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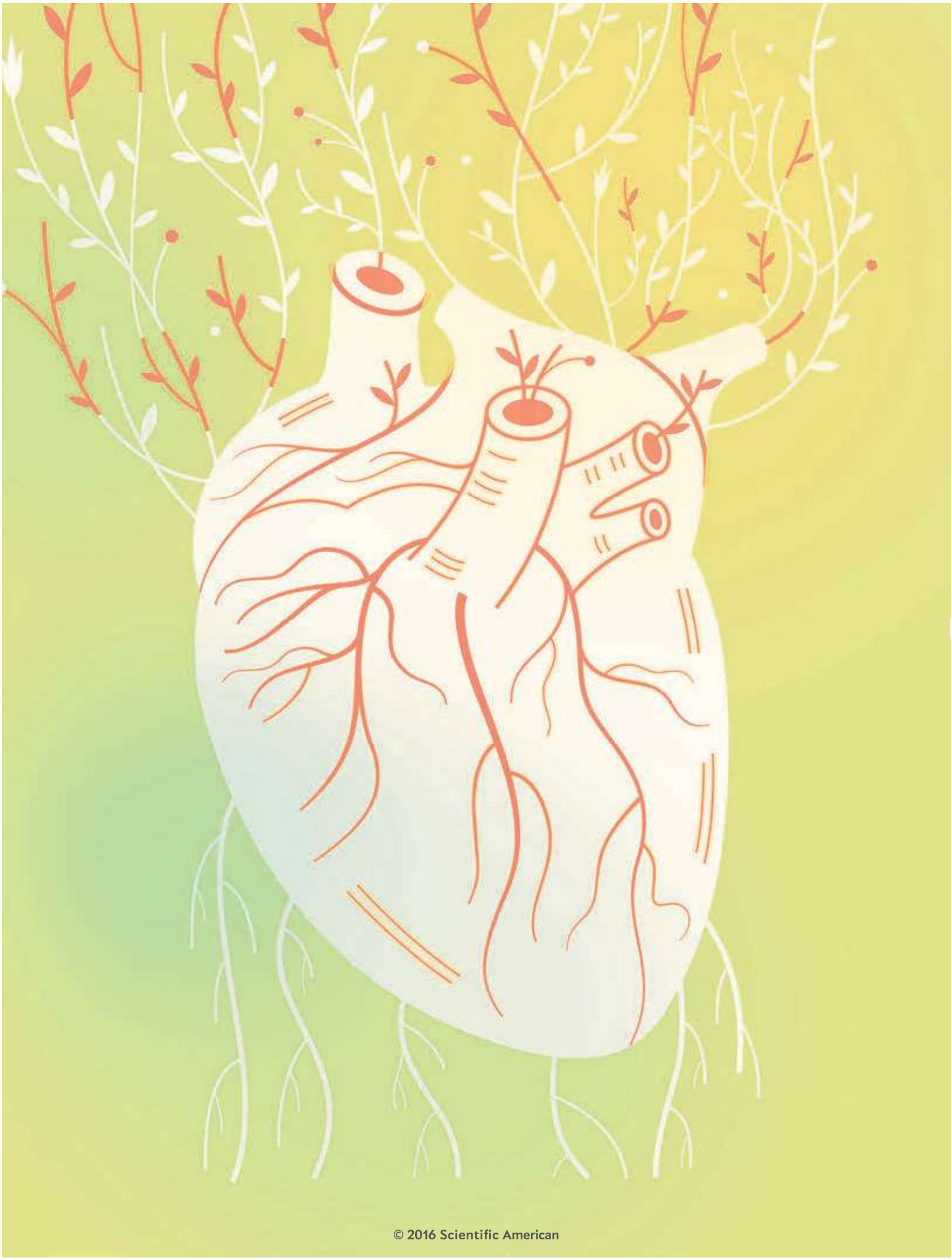

CARDIOLOGY

heart therapy

Harnessing the organ's own healing properties may help prevent heart attacks and lessen the painful effects of severely narrowed coronary arteries

By Gabor Rubanyi

Illustration by Harry Campbell

Gabor Rubanyi is a physician and co-founder of Angionetics, a company that is developing a gene therapy to grow new blood vessels in the heart.

