

## Hiroaki Shimokawa

### “Research Is a Hobby That Enhances My Life”

Susan Ince

**H**ow does a cardiologist end up conducting a randomized controlled trial on a possible dementia treatment, particularly one that uses an ultrasound device he developed?

For Hiroaki Shimokawa, MD, PhD, that surprising development is just one natural and exciting step in a career that began in basic research on coronary spasm and endothelial functions and gradually incorporated clinical research, applied engineering, and epidemiology as new questions emerged and opportunities presented themselves.

Shimokawa received his MD from Kyushu University Medical School in 1979, returning there for PhD studies after his internship. After several attempts, he developed the first animal (pig) model of coronary artery spasm.<sup>1</sup> At the time, there were conflicting theories about the pathogenesis of coronary spasm, and Shimokawa spent 1985 to 1988 with vascular biologist Paul Vanhoutte, MD, PhD, at the Mayo Clinic, investigating the role of endothelial dysfunction in animal models. During that time, they demonstrated the influence of diet,<sup>2</sup> endothelial regeneration,<sup>3</sup> hypercholesterolemia, and atherosclerosis<sup>4</sup> on endothelium-dependent relaxations in response to aggregating platelets and related vasoactive substances.

Since returning to Japan in 1989 and establishing an independent laboratory at Kyushu University and then Tohoku University, Shimokawa has been in the forefront of demonstrating the involvement of Rho-kinase in the pathogenesis of coronary artery spasm, atherosclerosis, reperfusion injury, hypertension, pulmonary hypertension, stroke, and heart failure.<sup>5-7</sup> Rho-kinase has become an important therapeutic target in cardiovascular medicine, and Shimokawa is currently conducting a randomized controlled trial of the Rho-kinase inhibitor fasudil in the treatment of intractable coronary spasm.

Shimokawa also continued basic research on endothelium-derived relaxing factors. In 2000, he found that a physiological concentration of hydrogen peroxide derived from the endothelium is an endothelium-derived hyperpolarizing factor (EDHF),<sup>8</sup> relaxing underlying vascular smooth muscle by opening potassium channels, with its importance increasing as vessel size decreases.<sup>9</sup>

The identification of hydrogen peroxide as an EDHF was subsequently confirmed in animals and humans by many other groups, although the nature of EDHF appears to be heterogeneous. Shimokawa's work on EDHF is considered some of his most

important basic research to date: researchers who identified the first 2 major endothelium-derived relaxing factors—prostacyclin and nitric oxide (NO)—were awarded the Nobel Prize in Physiology or Medicine.

While treating patients with end-stage coronary artery disease and multiple comorbidities, Shimokawa became intrigued by the idea that noninvasive therapies could reach the heart and stimulate the body's capacity for self-repair. After hearing a report in 2001 that low-energy shock waves (SW) could stimulate endothelial cells to generate NO in vitro, he embarked on a decade-long effort to translate that basic research insight into a viable treatment. After further in vitro work, his team demonstrated that low-energy SW ( $\approx 10\%$  of the energy density used for lithotripsy therapy) upregulate the expression of vascular endothelial growth factor, induce neovascularization, and

improve myocardial ischemia in a pig model.<sup>10</sup> The team then conducted an open trial followed by a placebo-controlled crossover study of the therapy in patients with severe coronary artery disease without indication for percutaneous coronary intervention or coronary artery bypass grafting. In both studies, the therapy improved symptoms, exercise capacity, and myocardial perfusion without complications.<sup>11</sup>

More recently, Shimokawa has found that therapy with low-intensity pulsed ultrasound (LIPUS) may provide an easier alternative to SW therapy for angina, potentially with far broader applications that include myocardial infarction, heart failure, and even dementia.

Shimokawa is currently professor and chair of the department of cardiovascular medicine at the Tohoku University Graduate School of Medicine in Sendai, Japan. He also directs Tohoku University Hospital's Clinical Research, Innovation, and Education Center, a highly active institute where professional staff support medical researchers at all stages of development,



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from seed research to large clinical trials. In 2017, the university founded the Big Data Medicine Center. Shimokawa also directs the center as it uses modern technologies to develop new basic, information, and clinical research.

