Pulmonary Hypertension: Deserving of Attention

Nazzareno Galiè, MD, associate professor of cardiology at the University of Bologna, Italy, says pulmonary hypertension is uncommon, but justifies the attention it receives in the scientific and clinical communities. He speaks to Ingrid Torjesen, BSc.

With a minimal prevalence of just 15 cases per million, pulmonary arterial hypertension is a rare condition, and, considering this fact, a great deal of attention is focused on it from a scientific point of view, according to Dr Nazzareno Galiè. “There are many ongoing trials with new pharmacological compounds,” he says, “and the interest among physicians is also quite high, as the symposia on the condition, organised within the main frame of institutional congresses, are always well attended.”

In addition, there are 2 sets of guidelines on pulmonary arterial hypertension — one from the European Society of Cardiology and the other from the American College of Chest Physicians. Dr Galiè believes that it is remarkable that such detailed diagnostic and treatment guidelines have been provided for a rare disease.

European countries, such as the United Kingdom, Italy, Belgium, Spain, Germany, Austria, and France, already have a small number of centres specialising in pulmonary hypertension, and Dr Galiè believes that this is the correct approach. “It is very important that there is not a proliferation of centres, because it is important for a centre to have a critical number of patients to gain experience and to provide the appropriate care,” he explains. “If a hospital has only a handful of patients, experience cannot be collected, and the organisation will not be efficient.”

He emphasises that pulmonary arterial hypertension is a very distinct condition and should not be confused with pulmonary hypertension presenting with diseases such as chronic heart failure or parenchymal lung diseases.

“Pulmonary hypertension in those settings cannot be treated with the same strategy,” he says. “We have learned from trials that when we try to utilise compounds developed to treat pulmonary arterial hypertension, such as prostanoids or endothelin receptor antagonists, in patients with chronic heart failure or parenchymal lung disease, they do not work and can be detrimental to those patients.”

The reason for this is the pathogenesis, he explains. “In these 2 conditions, the pulmonary hypertension is at least in part the consequence of a protective/compensatory mechanism. In chronic heart failure, reactive pulmonary hypertension is related to protection against pulmonary oedema, while in parenchymal lung disease, pulmonary hypertension is in part related to the mechanism of matching ventilation with perfusion.”

In these cases, he emphasises, it is therefore important to treat the underlying conditions responsible for the pulmonary hypertension, rather than the pulmonary hypertension itself, as the latter choice may be ineffective or even harmful to the patient.

Dr Galiè does not expect there to be huge developments in the treatment of pulmonary arterial hypertension in the next couple of years, but he expects that recently developed treatments will be refined. In the past few years, 3 classes of drugs have been developed and have proved effective: prostanoids, endothelin receptor antagonists, and phosphodiesterase-V inhibitors. Within these 3 classes, new compounds and new methods of administration are currently being tested in phase 3 clinical trials.

“I do not expect dramatic improvements with these trials, but refinements,” he says. “There may be compounds with fewer side effects or requiring fewer administrations. We will also learn more of the efficacy of combinations of these..."
classes of drugs and this will improve our treatment, although not dramatically.”

Dr Galiè does not expect there to be any new classes of drugs for pulmonary arterial hypertension before 2008–2009, as there are none currently in phase 3 clinical trials. However, there are a couple of promising prospects in phase 2 trials, he says, including a vasoactive intestinal peptide, which will be administered through inhalation, and a platelet-derived growth factor (PDGF) inhibitor (imatinib). Other interesting treatment approaches include the use of stem cells (endothelial progenitor cells) now being explored by a Canadian pilot study of patients with pulmonary arterial hypertension.

The low prevalence of pulmonary arterial hypertension means that no comparative trials have been conducted on existing treatments, so no evidence-based first-line therapy can be proposed. “We start with one officially approved drug, usually the cheaper and simpler one, and if results are not satisfactory, we add the second, and then the third,” Dr Galiè says.

“Even with this approach, there will still be a consistent number of patients for whom there will not be a satisfactory result.” He goes on to explain, “We still do not have an ideal drug, and it is possible that this is a disease that needs to be treated with concurrent multiple approaches as we do in heart failure, coronary artery disease, and systemic hypertension.”

Although there has been much progress in the treatment of pulmonary arterial hypertension in the past few years, the prognosis for the patient is still not good, Dr Galiè says. “As the mean age of diagnosis for pulmonary hypertension is around 50 years, an age at which work capability is very high, the patient is severely compromised in all aspects of quality of life,” he says. “This is why it is very important to continue to study and refine and maybe explore more creative approaches.”

The current theory on the pathobiology of pulmonary arterial hypertension is that there is an uncontrolled proliferation of the cells of the pulmonary arterial vessel walls. “This obliterates the lumen,” explains Dr Galiè (see Figure). “Almost all the new treatments have shown an antiproliferative effect in vitro,” he continues. “But we do not really know if this is the real effect of the drug on the patient.”