THE HUMAN HEART BEATS MORE THAN 100,000 TIMES EVERY DAY, PUMPING ALMOST 2,000 gallons of oxygen-rich blood through the aorta to the rest of the body. About 5 percent of that flow finds its way to two major vessels—the coronary arteries—which channel it to a network of progressively smaller blood vessels that feed each fiber of the cardiac muscle.

If something—such as a blood clot or a thick buildup of fatty material (atherosclerotic plaque) in the walls of the arteries—interrupts the circulation at one or more points in the coronary vessels, the blockage robs nearby cardiac cells of oxygen and nutrients. Unless the flow of blood resumes quickly, the starved part of the heart muscle dies: the person has a heart attack. Depending on how far the damage spreads, the heart may have trouble functioning properly or may even stop working altogether, leading to death.

Because cardiac muscle cells do not die immediately in response to a lack of oxygen, many of them can be preserved if a patient gets to the hospital quickly enough to allow doctors to act before permanent damage occurs. Among other things, physicians may prop open narrowed arteries with stents or surgically bypass the blocked section of an artery. These procedures are also used to try to prevent heart attacks from happening in the first place as well as to lessen the pain (angina) that often accompanies a severe narrowing of the arteries, but they do not always work and sometimes bring about new problems.

As it happens, the heart has its own way of dealing with blockages in the coronary arteries. It can develop new channels—called collateral vessels—that redirect blood flow from several new directions to oxygen-starved areas of the cardiac muscle. Collateral vessels are present from birth, but they do not usually carry blood. They grow larger and may also form anew after severe blockage or narrowing of coronary arteries takes place and then only after several weeks. In a person with a well-developed collateral system, the extra flow may be enough to keep heart tissue nourished even in the face of a fully closed vessel. But too often the natural collateral circulation is not up to the task.

A number of researchers—myself included—have spent the past two decades experimenting with ways to spur the heart to produce new collateral vessels that are able to provide adequate blood flow in the hearts of patients whose muscle fibers are not getting enough oxygen. By doing so, we hope to reduce the pain felt by many patients with advanced atherosclerosis as well as to avoid heart attacks in patients who can no longer be helped by stents or bypass surgery. So far our efforts—which have included injecting various proteins, genes and cells into the heart—have not yet yielded a remedy that works well enough for the majority of people whose arteries have become dangerously narrowed. Over the past few years, however, some of us in industry and at universities have refined our procedures dramatically. A number of these approaches are now being combined in human trials that should be completed in the not too distant future.

If we are successful, the first people to notice the difference will probably be those who suffer from angina, which manifests during stress or physical activity when coronary arteries damaged by atherosclerosis can no longer provide all the oxygen

IN BRIEF

The heart has the ability to grow extra blood vessels when under duress. This so-called collateral circulation can mean the difference between life and death after a heart attack by creating new channels to bring blood to damaged parts of the heart muscle. **For reasons** that are not completely clear, however, most cardiac patients are unable to develop a good collateral network.

Researchers are testing genetic and cellular therapies to promote new blood vessel growth in the heart. If successful, the treatments could help many avoid chest pain or prevent heart attacks.

New Pathways for a Struggling Heart

The heart sometimes has the ability to grow new arteries. Researchers are testing gene therapies to try to boost this regenerative capacity to restore oxygen-rich blood flow to a region of the cardiac muscle where normal circulation has dropped off because of a fatty buildup (atherosclerotic plaque) inside one or more major blood vessels. If successful, these treatments may one day be used, among other things, to lessen the chest pain that often occurs when part of the heart cannot get enough oxygen (a condition called ischemia).