“Unfortunately, basic research in Japan has been rapidly shrinking, and I hope that this unique approach will help activate basic cardiovascular research in the country,” said Shimokawa, who described the current situation as devastating in a 2017 review in *Circulation Research*.<sup>12</sup>

Among many awards, Shimokawa has received: the Jeffrey M. Hoeg Arteriosclerosis, Thrombosis and Vascular Award of the American Heart Association in 2006; the Japan Medical Association Award in 2012; and the William Harvey Lecture Award of the European Society of Cardiology in 2014. Shimokawa has published in *Circulation Research* since 1984 and has been a senior consulting editor for the Journal since 2009.

### **Where Did You Spend Your Childhood? What Kind of Area Was It?**

I was born and spent my childhood in Chikugo City, Fukuoka Prefecture (Kyushu Island), Japan, which was (is) a typical rural area with rice paddies. Before I entered primary school at the age of 7, I spent all day outdoors—catching insects, fishing, and playing baseball. My mother was from a family of farmers and I enjoyed planting rice in the spring and reaping rice in the autumn at their home.

### **If I Had Met You Then, Would I Have Pegged You as a Budding Scientist or Doctor?**

No. I played all kinds of sports, including running track in junior high school for 3 years and playing football for 9 years during high school and medical college. I did well in school, but perhaps you would not have guessed I would become a researcher.

### **How Did You Get Interested in Cardiovascular Disease?**

When I was an elementary school student, my grandfather had a stroke. When my parents explained it to me, I was shocked to learn that blood vessels can be plugged or ruptured and thereafter I gradually became interested in cardiovascular diseases and stroke.

Later, during the Fukuoka Drought in 1978 to 1979 (for 287 days!) when I was in the last 2 years of medical school, I realized the importance of lifelines, including water, electricity, and gas. This experience convinced me just how important the cardiovascular system is in maintaining our body homeostasis. Indeed, we cannot live without the heart (or cardiovascular system) even if we have very sophisticated brain or immune system. At that point, I decided to become a cardiologist.

### **Did You Go Directly to Medical School From High School?**

Yes, I went directly to Kyushu University Medical School from high school, a typical course in Japan.

### **Tell Me About Your Mentor Akira Takeshita. What Did You Learn From Him?**

A year after I returned to Kyushu University from the Mayo Clinic in 1989, Dr Takeshita was appointed as professor and chairman of the Department of Cardiovascular Medicine, Kyushu University. He kindly and continuously supported me, giving me a chance to become a lecturer in 1992 and associate professor in 1995.

From him, I learned the importance of continuing my research even under difficult circumstances. Almost all young researchers face tough situations in their research life in terms of human relationships, academic conflict, and financial problem, etc. I am convinced how important it is to have a reliable and respectable mentor like Dr Takeshita to overcome such situations, and I always try to be a good mentor for young researchers in my laboratory and throughout Japan.

Both Drs Vanhoutte and Takeshita were honest, prudent, and faithful mentors. Unfortunately, Dr Takeshita died of cancer in 2009 at the age of 69. However, he lives in my heart, and I talk to him almost every day.

### **Did You Ever Have an Experiment or Theory That Completely Failed? What Happened? What Did You Learn From It?**

Like other researchers, a number of my experiments or theories have failed. I learned from them that it is important to discuss your findings with other researchers and colleagues in detail so you can make an early decision to stop or change your protocol. But one must never give up on research.

### **What Was the Biggest Sacrifice You Had to Make to Pursue Your Scientific Career?**

I do not think that I have sacrificed anything to pursue my scientific career because research is just my hobby that enhances my life. Research opens the way to unexplored territory, and I don't know of anything more exciting.

