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IEPR Newsletter

Heart Failure

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In This Issue

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"The goals of heart failure treatment are to prolong active life by improving symptoms and delaying progression of the underlying ventricular dysfunction and heart failure. In addition, major morbid events, like infarction and stroke, should be reduced and mortality lowered."
Prof. John GF Cleland, University of Hull, UK

Heart failure is a common but complex diagnostic and therapeutic puzzle. It is also a deadly condition sometimes termed the 'cancer' of the heart, the commonest malignant disease in Europe and North America. This terminology is very apt in many ways and heart failure physicians may have more to learn from oncology than cardiology when it comes to patient management in terms of aetiology, therapeutic intervention, long-term strategy and psychological support.

Until recently heart failure was more or less an immutable death sentence. Some patients could have corrective surgery and some heart transplants, but very few patients developing heart failure at age 60 years would survive until age 70. This is changing, with the advent of beta-blockers and cardiac resynchronisation therapy we can begin to talk about 'remission' of heart failure for the first time. Note the analogy to cancer medicine. Remission, in the context of heart failure means relief of symptoms, an improvement in quality of life to the average in the healthy population, and a restoration of ventricular function to normal or near-normal levels. With modern treatment about 15% of patients with heart failure due to left ventricular systolic dysfunction (LVSD) can achieve this. The proportion is even higher if the problem is dilated cardiomyopathy. Just like cancer patients, just because you have been started on the right therapy it doesn't mean to say that the treatment will work, nor does it mean that the problem being treated won't change. For instance, atrial fibrillation, cardiac dyssynchrony, renal dysfunction and anaemia may all develop long after the onset of heart failure and require a change in management. Heart failure is not as readily amenable to the more direct approaches of interventional cardiology and electrophysiology, engendering some interesting differences of opinion amongst the cardiovascular specialties.

Just as it is very unlikely that there will be one treatment to cure all cancers so it is unlikely there will ever be one cure for heart failure, although that has been the thrust of research on heart failure for the last 20 years. Studies of ACE inhibitors, beta-blockers and aldosterone antagonists have been designed to identify benefits in large and relatively unselected populations of patients with heart failure due to left ventricular systolic dysfunction. These treatments have generally delivered modest benefits on average but importantly, this probably reflects a large benefit in some patients, no benefit in others and probably some harm in a minority of cases. These studies were generally not set up to look at differences in effect between patients. More recently, the treatment of heart failure has begun to become more diverse, seeking to obtain larger benefits for individual patients by targeting therapy at a specific aspect of their problem. Thus cardiac resynchronisation seeks to correct dyssynchrony in the 30% of patients with LVSD who have advanced symptoms and a QRS >120 msec on the ECG. Erythropoetin is targeted at the anaemia of heart failure. Renal dysfunction, atrial fibrillation and other complications of heart failure are also exciting possibilities.

What then of the myocardium? Patients with LVSD are often considered to have had myocardium replaced by scar tissue especially when the aetiology is ischaemic heart disease. This is clearly only part of the story. The failing myocardium is also very complex, especially in patients with ischaemic heart disease. In these patients, there often are large areas of myocardium replaced

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by scar but most patients also have areas of myocardium that are viable but fail to contract. This is termed 'stunning' if it occurs in the aftermath of ischaemia or myocardial infarction, and 'hibernation' if it persists weeks after any obvious ischaemic insult. About 25% of patients with ischaemic heart failure will also have painless myocardial ischaemia. The aetiology of these different phenomena is probably rather similar. They are probably all dependent on an impaired myocardial flow reserve leading to an insufficient blood supply to maintain normal activity either at rest or during a modest amount of stress. It is likely that there is an acceleration of programmed cell death (apoptosis) in myocardial regions affected by ischaemia/hibernation which will contribute to myocardial fibrosis and adverse LV remodelling.

How should myocardial ischaemia/hibernation be treated in these patients? To the interventional cardiologists the answer seems obvious. Many things are obviously the 'right' thing to do in medicine, until you check it! There is no evidence that revascularisation of the epicardial coronary arteries improves outcome for patients with hibernating myocardium, nor evidence that it is safe. This is being tested in two large multi-centre trials which have randomised about 1,000 patients and have not been stopped, so far, for benefit or harm. Remember that one of the greatest benefits of cardiology research in the last 25 years was stopping the proliferation in use of Class I anti-arrhythmic drugs. There are those of us who believe that stopping widespread use of aspirin (a COX-2 antagonist!) will similarly have a large benefit to patients (1). Things need checking!

