Could you provide an overview of your heart failure group and its different members’ strengths and interests?

Our group has a mutual interest in understanding the cellular and molecular mechanisms of heart failure (HF) and how this knowledge can lead to improved patient outcomes. Dr Rong Liang uses gene targeted mouse models to dissect molecular mechanisms of HF. Dr Youhua Zhang is an expert in arrhythmias and HF. Since about half of cardiac deaths are due to sudden death from arrhythmias, he brings an important and often neglected perspective to our collaborative work. Dr Ed Dedkov is an expert in vascular changes in HF. My current focus is largely on translating the exciting results from our animal studies to patients.

What initially led you to explore thyroid function in cardiac patients?

As a PhD student, I wanted to study HF but there was no one in my department conducting heart research. Luckily, an MD/PhD faculty member studying the effects of hyperthyroidism on the lungs agreed to serve as a mentor on a heart project using the same model. Over time, it became clear to me that normal thyroid hormone (TH) levels were critical in maintaining heart health and, most importantly, low TH function can actually cause HF. A natural progression was to use THs to treat animal models of HF and identify potential benefits that could be translated to humans.

Research suggests that there is a link between thyroid function levels and arrhythmia; could you elucidate this?

It has been known for many years that hyperthyroidism may increase the heart’s susceptibility to arrhythmias. Some clinical studies also suggest that low thyroid function may increase arrhythmias. In a recent animal study, Zhang clearly demonstrated this is the case. It is difficult to know the extent of this problem in patients with heart disease since serum TH levels may fail to accurately reflect the extent of cardiac TH deficiency.

How can low thyroid function be treated, and how can such treatments potentially benefit cardiac patients?

Unfortunately, there are currently no TH clinical treatment/monitoring guidelines for cardiovascular disease (CVD) and important questions remain unanswered. Which form of TH should be used, T3, T4, or both? Is it possible to restore cardiac tissue TH levels without overdosing? Which patients will benefit and what criteria should be used for selection? Fortunately, animal studies from our lab are providing valuable guidance. It appears that low doses of T3 can safely restore cardiac T3 levels and dramatically improve heart function without significantly increasing serum THs.

You have already conducted several animal studies investigating the effects of low thyroid levels on cardiac health. What have been your most promising findings? Are you close to beginning clinical human trials?

Results from animal studies have been remarkable. It appears that all types of heart disease lead to low cardiac tissue TH levels. TH treatment has led to improvements in survival, contraction, and relaxation of contracting muscle cells. Coronary blood flow improved and scar tissue was inhibited. Since it now appears that all of these benefits can be achieved with safe, low doses of T3, I believe we now have the information needed to proceed intelligently with clinical trials for the first time.

Would you like to highlight any student training or outreach initiatives that you’re involved in? What are the benefits of exposing members of the public and young people to active research?

I have always been interested in offering meaningful research experiences for students. Many medical and undergraduate students here are working in the labs of our HF group. Even if these medical students do not pursue a career in research, the critical thinking skills associated with research are valuable, particularly since we are in the age of evidence-based medicine.

Do you collaborate with other laboratories? What makes your team cohesive?

Everyone in our HF group has a significant history of outside collaborations. However, proximity makes a big difference. Each member also brings something different and highly complementary to the group. Liang is very good at molecular mechanisms. Zhang is an expert in cardiac electrical activity and arrhythmias. Dedkov has a strong background in coronary vessels. I have largely focused on contracting muscle cells and translational research during my career. Each member of the group is also very good at pathophysiology. We make a strong team.
Although it is known that cardiovascular disease and low thyroid function are intrinsically linked, further research is needed. The Cardiovascular Research Group at the New York Institute of Technology, USA, is investigating this and other unanswered questions in the circulatory system.

**RECENT ANIMAL RESEARCH** has shown that cardiovascular disease (CVD) leads to low cardiac tissue thyroid hormone (TH) levels and evidence suggests this is also the case in humans with CVD. For instance, a clinical study by Giorgio Iervasi in 2003 found that 20 per cent of patients with CVD had overt hypothyroidism and 30 per cent of the study group had low T3 syndrome. Based on insight from animal studies, it is likely that many more had low cardiac tissue T3 levels. Recently, two clinical studies (CP Chuang, 2013; JE Mitchell, 2013) also showed that mortality increases in heart failure (HF) patients as TH levels decline. It has been known for many years that TH can reduce atherosclerosis, stimulate blood flow to the heart, increase contractile strength and improve cardiac relaxation. However, the Coronary Drug Project (1973) and the DITPA trial (2009) demonstrated that treatment with excess THs or analogues can lead to an increase in heart arrhythmias and possible death. Conversely, low thyroid function can also promote arrhythmias.

**THYROID HORMONE LEVELS**

Dr A Martin Gerdes, who leads the Cardiovascular Research Group at the New York Institute of Technology (NYIT)’s College of Osteopathic Medicine, believes researchers urgently need to determine how much of the symptoms in heart failure patients is due to an underlying disease (such as ischemic cardiomyopathy, hypertension or diabetes) and how much is due to a superimposed low thyroid condition in the heart, which is indistinguishable symptomatically from heart failure. “The extent to which low thyroid function contributes to cases of CVD leading to heart failure is not clear at present, but I suspect that nearly all CVD patients may be affected,” he asserts. At present, there are no published data regarding TH levels in heart tissues of CVD patients. “However, low cardiac tissue TH levels have now been observed in all animal models of CVD studied to this point, and it has become clear that serum TH levels may underestimate the extent of the problem,” Gerdes adds.

