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Pioneer in cardiology

Hiroaki Shimokawa MD PhD

In the latest of our series featuring pioneers in cardiology, Mark Nicholls speaks to Hiroaki Shimokawa, Professor and Chairman, Department of Cardiovascular Medicine at Tohoku University, Japan, about his career, research and innovative work



A substantial portion of patients with coronary artery disease still complain of angina even after coronary intervention, suggesting involvement of coronary vasomotion abnormalities. Prof. Shimokawa at Tohoku University, Japan, has made a significant contribution to the understanding of the pathogenesis of coronary vasomotion abnormalities and endothelial dysfunctions over the last 35 years as a pioneer in this research field.

He has also led advances in the development of advanced non-invasive therapies with sound waves and epidemiological studies on heart failure, coronary vasospastic disorders, and acute myocardial infarction. That has included identifying that Rho-kinase, a molecular switch for vascular smooth muscle cell (VSMC) contraction, plays a key role in the molecular mechanisms of the spasm and also demonstrating for the first time that physiological concentration of endothelium-derived hydrogen peroxide (H₂O₂) is an endothelium-derived hyperpolarizing factor (EDHF).

Born in 1954, he grew up in the Fukuoka prefecture of Kyushu Island in Japan where his father Keiichiro was an engineer and his mother Shizuko a junior high school teacher. The first person in his family to become a medical doctor, he was followed by his younger brother Toshihiro, who became a surgeon. Hiroaki Shimokawa, who is Professor and Chairman, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, recalled how his interest in a career in cardiology and science was stimulated through two quite different life experiences.

'First, when I was an elementary school student, my grandfather was recuperating at home from a stroke', he said. 'My parents explained to

me about stroke, and I was shocked to learn that blood vessels can be plugged and/or ruptured. After that, I gradually became interested in cerebral and cardiovascular diseases. Secondly, in 1978, when I was in the last grade of medical school, I experienced the Fukuoka Drought, in which water was supplied only for 1–2 h a day. At that time, I was wondering which way I should go, stroke specialist or cardiologist. This unexpected experience convinced me about the importance of the cardiovascular system, the heart and blood vessels (water supply), to maintain homeostasis (civil life), and I decided to become a cardiologist'.

He graduated from Kyushu University in 1979 and obtained his MD degree, before undergoing his medical training at Kyushu University Hospital and Kyushu Welfare and Pension Hospital. Later, in 1985, he went to study endothelial functions at Mayo Clinic under the guidance of Professor Paul M. Vanhoutte. The two main mentors in his scientific and professional life were Professor Akira Takeshita (Kyushu University) and Paul Vanhoutte (Mayo Clinic). 'From Takeshita, I learned the importance to continue research based on my belief even under any difficult situations, and from Vanhoutte, I learned the pleasure of research where we can discover unknown facts and contribute to society', he said.

Over the past four decades, Hiroaki Shimokawa's research interests have covered four main areas: coronary artery spasm and coronary microvascular dysfunction; endothelial functions; development of non-invasive advanced therapies using ultrasound; and epidemiological studies on heart failure, vasospastic coronary disorders, and acute myocardial infarction.



Medical campus Tohoku University



Dept of Cardiovascular Medicine, Tohoku University

That research has 'evolved step by step' since 1981 when he finished internship and started research on coronary artery spasm, as the prevalence of spasm is high in the Japanese population. 'After many failures, I finally succeeded in developing an animal model of the spasm in pigs, in 1983', he said. 'For 37 years since then, as the first research theme, I have been studying coronary spasm and coronary microvascular dysfunction in animals and humans'.

