Dysfunction of Myoplasmic Ca^{2+} Regulation in Skeletal Muscle from Predialytic Uremic Patients

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Dear Sir,

Several reports have suggested that some patients with chronic renal failure may develop muscle weakness and pain due to a primary disorder of skeletal muscle functions [1]. The maintenance of transmembrane Ca^{2+} gradient is essential for the function and viability of muscle cells. The Ca^{2+} overload has been supposed to be a final pathway of cellular injury in a wide range of conditions [2, 3]. The myoplasmic Ca^{2+} concentration in skeletal muscle is primarily regulated by the $\text{Na}^{+}/\text{Ca}^{2+}$ exchange and the Ca^{2+} pump at the sarcolemma and by the Ca^{2+} pump at the sarcoplasmic reticulum [4]. In the present investigation, we studied the resting myoplasmic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$) in predialytic uremic patients.

This study was carried out in 10 uremic patients (8 men and 2 women) with chronic renal failure with a mean age of 48 ± 3 years (mean $\pm$ SE) and an average glomerular filtration rate of 19 ± 3 ml/min, $\times 1.73$ (clearance of inulin, corrected to 1.73 m² body surface).

Hypertension was present in 2 of 10 patients. Patients presented with muscle weakness predominantly in the lower limbs. On physical examination, no objective evidence of a sensory deficit was found in any of these patients. In the uremic patients external intercostal muscle biopsies (7th to 8th intercostal space) were removed under local anesthesia. Control muscle biopsies were obtained from 4 subjects under a general anesthetic with no neuromuscular or renal disease at the time of thoracotomy performed for different surgical indications. All the patients included in the study were nondiabetic and did not have any other systemic disease.

The $[\text{Ca}^{2+}]_i$ was measured by means of double-barreled Ca^{2+} -selective microelectrodes which were prepared and calibrated as described previously [5]. In muscle fibers from control subjects the $[\text{Ca}^{2+}]_i$ was 110 ± 10 nM ($n = 23$, n = number of measurements; range 90-130 nM), while in the uremic patients it was 670 ± 56 nM, ($n = 45$; range 450-834 nM). This high $[\text{Ca}^{2+}]_i$ was observed in all the muscle biopsies regardless the sex and age. The muscles used for the myoplasmic Ca^{2+} measurements were the external intercostal muscles, since they represent the only muscle preparation that can be removed preserving intact conditions in the muscle fibers. However, despite the fact that these groups of muscle did not show any

evidence of weakness, such muscles did show a significant alteration in resting myoplasmic Ca^{2+} regulation. This finding suggests that the muscle disorder observed in chronic renal failure is a generalized myopathy.

Despite the fact that in previous studies the absence of distinguishing morphological and electromyographic features has been reported [6, 7], we have found a remarkable consistent alteration in $[\text{Ca}^{2+}]_i$ in all the uremic patients included in this study. However, these observations do not suggest a unified concept for the pathogenesis of myopathy in chronic renal failure. It seems likely that dysfunction in myoplasmic Ca^{2+} regulation may be a secondary effect of several etiologic factors, acting separately or in combination, which may contribute to the myopathy observed in these patients. Perhaps a common metabolic basis, such as deficiency in adenosine triphosphate and/or a disturbance in myoplasmic pH, may compromise the efficiency of some of the myoplasmic Ca^{2+} -regulatory mechanisms, making possible an increase in the myoplasmic Ca^{2+} concentration. Further studies are necessary to clarify this point.

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