Viral Vectors delivery new calcium pumps for ailing hearts

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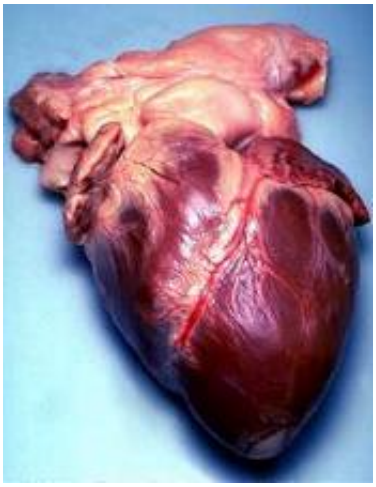

Human heart from 64-year-old man. Credit Wikipedia Commons

(Medical Xpress)—A fresh round of trials to evaluate gene therapy for the heart is set to begin in a couple of weeks. The British Heart Foundation will be sponsoring the study, which seeks to replace defective calcium pump genes inside cells, with new ones delivered by a virus. The main trials will look at a group of around 200 patients worldwide, and a separate trial will look at 24 patients who already have a mechanical heart-assist device implanted.

The trials build on previous work published in 2011 by researchers at the University of Pennsylvania. That study established the potential viability of using viral vectors to deliver genes into the heart. The virus used is

known as a recombinant adeno-associated virus (AAV), which is apparently much safer than adenovirus vectors which has been problematic in the past. Recombinant AVVs are able to infect nondividing cells, and they consist only of the shell of the virus. Since they do not contain any viral genes they are therefore much less immunogenic.

The vector will be delivered specifically to the heart by a catheter threaded through the vasculature from an entry point in the groin. The gene introduced by the vector codes for a calcium pump known as SERCA2a. Once the gene is inside the cell, the normal protein construction machinery takes over and translates the gene into the protein pump. Provided everything works properly, the pump is then targeted to right spots in the cell. SERCA2a is normally localized exclusively the the region of the cell known as the sarcoplasmic reticulum (SR).

In everyday operation, the heart contracts when calcium enters the smooth muscle from the extracellular space. Calcium also then gets released internally from the SR. After the beat, the calcium is pumped out of the cell, and back into the SR. SERCA2a is one of two kinds of pumps that are used exclusively by the SR. In those patients with defective genes for SERCA2a, free calcium lingers longer inside the cell, and the heart can not be primed for the next beat as efficiently.

Gene therapy was stalled years ago when an 18 year-old patient, Jesse Gelsinger, died from a massive immune response to the adenovirus that was used. The new recombinant AAVs should not have this problem, although it is not clear if the patients in the new study will be given immunosuppressive drugs as a precaution. AAVs also have the advantage that they do not integrate within the genome of the host cell, instead they remain in single-stranded form in the cytoplasm. Other studies in the past have looked at using another kind of vector called a

lentivirus, which can apparently deliver genes larger than the 4.8 kilobase size which has been a cited as a constraining factor for AAVs. New techniques may now be able to deliver larger cargoes by using different vectors for different subunits of the gene.

As no study is perfect, individual variances in the genetic defects of SERCA2a genes will add a layer of complexity to the study. Some patients may have some residual SERC2a function intact, while others none at all. There are at least three kinds of SERCA2a genes, each for different cell types. Fortunately the proteins encoded by these genes only appear to have function in muscle cells. They therefore should not be a complicating factor if they are introduced into other kinds of cells. One exception to this may be that SERCA2a could have some additional role in adipocytes (fat cells), where it can act in a thermogenic (heat generating) capacity. The protein itself is highly regulated by other factors including phosphorylation secondary to control by adrenalin.

The heart operates across a wide range of speeds and loads according the demands placed on it by the body. Fine tuning of the waveform to meet these demands by the hundreds of different ion pumps and channels in the cell is essential for optimal function. In diseased hearts, the immediate goal is just to extract some stable performance in the resting state. If successful, replacement of defective proteins through the new recombinant viral vector therapies could become a common alternative to cardiac assist devices.

More information: Release: www.bhf.org.uk/media/news-from … e-therapy-trial.aspx
Earlier study: Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID), circ.ahajournals.org/content/124/3/304