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# HEART FAILURE RESEARCH: TRANSLATING BASIC SCIENCE INTO THERAPIES

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## Overview

Congestive heart failure is a syndrome characterized by decreased cardiac output with consequent neurohormonal activation leading to water and salt retention. This ultimately results in pulmonary and vascular congestion with eventual organ hypoperfusion and death. Often described as a "vicious cycle," congestive heart failure is responsible for more than 40,000 deaths per year in the United States and plays a substantial role in another 250,000 deaths; it takes a financial toll as well, with approximately $34 billion spent each year on the medical care of patients.[1] The key to ending this vicious cycle is applied research. The Department of Cardiology within The Methodist Hospital is conducting research aimed at understanding heart failure and working towards therapies to improve patient care.

## Resources

The Methodist Hospital's Heart Failure Research Laboratory includes basic scientists and clinicians working side by side to understand the mechanisms involved in translating laboratory work into eventual clinical care (Figure 1). Located within The Methodist Hospital Research Institute, the laboratory provides access to state-of-the-art equipment and facilities to aid this research (Figure 2). The close association between the clinical and research personnel provides an opportunity to access research and apply laboratory findings to the clinical setting. For example, this collaboration has led to the creation of one of the largest cardiac tissue collections, allowing researchers to study the underlying mechanisms involved in heart failure. The study of heart failure would be impossible without these resources, and the develop-

**Figure 1.** The Methodist Hospital's Heart Failure Research Laboratory allows basic scientists and clinicians to collaborate in translating laboratory research into clinical care.

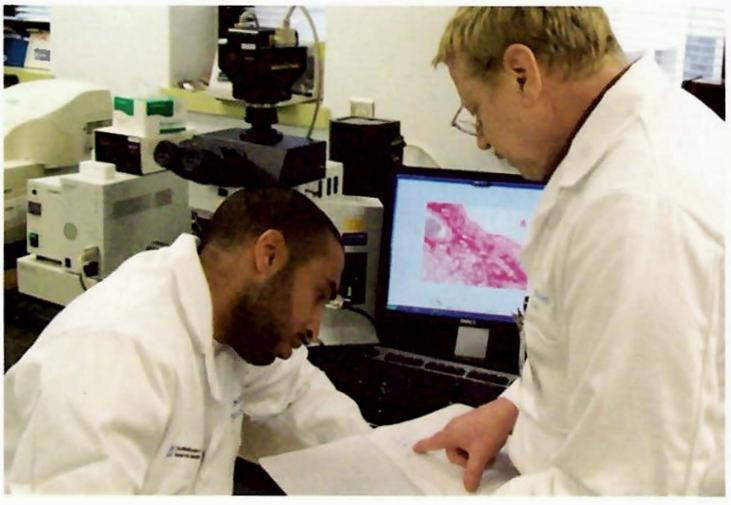
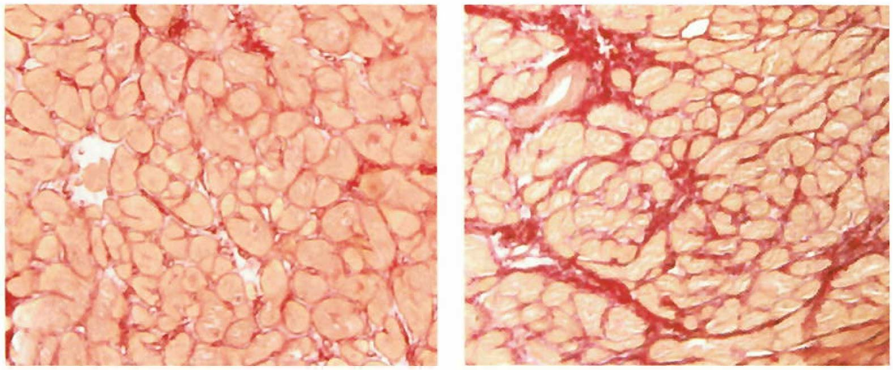


**Figure 2.** The Methodist Hospital Heart Failure Research Laboratory provides access to state-of-the-art equipment and facilities.



Normal Myocardium | Failed Myocardium

**Figure 3.** While collagen is normally present in heart muscle tissue, abnormal amounts of collagen are believed to be an underlying mechanism in heart failure.

ment of new therapies depends on these studies. Collaboration is an essential component of any translational research program, and our collaborations extend beyond the walls of the clinic, the hospital, and even Houston.

