

# Stress and natural disasters may pose high risks for coronary artery spasm

## William Harvey lecture today on research in coronary spasm

IN THE WILLIAM HARVEY Lecture this morning Hiroaki Shimokawa will urge cardiologists to pay more attention to coronary artery spasm. The condition, he says, can sometimes be overlooked by cardiologists in the West, who are often cautious about provocation tests.

‘We used to think the incidence of coronary spasm was three times higher among Japanese populations than Caucasians,’ he explains. ‘But now we believe the incidence probably isn’t that different – it’s just that Western cardiologists are less likely to perform the tests.’

Diagnosing coronary spasm, adds Shimokawa, who is director of the Cardiovascular Centre at Tohoku University Hospital, Japan, is of vital importance as a trigger of myocardial ischaemia in patients with and without obstructive CAD and may result in life-threatening ventricular arrhythmias.

In today’s lecture Shimokawa will provide an overview of his translational research suggesting that Rho-kinase has a crucial role to play in the pathogenesis of coronary spasm. Rho-kinase enhances myosin light chain phosphorylation through inhibition of myosin-binding subunits of myosin phosphatase, leading to vascular hyperconstriction or vasospasm.

In his studies, Shimokawa has been greatly helped by the first ever animal model of coronary spasm. The porcine model, which he developed in 1983, used a combination of balloon damage to the endothelial cells followed by high-



Hiroaki Shimokawa: ‘Our research suggests new approaches to the treatment of vasospasm.’

cholesterol feeding. After six months, Shimokawa was able to induce spasm by intracoronary histamine or serotonin, and show that inflammatory changes of the coronary artery play an important role in its pathogenesis in pigs.

Using the porcine model, Shimokawa and his group showed significant correlations between the extent of myosin light chain phosphorylation and vascular smooth muscle contractions. ‘We believe Rho-kinase activation plays a major role as the molecular switch that triggers not only coronary artery spasm but also atherosclerosis in general,’ he explains.

In clinical studies Shimokawa showed that the selective Rho-kinase (ROCK)

inhibitor, fasudil, prevents myocardial ischaemia in patients with coronary spasm. Furthermore, he showed that Rho-kinase activity in circulating neutrophils provided a useful biomarker for diagnosis and disease activity assessments in patients with vasospastic angina. At the molecular level, he has also demonstrated that Rho-kinase downregulates the enzyme endothelial nitric oxide synthase. In a separate series of experiments, he showed that endothelial nitric oxide synthase provides a source of hydrogen peroxide, which in turn he found to be the substance responsible for dilating small resistance vessels as an endothelium-derived hyperpolarising factor.

‘Taken together,’ he says, ‘our research suggests new approaches to the treatment of vasospasm. You can give drugs like fasudil to suppress Rho-kinase activity or promote healthy levels of endothelial nitric oxide synthase through exercise, female hormones and ACE inhibitors.’

Shimokawa believes that psychological stress also plays a major role in coronary artery spasm. In the studies he undertook in patients with coronary artery spasm following the 2011 Great East Japan Earthquake (which he experienced first hand), Shimokawa showed that Rho-kinase activity in the circulating neutrophils of patients with vasospastic angina correlated with post traumatic stress disorder scores six months after the event.

‘In separate research, we showed that cardiovascular events rose after the disaster and, taking these studies together,

it’s conceivable that transient enhanced coronary vasospastic activity increased the number of fatal arrhythmias,’ he says. ‘Clinicians need to be made aware that patients may be at greatest risk of suffering spasm at times of natural disaster or psychological stress.’ The mechanisms for Rho-kinase activation during stress, he adds, remain to be clarified.

For such situations, Shimokawa firmly believes that it is important to identify those patients at greatest risk. Working with the Japanese Coronary Spasm Association, he developed a database of nearly 1500 patients with coronary spasm and from their outcomes used a multivariable model to select seven variables representing predictors of major adverse events. ‘Ultimately this model should help us decide who to focus on,’ he explains. ‘Patients found to be at high risk can now be treated with calcium channel blockers, ACE inhibitors and statins.’

Shimokawa feels especially honoured to be the first Japanese scientist invited to give the William Harvey Lecture. ‘For Japanese cardiologists the ESC Congress has become our overseas meeting of choice,’ he says. ‘We find opportunities to take a generalist approach help our translational science and we feel comfortable that not all European doctors speak English.’

31 August, 08:30-09:10

**Skopje (The Hub) - Central Village**  
ESC William Harvey Lecture on basic Sciences