Beta-blockers have been tested in the large multi-centre CHRISTMAS trial for the treatment of ischaemic or hibernating myocardium (2,3). The CHRISTMAS (**C**arvedilol **H**ibernating **R**eversible **IS**chaemia **T**rial: **MA**rker of **S**uccess) trial showed that the patients who had a large volume of myocardium affected in this way obtained significantly greater benefit in terms of improved LV function. Interestingly, patients with dilated cardiomyopathy did too! At first sight this seems odd. However, the myocardial microcirculation may be rather similar in dilated cardiomyopathy and hibernating myocardium and may be the common link in terms both of aetiology and therapy (4).

Does EECP have a role in the management of myocardial microcirculatory disorder? EECP certainly works for angina, although the mechanism remains uncertain. Improvement in the microcirculation, akin to the benefits that might be obtained by a cardiovascular fitness programme (which can also reduce angina), is a pretty good candidate mechanism. One potential way of addressing this whole issue is to carefully characterise the myocardial substrate of patients with ischaemic heart disease and LVSD prior to and after EECP. Cardiac magnetic resonance imaging provides an highly accurate method for assessing global and regional LV function. Also, by injecting gadolinium during adenosine stress and then at rest, and by looking at early and delayed uptake, the volume of myocardium affected by ischaemia and by scar can be assessed. Accordingly, in 2004 we started a project called ECCE (**E**nhanced External **C**ounterpulsation in **C**hronic Left Ventricular Systolic Dysfunction **E**valuation). If EECP specifically improves the function of myocardial segments identified as being affected by ischaemia and or hibernation, then this is powerful evidence not only of how EECP works but also in whom. Recruitment for ECCE is about 50% complete and we look forward to presenting our results in 2006. Hopefully, this will be a great follow-on from the PEECH study, for which we were proud to be the only European representative.

References

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(2) Cleland JGF, Pennell DJ, Ray SG, Coats AJ, MacFarlane PW, Murray GD, Dalle Mule J, Vered Z, Lahiri A, on behalf of the CHRISTMAS (carvedilol hibernating reversible ischaemia trial: marker of success) investigators. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. Lancet 2003; 362:14-21.

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Recent Publications:

Lawson WE, Silver MA, Hui JCK, Kennard, ED, Kelsey SF (for the IEPR investigators). Patients with Diastolic or Systolic Heart Failure Demonstrate Comparable Immediate and One-Year Benefit from Enhanced External Counterpulsation. J Card Fail 2005;11:61-66

Michaels AD, Barsness GW, Soran ZO, Kelsey SF, Kennard ED, Hui JCK, Lawson WE, (for the IEPR investigators). Frequency and Efficacy of Repeat Enhanced External Counterpulsation for Stable Angina Pectoris (from the IEPR). Am J Cardiol 2005; 95:394-397

Recent Presentations:

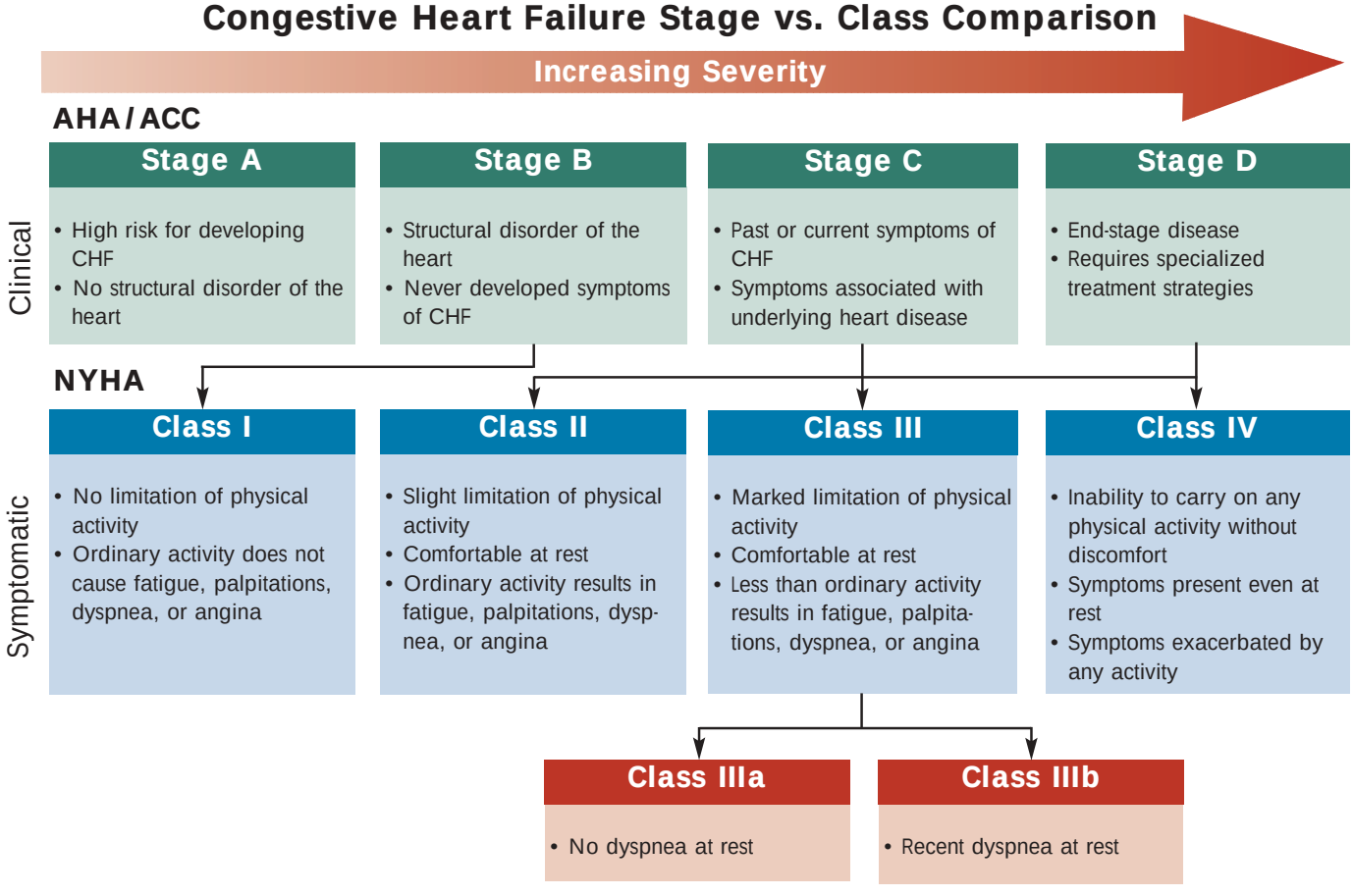
American College of Cardiology Annual Scientific Session, Orlando, FL, March 6-9, 2005

Sustained One-Year Benefit of Enhanced External Counterpulsation in Relieving Mild Angina in Patients with End-Stage Coronary Disease

WE Lawson

The ACC/AHA[1] has created guidelines that divide heart failure (HF) patients into stages reflecting clinical signs of disease. The NYHA[2] classification categorizes the HF patient by symptomatic impact on ability to function and is the classification tool most commonly used in clinical practice.

Congestive Heart Failure Stage vs. Class Comparison



1. American College of Cardiology/American Heart Association
2. New York Heart Association

The IEPR Manuscript Writing Group Develops and Implements Publication Guidelines

One of the primary objectives of the IEPR has been to disseminate significant findings regarding the safety, efficacy and treatment outcomes of EECP therapy in daily clinical practice to the wider medical community through presentations at national and international cardiology meetings, and publication of manuscripts in peer-reviewed journals. With the completion of follow-up for Phase I, and the completion of enrollment for Phase II, a larger and more comprehensive body of information is available for analysis, presentation and publication. To make best use of the resources of the IEPR Coordinating Center and the time of the IEPR investigators, the Manuscript Writing Group was formed to optimize the publication process. Currently the Group is chaired by IEPR Medical Director, Dr. Andrew Michaels and is comprised of ten experienced IEPR investigators, and doctors Sheryl Kelsey and Elizabeth Kennard of the IEPR Coordinating Center. The Manuscript Writing Group has developed and implemented guidelines for submission of proposals for data analysis, approval of projects, ensuring scientific content, setting priorities for analysis, assigning authorship of manuscripts, and ensuring that abstracts and papers are completed and submitted in a timely fashion. Members of the Writing Group have found formalizing the publication process efficient and productive, and look forward to continuing analysis of the combined Phases I and II databases for topical and dynamic meeting presentations and publications in peer-reviewed journals.

IEPR investigators and coordinators interested in participating in the publication process, i.e. developing an abstract for presentation at a scientific meeting and preparing a manuscript, should contact Dr. Michaels by email: andrewm@medicine.ucsf.edu. For a complete list of IEPR publications and presentations go to the IEPR website at www.edc.gsph.pitt.edu/iepr and click on 'Publications'.