## Current Projects

Currently, we are using our cardiac tissue collection to look at alterations associated with different types of failure, applying genomic and proteomic studies to identify these differences and understand the mechanisms involved. One of our ongoing projects involves collaborating with other researchers at both Methodist and the University of Houston to understand metabolic abnormalities related to heart failure. This group is studying mitochondrial changes and changes in glucose utilization and testing therapies designed to identify or relieve these abnormalities.

Another study involving immunity in heart failure has helped us better understand how the immune system responds in acute decompensation and led to the testing of immune modulation and plasmapheresis as adjunct therapies to alleviate or possibly reverse certain types of heart failure. In another ongoing project, we are finding ways to alleviate fibrosis as an underlying structural abnormality that exacerbates heart failure.

## Cardiac Fibrosis: One Example of Translating Research into Possible Therapies

### *The Underlying Problem*

At the cellular level, the human heart is a highly ordered structure that includes nonreplicating myocytes arranged in myofibrils surrounded by an intricate scaffold of collagen matrix. This matrix is composed of elastin, fibronectin, laminin, and struts of collagen that interconnect myocytes and capillaries. Collagen, a major constituent of fibrous tissue, is a biologically active substance, with collagen I and ill predominating in the heart. Collagen I provides tensile strength needed for systolic contraction and with collagen III comprises two-thirds of the matrix proteins. Both dilated and ischemic cardiomyopathies are characterized by a dramatic increase in the accumulation of interstitial collagen (Figure 3), especially collagen I, which leads to ventricular stiffness and diastolic dysfunction that exacerbates the heart failure cycle. One study demonstrated that increasing myocardial collagen I density correlated directly with higher NYHA class heart failure.[2] Experiments in our lab conducted on myocardial biopsies, taken from heart failure patients bridged to transplantation with ventricular assist devices, revealed reductions in collagen I, collagen III, and myocyte size with chronic mechanical unloading.[3] These changes are associated with improvement in cardiac function and point to abnormal collagen as an underlying mechanism in heart failure.

### *Looking for a Therapy*

Understanding the aberrant fibrosis is critical, but finding a therapy is a different issue. Our search for a therapy led us to Technologico de Monterrey (Monterrey Tech) in Mexico, where researchers had demonstrated that a simple vegetable extract was capable of decreasing fibrosis in a liver model. We formed a collaboration with these researchers to determine whether this phenomenon was more universal and may be applied to heart failure where fibrosis, or collagen deposition, was an underlying problem.

### *Tissue Culture Studies of "Extract"*

We obtained the natural extract and began laboratory studies to try and understand its effect Our first studies used cardiac fibroblasts, the cells responsible for production n of collagen, grown in tissue culture. The extract was applied to cells and stimulated to produce collagen. Real-time polymerase chain reaction (PCR) was employed to look at the expression of collagen I in the cells as well as TGF- , which is the molecule most responsible for collagen increases. The extract decreased both the TGF- and the collagen I

