PRACTICES

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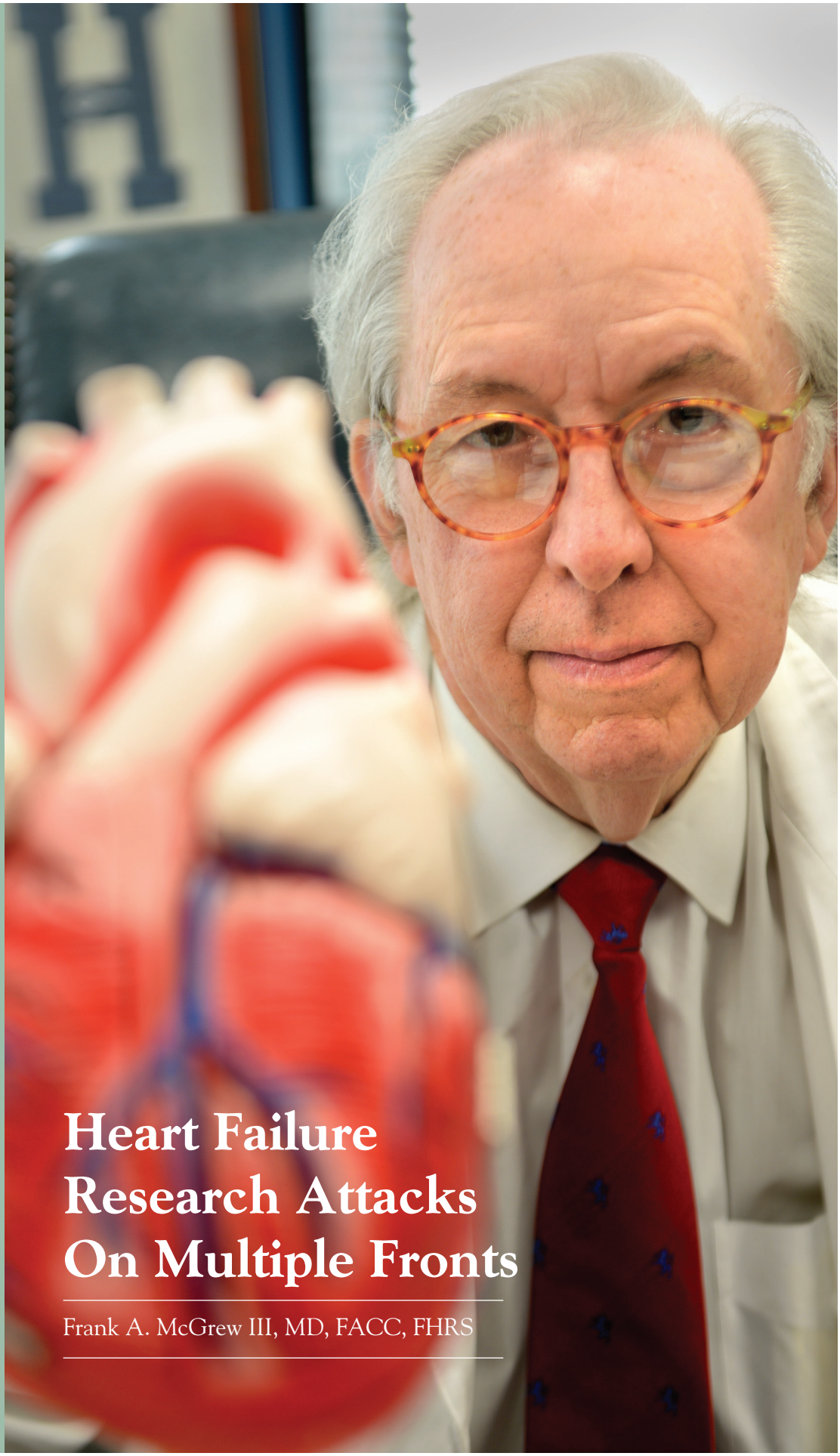

Heart Failure Research Attacks On Multiple Fronts

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Our search for a real answer to heart failure continues, even as we follow current care guidelines to provide the best quality care to our patients. We have many tools in our bag to help patients with a weak heart muscle: digitalis; diuretics; beta blockers; ACE inhibitors; angiotensin receptor blockers; aldosterone blockers; statin therapy; defibrillators; and resynchronization pacemaker/defibrillators. All have dramatically improved patients' outlook. Even with these multifaceted approaches, however, many patients still experience disability and premature death. Therefore, the search for new therapies is being avidly pursued.

Due to our imperfect knowledge of the actual fundamental problem in heart failure, our research therapies have necessarily approached this from different viewpoints. No true unified therapy is yet available to attack the fundamental mechanisms of heart failure, but investigations hope to realize a complete therapy.

