Dr. Piotr Ponikowski is professor of cardiology at the cardiology department, Military Hospital, Wroclaw, Poland, and his training as a clinical cardiologist was mainly in his home country. However, he spent 3 years in the United Kingdom, supported by fellowships from the British Council and the European Society of Cardiology. There, in the mid-1990s, as a young medical registrar, he trained under Phillip A. Poole-Wilson, MD, FRCP, FESC, and Andrew J.S. Coats, FRCP, FESC, FAHA, at the National Heart and Lung Institute and the Royal Brompton Hospital, London. It was here that his general interest in heart failure (HF) developed.

Dr. Ponikowski's work on anaemia and HF started about 5 years ago, and his paper written on the subject in 2001 was eventually published in 2003.1 Anaemia is now recognised to be an important and frequent comorbidity in HF, associated with poor quality of life, high morbidity, and mortality, and is caused by a complex mechanism that has yet to be fully described.2 This article focuses on the work being done on the treatment of anaemia in HF.

The Rationale for Treatment

The reasonable theory that treatment to correct anaemia will benefit HF patients needs to be proved in large-scale well-controlled studies, but Dr Ponikowski warns that studies of anaemia in patient groups with other pathologies suggest that a total correction may not always be beneficial.

For instance, Anatole Besarab, MD, and his colleagues treated anaemic patients with haemodialysis-dependent end-stage renal disease with erythropoietin to different haemoglobin targets.3 In one group the aim was to keep the haemoglobin at near normal levels, while in the other group patients were kept mildly anaemic. The study was terminated early because a trend was observed toward higher risk of death and myocardial infarction in those randomised to normal target haemoglobin levels.

Available Treatments

Blood transfusion is not a good option in HF. However, the erythropoiesis-stimulating proteins (epoetin-α, epoetin-β, or darbepoietin-α), most likely in combination with iron, appear to be logical treatments. Again, this has to be proved in large-scale, well-controlled trials, because, Dr Ponikowski says, as yet only a few small studies on treating anaemia in HF exist. Donald S. Silverberg, MD, and his coworkers, in an open-label study in 2000 with 26 patients, showed for the first time that the use of subcutaneous recombinant human erythropoietin and intravenous iron for the treatment of anaemia in severe, resistant, chronic HF, improves cardiac and renal function and New York Heart Association functional class, while markedly reducing hospitalisations.7 A series of seminal papers from the same group further confirmed clinical benefits of the correction of anaemia with erythropoietin in HF.8

Subsequently, Donna M. Mancini, MD, and colleagues published a single-blind, randomised, placebo-controlled trial demonstrating favourable effects of erythropoietin therapy in 26 patients with advanced HF and anaemia.7 Compared to placebo, those receiving erythropoietin had an increase in peak oxygen consumption and improvement in quality of life (measured by the Minnesota Living with Heart Failure score). Interestingly, there was a linear correlation...
between improvement in peak oxygen consumption and improvement in haemoglobin.

Dr Ponikowski’s group, together with other coinvestigators, has recently completed studies with the long-acting erythropoiesis-stimulating protein, darbepoetin-α. The first was a multicenter, randomised, double-blind, placebo-controlled study, with 41 symptomatic HF patients with anaemia (haemoglobin 9.0-12.0 g/dL). A 26-week treatment with darbepoetin-α safely and effectively increased haemoglobin concentrations and improved health-related quality of life as evaluated by patient global assessment. Trends toward improved exercise tolerance, as measured by peak oxygen consumption and exercise duration, were observed.9 Earlier this year, in a paper presented at the American College of Cardiology meeting, these observations were further confirmed and strengthened in a study comprising a larger population of 150 patients.9

Before anaemia becomes widely accepted as a therapeutic target in HF, large multicentre clinical trials investigating the safety of long-term treatments with erythropoiesis-stimulating proteins and their effects on patient outcomes are needed. One such trial will start later this year: the Reduction of Events with Darbepoetin α in Heart Failure study (RED-HF). It will evaluate whether treatment of anaemia with darbepoetin-α reduces the risk of morbidity and mortality in symptomatic, anaemic HF patients.

What Will Be the Optimum Treatment?

Dr Ponikowski feels that the optimum treatment may be an erythropoiesis-stimulating protein combined with intravenous iron, because functional iron deficiency is a common but much overlooked problem in HF.