### **In Looking Back at American Heart Association Press Releases for Many Years, I Can't Find a Single Time When Research on Coronary Spasm Was Featured. Do You Think It Has Been an Underappreciated or Understudied Aspect of Heart Disease?**

Yes. There are 3 mechanisms involved in the pathogenesis of stable angina pectoris, including (1) atherosclerotic stenosis of epicardial coronary arteries, (2) epicardial coronary artery spasm, and (3) coronary microvascular dysfunction. Although the first mechanism is easily visualized by coronary angiography, the functional abnormalities of the second and third cannot be seen by routine coronary angiography alone. Because cardiologists and cardiac surgeons can only treat the first mechanism with stent and bypass surgery, most of them are not interested in the second and third mechanisms that I study. Thus, my research has not attracted much attention of western researchers/doctors until recently. However, many researchers in the United States and especially in Europe are now getting interested in the second and third mechanisms (functional coronary abnormalities) because 40% to 50% of patients still complain of chest pain after coronary stenting or bypass surgery.

### **How Did You Get Interested in Investigating the Possibility That SW Could Treat Angina? Clinically, Where Do Things Stand Now in Japan and Elsewhere As Far As Using This Approach?**

In 2001, when we organized the first annual scientific meeting of NO in Japan, an Italian group reported that low-energy SW could stimulate NO release from human endothelial cells in vitro. Because NO is known to promote angiogenesis, I got the idea to use low-energy SW to treat patients with severe angina. Since there was no SW company in Japan, I finally started to develop

extracorporeal cardiac SW therapy in collaboration with Storz Medical, a Swiss SW company that obtained CE mark approval to sell the product in the European Union in 2003. After confirming its efficacy and safety in a pig model, I conducted 2 clinical trials (open trial and then double-blind trial<sup>13</sup>) and finally obtained an official approval in Japan in 2010. To date, >10000 patients have undergone cardiac SW therapy in >25 countries with good results.

### **Why Did You Switch Your Focus From SW to Ultrasound for Angiogenic Therapy?**

Partly because ultrasound is safer and easier to handle than SW and partly because Japan is good at ultrasound (compared with SW) and there are several major Japanese ultrasound companies. After 2 years of preliminary experiments, in collaboration with the Department of Technology at Tohoku University, I was able to identify the specific conditions of ultrasound (LIPUS) that stimulate NO release from endothelial cells in vitro and promote angiogenesis in pigs in vivo, levels which are different from those used in routine diagnosis but still within the safety level of ultrasound. Of course, I am not a physicist, but I was able to develop such a LIPUS machine in collaboration with a Japanese US company. Now, as a principal investigator, I am conducting a randomized controlled trial using LIPUS therapy in angina pectoris, which will be completed within the next year. Experimentally, we also demonstrated that the LIPUS therapy is effective and safe for the treatment of myocardial infarction<sup>14</sup> and heart failure.<sup>15</sup>

Even more interesting, I have recently confirmed that whole-brain LIPUS therapy is also effective and safe in mouse models of dementia (vascular dementia and Alzheimer disease).<sup>16</sup> Indeed, a circulatory disorder is the common underlying mechanism for both cardiovascular disease and dementia, which could be ameliorated by the LIPUS therapy. Supported by the Japanese government, I have just started a randomized controlled trial of the LIPUS therapy for the treatment of Alzheimer disease in Japan. The additional advantage of LIPUS therapy is that we do not need to worry about the blood-brain barrier, which seriously matters when we plan to use drugs or gene/cell therapies for patients with dementia. If the efficacy and safety of LIPUS therapy for dementia is confirmed, this should be great news for many patients with dementia and their families in the world.

### **You've Done Many Types of Research—Animal Models, Clinical Trials, Applied Engineering, Epidemiology, etc. How Important Is It for a Researcher to Have the Flexibility to Pursue Many Different Approaches to Important Questions?**

I started my research life with basic research on coronary spasm and endothelial functions, then added clinical research because I was (am) a cardiologist. I got involved in applied engineering because I felt a need to develop non- or less-invasive therapies to treat patients with coronary artery disease, and hopefully those with dementia. Once I became the chairman of the Department of Cardiovascular Medicine at Tohoku University, that position allowed me to start several epidemiological studies in collaboration with affiliated hospitals and many other universities in Japan and abroad. So, it was quite natural for me to add new types of research step-by-step in my career.