Dr Galiè says the development of highly sensitive radiological or magnetic resonance techniques showing the lung microcirculation clearly will improve understanding of the pathophysiology of pulmonary arterial hypertension. These techniques will also enable researchers to look at the correlation between the “virtual” histology and the outcome of treatment.

“We do not need very sophisticated approaches for diagnostic purposes, but we do need them for the understanding of the disease and for epidemiological and pathological correlation with treatment,” he says, “because it is neither practical nor ethical to use lung biopsies for this. Biopsies cannot be used for the study of the disease because they are dangerous and demanding for the patient, and do not provide any patient-specific treatment information.”

Dr Galiè goes on to say, “If we can develop noninvasive assessments showing changes in microcirculation based on the new imaging techniques, this can help us to understand the pathobiology better and why the existing drugs are working.” He concluded, “Then maybe we can learn how to improve efficacy, or find other methods of treatment.”

Ingrid Torjesen is a freelance health writer.

A National Audit of Care for Myocardial Infarction

The Myocardial Infarction National Audit Project (MINAP) is helping to raise the standard of care offered to heart attack patients within the UK’s National Health Service, reports Mark Nicholls.

The Myocardial Infarction National Audit Project (MINAP) was established as a response by the profession to the audit requirements of the National Service Framework (NSF) for Coronary Heart Disease in England and Wales, and is now in its fifth year. In that time, it has evolved into a comprehensive and transparent means of monitoring, maintaining, and improving how the National Health Service (NHS) manages heart attacks.

The fifth MINAP report, published in June, stated that “patients with heart attack are being treated at a level of excellence that is unsurpassed anywhere in Europe or beyond.” The report presents data from all hospitals about patients who have had a myocardial infarction (MI), and for the first time includes ambulance services in England and Wales that provide care for patients with suspected MI. Most of the work relating to the MINAP report was performed by the Royal College of Physician’s Clinical Effectiveness and Evaluation Unit. The project is undertaken in collaboration with the Central Cardiac Audit Database (CCAD) and funded by the Healthcare Commission. The main findings of the report are summarised in the box on the next page.

Cardiologists believe the MINAP report has played a valuable role in raising the quality of care for MI patients. The associate director of MINAP, Clive Weston, FRCP, reader in clinical medicine at the School of Medicine, University of Wales, Swansea, said, “It allows an assessment of the performance of individual hospitals in the management of acute MI against a small number of pre-specified targets. While each hospital can access its own data and compare this against a national aggregate at any time,
Main findings of the 2006 MINAP report

- Patients now receive thrombolytic treatment faster. A total of 83% of eligible patients in England and 74% in Wales received thrombolytic treatment within 30 minutes of arrival at hospital, compared to 44% in England in 2001 and 65% in 2003–2004 when the Welsh hospitals were first included.
- A total of 58% of patients received thrombolytic treatment within 60 minutes of calling for professional help in England, compared to only 22% in 2001 (30% in Wales, compared to 22% in 2003–2004).
- More hospitals are now using angioplasty as an emergency treatment for MI. In 2005–2006, 1647 patients were treated with primary angioplasty in preference to thrombolytic treatment, compared to 1087 in 2004–2005.
- The proportion of MI patients prescribed secondary prevention medication on discharge from hospital continues to increase, at 97% for aspirin, 92% for beta-blockers and 96% for statins in England, with corresponding increases to 98%, 91% and 94% in Wales.

Dr Weston continued, “The management of ACS, and STEMI in particular, is changing in the UK, where historically high rates of thrombolytic therapy use have been reported. Ambulance paramedics are giving prehospital thrombolytic drugs, while some hospitals operate primary percutaneous coronary intervention services for their own patients and those of neighbouring hospitals. MINAP is attempting to capture this activity, though of course performance indicators may have to change to reflect new systems of delivering care.”

He explained that there has been interest in the MINAP concept from hospitals in Northern Ireland, Scotland, the Irish Republic, and also from much further afield, such as the Middle East and New Zealand.

Peter Weissberg, MD, FRCP

Peter Weissberg, MD, FRCP, medical director of the British Heart Foundation, based in London, United Kingdom, said the value of MINAP is that it is a “transparent and objective” way of monitoring how hospitals are performing in the treatment of MI, and can help identify and remedy problems. “It produces a greater homogeneity of MI management across England and Wales,” he said.

“What it has done is to follow the patient journey, encapsulating everything from the moment the patient gets symptoms right through until they are discharged from hospital, and the drugs they are taking on discharge.” He continued, “That means it enforces coordination of the process between various different agencies that are involved with patient care. MINAP is a tool that monitors the total package of care and shows up where that package is falling down. It identifies where the problems are, and because the data is available for everybody to see, it puts pressure on those responsible for provision to remedy those problems.” Dr Weissberg concluded, “There is no doubt in my mind that it is a major instrument for maintaining and improving care for patients with a heart attack.”