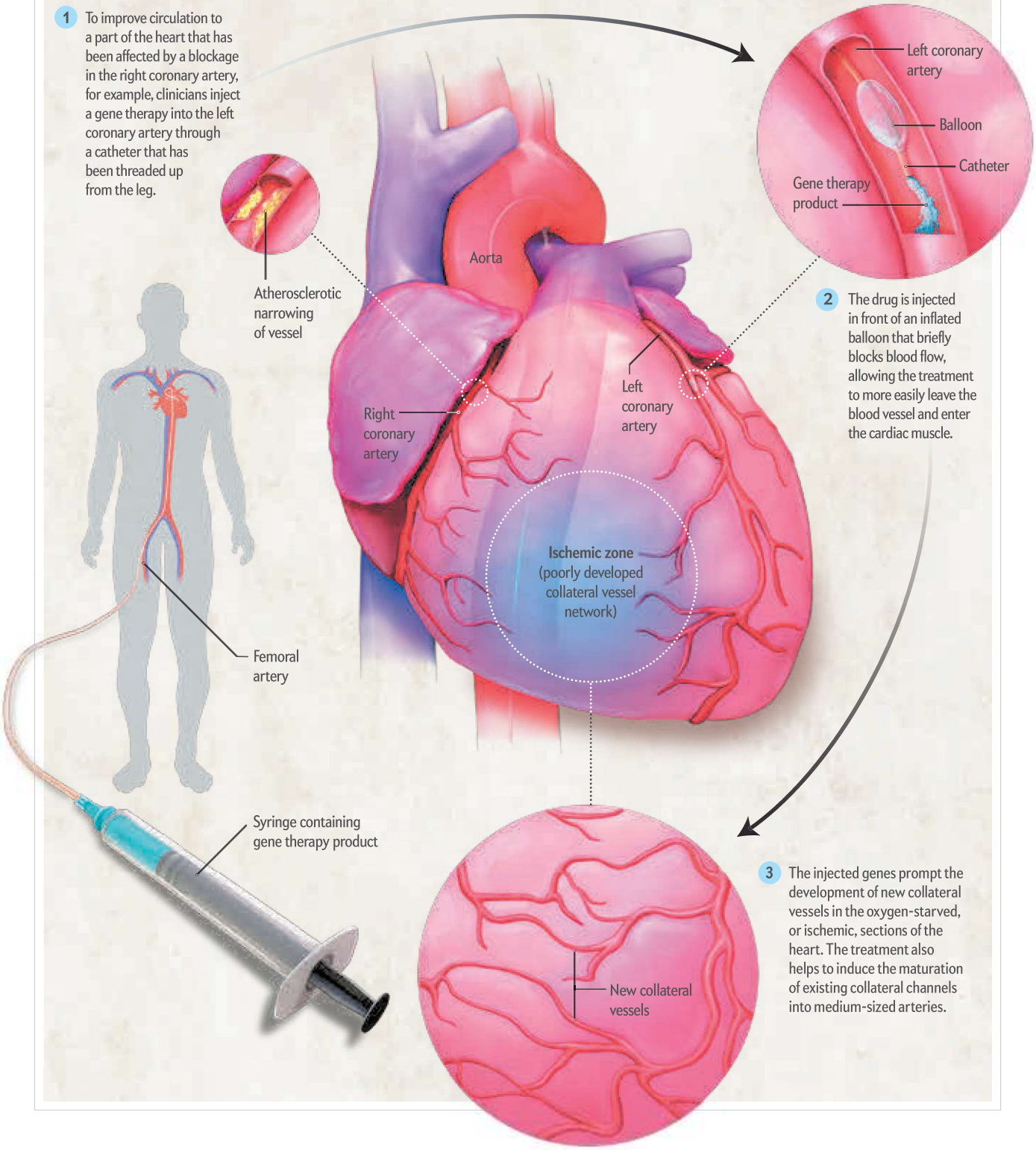

Illustration by Mesa Schumacher

needed by the cardiac tissue. For a variety of reasons, standard treatments with medication, stents or surgery cannot help several million angina patients around the world—an estimated 850,000 of whom live in the U.S. A brand-new therapy that relieved their symptoms would dramatically improve their quality of life, allowing many, for example, to walk around the neighborhood instead of being confined indoors. It should also aid at least some fraction of them to avoid having a first or a repeat heart attack.