IEPR-2 Form Compliance

Six Months: 94% • One Year: 95% • Two Years: 93%

IEPR Site Spotlight:

Hull Royal Infirmary, Hull, East Yorkshire, UK

Prof. John GF Cleland, Medical Director - Dr. Poay Huan Loh, Fellow - Jocelyn Cook, RGN, Sr. Research Nurse Coordinator

Kingston-upon-Hull is an old city (1299 AD), established by King Edward I of England (aka Hammer of the Scots) to build a fleet for the invasion of Scotland. It has very strong ties with the USA. The refusal to let King Charles I into Hull (the major weapons arsenal in the North of England in 1640) precipitated the English Civil War and was the English-speaking world's first shot at republicanism. The Washington family came from Selby – just outside Hull. During the American Revolution the Americans attacked the east coast of England near Hull and in a naval engagement the Americans lost their first-ever flagship (Bonhomme Richard) under the command of Paul Jones (in fact the Americans won the engagement but it was a Pyrrhic victory). William Wilberforce was the Member of Parliament for Hull at the start of the 18th Century and led the anti-slavery campaign that led to the British taking affirmative action against slavery worldwide around 1830. His policy also stopped the British joining the American Civil War on the Confederate side. The first aircraft (in fact an airship) of the US Air Force crashed into the Humber (a large two-mile wide river on which Hull is situated). Over two million immigrants from Europe passed through Hull on their way to the New World. Many Americans served in the many airbases in and around Hull during World War II. Some eminent American cardiologists started their careers in Hull, including Udo Thadani, Wallace Portal, and the redoubtable Clive Aber. Doubtless many Americans will know of other connections.

Jocelyn Cook, RGN, Prof. John Cleland, Dr. Huan Loh

Well, now you know a little bit about Hull. What about its cardiology department and who does it serve? The department belongs to the National Health Service (NHS) and has eight consultant cardiologists (including Professor Cleland) who provide a comprehensive cardiology service to about a half million people. It is the regional referral centre for a population of about 1.5 – 2 million which extends from Boston (Lincolnshire) to (Old) York, Scarborough (of Scarborough Fair fame), Whitby (Bram Stoker and the Dracula legend) and the North York moors (the Brontes and Wuthering Heights). The patient population includes some of the wealthiest in England and some of the most deprived. The city is still scarred by the devastation of world wars and the loss of its fishing fleet but has large aerospace, information technology, chemicals and engineering industries. Its main trading partner of the 18th century, St. Petersburg in Russia is coming back on line and in many ways Hull is Britain's most progressive city. The Hull cardiology department provides a full range of services for cardiac emergencies, deals with about 1,000 myocardial infarctions each year, conducts about 2000 revascularisation procedures and has one of the UK's largest ICD (currently about 300 patients) and CRT programmes (currently about 100 patients).

Since 1999, there has been a growing interest in research under the auspices of Professor John Cleland. Hull has Europe's largest longitudinal epidemiological programme on heart failure, is one of its most active cardiac magnetic resonance imaging centres, has expert echocardiography, nuclear cardiology, electrophysiology, interventional cardiology and cardio-thoracic surgery. Professor Cleland chairs the Steering Committee of a number of important studies including the CHRISTMAS trial (that investigated the clinical relevance of the ischaemic myocardial substrate as a determinant of the response to beta-blockers), CARE-HF[1], and PEP-CHF[2] (an ongoing study of ACE inhibitors in patients with diastolic heart failure). The department regularly publishes in high-quality journals (including New England Journal of Medicine, Lancet, Circulation and Journal of the American College of Cardiology).

What about EECP in Hull? Hull started its EECP programme in 2000 AD and until last year was one of only two centres providing this therapy in the UK (population ~60 million). Two more centres (one private) started offering EECP in 2004. EECP is paid for by the National Health Service (NHS) but patients have to get the support of their family doctor to have the treatment. Excluding research patients, we have 78 patients who have completed therapy with at least one-year follow-up to assess outcome. Our results are very similar to those observed in US centres with about 86% of patients feeling they obtain an important short-term benefit which is sustained in about 90% of patients out to at least one year. Many of our cardiologists were sceptical about EECP to begin with. However,

1. CARE-HF=**CA**rdiac **RE**synchronization and **H**eart **F**ailure
2. PEP-CHF=**P**erindopril for **E**lderly **P**eople with **C**hronic **H**eart **F**ailure

attitudes changed after the first dozen patients had been treated. Some of these patients were real 'cardiac cripples' who had failed all other available treatment. In many of these patients the results were astounding. Now, the cardiologists and even the cardiac surgeons regularly refer patients to the programme for the management of angina.

