Targeted Uptake-1 Carrier to Rescue the Failing Heart

Fabio A. Recchia, Mauro Giacca

Heart failure is characterized by sympathetic nervous system activation with consequent increase in cardiac and systemic norepinephrine (NE) release. Sympathetic hyperactivity preferentially targets the heart during early stages of failure and subsequently involves other organs. A landmark study published in 1984 by Cohn et al showed that plasma NE concentration in venous blood sampled at rest provides a better guide to the prognosis of chronic congestive heart failure than other indexes of cardiac performance. 

Although the augmented adrenergic drive in the failing heart is initially a compensatory mechanism to preserve contractility and cardiac output, in the long term it leads to very complex maladaptive phenomena (Figure). In particular, two deleterious effects must be mentioned, both caused by excessive catecholamine release: cardiomyocyte injury and functional denervation. NE is indeed markedly toxic for cardiomyocytes at concentrations typically found in the failing heart. Sustained β-adrenergic stimulation leads to cAMP-mediated calcium overload of the cardiac cell, with a resulting decrease in synthetic activity and/or viability and contractile impairment. It can also trigger myocyte apoptosis mediated by protein kinase A and calcium entry via voltage-dependent calcium channels. On the other hand, functional denervation of the failing heart is responsible for reduced inotropic support, especially during exercise, and can be attributed to at least three mechanisms: depletion of NE stores in cardiac nerve endings, selective downregulation of β1-adrenoceptors, and desensitization of the intracellular β-adrenergic signaling cascade, mainly mediated by β-adrenergic receptor kinase and β-arrestin. The excessive NE release in myocardial interstitial space is not counterbalanced by adequate sympathetic nerve ending reuptake, because the principal NE carrier, namely uptake-1, is downregulated or displays decreased efficiency. Further worsening the condition of reduced NE availability, tyrosine hydroxylase, the rate-limiting enzyme in the catecholamine synthetic pathway, was also found downregulated in animal models of heart failure. Such molecular alterations, some of which have been elucidated only recently, can now explain, at least in part, the well-known beneficial effects of β-blockers, pharmacological agents introduced many years ago and still considered a pillar in the treatment of heart failure. The concept that the local accumulation of NE in myocardial tissue, with consequent hyper-stimulation of β-receptors, is a major cause of long-term cardiac structural and functional impairment during heart failure is strongly supported by the remarkable efficacy of chronic β-blockade in improving β-adrenergic and calcium signaling and in reversing cardiac remodelling.

Direct competitive inhibition at the cardiac receptor level seems more beneficial than lowering systemic sympathetic drive, a therapeutic strategy that has even resulted harmful in recent clinical trials. Therefore, if the key factor that determines adverse effects of sustained sympathetic activation on cardiomyocytes is NE accumulation in the presynaptic cleft, it is conceivable that enhancing NE removal may effectively counter the progression of heart failure. This interesting hypothesis has been tested by Münch and collaborators in their study published in the present issue of Circulation Research. Because no pharmacological agents are presently available to potentiate NE synaptic reuptake in vivo, these authors chose a different experimental approach, based on the powerful tools now offered by genetic engineering. They selectively transduced the heart with an adenovirus-based vector delivering the gene for the NE carrier uptake-1 protein. The experimental model of choice was rabbit pacing-induced heart failure, characterized by a number of biochemical, molecular, functional, and microstructural alterations of cardiac adrenergic terminals extensively described by Liang’s group. Uptake-1 carriers are downregulated after only two weeks of rapid cardiac pacing in rabbits, with a further and pronounced fall in density and activity occurring at the eighth week. Based on the well-defined and predictable time course of uptake-1 downregulation, Munch and coworkers administered recombinant adenoviruses before starting the pacing protocol and euthanized the animals two weeks later. A first remarkable finding was that uptake-1 gene transfer normalized not only protein expression of the uptake-1 carrier, but also of β1-adrenoceptors and of sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA-2), thus reproducing some of the molecular effects of β-blocking therapy. A second important finding was the complete recovery of NE uptake by cardiac tissue taken from septum, anterior, and inferior wall of the left ventricle. This is a major accomplishment, because one of the main problems presently afflicting gene transfer approaches is the difficulty, if not the impossibility, to obtain a global and homogeneous expression of transgenes in target organs. The method of vector delivery to the heart adopted by Munch and collaborators, based on aorta and pulmonary artery cross-clamping, has found several successful applications by different authors during the last few years.

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adenoviral transduction of uptake-1, cardiac NE content increased by $\approx 25\%$ compared with GFP-transduced failing hearts. Albeit indirectly, this indicated efficient reuptake in nerve terminal vesicles rather than in myocytes, where NE would have been rapidly degraded. In spite of the successful reversion of the molecular alterations, hemodynamic and cardiac functional improvements were not equally striking. It must be considered, however, that these animals were studied at a very early stage of failure, when cardiac function was still relatively preserved and the potential beneficial effects of uptake-1 gene transfer were possibly underestimated. Whether uptake-1 gene transfer might exert more pronounced benefits at later time points will probably require gene transfer with other vector systems, in which the transduced cells persist and maintain gene expression for longer periods.

As commonly occurs in science, the findings reported in this study present several limitations and raise as many questions as they answer. As recognized by the authors themselves, gene delivery after adenoviral transduction using aorto-pulmonary cross-clamping produces nonspecific gene transfer, thus leaving the relevant cell type that mediates the beneficial effect of uptake-1 overexpression unclear. Furthermore, the observation that uptake-1 overexpression slows the progression of heart failure is equally compatible with the possibility that a reduced NE uptake is a primary causal trigger of the heart failure itself, or that it represents the exhaustion of a secondary compensatory effect.

Can these new results find a clinical application in the near future? The likelihood of exploiting gene transfer technologies for therapy of heart failure in patients is undoubtedly an exciting prospect. For this purpose, uptake-1 joins the growing number of genes recently purported to be of therapeutic value, including adenylyl cyclase VI $^{17}$ and the SERCA2a $^{18}$ which are now considered for clinical trials. Despite successful identification of these potential therapeutic genes, however, several issues concerning gene delivery vectors, the route of administration, and timing of gene expression, still remain to be solved. First generation adenoviral vectors are highly immunogenic and proinflammatory, a property that severely hampers their clinical exploitation and limits the temporal therapeutic window of their effectiveness. $^{19}$ Other vectors might be better suited to gene therapy of heart failure, particularly those based on the new serotype-8 adenovirus, $^{20}$ which transduce the heart with high efficiency and persist in vivo for indefinite periods of time. Additionally, we might envisage that therapeutic gene expression should be regulated in an appropriate way by physiological promoters or, even better, that it should be switched on and off at will, using drug-regulated transactivators. Finally, other procedures are needed to obtain homogeneous gene delivery to the whole heart other than aorto-pulmonary cross-clamping, which is evidently not applicable to patients.

While awaiting important progress in these areas, the possibility of transferring genes to the heart using viral vectors and whole-organ delivery, as in this study, represents an outstanding investigational tool to determine gene function in physiological and pathological settings. We can easily predict that this tool will be increasingly exploited in the near future by a number of investigators, particularly because the information it provides in adult non–genetically engineered organisms appears to perfectly complement that obtained through the use of transgenic animals.

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**References**


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