At this year’s Heart Failure Association meeting, his group presented a study demonstrating that among 218 consecutive, symptomatic HF patients, nearly half fulfilled the criteria for iron deficiency. They found that iron deficiency frequently coexists with HF irrespective of the presence or absence of anaemia, and is related to exercise intolerance and status of low grade inflammation.10 At the same meeting, Dr Ponikowski presented the first results of the Ferric iron sucrose in Heart Failure (FERRIC-HF) study, which showed that iron repletion with intravenous iron sucrose was safe and improved exercise capacity and symptom status in iron-deficient HF patients. Benefits were much more evident in anaemic patients (see Figure).

In summary, Dr Ponikowski said, “I am positive and enthusiastic about the benefits of treatment of anaemia in HF seen so far. However, it is important not to overestimate at this stage the potential benefits that HF patients may achieve by correction of anaemia. We are still waiting for really firm data from large morbidity and mortality trials.”1

He stressed the need for double-blind, placebo-controlled studies with the different erythropoietin-stimulating proteins in combination with iron before the treatment of anaemia can be considered as a goal of therapy in HF. He added that while there are some hypothetical negative effects, such as increased thrombotic risk and increased blood pressure, the authors of reports generally presented so far have not seen such problems.

Robert Short is a freelance medical journalist.

References

Centres of Excellence in Cardiology: The Hammersmith Hospital

In the first of an occasional series looking at centres of excellence across Europe, Kenneth Taylor, MD, FRCS, FESC, (above) and Christopher Baker, PhD, FRCP, (below) talk to Barry Shurlock, MA, PhD, about their institution and how it functions.

Now treating more patients than ever, Hammersmith Hospital still throngs with academics exploring new and more effective treatments for heart disease, especially in patients with multisystem disorders. The clinical director of cardiac sciences at Hammersmith Hospital is Dr Kenneth Taylor. He also holds the British Heart Foundation (BHF) Chair of Cardiac Surgery of Imperial College, London. The chief of service for cardiology is consultant cardiologist Dr Christopher Baker. These 2 doctors are key players in organising and managing cardiology services at this famous institution.

Eponymous recognition is an accident of history that may happen to individuals and institutions. In the case of the Hammersmith Hospital, it is “the Hammersmith regime,” referring to the high doses of the protease enzyme inhibitor aprotinin that is used to protect patients on heart-lung bypass from excessive bleeding, systemic inflammation, and multi-system organ failure. The Hammersmith regime has become a worldwide best practice in these situations, which was the result of an educated guess by the Hammersmith cardiac surgical team, who verified their early findings in clinical trials.

This is a good example of the cross-specialty expertise that the hospital prides itself on, because this particular use of aprotinin might not have been developed without local pharmacological and immunological expertise combined with the department’s own deep understanding of the processes of extracorporeal circulation. The Hammersmith goes back a long way in open heart surgery, as it was here that, in 1956, the Melrose heart-lung machine was first used in an open-heart operation in the United Kingdom.

At the hospital, in basic science, medicine, and surgery, academics work together in an environment where the specialties are not in watertight compartments, according to Dr Taylor. He said, “The Hammersmith has always been a multi-specialty, integrated academic hospital, specialising in both clinical service delivery and basic science research.” Thus, when he wanted to understand in more detail the effect of aprotinin in systemic inflammation in the patient on bypass, he turned to Dorian Haskard, DM, FRCP, FMedSci, FAcR, a rheumatologist by training, who holds the BHF Sir John McMichael Chair of Cardiovascular Medicine at the National Heart and Lung Institute, Imperial College London, which is on the Hammersmith campus. This capability for inter-speciality interaction at the Hammersmith is backed up by Dr Baker, who said, “If you have an idea to research, there will be somebody within the hospital [and its associated institutions] who is a world authority on it, or knows someone who is. I was supervised for my PhD by Julia Polak, MD, DSc, FRCP, FMedSci, and Roger Hall, MD, FRCP, FESC, and if we came up with an idea outside our direct expertise, there was always someone else who knew how to do it.”

