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Commentary: Spinach for Popeye, autogenous mitochondria for us!!

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In one of the latest movies on Netflix, *Project Power*, villains and heroes take a pill that reveal the extraordinary super powers that reside in any of us. The concept is not new: vampires drink blood to keep their eternal youth; Popeye eats spinach because of its high content of iron, as the strength of iron symbolizes power. In their latest research, the team of Weixler and colleagues¹ proposes to inject autogenous mitochondria from skeletal muscles to the free wall of the failing right ventricle (RV) of animal models to increase the mitochondrial function in the RV cardiomyocytes and decrease their apoptosis rate. What is more symbolic for energy than mitochondria, which we have always been taught is the power plant of the cells? But can it work?

There are few data on the remodeling mechanisms of the RV in response to pressure and volume overload and its subsequent transition to RV failure. Downregulation of the mitochondrial enzymes seems to be a key phenomenon of this process.² Obviously, targeting this maladaptive pathway is an appealing goal. Research in this area is still at its dawn,³⁻⁵ and the innovations seem to produce feverish enthusiasm⁶ in a similar way than stem cells research was embraced a few years ago. The authors expanded the already-ongoing research on mitochondrial transplantation, mainly involving the potential treatment of left ventricular failure,^{4,5,7,8} to an animal model of failing RV, obtained by surgical pulmonary artery banding.

Yves d'Udekem, MD, PhD (right), and Federica Caldaroni, MD (left)

CENTRAL MESSAGE

Autologous mitochondria injection for the treatment of right ventricular failure is appealing; however, more extensive research is needed to identify its real clinical potential.

The RVs of 2 different groups of animal models were injected, respectively, with autologous mitochondria and inactive vehicle. The authors demonstrated that 4 weeks following mitochondrial transplantation, the mitochondria-treated hearts were functionally better than vehicle-treated hearts in terms of contractile function and histologic findings of decreased cardiomyocyte apoptosis, claiming a protective effect induced by the mitochondria injection on the myocardial cells.¹

Can we be convinced at this stage and are we getting close to the use of this self-described “therapeutic intervention” in clinical practice? First of all, it is likely that this approach would only be useful for a limited subset of patients. Of course, RV pathology is at the core of congenital heart disease in the same way that left ventricular pathology is at the center of acquired adult heart disease. But unlike what is seen in the left ventricle, we only rarely observe failure of the RV that is primarily related to myocardial dysfunction in the setting of hypertrophied RV.⁹ Which failing hypertrophied RVs do we want to help? Patients with old Mustard and Senning? Are they not primarily failing because of arrhythmias¹⁰? Do we not think that many patients with RVs sustaining the systemic circulation are failing because of the unsuitable geometry of the valve annulus that causes these valves to leak? Patients with pulmonary atresia and intact ventricular septum? They are usually failing because of residual obstruction. The patients with single-ventricle

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circulation? Only one-third of them fail because of myocardial dysfunction and only a few because of isolated decreased myocardial strength.¹¹ Therefore, there are some doubts that injection of mitochondria would be a universal solution.

But even so, can we believe that injection of mitochondria will work? The present work looks extremely convincing, but those who are not specialists in this topic may have some doubts because of what we witnessed with stem cell therapy research. It has been repeatedly demonstrated that injected stem cells do not stay in the heart for more than a few hours. Why would it be different with mitochondria which are smaller? In addition, one should remember the noise made by the discovery that the injection of dead stem cells and agents promoting inflammation into failing hearts was as efficient as the injection of stem cells.^{12,13}

Therefore, the dream of injecting autogenous mitochondria to our defective hearts still remains a sweet dream. It comes from a “high-tech” side of research that has been very promising without yet delivering much of its promises. However, one should be open-minded because often we have seen our wildest dream become reality. People of older generations can look back and imagine what we would have thought if we were said that, one day, we would have in the palm of our hands a phone that would bring at all times information on the entire knowledge of humanity ... and the latest movies from Netflix.

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