These multidisciplinary approaches have deepened my knowledge and allowed me to better understand the pathophysiology of cardiovascular disease. Importantly, the addition of new

types and methods of research has substantially promoted my research in a synergistic manner. For example, thanks to my basic research experience, I can see many invisible things from a single coronary angiogram, such as endothelial function, vascular smooth muscle function, and coronary microcirculation. I always try to be flexible to pursue many different approaches to research questions, and I advise young researchers to do the same.

### **How Did You Meet Your Wife? Have You Ever Collaborated?**

We met when we were both residents at Kyushu University Hospital, me in cardiology and my wife Hiroko in pediatric neurology. My wife went to the United States with me in 1985 and when we returned to Japan in 1989, she switched her focus to public health and got a job at the Fukuoka City Office. Almost 30 years have passed since then, and she is now the director of the Public Health Department of Sendai City. Theoretically, she could investigate the Tohoku University Hospital at any time if needed! We haven't collaborated on any research.

### **Do You Think Your Children Grew Up Thinking That Medical Research Was an Enjoyable Career?**

My son Tomonori is a hematologist and my daughter Eriko is training to be a pharmacist. My wife and I did not ask them to go into medicine, but they may have been influenced by us.

### **You Have Mentored Many Doctoral Students Who Have Gone on to Successful Careers. Why Is This Important to You?**

I believe that it is very, very important to raise young doctors/researchers for future medicine/medical research. Current medical diagnoses/treatments are all based on previous collaborative work by researchers and patients. I always tell doctoral students that 100 years ago, during World War I, pulmonary tuberculosis was a fatal disease, but now it is a completely curable disease thanks to chemotherapy. Many currently incurable diseases could be curable 100 years from now, but we are responsible for training the doctors and researchers to make that possible.

I am very pleased to see that young fellows are growing into established researchers, step-by-step, in my laboratory. Perhaps this feeling is similar to that of parents as our DNA is passed on to the next generation. In this sense, Dr Takeshita's DNA is definitely present in me, and both my DNA and Dr Takeshita's DNA will be inherited by the next generation.

### **What Do You Tell Young Researchers About How Hard They Must Work to Be Successful?**

In my experience, and generally speaking, I believe that researchers work hard to discover the facts, not to succeed. The many positions I hold resulted from my efforts but were never the goals of my efforts. So my advice to young researchers is simple: keep working to discover the facts and never give up. If you never give up, you will never fail.

### **How Hard Do You Work at This Stage of Your Career? What Is the Breakdown of Your Time Commitments?**

I think that I am a typical Japanese hard worker, going to work at 7:00 AM and going back home at around 9:00 PM. In terms of the percentage of my efforts, I would say research (including teaching PhD students) 40%, administration 40%, other teaching 10%, and clinical work 10%.



### What Do You See Ahead for the Next Few Years of Your Career? Anything You're Particularly Excited About?

I am now conducting 3 randomized controlled trials, including the separate LIPUS trials for angina pectoris and dementia, and the trial with a selective Rho-kinase inhibitor for intractable coronary spasm. I am particularly excited about the LIPUS trial for dementia. If LIPUS therapy is confirmed to be effective and safe, this new treatment would be a tremendous good news for patients with dementia and their families in the world.

### What Do You Like to Do Outside of Work?

I like to travel in Japan and abroad with my wife and to read books and listen to music, especially classical music. I watch football and occasionally run (mainly jog) near my home in the dry riverbed of the Hirose River. But I enjoy research and education more than my other hobbies.

### Have You Read Anything Recently That You Would Recommend?

I recently reread *Man's Search for Meaning*, by Viktor Frankl. This unrivaled book teaches us that our life has value in any situation. "It did not really matter what we expected from life, but rather what life expected from us." In the past, this notion from the book has helped me overcome difficult situations.

### What Would Surprise Readers to Learn About You?

Readers may be a little surprised that a cardiologist like me is going to start a clinical trial for dementia in collaboration with geriatricians. However, I am ready to do any research if it is scientifically exciting and meaningful for patients.

### Disclosures

None.

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