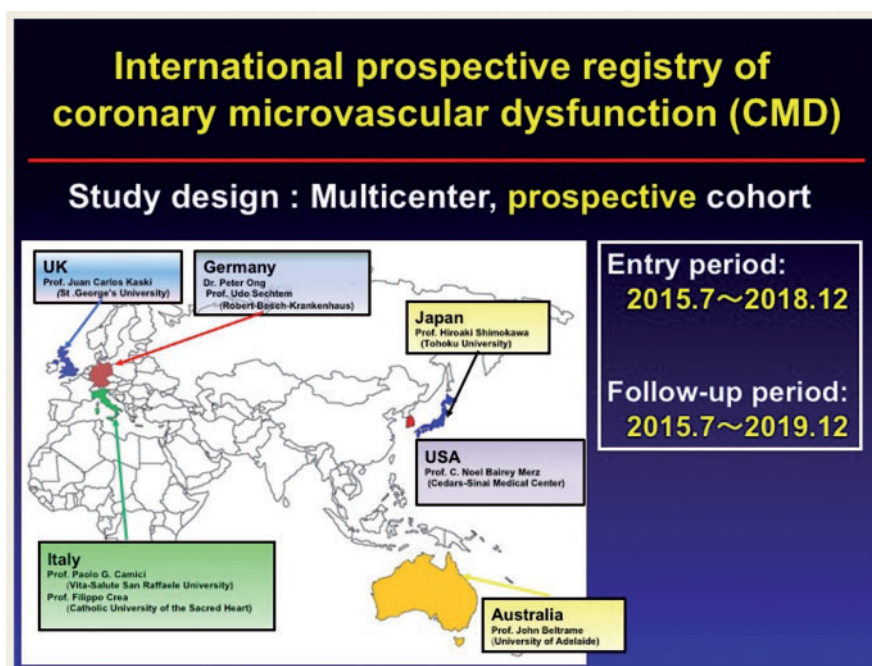
Since his time at Mayo Clinic studying endothelial function, especially endothelium-derived relaxing factors, he has been studying endothelial functions/dysfunctions as the second theme of his research. On returning to Japan from America, he also became interested in developing non-invasive therapies using sound waves after seeing a rapid increase in the number of elderly patients with severe angina without indication for PCI or CABG, and since 2001, this has been a third theme of his research.

And following his appointment as Professor and Chairman of Tohoku University in 2005, he began several epidemiological studies on heart failure, coronary vasospastic disorders, and acute myocardial infarction as the fourth theme of research.

He succeeded in developing two animal models of coronary spasm in pigs; experimental atherosclerosis with balloon endothelial injury and high-cholesterol feeding¹ and experimental coronary inflammation with long-term adventitial treatment with an inflammatory cytokine.²

'In those models, I identified that Rho-kinase, a molecular switch for VSMC contraction, plays a key role in the molecular mechanisms of the spasm.³ I subsequently performed a series of experimental and clinical studies, demonstrating that Rho-kinase also plays a key role in the pathogenesis of atherosclerosis in addition to vasospasm.^{4,5} I also demonstrated that activated Rho-kinase plays an important role in the pathogenesis of microvascular angina (MVA), which is a third type of angina frequently noted in post-menopausal women, an important topic in gender-specific medicine.^{4,5} Currently, several pharmaceutical companies are developing selective Rho-kinase inhibitors and one of the major indications is MVA'.

Prof. Shimokawa said that although it is widely known that nitric oxide (NO) plays a major role in relatively large arteries and the importance of EDHF increases as the vessel size decreases, the nature



With his work on the mechanisms for coronary atherosclerosis and vasospasm, Hiroaki Shimokawa explains there are three major mechanisms of stable angina pectoris, including (i) atherosclerosis of large epicardial coronary arteries, (ii) vasospasm of epicardial coronary arteries, and (iii) coronary microvascular dysfunction.

'Many people still believe that (i) is the only mechanism because (ii) and (iii) cannot be visualized by simple coronary angiography. However, since the strategy to treat (i) alone (e.g. PCI) failed to fully improve symptoms and long-term prognosis of ischaemic heart disease patients, the importance of (ii) and (iii) has been emerging. Indeed, even after successful intervention with stents, 30–40% patients still experience chest pain, which is the case not only in Japan but also worldwide. For this reason, the prevalence of coronary vasospastic disorders is now considered higher, even in western countries than ever before'.

of EDHF remained to be identified for a long time since the first report of its existence in 1988. He noted some similarities between NO and EDHF in terms of susceptibility to risk factors and improved responses to some drugs and hypothesized that EDHF may be a reactive oxygen species derived from endothelial NO synthase (eNOS). By testing this hypothesis with eNOS-deficient mice, he demonstrated for the first time in 2000 that physiological concentration of hydrogen peroxide (H_2O_2) derived from eNOS is an EDHF.^{4,6,7} His H_2O_2 /EDHF theory was subsequently confirmed in humans by his group and in other animals by other research groups.

He said: 'The important point of this theory is that we definitely need a low and physiological concentration of reactive oxygen species (e.g. H_2O_2) to maintain cardiovascular homeostasis, although they are widely and simply believed to be harmful for oxidative stress'.

Another area of his work is in applying advances in biomedical engineering to cardiovascular medicine. From about 2000, he realized a need to develop non-invasive therapy with sound waves to treat patients with severe angina pectoris who do not have indications for PCI or CABG. He studied how low-energy shock wave (SW) could stimulate endothelial cells to generate NO *in vitro*.

'Since NO is known to exert effective angiogenic effects, I had the idea to use low-energy SW to stimulate the heart to generate NO for the treatment of severe angina'.

