Impact Objectives

- Study the pathophysiological condition of pulmonary arterial hypertension (PAH)
- Develop therapeutic methods for the prevention of progressive pulmonary arterial remodelling and treatment of right ventricular heart failure

The secrets of pulmonary arterial hypertension

__Professor Yasunobu Hayabuchi__ from the Department of Paediatrics, __Tokushima University__ in Japan uncovers the role of potassium channels and vasa vasorum in pulmonary hypertension, and discusses innovative therapeutic applications to prevent progressive pulmonary arterial remodelling

Firstly, can you talk a little about pulmonary arterial hypertension (PAH)?

PAH is a chronic and progressive disease that is characterised by the development of increased blood pressure (hypertension) in the arteries of the lungs. Owing to the fact that pulmonary arteries are responsible for carrying blood from the right side of the heart to the lungs, right heart failure is the most common and prominent complication of this disease. Eventually, and because of its progressive nature, PAH will undermine the efficiency of the heart muscle if left untreated and ultimately lead to death.

Despite the fact that PAH was first reported in the end of the 19th century, its respective diagnosis can be very difficult, even in cases where PAH has significantly progressed. This is because the respective symptoms can be easily mistaken for other diseases that propel hypertension. The most commonly described symptoms reported by patients diagnosed with PAH are shortness of breath and fatigue. The time between patient recognition of symptoms and a definitive diagnosis of PAH is consistently delayed. Therefore, what is important right now is to investigate the pathophysiology of this disease and focus on preventing progressive pulmonary arterial remodelling and on treating right ventricular heart failure.

Why are potassium channels important for the development of new therapeutic strategies?

First of all, potassium channels are ion channels present in cell membranes that are selectively permeable to potassium ions. There are many different types of potassium channels that exist in pulmonary artery smooth muscle, each one with different and distinct functions that contribute to the manifestation of various physiological actions and pathological conditions.

Recently, it was found that the KCNK3 (TASK1) gene, which encodes a type of two-pore domain potassium channel, is a predisposing gene for PAH by genetic mutation. In addition, we have identified that calcium-activated potassium channels seen in smooth muscle cells have the capacity to change from BKca ($Kca1.1$) to IKca ($Kca3.1$) predominance in PAH, and hence facilitate smooth muscle cell migration, enhance proliferation and inhibit apoptosis.

Therefore, our research focuses on the regulation of potassium channels in the pulmonary smooth muscle cells and on the effects of this regulation on the remodelling, proliferation and migration of pulmonary artery smooth muscle cells. We need to keep in mind that some agents or medications can control potassium channel regulation. Hence, we are currently investigating the effect of several agents on pulmonary arterial tone and remodelling. Elucidation of the effect of potassium channels on pulmonary vasoconstriction and remodelling is bound to bring new therapeutic strategies into the forefront of our minds.

What are the most important findings of your research so far?

One of the primary targets of our research is to use Optical Coherence Tomography (OCT) in order to investigate and depict pulmonary vascular pathologies, and hence evaluate pulmonary arterial compliance in PAH patients. Our OCT studies have already demonstrated that vascular diseases are frequently accompanied by prominent development of the vasa vasorum - a network of small blood vessels that supply the walls of large blood vessels. This development contributes to vascular remodelling because it acts as a mediator, a conduit if you will, that allows the delivery of both leukocytes and progenitor cells. Moreover, the development of vasa vasorum can also have a profound effect on the development of systemic-to-pulmonary arterial blood flow. Furthermore, our investigation demonstrated the significant correlations between pulmonary arterial intima-media layer thickness and pulmonary hemodynamics, including pulmonary arterial pressure and resistance.

Hence, our OCT findings can be very useful when it comes to observing the change of pulmonary arterial pathological condition along with the treatment. We have also implemented an innovative echocardiographic technique that when used in combination with cardiac catheterisation assessment can allow the efficient and accelerated early detection and evaluation of right heart failure induced by PAH.