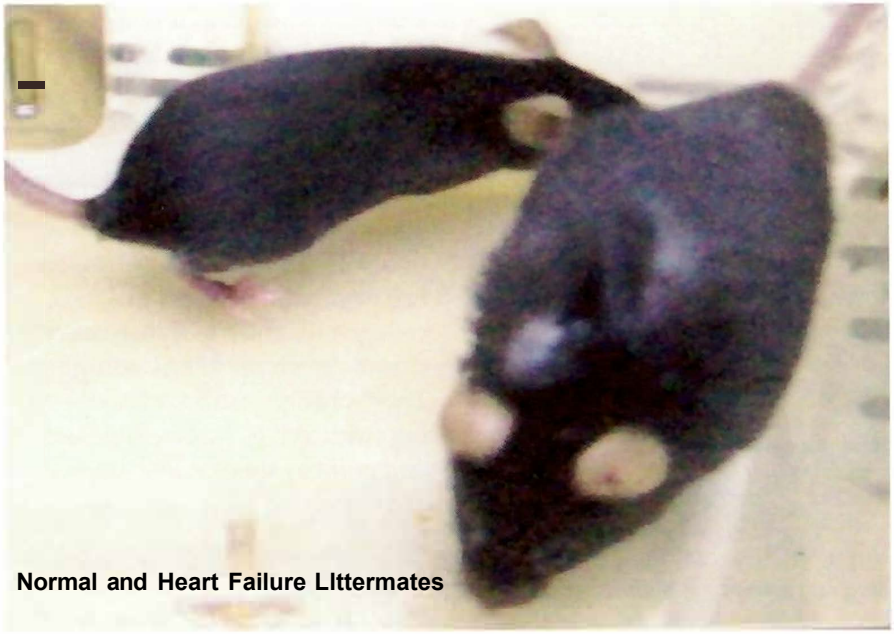
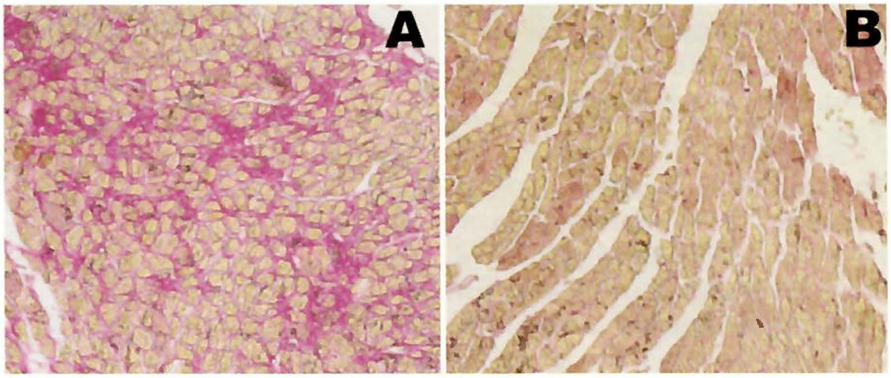



**Figure 4.** Researchers use C57BL/6 mice to study a model of nonischemic heart failure.




**Cardiac Fibrosis in Heart Failure Mice (A) and in extract treated mice (B)**

**Figure 5.** Mice treated with extract showed decreases in cardiac interstitial fibrosis, TGF-. and inflammatory cardiac cells.

production. While this is promising for reducing fibrosis, it is still necessary to determine if this effect occurs in a whole organism. To pursue this further, we studied an animal model of heart failure.

### *The Heart Failure Mouse*

Our laboratory has built upon a model of injured myocardium initially developed by Oestreicher et al.4 and expanded it to what we believe is a model of nonischemic heart failure. Our model uses C57BL/6 mice (Figure 4) that received L-NAME (an inhibitor of nitric oxide production) and NaCl in their drinking water to increase vascular resistance and raise blood pressure for five weeks. For the final four weeks, an osmotic minipump continually administered angiotensin II to further increase vascular pressure, mimic activation of the renin-angiotensin system, and promote fibrosis. Real-time PCR, echocardiography, immunohistochemistry, hematoxylin and eosin stain, and picrosirius red staining techniques were employed to characterize this model. This model demonstrated decreased cardiac ftmction as measured by echocardiography as well as increases in cardiac BNP and ET-1 (known markers of heart failure) and increases in body weight, body fat, and glucose levels. Furthermore, inflammatory cytokines were activated the same as in human heart failure and, more importantly for our studies, a dramatic increase in cardiac fibrosis was seen. In age experiments, mortality was highest in older mice much like human cardiomyopathies.

### *"Extract" Therapy in the Mouse Model*

In our next set of experiments using our mouse model, extract was mixed into the food of mice undergoing the heart failure protocol. Cardiac collagen was measured along with other cardiac markers of heart failure and cardiac function. The extract-treated mice did not demonstrate the increased body weight seen in the nonextract-treated group. Both heart failure markers BNP and ET-1, which were increased in heart failure versus control mice, showed no increase when treated with the extract-containing food. Decreases in cardiac interstitial fibrosis in the extract-treated group were documented, as were decreased TGF- and a decreased presence of inflammatory cells in the heart (Figure 5). Fractional shortening and ejection fraction, which were recorded and measured by a blinded observer, were found to be preserved in the treated mice.

## Conclusion

The vegetable extract experiments are one example of the heart failure studies we are actively pursuing at the Methodist DeBakey

Heart & Vascular Center. Ongoing research provides the opportunity to help us understand heart failure and may lead to new therapies. While the extract studies look promising, it should be noted that our theory has only been tested in this one mouse model, and the effect it may have on existing heart failure is currently unknown. Further research and collaboration between the basic science and the clinical arenas will hopefully result in translational therapies aimed at treating heart failure and its symptoms to end the vicious cycle.

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