Resynchronization therapy uses pacemaker leads placed on the left ventricle of the heart to make it work in synchrony with the right side of the heart. While these have been available for some time, at least one third of patients do not fully benefit from this therapy.

New research involving "adaptive ventricular pacing" shows promise for improving heart muscle function. This therapy is when the right ventricle impulse is sensed, and the left ventricle is paced, therefore utilizing the normal electrical pathway to the right side of the heart.

Other electrical therapies of the heart include the use of "cardiac contractility modulation," which provides low levels of electrical current during parts of the cardiac cycle that are responsible for strengthening the heart muscle contraction. While these devices are like pacemakers, they make the heart muscle beat stronger, not merely faster. Preliminary trials have shown great promise and longer trials with technological

Injecting stem cells into heart muscle

modification are about to be initiated.

Another exciting area of research involves the use of stem cells. The human body harbors the stem cells in various tissues. Some of these originate in the bone marrow, some actually reside in the heart itself. They have the

Harvesting stem cells from bone marrow

capability of being transformed from immature, fetal-like cells into cells resembling heart-muscle pumping cells and new blood vessels. Work progresses on many fronts to harness these cells to repair injured heart tissue. Our investigation has approached this from different aspects. Our initial study involves using stem cells intravenously immediately after a heart attack and utilizing the property of the injured heart to attract stem cells from the

Injecting stem cells into artery

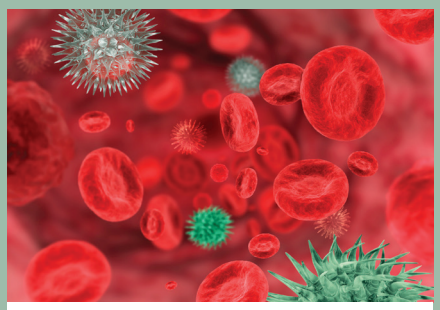
general circulation. This provides rapid access to injured tissue and should help to promote healing. Another approach to stem cells is to harvest them from peripheral blood and to inject them into the heart muscle using special guiding catheters that target areas of heart muscle not yet permanently scarred. These stem cells can be injected into the heart muscle using techniques much like standard cardiac catheterization. In this manner, stem cells can be used to strengthen weakened heart muscle and to promote blood vessel growth in patients with incapacitating chest pain due to coronary artery blockage.

Another similar technique uses a bone marrow harvest of stem cells to inject directly through a heart artery that has recently been opened with an acute heart attack, but yet would supply the area of heart muscle that has been weakened by this initial insult. Most heart muscle that exhibits heart

Injecting enzyme SERCA

failure is deficient in an enzyme known as SERCA.

We now have the capability of injecting the human gene that



Viral particle infects heart cells

forms this enzyme into the heart via standard cardiac catheterization technique. This gene is encapsulated into a viral particle, which is stripped of its own intrinsic DNA, and the viral particle infects the cardiac cells squirting in the human gene, thus making the patient's heart cells a factory to produce this deficient protein, hopefully improving heart muscle strength.

The search for medications – both intravenous and oral – that can directly stimulate stronger force pumping of the heart has been viewed as the quest for the Holy Grail of cardiology. Previous molecules have produced transient improvement in heart muscle

Molecule Omecamtiv

function, but at the price of producing heart rhythm irregularities and overworking the heart muscle, causing damage later. A new molecule, Omecamtiv, is available in both oral and intravenous forms and seems to provide direct heart strengthening ability without these side effects.

Another approach to the treatment of heart failure is to actually try to prevent it by reducing the likelihood that diseased arteries progress to total blockage and cause heart attacks or permanent heart muscle damage. It has long been felt that some patients harbor inflammation within their blood vessels and contribute to this accelerated hardening process. The protein circulating in the blood known as C-reactive protein seems to be an indicator of which patients harbor this inflammation. Using this as an identification point, patients who have had previous heart attacks are identified and given a vaccine that blocks inflammatory compounds within the body known as cytokine. Approximately 10 percent of all patients with a history of a heart attack will be eligible for this treatment. Diabetic patients who have had previous heart attacks also have evidence of inflammation and may respond to the use of methotrexate in very low doses. This drug is used to treat inflammatory disorders such as rheumatoid arthritis and shows promise in preventing recurrent heart attacks in diabetic patients.

C-reactive protein

The treatment of congestive heart failure is a great challenge for physicians, and most patients who exhibit this condition today will ultimately need additional therapy. The current guideline therapies are only partially adequate. We believe the patients who suffer from congestive heart failure should be considered for clinical trials to improve their ultimate prognosis.

Dr. McGrew and his staff with a model of a gene similar to the one that forms SERCA.