COLLATERAL FORMATION

THE FIRST STEP toward devising a treatment for spurring the growth and development of new blood vessels in the heart is to figure out why collateral vessels sometimes appear and mature on their own. For years investigators have debated which of two different forces prompts existing collateral channels to turn themselves into medium-sized arteries: Increased blood flow in the collateral channels or decreased oxygen in ailing cardiac muscle? These conditions may ensue whenever the inside of a coronary artery becomes severely narrowed. The pressure inside the artery beyond the choke point decreases because less blood can get through the smaller space. This decrease causes an imbalance that starts the flow of blood into the "downstream" collaterals from other unaffected areas of the heart. At the same time, the cardiac tissue beyond the narrowed passage of the artery receives less oxygen because less blood is getting through. Some studies found more evidence for the blood flow explanation; others pointed to lower oxygen levels.

It now looks as though both processes play an important role in the development of collateral circulation in the human heart. The new blood flow into ancillary channels creates shear forces that cause the inner lining to release proteins called growth factors that in turn prompt the walls to become stronger and the inner diameter to grow. Subsequently, the newly maturing arteries can handle an increased flow of blood. Meanwhile the lack of oxygen in the heart muscle stimulates the release of other growth factors that trigger the formation of new collateral channels, which can become small arteries.

Over the past 15 years investigators have found that just 20 to 30 percent of cardiac patients have a well-developed collateral circulation. No one is quite sure why, but the collateral network in most people with coronary artery disease does not develop enough to get around the blockages in their coronary arteries. Some studies suggest that high blood cholesterol levels and the damage to small blood vessels caused by diabetes, in particular, may interfere with collateral vessels' ability to change.

Having useful collateral vessels in the heart can, however, mean the difference between life and death. In a study of 845 people with serious heart disease published online in 2013, Christian Seiler of University Hospital of Bern in Switzerland and his colleagues showed that those patients whose collateral blood supply could replace at least 25 percent of their once normal coronary blood flow were 67 percent less likely to die from their heart problems over the course of 10 years.

RESEARCH CHALLENGES

OVER THE PAST FEW YEARS research has revealed just one proved method for boosting collateral circulation in the heart: exercise that pushes the organ to perform at a higher level than normal for an extended period. A German study of 60 men with serious coronary artery disease published in 2016 demonstrated that 10 hours of high-intensity or 15 hours of moderate-intensity exercise each week for a month increased the amount of blood that could flow through the men's collateral network by about 40 percent. The moderate group exercised six to eight times a day at 60 percent capacity—with 100 percent being the most effort they could expend without triggering chest pain. The high-intensity group exercised four times a day at 95 percent capacity (a level at which people sometimes felt chest pain)—all under the supervision of experienced physicians and personal trainers. The 40 percent improvement is probably about at the theoretical maximum of what is physiologically possible, based on laboratory studies with dogs, which showed that the collateral network can replace about a third of normal circulation through the coronary arteries.

A brand-new therapy that relieves symptoms of angina (chest pain) would dramatically improve the quality of life of many patients, allowing them, for example, to walk around the neighborhood instead of being confined indoors.

Presumably the greater physical activity increased the pressure in study participants' coronary arteries, which in turn forced the blood into the collateral vessels. The regular daily workouts then stimulated the walls to widen and thicken to handle more blood. Whether exercise also triggered the growth of new collateral vessels is unclear because such vessels, even if they had formed, would have been too small at first to show up on an angiogram, a type of x-ray scan used to visualize coronary arteries.

Even moderate exercise is not an option, however, for many people with advanced heart disease—hence the search for the right combination of designer proteins, genes or cells to push the heart to expand its collateral network.

SCIENTIFIC AMERICAN ONLINE Find out more about how researchers hope to coax the heart into repairing itself at ScientificAmerican.com/jan2017/heart

Some of the earliest efforts focused on two different proteins—known by their acronyms VEGF and FGF—that stimulate the growth of blood vessels. Whereas several initial, small studies with these and other growth factors seemed promising, follow-up studies with a larger number of patients revealed numerous issues. Perhaps the biggest problem was that clinicians had to deliver high amounts of proteins over a long period to get any new blood vessels to form in the heart. Meanwhile other parts of the circulatory system elsewhere in the body reacted badly, causing blood pressure to fall—sometimes severely—and the experimental treatments had to be stopped.