Working with a Swiss SW company, he developed a SW machine and confirmed its efficacy and safety in patients with severe angina pectoris through animal models and clinical trials.^{8,9} 'Based on these positive results, our cardiac SW therapy (CSWT) was approved as an advanced therapy by the Japanese government in Japan and also for CE mark in Europe. Since then, CSWT has been used to treat more than 10 000 patients with severe angina in 25 countries with good effectiveness and acceptable safety'.

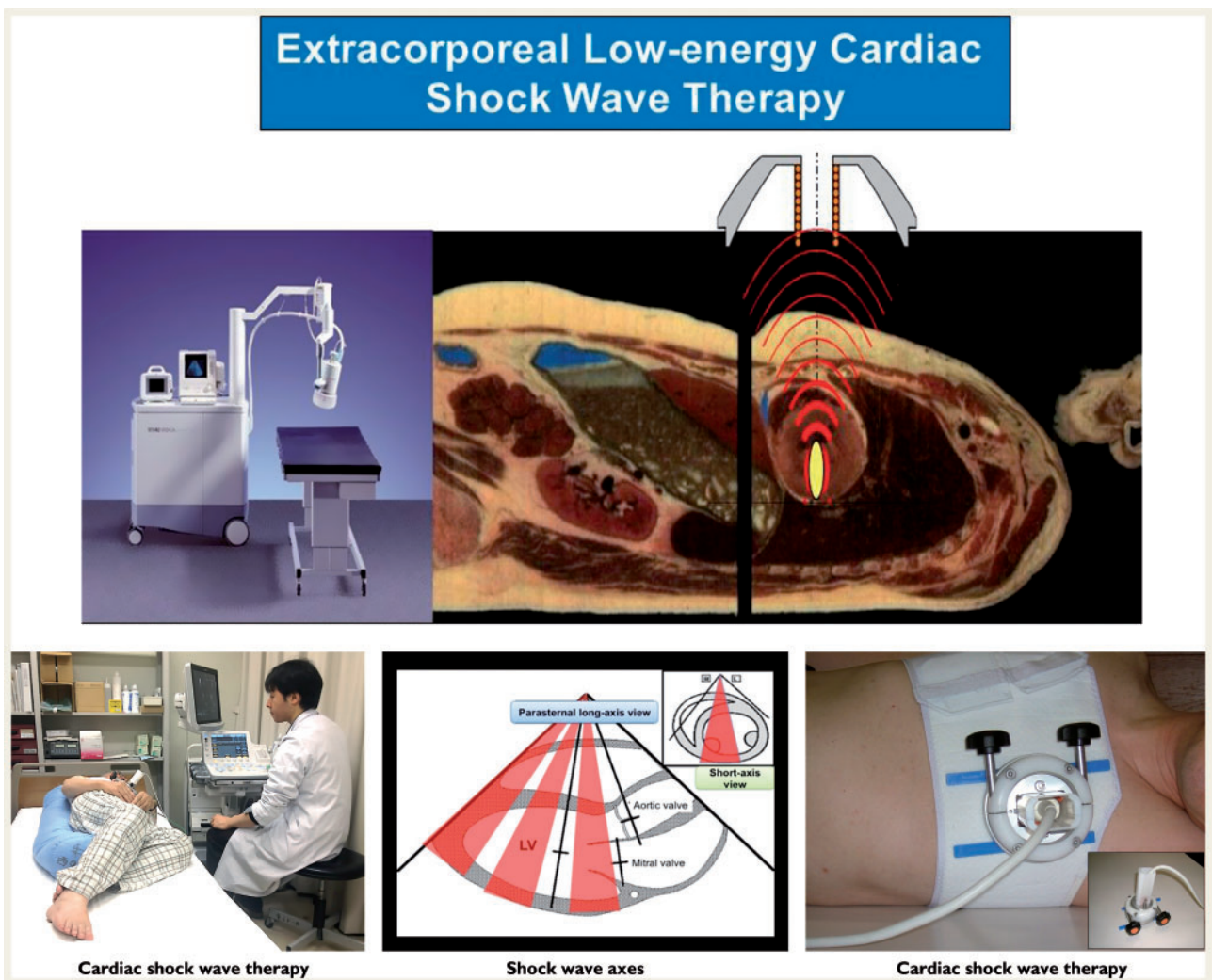
He followed that by examining whether low-intensity pulsed ultrasound (LIPUS) could reproduce the effects of SW because LIPUS

could be safer than SW (although both are safe at lower levels) and requires shorter treatment time than CSWT (point-to-point treatment by SW vs. cross-sectional treatment by LIPUS). After 3 years of preliminary experiments, his team identified the specific condition of LIPUS, with which they could reproduce the effects of SW.¹⁰ He is now conducting an investigator-initiated double-blind, placebo-controlled trial in Japan in collaboration with 10 university hospitals.

