And… relax! An off-beat approach to treating heart disease

Half of all cases of heart failure are caused, not by the heart's inability to contract and pump blood through the body, but by its failure to relax and refill with blood. Sadly, standard heart failure treatments are not effective against this form of the disease. **Dr Timothy O'Connell**, of the University of Minnesota, is developing novel ways to treat and prevent such cases using the omega-3 fatty acids found in fish oils.

Heart failure is a major cause of disability and death, affecting 5.7 million people in the USA alone. Of these, around half will die within five years of developing the condition.

But heart failure is complex, with multiple causes and manifestations. Although many people assume heart failure results from the heart's inability to pump blood through the body, in fact, around half of all cases are due to the opposite problem – a failure of the heart muscles to relax, preventing the heart from refilling with blood.

WHAT'S IN A HEARTBEAT?

The human heart comprises four muscular chambers – two atria and two ventricles, separated by valves – which contract to pump blood around the body (known as 'systole') and relax to fill with blood for the next contraction ('diastole'). A cardiac cycle is defined by systole and diastole. During a systole or the contractile phase, blood is pumped from the left ventricle to the body and from the right ventricle into the lungs, where it is oxygenated, and returns to the atria. During diastole or the relaxation/filling phase, blood initially flows into the ventricles from the atria as the ventricles relax and ventricular filling is completed by atrial contraction, thus completing the cycle.

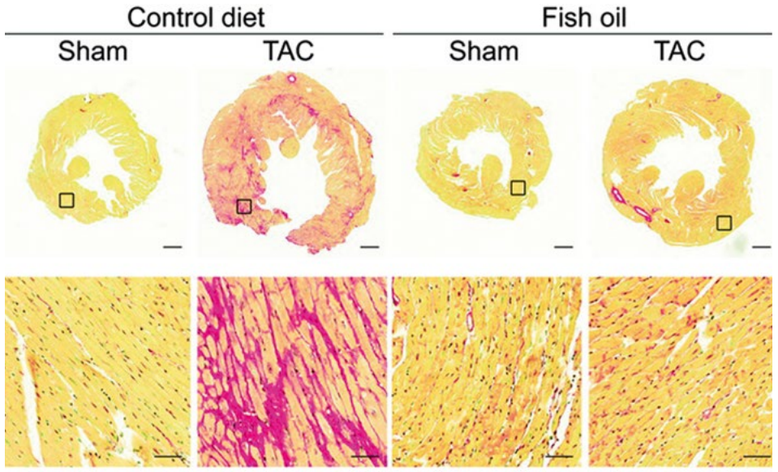
Therefore, both contraction and relaxation are crucial to the normal function of the heart, and the provision of an adequate supply of blood and oxygen to the rest of the body. Dr O'Connell's interest lies in cases of heart failure where the heart is unable to relax and fill properly, known as 'heart failure with preserved ejection fraction (HFpEF)'.

HFpEF

HFpEF is most common in older patients and women. It is also commonly associated with related conditions (called co-morbidities) such as high blood pressure, obesity, diabetes and lung or kidney diseases. However, unlike other forms of heart disease, there are currently no successful treatments available for HFpEF.

Current research, using both laboratory animals and clinical data, has led to an emerging hypothesis about the causes of HFpEF. A leading hypothesis suggests that chronic conditions, such as obesity and diabetes, lead to a permanent ('systemic') state of inflammation throughout the body.

Both contraction and relaxation are crucial to the correct functioning of the heart



Omega-3 supplementation prevents fibrosis in pressure overload induced heart failure. Mice were fed an omega-3 (or control) diet for 8 weeks, pressure overload on the heart was induced (TAC), and fibrosis was measured after 4 weeks. Pressure overload induced significant fibrosis (red staining) in control hearts, which was prevented by omega-3s.

This, in turn, damages the small blood vessels supplying the heart, and causes scarring and thickening of connective tissue cells in the heart ('fibroblasts') – known as fibrosis.

In turn, fibrosis causes the heart muscles to stiffen, impairing their ability to relax fully during diastole. This causes the symptoms of heart failure, particularly during exercise when the body needs a greater flow of blood to fulfil its oxygen requirements.

ENTER OMEGA-3S

Omega-3 polyunsaturated fatty acids are one of the dietary heroes of our time. Found mainly in fish oils, they have been proposed to help treat and prevent rheumatoid arthritis, depression, asthma, Alzheimer's disease, and childhood neurological disorders, as well as heart disease through their effect in reducing triglycerides (which have been linked to high cholesterol levels).

Dr O'Connell's research focuses on one omega-3 fatty acid – eicosapentaenoic acid (EPA) – found predominantly in oily fish. Although omega-3 fatty acids are known to contribute to cardiovascular health, to date, the development of omega-3-based treatments has been hampered by a lack of conclusive evidence from clinical trials, and a poor understanding of the mechanism by which omega-3 fatty acids work. Dr O'Connell's research is helping to address both these issues, focusing particularly upon the role of EPA in preventing HFpEF.

Breakthrough mechanistic studies carried out by Dr O'Connell, with colleague Dr Gregory Shearer at Pennsylvania State University, suggest that EPA molecules work through a cell surface receptor known as 'free fatty acid receptor 4 (Ffar4)' found on fibroblasts and cardiac muscle cells. Ffar4 is a 'G-protein coupled receptor', one of the largest family of receptors found in the membranes bounding animal cells, which mediate interactions between cells via signalling molecules such as EPA. Dr O'Connell's studies on heart failure in mice suggest that when EPA activates Ffar4 in fibroblasts, fibrosis is reduced. In isolated and cultured fibroblasts, Dr O'Connell states, Ffar4 is both "sufficient and required" to prevent fibrosis.

