prevalence of cardiovascular disease and hypertension seen in this patient population.

PTH (and also PTHrP) have been shown to increase acutely the force and frequency of contraction of isolated, beating rat cardiomyocytos. It has been, suggested that increased inotropy produced by PTH and PTHrP is due to effects on coronary flow and heart rate and not to effects on contractile function. However, changes induced by PTH occur in association with an increase of cell calcium and cyclic AMP. In isolated myocardial mitochondria PTH uncoupled oxidative phosphorylation and inhibited myocardial energy production, leading to reduced ATP content and impaired activity of creatine kinase. Like the chronic inhibitory effects of PTH on myocardial contractility, these responses could be reversed by verapamil. In a uremic rat model elevated cytosolic Ca^{2+} in cardiomyocytes was associated with attenuated IGF-1 stimulated protein synthesis that could be reversed either by parathyroidectomy or felodipine, suggesting yet another mechanism by which elevated intracellular calcium and 2.º hyperparathyroidism might modulate myocardial growth and structure in uremia. The above noted experimental studies suggest that prolonged exposure to PTH is associated with a greater intramyocardiocyte Ca^{2+} and with adverse effects on myocardial metabolism, structure, and function. An increase of cytoplasmic Ca^{2+} by excessive PTH levels has also been found in uremic patients in whom elevated platelet Ca^{2+} was correlated with plasma PTH and which could be corrected by parathyroidectomy of calcitriol treatment.

In rats with CRF the PTH/PTHrP receptor is downregulated. This may serve to desensitize tissues to PTH effects and thus minimize increases in cellular calcium, possibly as part of a negative feedback mechanism.

In humans with CRF, as in 1.º hyperparathyroidism, the presence of 2.º hyperparathyroidism has been associated with increased myocardial calcium content and impaired ventricular systolic and diastolic function. Moreover, both 1.º and 2.º hyperparathyroidism are associated with left ventricular hypertrophy (LVH). There are theoretically several mechanisms by which parathyroid excess could favor LVH and cardiac dysfunction. They include direct trophic effects on cardiomyocytes and interstitial fibroblasts and indirect effects such as a blood pressure increase via hypercalcemia, hyperphosphatemia and anemia, as well as pathologic large and small vessels changes secondary to disturbances of lipid and carbohydrate metabolism and to soft-tissue calcifications associated with chronic PTH excess However, parathyroidectomy is not consistently associated with improvement in left ventricular hypertrophy and function, suggesting either PTH-induced changes became irreversible in the case of long-standing, severe hyperparathyroidism, for example by the induction of interstitial fibrosis, or that other factors contributing to myocardial dysfunction were more important than parathyroid overfunction.

In conclusion, the hyperparathyroid stale of chronic renal failure contributes to the cardiovascular pathology seen clinically in uremic patients and also to the excess mortality from cardiovascular causes found in this patient group.

REVIEW ARTICLE

Rostand SG, Drüeke TB: Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 56: 383-392, 1999.