A few researchers turned to gene therapy as a way of getting around some of the problems caused by the use of proteins. The idea is to inject genes that contain the molecular instructions for creating VEGF, FGF or other proteins directly in the heart, usually by placing the genes into a relatively benign virus that infects cardiac cells. Once implanted successfully, the genes can churn out the necessary growth factors for an extended period right where they are needed. Although scientists have in fact induced the appearance and maturation of collateral blood vessels in the hearts of lab animals, no large-scale clinical trials of gene therapy for human hearts have so far demonstrated significant benefit—perhaps because the injected genes did not reach enough cardiac muscle cells. Full disclosure: my company, Angionetics, is trying to develop one of these remedies, based on the gene for FGF. Our studies have identified what may be a more effective method of delivering the genetic material to a broader area of the heart, which is essential to form enough new collateral vessels. The U.S. Food and Drug Administration gave us permission in September 2016 to begin advanced testing of our product in 320 people.

Finally, some investigators have tried using so-called adult stem cells, taken from a patient's own bone marrow or blood, to try to entice an ailing heart to develop extra blood vessels. The rationale is that these stem cells can produce a variety of growth factors, and it may well take multiple growth factors—in carefully calibrated combinations—to generate the appropriate number of collateral blood vessels. One of the complicating issues is that it is not always easy to identify how many of the injected cells remain functional in the heart. Nevertheless, several small clinical trials over the past 10 years have resulted in some encouraging findings—such as allowing treated patients to exercise a few minutes longer than untreated patients on a treadmill without pain. But as with the protein and gene therapy techniques, no substantive benefit has so far been documented in large-scale clinical trials of cell therapy.

LESSONS LEARNED

TWENTY YEARS may seem like a long time to spend trying to figure out how to grow collateral blood vessels in the heart without finding a broadly effective solution or giving up. But everything my colleagues and I in the field have learned so far confirms our sense that boosting collateral growth is achievable and could help many people. What we need to do now is pull together the many insights that we have gleaned from the research so far and start applying them more systematically to each new endeavor we undertake.

For example, we have a better understanding today of how any potential treatment should be delivered to the heart to provide the maximum response. Historically, researchers have injected their favored experimental therapy in one of three ways: directly into the cardiac muscle, from which it spreads in a small area between the fibers; through a vein in the heart, pushing it backward against the blood flow; or through a coronary artery, which carries it in the same direction as the flow of blood. Several studies have now shown that the only way to reach the existing collateral channels while stimulating the formation of new collateral networks is to inject experimental drugs into one or more of the coronary arteries. Existing coronary collateral channels are just too far from the injection sites in either the cardiac muscle or veins to benefit from the treatment. We have also learned that temporarily blocking circulation by inflating a tiny balloon inside the artery at the same time that we deliver the drugs makes the vessel walls more permeable, allowing a larger dose to reach the heart.

In addition, one of the most challenging obstacles to demonstrating that a treatment can generate useful collateral vessels in humans is making sure that we are treating the right patients in clinical trials. In all likelihood, remedies to expand existing collateral vessels and grow new ones are not going to do anything for the 20 to 30 percent of cardiac patients whose collateral circulation is already well developed. If such people take part in our experimental studies, their lack of improvement could obscure gains for others; averaging their results with everyone else's would artificially depress the findings, making it seem as though the treatment has failed.

To date, the most accurate method for measuring a person's collateral circulation involves inserting a small balloon through a catheter into a coronary artery, inflating the balloon to block circulation briefly and then measuring how much blood still manages to flow around the obstruction, presumably through the collateral vessels. Realistically, such a procedure is too complex and expensive to identify the majority of patients who could benefit from the production of extra blood vessels in their heart and to verify whether treatment has helped them. Less invasive techniques to estimate collateral circulation have been developed but are not yet as accurate as they need to be. We have to come up with a simple, standard way of measuring collateral flow so that we can identify good candidates for the approach and recognize success when we achieve it.

Taking these and other hard-won lessons into account, I believe we are well on our way to developing new treatments to boost the growth of collateral arteries in the heart. Within the next several years we should finally be able to offer a successful alternative to hundreds of thousands of cardiac patients who currently have no other options. SA

MORE TO EXPLORE

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