Dr O'Connell's research may fundamentally redefine our understanding of how omega-3 fatty acids contribute to heart health

Other scientists have also shown that Ffar4 can be involved in the regrowth of damaged blood vessels. These findings indicate that EPA, through Ffar4, may impact both of the key characteristics of HFpEF: fibrosis and blood vessel damage. This therefore suggests two mechanisms for how EPA works to prevent heart failure: preventing fibrosis and promoting blood vessels.

Dr O'Connell's mouse studies have also shown that the action of EPA in HFpEF may be heavily dependent on the amount of EPA present – with a threshold concentration needing to be attained in the body before any effect is seen. This may explain the failure of previous clinical studies to find conclusive support for EPA as an effective treatment for heart failure: human clinical trials simply failed to achieve high enough levels of EPA in the body.

MOVING ON FROM THE MODEL

In a study funded by the US National Institutes of Health, Dr O'Connell now plans to draw these results together using both human clinical trials and mouse models. The project will test the hypothesis that, if EPA is ingested in sufficient quantities to reach therapeutic levels in the body, Ffar4 activation will prevent fibrosis, regenerate damaged blood vessels, and ultimately restore the ability of the heart to relax and fill with blood during diastole – thus preventing heart failure.

Dr O'Connell believes this research may fundamentally redefine our understanding of how omega-3 fatty acids contribute to heart health. Eventually, he hopes his lab's work will provide evidence for the importance of EPA and elucidate its role in preventing heart failure, and lead to the development of novel therapies targeting Ffar4 capable of preventing and treating HFpEF, the hidden half of heart disease.

Q&A

Why is HFpEF so important?

Heart failure is a leading cause of death and morbid sickness world-wide. Recently, the incidence of HFpEF surpassed HFrEF (heart failure with reduced ejection fraction or systolic heart failure) in the US, and with the incidence of co-morbidities like diabetes and obesity increasing, the problem will only get worse. And, as already mentioned, there are no effective treatments for HFpEF. It is also now clear that HFpEF is mechanistically entirely different than HFrEF, suggesting that more research is needed to understand HFpEF. I recently searched the NIH reporter database of funded grants and found that a search for 'Heart Failure' identified 2,695 grants across all institutes and 1,517 from NHLBI. However, a similar search for 'Heart Failure Preserved Ejection Fraction' identified only 54 funded grants across all institutes (2.0%) and only 39 from NHLBI (2.5%). Certainly, we need to do more to understand HFpEF and develop new therapies.

Why do you think the HFpEF form of heart failure has been so overlooked and understudied?

I'm not sure I would say HFpEF has been overlooked, at least not recently. I would say that HFpEF as a clinical syndrome is relatively new – certainly more so than HFrEF, the latter being what most people think of when they think of heart failure. Also, HFpEF being a newly recognised syndrome, we lack much of the basic knowledge that has been accumulated over time from studies of HFrEF. In truth, there is still a lot to learn about the disease mechanisms underlying the development and progression of HFpEF.

How do animal models help in understanding the causes of, and developing treatments for, diseases like HFpEF?

Animal models are useful for understanding basic underlying disease mechanisms. Unfortunately, there are currently no small animal models of HFpEF that exactly recapitulate human HFpEF. There are several potential reasons including the fact that rodents are not little humans. Mice, which we use because of the availability of genetic models, have their own unique physiology. Further, and maybe more important, is the multifaceted nature of HFpEF. It co-occurs more often with other diseases such as obesity or diabetes making it harder to distinguish the specific role of HFpEF. Ultimately, that is very difficult to replicate in animals. At the end of the day though, work in animals will likely help uncover basic mechanisms that drive HFpEF progression, such as the role of Ffar4 in cardiac muscle cell and fibroblast function.

Why have clinical trials so far been inconclusive with regard to the efficacy of EPA in heart disease?

Based on our recent analysis of EPA levels and outcomes in 18 different clinical trials in heart disease (mostly coronary heart disease), we found that improved outcomes were associated with higher EPA doses and higher EPA accumulation achieved during the trial. This is in line with what has recently become apparent, namely that one must achieve a threshold level of omega-3 accumulation in order to see a clinical benefit. We suspect the same is true for EPA in heart failure, and we think about it as an EPA-therapeutic index – or the amount of EPA needed to observe a benefit.

How do you see your research moving forward over the next few years?

Given the proposed importance of peripheral inflammation in heart failure, we are interested in the role of EPA in preventing inflammation. It turns out that Ffar4 is expressed in macrophages, an immune cell that might have an important role in heart failure. Currently, we are looking at how EPA might induce an 'anti-inflammatory' state in macrophages and thus help to alleviate heart failure.

Detail

RESEARCH OBJECTIVES

Dr O'Connell's research focuses on advancing the science of heart failure treatment and prevention. His current research is looking into the mechanisms of omega-3 fatty acids – particularly eicosapentaenoic acid (EPA) – in offering cardioprotection against heart failure.

FUNDING

- National Heart, Lung, and Blood Institute (NHLBI)
- American Heart Association (AHA)
- Amarin Corporation

COLLABORATORS

- Dr Gregory C Shearer (Pennsylvania State University)
- Dr William S Harris (OmegaQuant Analytics & University of South Dakota)
- Dr Paul C Simpson (University of California San Francisco & San Francisco Veterans Affairs Medical Center)

BIO

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