With better information technology to improve the collection and the quality of the data, Dr Weissberg believes the next step is to use the data as a basis for monitoring further improvement, and to investigate the delivery of immediate angioplasty and thrombolysis in the community.

Mark Nicholls is a freelance medical journalist.
History of Cardiology: Étienne-Louis Fallot, MD

The famous French physician may not have been the first to describe his eponymous tetralogy, but he will forever be associated with it. Diana Berry explains.

Étienne-Louis Arthur Fallot, MD, was a very private man, and biographical details of his personal life are extremely limited. He would not even countenance the writing of an obituary after his death. He was born in Sète, France, on 29 September 1850, and was educated at the lycée in Marseilles, where he was awarded a prize for high scholastic achievement. He remained in Marseilles throughout his life and achieved his degree in medicine at the city’s École de Médecine.

He did once visit Montpelier, where in 1876 he wrote a dissertation on the subject of pneumothorax. In the same year, Fallot was appointed director of a medical clinic in Marseilles. In 1883, he was appointed assistant professor in forensic medicine and hygiene at the medical school, and in 1888 he became professor of hygiene and legal medicine, a post that he held until his death in 1911.

Dr Fallot had an excellent reputation as a clinician and diagnostician who was known to be painstaking in the physical examination of his patients. It is said that he always displayed compassion for the weak and less fortunate in society. His scientific writing was quite prolific, and included papers on a local epidemic of cholera, congenital pectoralis aplasia, a case of hysterical hemiplegia, and the incidence of encephalitis in Corsicans.

It was, of course, Dr Fallot’s classical study of the congenital malformations which, recognised as the common cause of maladie bleue (morbus caeruleus), resulted in the eponymous title of the “tetralogy of Fallot.” He described the malformations as consisting of “a true anatomicopathologic type represented by the following tetralogy: (1) stenosis of the pulmonary artery; (2) interventricular communication; (3) deviation of the origin of the aorta to the right; and (4) hypertrophy, almost always concentric, of the right ventricle. Failure of obliteration of the foramen ovale may occasionally be added in a wholly accessory manner.”

As with so many other advances in medical knowledge, there is inevitably the question, is it clearly attributable to a specific individual? In this case, in the preceding 2 centuries other well-known medical personalities had apparently described the same congenital cardiac malformation. One of the first to describe the abnormality was Niels Stensen, MD (1638–1686), a Danish anatomist and theologian famous for his discovery of the parotid duct. Dr Stensen found the abnormality in a fetus and used his excellent anatomical skills to describe in detail the cardiac defects that he encountered at autopsy.

Just over a century later, in 1777, the Dutch physician Eduard Sandifort, MD, (1742–1814) who held the chair of anatomy and surgery at Leiden University, The Netherlands, wrote Observationes Anatomico-Pathologicae, which contained a description of what he considered to be a rare and unusual cardiac pathology. His young patient suffered cyanosis in infancy and later complained of headaches, severe fatigue, palpitations, fainting fits, and pedal oedema. He died at the age of 12, and at postmortem Dr Sandifort discovered the same defects as those previously described by Dr Stensen.

Further accounts of the malformation were given by William Hunter, MD, (1718–1783) in Medical Observations and Inquiries, by John Richard Farre, MD, (1775–1862) in On Malformations of the Human Heart, and by Thomas Bevill Peacock, MD, (1812–1882) in Malformations of the Human Heart.

In his paper, Dr Fallot mentioned observations on cyanosis that were written during the preceding century and more contemporaneously as offering “the interesting peculiarity that the existence of the various cardiac lesions previously mentioned is met with and fully described.” He concluded by suggesting that it was logical “and more in conformity with the laws of physiology to regard the whole series of cardiac changes enumerated as wholly the result of pulmonary stenosis.” He wrongly believed the cause of the pulmonary stenosis to be attributable to a pathological process developing during the intrauterine period at the level of the pulmonary valves and the contiguous infundibulum region.

Some variants of Dr Fallot’s tetralogy included a “balanced shunt syndrome” characterised by spells of intermittent cyanosis, hyperpnoea, and syncope; Fallot’s trilogy (a triad of pulmonary stenosis, intraatrial septal defect, and a closed interventricular septum); and Fallot’s pentalogy, where in addition to the four characteristics of the original tetralogy, there was also a patent foramen ovale or atrial septal defect.

Dr. Fallot’s work and accomplishments do not appear to have been greatly appreciated during his lifetime, and he suffered from illness relatively early in his life. He died at age 61 in May 1911, after what has been described as “a period of purifying loneliness.” He would no doubt be amazed and perhaps a touch dismayed to discover the immortality he has achieved through the eponym which bears testimony to his medical achievements.

Diana Berry is a medical historian and freelance journalist.

References