Currently, the main referrals for EECP in our centre are:

1. Patients with persistent, troublesome angina despite pharmacological therapy for whom no further revascularisation procedure is considered possible.
2. Patients with recurrent angina after a first coronary artery bypass in preference to repeat surgery, since these patients have an increased risk and poorer result from repeat surgery and there is no evidence of prognostic benefit. Only patients who fail repeat EECP would be referred back to the surgeons.
3. EECP is considered the treatment of choice above all other interventions in patients who have failed conventional pharmacological therapy and/or revascularisation.

Patient successes:

'Before EECP, I would call myself a cripple and suffered from daily angina. Now, I have infrequent angina and can get on with my daily activities without much problem. It has been two years since I had my treatment!'

'Without EECP I would not have been able to have my hip replacement. After my first treatment the effect was amazing. Two years later I could hardly walk and I was in need of another hip replacement. My anaesthetist was so impressed by my EECP story that he requested a second lot of treatment before he would operate. After the second treatment the operation went ahead, not only has it improved my heart but also my hip.'

'My wife's angina was so bad she couldn't even get out to shop for food for over a year. Even the effort of making a meal was often too much. Now she is back to her 'old' self. Thanks to EECP my diet and lifestyle have improved enormously. My wife's too!'

As might be expected in a British public service hospital, EECP is provided in a fairly rundown Victorian building. However, it is what is inside that counts. EECP is administered by one lead nurse with back up to cover absence, and with a cardiology trainee on the same floor. All patients are thoroughly assessed for coronary risk factors, aortic valve disease or aneurysms prior to receiving EECP. Patients are advised that this is a treatment for symptoms and is safe but that we do not know if it will alter the risk of future cardiovascular events. This is important in the UK because most patients when offered an alternative to revascularisation will choose it (we hear patient attitudes may be different in the US). Perhaps one day we will see a trial of EECP versus angioplasty for chronic stable angina – my money will be on EECP!

A few words from Joss, our lead nurse and EECP Coordinator:

'We have a fairly informal setting as a number of our patients come quite a distance therefore can not guarantee prompt arrival. This leads to flexibility they all appreciate. With patients coming from all parts of the UK the atmosphere is very sociable and good friendships have formed with requests for follow-up visits to be made the same day as their new friends.

We have a TV, radio and video in the treatment room. We provide refreshments and all the usual comforts for the treatment such as padding for the shins and ladies' tights (when the male patients bring their wives the tights usually provide some hilarity).

Even though I am the primary EECP therapist, the rest of the staff always make the effort to get to know all the patients during their treatment course.

Patients are very enthusiastic about the treatment, and have been very proactive in spreading the news. Down the line they have usually been told that there is nothing else that can be done for their condition. EECP for them has therefore been a life changer physically and psychologically, without which their future would have remained bleak.'

Our staff includes:

Prof. John Cleland, MD, FRCP, FESC, FACC

Prof. Cleland is Professor of Cardiology at the University of Hull, a Consultant Cardiologist and an expert on many aspects of heart failure. He is Chairman of the British Society for Heart Failure, past-chairman of the European Society of Cardiology Working Group on Heart Failure, and an adviser to the UK National Institute for Clinical Excellence (NICE). He is an author on more than 250 peer-reviewed papers in cardiology, mostly related to heart failure.

Poay Huan Loh, MB, ChB, MRCP, BMedSc(hons)

Dr. Loh is a Clinical Lecturer/Research Fellow in our Academic Cardiology Department. He joined the team in August 2003 and has a main research interest in EECP. Dr. Loh has had two EECP abstracts accepted for the May 2005 British Cardiac Society meeting, and one for the June 2005 meeting of the Heart Failure Association of the European Society of Cardiology.

Jocelyn Cook, RGN

Jocelyn is a Senior Research Nurse, EECP therapist and Coordinator. Joss, 'converted' after fifteen years in interventional cardiology in Sheffield and London, has been working with EECP for four years, and is an active member of the International EECP Therapists Association (IETA).

Peter Jones, RNC, BSC

Peter is a Senior Research Nurse with 7 years of experience in cardiology research. He became involved with EECP to assist in the PEECH Trial and has continued to take an active part in EECP treatment and research since.

Janet Bristow, RGN, Dip ED

Janet has 20 years of experience in cardiology care. She has been the Project Leader in the Primary Care for a heart failure research study within our Academic Cardiology Clinics. Janet was introduced to EECP at the same time as Peter. She also assisted with the PEECH Trial and has continued her involvement with EECP treatment and research since.

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