Novel therapeutic approaches in pulmonary vascular pathologies

*Researchers at the **Tokushima University**, Japan, are creating a step change in the development of innovative techniques that depict pulmonary vascular pathological findings and provide an effective tool for improving diagnosis and treatment in patients suffering from pulmonary arterial hypertension (PAH)*

A significant proportion of patients with congenital heart disease, in particular those with increased pulmonary blood flow, will develop pulmonary arterial hypertension (PAH). Research underway by a team at the Tokushima University's Department of Paediatrics aims to investigate and eventually implement innovative methods to diagnose and treat patient suffering from this condition. The team is led by Professor Yasunobu Hayabuchi, a paediatric cardiologist who has published more than 100 articles in cardiology and cardiovascular pathophysiology and is primarily involved in treating infants and children suffering from congenital heart diseases, who is working closely with his colleague Dr Yukako Homma.

PREVENTION IS KEY

'PAH is a chronic refractory disease with the clinical conditions of persistently elevated pulmonary arterial pressure and pulmonary vascular resistance from various causes, and a poor prognosis with progressive exacerbation of right heart failure and respiratory failure,' explains Hayabuchi. What makes this disease very difficult to diagnose in the first place, but even in cases where the disease has significantly progressed, is that hypertension in the pulmonary artery manifests with no apparent reason. Despite the fact that the respective symptoms of this disease are evident, such as shortness of breath, especially during walking or exercise, chest pain and fainting episodes, it is often hard to identify PAH because these symptoms may be confused with other diseases that cause hypoxia in blood and promote hypertension.

Nevertheless, say Hayabuchi, the major pathological finding that characterises PAH is the narrowing of the pulmonary arterial lumen that can come as a result of three distinct factors. 'These include abnormal constriction of peripheral small pulmonary arteries to less than 500μm in diameter, vascular remodelling from the over-proliferation of vascular endothelial, smooth muscle, and other cells and resistance to apoptosis, and the formation of thrombus in the respective affected sites.'

However, and owing to the fact that pulmonary arteries carry blood from the right side of the heart to the lungs, PAH leads to right heart failure and ultimately death if left untreated. This is exactly why Hayabuchi and his team have dedicated their research on investigating the pathophysiology of this disease in order to implement innovative approaches that can improve the diagnosis and the treatment of this disease. 'We study the pathophysiological condition of pulmonary arterial hypertension and therapeutic methods from the viewpoint of the prevention of progressive pulmonary arterial remodelling and treatment of right ventricular heart failure,' outlines Hayabuchi.

ROLE OF POTASSIUM CHANNELS

First of all, there are many different types of potassium channels with various functions that exist in pulmonary artery smooth muscle cells, contributing to many physiological actions and pathological conditions. 'The potassium channels that exist in vascular smooth muscle cells are broadly divided into four classes: voltage-gated K+ channels (Kv), Ca2+ -activated K+ channels (Kca), two-pore domain K+ channels (K2P), and inwardly rectifying K+ channels (KIR),' highlights Hayabuchi. The connection between these channels and the manifestation of PAH in patients is a prominent field of study that has propelled various innovative findings. 'For instance, we identified that KCNK3 (TASK1), which encodes a type of two-pore domain potassium channel, is a predisposing gene for PAH by genetic mutation,' he says. 'Furthermore, PAH is also characterised by a distinctly decreased expression of voltage-gated potassium channels, particularly KCNA5 (Kv1.5).'

Therefore, researchers have shifted their focus on investigating and evaluating the level of involvement of these channels in the onset and exacerbation of PAH with the goal of regulating and controlling these channels. In fact, the latter can be succeeded by means of agents or medication that can improve the underlying pulmonary arterial tone and remodelling. 'The calcium-activated potassium channels seen in smooth muscle cells also change from BKca (Kca1.1) to IKca (Kca3.1) predominance in PAH due to transformation and have effects including the facilitation of smooth muscle cell migration, enhancement of proliferation, and inhibition of apoptosis,' outlines Hayabuchi. Hence, the elucidation of the roles of potassium channels in pulmonary vasoconstriction and remodelling is promising for the establishment of new therapeutic strategies for PAH.