Shimokawa said: 'These exciting findings with sound wave therapies (SW and LIPUS) indicate that there are substantial self-repairing capacities left in our body, which could be effectively activated by appropriate physical stimuli. My approach to use self-repairing capacities with sound wave is in huge contrast to cell or gene therapies, in which exogenous materials (even iPS cells) are used for treatment'.

With a translation focus at the forefront of his research, and also homing in on areas the researcher cannot always see.

'What you can see (e.g. coronary angiography, imaging data, laboratory data) is not everything, and rather what you cannot see (e.g. coronary spasm, coronary microcirculation, endothelial functions, sound waves) may be more important than what you can see', he said.



He sees his work on Rho-kinase (coronary spasm and coronary microvascular dysfunction) as the most important, although he expects his work with sound waves will also become more important worldwide over the next decade. In terms of how this has advanced the field within cardiology, Shimokawa suggests that in addition to coronary atherosclerosis (Type 1 angina), more attention should be paid to vasospastic angina (VSA, Type 2 angina) and MVA (Type 3 angina).

'Rho-kinase plays an important role in the pathogenesis of both VSA and MVA', he continued. 'Thus, Rho-kinase should be an important therapeutic target in cardiovascular medicine and of drug development as well. Non-invasive therapies with sound waves (CSWT and LIPUS therapy) are also important. We have self-repairing capacities unused in our body and appropriate physical stimuli can activate these capacities. It seems that these non-invasive therapies with sound waves are effective not only for the heart but also for other organs. I believe that these therapies should be developed in the global super-aging society as they are non-invasive in nature and markedly reduce medical costs as well'.

For his long-time basic, clinical, and translational research, Shimokawa received many awards, including Jeffrey M. Hoeg Award of the American Heart Association in 2006, Japan Medical Association Award in 2012, and William Harvey Lecture Award of the European Society of Cardiology in 2014. He is the President of Japanese Association for Gender-specific Medicine; vice president of the Japanese College of Angiology; a board member of the Japanese Circulation Society, Japanese Society of Internal Medicine, and Japanese Heart Failure Society; and an Associate Editor of the *European Heart Journal* representing the Asia region and the Arteriosclerosis, Thrombosis and Vascular Biology; a Senior Consulting Editor of the

Circulation Research; and a Senior Guest Editor of the *International Journal of Cardiology*. He also serves as the director of the Clinical Research, Innovation and Education Centre, Tohoku University Hospital, one of the most active clinical research institutes in Japan.

Away from medicine, his hobbies are reading books (especially historical novels), music, and sport.

While proud of his research, Professor Shimokawa takes great pride in the fact that over the last 25 years, he has supervised ~100 doctoral students for their PhD thesis study, with 82 of them winning more than 200 young investigator awards of major academic societies.

Advice he gives to young researchers is to select an original theme of research, pick good mentors, and continue research despite any difficult situations that arise.

'Future medical research and practice will depend on the achievements of the young generation', he added. 'I am very proud of their achievements and look forward to their progress as a cardiologist and cardiovascular researcher'.



Conflict of interest: none declared.

References

References are available as [supplementary material](#) at *European Heart Journal* online.

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State of the art in TAVI

A revolution in patient care is taking place, but there is much still to learn as discussed by Dr Miles Dalby

Together with Professor Magdi Yacoub, Dr Miles Dalby reflected on the revolution in intervention for aortic stenosis, as well as the challenges of trying to recreate the incredible biological function of the native aortic valve and root complex, at the Royal Society of Medicine Cardiology Update Meeting in London.

The aortic valve and root are a dynamic part of the central arterial vasculature with exceptional haemodynamic properties.^{1,2} Aortic stenosis however is the commonest single valve disorder in the developed world and is increasing in frequency in an aging population.³

Mechanical aortic valve replacements (AVR) have been developed from the 'ball in cage' design (Figure 1). Albert Starr implanted in 1960 through to tilting disc and bi-leaflet designs optimized with haemodynamic optimization and thrombo-resistant coatings.⁴ Although mechanical valves are very durable and can last for decades, biological valves were developed to avoid anticoagulation and to be more physiological. Elegant solutions have been developed to preserve

the natural function of the aortic valve and root, including a large orifice area and low trans-valvar gradient with stentless xenograft, homograft, and autograft techniques. These procedures however are complex, technically demanding and supply can be an issue. Alternative surgical solutions include 'sutureless' surgical valves⁵ and the exciting innovative



**Sir Magdi Yacoub (L) and Miles Dalby (R)
at Royal Society of Medicine**