CARDIAC RESUSCITATION

Cyclosporine cocktail for cardiac arrest?

Cyclosporine does not prevent early multiple organ failure in patients with nonshockable cardiac rhythm after out-of-hospital cardiac arrest, according to the results of the CYRUS trial. By binding to cyclophilin D, cyclosporine prevents the opening of the mitochondrial permeability transition pore. Opening of this pore at the time of reperfusion is thought to contribute to multiple organ damage. Accordingly, the CYRUS investigators hypothesized that early administration of cyclosporine immediately after resuscitation would prevent multiple organ failure.

The researchers randomly assigned 794 patients with nonshockable out-of-hospital cardiac arrest (asystole or pulseless electrical activity) to receive an intravenous bolus of cyclosporine (2.5 mg/kg) at the onset of advanced cardiovascular life support, or no additional intervention (control). The primary end point (Sequential Organ Failure Assessment score) was not significantly different in the cyclosporine

and control groups (median 10.0 vs 11.0). Similarly, survival was not significantly different between the two groups at hospital admission (24.5% vs 25.6%), at 24 h (16.8% vs 15.7%), or at hospital discharge (2.5% vs 1.3%). Favourable neurological outcome at hospital discharge was similar in the two groups (1.8% vs 1.3%).

“The main limitation of our study,” say the investigators, “is probably the delay in administration of cyclosporine after the resumption of circulation.” The median delay from arrival of the advanced cardiovascular life support team to injection of the study drug was 8 min. “Earlier administration of cyclosporine would result in better prevention of post-cardiac arrest syndrome,” speculate the researchers.

In an Editorial that accompanied the trial report in *JAMA Cardiology*, Lance B. Becker and Peter B. Berger suggest that “the low dose of cyclosporine A administered ... is as likely to contribute to the negative findings as

the delay in treatment”. Many preclinical studies used dosages of 10 mg/kg. Becker and Berger also question whether “administering a single therapeutic agent in the setting of cardiac arrest in an attempt to treat reperfusion injury [is] the optimal approach. The hope that a single agent directed at a single molecular pathway might correct the great many metabolic derangements that occur during reperfusion injury may be wishful thinking.”

They suggest that “perhaps an antireperfusion ‘cocktail’ consisting of a combination of agents would be more successful than our current approach”.

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ORIGINAL ARTICLE Argaud, L. et al. Effect of cyclosporine in nonshockable out-of-hospital cardiac arrest: the CYRUS randomized clinical trial. *JAMA Cardiol.* <http://dx.doi.org/10.1001/jamacardio.2016.1701> (2016)

FURTHER READING Hausenloy, D. J. & Yellon, D. M. Ischaemic conditioning and reperfusion injury. *Nat. Rev. Cardiol.* **13**, 193–209 (2016)