

Commentary

Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance

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Abstract

Rhabdomyolysis is a pathogenetic cause of acute kidney injury. In such circumstances, not only should therapeutic strategies to replace the failing kidney be implemented, but measures should also be explored to prevent further damage by circulating myoglobin. Volume expansion and forced diuresis have been used, but when a kidney fails, renal replacement therapies are instituted. The techniques and devices used for classic dialytic techniques have displayed a limited capacity for the removal of circulating myoglobin. In a recent paper, Naka and colleagues have proposed the use of a super-high-flux membrane in continuous hemofiltration. The removal of myoglobin was greater than in than any previous report. Thus, if the removal of myoglobin is desirable, a combination of continuous hemofiltration and hyperpermeable membranes seems to be the most effective. However, care must be exercised to prevent unwanted albumin losses.

Rhabdomyolysis is a pathogenetic cause of acute kidney injury in a large number of cases where traumatic or non-traumatic causes induce muscle cell disruption [1]. Naka and colleagues concluded an interesting study on myoglobin clearance by hemofiltration using a 'super-high-flux' membrane in a case of acute rhabdomyolysis [2].

The paper is of peculiar interest for several reasons. First, because of the renal damage induced by circulating myoglobin, not only should therapeutic strategies be implemented to replace the failing kidney function, but preventive measures should also be explored to prevent further damage due to renal tubular obstruction, altered intrarenal hemodynamics and tubular cell dysfunction. So far, acute kidney failure has been treated by classical methods of renal replacement therapies, while protective measures have been limited to volume expansion by alkaline fluids and forced diuresis by osmotic diuretics. Second, all attempts to produce a significant removal of myoglobin by extracorporeal

therapies have so far displayed controversial results but in general they have been proved to be modestly useful. Thus, although the rationale for a quick and effective removal of myoglobin in acute rhabdomyolysis would be strong and logical, the practical results obtained with traditional methods have been disappointing. The inefficient removal of myoglobin results in a permanently high circulating level of the molecule and a perpetuation of the pathological insult with prolongation of anuria and delay of renal function recovery.

Why are extracorporeal techniques hardly effective in removing myoglobin? There are several reasons that depend on the nature of the molecule, on its distribution in the organism, on the mechanism of solute transport and on the structure of the membrane in the extracorporeal technique.

Myoglobin has a molecular mass of 17 kDa but because it is non-spherical and carries electrical charges it can be considered to be a solute with an Einstein-Stokes radius greater than expected. In these circumstances, not only does the solute have a very low diffusion coefficient, thus requiring transport by convection, but it also possesses a steric magnitude that is likely to be rejected by the membrane pores. The volume of distribution in the human body is not known but the molecule has been estimated to be distributed into two pools: one is in equilibrium with the vascular circulation, which should be about one-tenth of the body weight; the other is in equilibrium with the muscle tissue, which is hard to define. The two pools do not equilibrate rapidly, so a very efficient system of blood purification will cause a significant decrease in the circulating levels, suggesting that optimal application will involve intermittent frequency. In contrast, a less efficient system, capable of maintaining the levels at a steady state, can cope with the daily generation but needs to be administered 24 hours a

day. Finally, the membrane and technique used for the membrane separation process are crucial for the efficiency of the therapy. There is no question that convection should be used, because of the molecular mass of the solute. However, standard cellulosic membranes are practically impermeable to the molecule; high-flux membranes should be used.

The limitation imposed by high-flux membranes in convective therapies such as hemofiltration is that in the presence of a low sieving coefficient for myoglobin, even high-volume hemofiltration or pulse high-volume hemofiltration may be inefficient [3]. Theoretically the sieving for myoglobin should be in the range 0.4 to 0.6, but this is only true in optimal conditions, with aqueous solutions and in the absence of concentration polarization. The average pore size is a statistical function and very little is known about the shape of the Gaussian curve of the pore size distribution when the membrane is used *in vivo* with the interference of high filtration fractions and plasma proteins. Under these conditions the sieving value may fall below 0.1, so that even in the presence of high filtration volumes the final clearance will be negligible.

Attempts to use plasmapheresis have resulted in higher sieving coefficients, but the final clearance is minimal because of the limitations imposed by low volume exchanges. A different approach could be tried either using adsorption directly on whole blood or using coupled plasma-filtration adsorption in which the patient's plasma is reinfused after being regenerated by passage through a sorbent cartridge. Results with such systems are under evaluation and seem encouraging.

The solution proposed by Naka and colleagues seems to be feasible and effective. The use of a continuous technique in conjunction with a hyperpermeable membrane with a myoglobin sieving well beyond the classic values observed with high-flux membranes seems to provide clearance and removal values previously unobtainable. One of the possible limitations is represented by albumin leakage, which should be rigorously tested and evaluated in a wider series of patients and treatment conditions. In the case described in this study, myoglobin clearance was significantly greater with the hyperpermeable membrane than the control treatment with a standard high-flux membrane.

In conclusion, the use of hyperpermeable membranes in continuous veno-venous hemofiltration (CVVH) might represent a novel approach to the treatment of acute rhabdomyolysis not only because efficient renal replacement is provided but also because a potential protective effect can be envisaged in the rapid and efficient removal of circulating myoglobin. Potential drawbacks due to unwanted loss of beneficial molecules should be carefully explored; nevertheless, the therapy could be of enormous advantage and, in the case of excessive albumin losses, pulse super-

high-flux therapy could be used in conjunction with standard CVVH for a few hours each day as a compromise between the beneficial effects of myoglobin removal and the negative effects of excessive albumin losses in continuous treatments. A randomized controlled trial would be of interest in comparing the innovative and traditional approaches, using as the primary end-point the time to renal recovery. Such a trial will probably be difficult to perform for several reasons; nevertheless, the rationale for the new therapy is known and we should try to provide a certain level of evidence from observational studies and case series if studies at a higher level are not yet available or are impossible to perform. The commercial availability of such new membranes in daily practice will definitely broaden the possibilities of the clinical application of super-high-flux hemofiltration techniques.

Competing interests

The author(s) declare that they have no competing interests.

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