OPTICAL COHERENCE TOMOGRAPHY STUDIES

Optical coherence tomography (OCT) is ▶

Our OCT studies elucidate that pulmonary arterial vaso vasorum increased under the condition with hypoxia in complex congenital heart disease

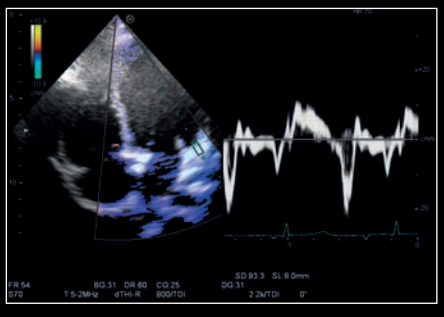
a non-invasive intravascular imaging modality that uses light waves to take cross-section pictures with high resolution of up to 10–20μm. In fact, this imaging modality has proven to be a very efficient method in terms of identifying and underlying the pathophysiology of coronary arteriosclerosis in adults, and hence providing an effective tool for improving diagnosis and treatment.

Recently, Hayabuchi and his team have published an innovative research study in which OCT was also found to be a promising tool for the evaluation of the pulmonary artery (PA) wall in children suffering from congenital heart disease. Furthermore, it was also identified that vascular diseases are frequently accompanied by prominent development of the vasa vasorum - a network of small blood vessels that supply the walls of large blood vessels - which contributes to vascular remodelling. 'Our OCT studies elucidate that pulmonary arterial vaso vasorum increased under the condition with hypoxia in complex congenital heart disease,' he explains. 'Development of vaso vasorum contributes to vascular remodelling by acting as a conduit for the delivery of leukocytes and progenitor cells.' Therefore, OCT is an ideal way to observe the change of pulmonary arterial pathological condition along with the treatment but also to foresee the prognosis of the disease.

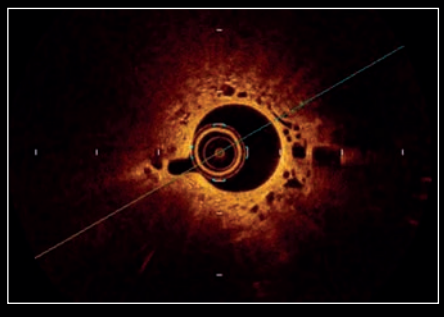
FUTURE PLANS

The most critical challenge in the quest of unlocking the secrets of this disease, and hence introducing novel diagnostic and therapeutic approaches is that PAH is classified into several groups where each one may require a unique approach and strategy. For instance, idiopathic PAH is caused by a specific gene mutation that can cause pulmonary hypertension to develop in families, also called heritable PAH, whereas congenital heart disease patients have progressive PAH. 'PAH and low pulmonary arterial compliance induce right heart failure,' observes Hayabuchi. 'On the other hand, in complex congenital heart disease, vasa vasorum of pulmonary artery develops and results in the pulmonary arterial remodelling.'

This underlines that future research needs to consider the treatment and prevention of these diseases on an individual level. Hayabuchi and his team are progressing well towards identifying definitive novel methods to treat and prevent these conditions, and the extensive research already completed by this team provides the scaffold upon which future studies can be built upon.



Tissue Doppler Imaging for the evaluation of cardiac function in a PAH patient



OCT imaging showing pulmonary artery morphology and pathological findings. Development of vasa vasorum is shown

Project Insights

FUNDING

This study was supported by funding from the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research grant numbers 22591180, 25461621 and 16K10068.

TEAM MEMBERS

Dr Yukako Homma

CONTACT

Professor Yasunobu Hayabuchi

T: +81 88 633 7135
E: hayabuchi@tokushima-u.ac.jp
W: http://pub2.db.tokushima-u.ac.jp/ERD/person/122001/profile-ja.html

BIO

Professor Yasunobu Hayabuchi's major area of clinical and research interest lies in paediatric cardiology and pulmonary arterial hypertension. He graduated from School of Medicine, Tokushima University in 1989. Hayabuchi received his PhD degree in 1997 and became a clinical and research fellow at Tokushima University from 1989. In 1999, he became a research fellow in Department of Cell Physiology and Pharmacology, University of Leicester, UK. He started at the Department of Pediatrics, Tokushima University as a senior lecturer where he was promoted to professor in 2018. As the activity of academic society, He is a councillor of the Japanese Society of Paediatric Cardiology and Cardiac Surgery and delegate of the Japan Paediatric Society.