His current research, supported by the National Institutes of Health, focuses on TH and HF. In a previous study, his group was able to demonstrate, using rodent models of heart disease, that with hypertension and ischemia the heart actually makes itself hypothyroid by activating an enzyme that deactivates THs. “It is not clear why this occurs, but animals are evolutionarily programmed to lower TH function during periods of starvation. It is possible that CVDs trigger this response in the heart. Low TH function in the heart may occur in the background of normal thyroid gland function,” Gerdes explains. His group was able to show that hypothyroidism alone can cause HF characterised by systolic and diastolic dysfunction, maladaptive cardiac myocyte remodelling and impaired coronary blood flow due to adverse vascular remodelling. However, following treatment with THs, they have observed remarkable benefits in several rodent models of heart failure, with improved survival and function of contracting muscle cells in the heart.

**ARRHYTHMIAS AND MITOCHONDRIA**

The Cardiovascular Research Group is a collaboration between several scientists within the Department of Biomedical Science at NYIT, who have a shared interest in elucidating the cellular and molecular mechanisms of HF. Dr Youhua Zhang is a group member whose research interests are in cardiac electrophysiology, arrhythmias and HF; preclinical and translational research; the autonomic nervous system in atrial fibrillation; and HF and atrioventricular (AV) node dual pathway electrophysiology. His current research focuses on studying the potential role of the cardiac autonomic nervous system in atrial fibrillation, increased atrial fibrillation arrhythmogenesis in a rat myocardial infarction/HF model, and determining possible treatment options to improve patient outcomes. He is also investigating the potential functional and histological basis responsible for AV nodal dual pathway electrophysiology, and this work is guided by a novel index he discovered.

Dr Qiangrong Liang, meanwhile, studies mechanisms that mediate myocardial protection against HF induced by various stressful conditions, and is currently investigating the role of mitochondria in CVD. His work, funded by the American Diabetes Association, is addressing three questions: why diabetic patients are more susceptible to HF, how a widely-used anti-
Evidence suggests that a majority of cardiovascular disease patients could have low cardiac thyroid hormone levels, a condition that, by itself, can cause heart failure.

cancer drug may contribute to HF, and how caloric restriction can protect the heart. Central to each question is the role of mitochondria. Mitochondria are the power plant of heart cells, generating energy for heart contraction. A healthy mitochondrial network is extremely important for normal cardiac function. Using both cell culture and animal models, Liang is investigating the molecular underpinnings of mitochondrial quality control processes including mitochondrial biogenesis and energetics, mitochondrial fission and fusion, and mitochondrial degradation known as mitophagy. "Intriguingly, TH can positively affect mitochondrial number and function, which may be another mechanism of their cardioprotective effects," Gerdes adds.

VASCULAR CHANGES

A third group member, Dr Eduard Dedkov, specialises in gender and age-related differences in the cardiovascular system. The main goal of his current research is to understand the mechanisms involved in the growth and adaptation of cardiac coronary vessels during development and under pathological conditions. One area of his investigations concerns the role of neurogenic peptide and growth factor interactions during development of the coronary vascular system. The results of this study will provide a better understanding of the congenital anomalies of this human system.

THERAPEUTICS FOR CVD PATIENTS

Findings from this series of investigations could have major implications for CVD patients in the future. Despite previous clinical studies that used excessive doses of TH and led to slight but significant increases in arrhythmias, Gerdes believes that his group’s and others’ recent animal studies and short-term clinical studies with TH in HF patients offer too much encouragement to ignore: "Clinical studies to test long-term therapeutic doses of T3 that restore normal TH function in the heart are needed. Our group is in the final stages of establishing a safe and effective T3 treatment/monitoring protocol that can be used in patients". These studies could show that therapeutic doses of TH have a range of beneficial effects such as improved exercise performance, improved left ventricle function, reduced depression and reduced neurohormonal activation, as demonstrated in animal models. Translating these benefits safely to humans is now a major objective. Furthermore, treating CVD patients with THs will cost only a few dollars per month, making it an economically viable treatment option which could dramatically impact HF outcomes. "There is a growing body of evidence that suggests this approach is low-hanging fruit, and we really should look at it more closely," Gerdes concludes.

INTELLIGENCE

COLLEGE OF OSTEOPATHIC MEDICINE

OBJECTIVES

• To understand the mechanisms involved in growth and adaptation of cardiac myocytes and coronary vessels during development and under pathological conditions
• To translate important results of our animal experiments into new treatments for patients with heart diseases

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A MARTIN GERDES graduated in 1978 with a PhD in Anatomy from the University of Texas Medical Branch at Galveston and was their ‘2013 Distinguished Alumnus of the Graduate School of Biomedical Sciences’. He is on the editorial board of eight cardiovascular journals and has over 100 peer reviewed journal articles. Gerdes is internationally known for his work on ventricular remodelling in heart failure. He has been the principal investigator on ~US $30 million in funding from the NIH during his career.