The role of the Hammersmith as a major British postgraduate centre has sometimes led to some unkind jibes, such as comments that there are more professors than patients, but over the last decade it has expanded its service commitment dramatically. Each year, 700 open-heart procedures, up to 350 thoracic operations, and more than 2000 angioplasties are performed in the hospital. Its catchment area in North West London includes a large number of people of Indian Asian origin, who have a much higher incidence of severe coronary artery disease than average, often associated with type 2 diabetes. The hospital also takes difficult patients from the rest of the United Kingdom and from many other countries.

Hammersmith has the largest renal centre in Europe, housed in new purpose-built premises, which allows Dr Baker, in conjunction with the nephrologists, to study the management of cardiac disease in patients with renal failure. Similarly, the presence on the Hammersmith site of the Queen Charlotte’s and Chelsea Hospital, the leading UK specialist maternity hospital, enables cardiologists and obstetricians to cooperate in the study and treatment of women with conditions such as pulmonary hypertension, coronary artery disease, and valvular disease due to rheumatic fever, a condition still seen in immigrants from South East Asia, Somalia, and other African countries.

Over the past 20 years, the organisation of medical education and national healthcare services in London, and in the United Kingdom in general, has changed out of all recognition. It is not possible to cover the subject in a short article, but in essence a large number of small but world-renowned medical schools have been amalgamated to form larger units, and their associated hospitals have also been combined to provide...
economies of scale and to give them more leverage in selling their healthcare services within a cost-conscious “internal market.”

This process is reflected in the complex institutional structure of the Hammersmith. The Hammersmith Hospitals National Health Service Trust (comprising Hammersmith, Charing Cross, and Queen Charlotte’s and Chelsea Hospitals) treats patients referred by general practitioners, local hospitals, and hospitals from throughout the United Kingdom and internationally. It is also the main academic multispeciality hospital of the Faculty of Medicine of Imperial College, London, a world-renowned institution for science, technology, and medicine. And within the Faculty, cardiothoracic surgery and cardiology are the remit of its heart and lung division, the National Heart and Lung Institute.

Two of the chairs are funded by the BHF, whilst the Medical Research Council Clinical Sciences Centre, as its name suggests, is supported by the national body for funding medical research. As if this were not enough, the Hammersmith is seeking a marriage with St Mary’s Hospital, London, where Sir Alexander Fleming, FRCP, discovered penicillin. To this end it has applied to be one of the handful of centres of excellence, called Biomedical Research Centres, planned by the UK Department of Health.

Formally, Dr Taylor heads up the Directorate of Cardiology and Cardiothoracic Surgery of the Hammersmith and was, until 3 years ago, operating 2 days a week. He admits to liking “the jousting of politics,” and says his new job is “like three-dimensional chess.” He is also director of the UK Heart Valve Registry, which was established at the Hammersmith in 1985, following withdrawal of the Björk-Shiley valve. He commented, “At the time no country had a registry, so although 100 000 patients worldwide had received the valve, no one knew who they were. The UK registry is the ‘gold standard,’ and it seeded others. It has allowed us to understand what went wrong in the manufacturing process. Also, we have been able to look in detail at the demographics of valve surgery.”

Amongst the subspecialties of the cardiac surgical department are conservative surgery of the mitral valve, headed by Prakash Punjabi, MS, FRCS, and thoracic aortic surgery, led by Jonathan Anderson, MB, ChB, FRCS. The department has a great deal of experience with “difficult” patients, according to Dr Taylor, who said, “We manage complex multipathology very well. Our results, judged against the risk profile of what we would anticipate, are consistently better than expected. We can handle people with complex renal disease, strange vasculopathies and the like — the interactions of the various departments, not just clinically but academically, are outstanding.”

Cardiologist and general physician Dr Baker, who was appointed to his consultant post in April 2002, is chief of service for cardiology of the National Health Service Trust, and lead catheter laboratory clinician at the Hammersmith. He also points to his consultant post in April 2002, is chief of service for cardiology of the National Health Service Trust, and lead catheter laboratory clinician at the Hammersmith. He also works at the Charing Cross Hospital, London, its sister institution, where the department focuses on rapid-access chest pain clinics and cardiac rehabilitation. Interventional cardiology at the Hammersmith is served by 3 catheter laboratories, including a brand new one with the latest state-of-the-art technology (Figure 2). The hospital is one of 8 centres nationwide where the logistics of primary angioplasty are being studied. The
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