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EDITORIAL

Foreword

Coronary Artery Spasm: A Special Focus Issue

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This special focus issue on coronary artery spasm is dedicated to the memory of Prof Attilio Maseri, a cardiology giant, who sadly died in 2021 but not without leaving an indelible legacy.

Attilio Maseri (1935–2021): In Memoriam

Born in Udine, Italy, Prof Maseri trained in cardiology and nuclear medicine. He held fellowship positions at Columbia University and Johns Hopkins University in the US. He was head of the Coronary Research Group of the Institute of Clinical Physiology in Pisa and, in 1979, was appointed professor of cardiovascular medicine at the Royal Postgraduate Medical School and director of cardiology at Hammersmith Hospital, London. In 1991, he returned to Italy as professor of cardiology at the Catholic University of the Sacred Heart in Rome and, from 2001 to 2008, was a professor of cardiology at the Vita-salute San Raffaele University in Milan. He died in Udine in 2021.

A philanthropist, a sagacious clinician and a charismatic and innovative scientist, Maseri has left a legacy that will be remembered for many decades. Challenging long-established dogmas through clinical observation and elegant research protocols were Maseri's hallmarks as a clinical academic.

He was fascinated by Prinzmetal's description of a type of angina likely to be caused by an increase of "coronary tonus" rather than by "fixed" coronary artery atherosclerotic stenoses. Research by Maseri and his collaborators proved not only the existence and importance of coronary artery spasm as a valid cause of myocardial ischaemia and infarction but also the role of changes of coronary vasomotor tone – including in the coronary microcirculation – in the genesis of angina pectoris.

His findings were received with scepticism by many leading cardiologists at the time. Indeed, his angiographic demonstration of coronary spasm was immediately dismissed as "catheter-induced spasm" and, in the 1970s, vasospastic angina was mockingly referred to as "the Pisa angina" because some renowned physicians claimed that coronary spasm could only be found in Pisa, where Maseri carried out the initial research work on the condition.

Rather than being discouraged by those negative remarks, he continued to push forward the many hypotheses that emerged from his clinical observations and creative mind. Among these was the role of inflammation in atherogenesis and the concept of dynamic stenoses as a cause of mixed angina.

Maseri was a true giant in the world of cardiology, a living legend who inspired legions of clinicians and researchers worldwide, and also a supportive mentor of hundreds of individuals who joined his quest for patient-centred, personalised medicine and true, meaningful translational research.

In the early 1970s, Maseri, as head of the Coronary Research Group in Pisa, started his fascinating research journey, which continued at the Hammersmith Hospital in London a decade later, to unravel the true role of coronary artery spasm in ischaemic heart disease.

Few mechanisms of myocardial ischaemia have attracted more attention and generated such a degree of controversy as coronary artery spasm. From being a plausible mechanism of angina more than two centuries ago and a credible cause of myocardial ischaemia in the early 20th century, coronary spasm became "the resort of the diagnostically destitute" for decades thereafter, until scientific evidence started to emerge in the late 1970s as to the true nature and importance of increased coronary vasomotion in the genesis of myocardial ischaemia.[1–5]

Despite the growing clinical and experimental evidence in the late 1980s and 1990 supporting the role of coronary vasoconstriction in angina, the concept of this condition has been strongly supported and vilified to similar extents.[1–5] However, coronary artery spasm is now an accepted cause of angina pectoris and, although its molecular mechanisms remain to be fully elucidated, its clinical presentation, diagnosis and treatment are now well established.[6,7]

That such controversial a cause of angina finally became recognised as a true diagnostic entity is due to a great extent to the indefatigable and elegant research work that Maseri and his collaborators carried out over two decades in Pisa and London.

Coronary artery spasm – excessive coronary vasoconstriction caused by vascular smooth muscle hypercontraction – can develop on angiographically normal or atherosclerotic coronary arteries and reduce myocardial blood flow to variable degrees.[7–9] As Beltrame et al. discuss in this issue, coronary artery spasm presents clinically with chest pain

Prof Maseri during the inaugural lecture at the opening of the academic year at the Catholic University of the Sacred Heart. Source: Crea et al. 2021.[1] Reproduced with permission from Oxford University Press.

Personal recollections by the authors

Juan Carlos Kaski For over a decade, I had the privilege to work with Attilio Maseri at the Royal Postgraduate Medical School, Hammersmith Hospital, in London. He was the reason why I decided to make London my and my family's home and pursue my research career in the UK. My wife Marta and I enjoyed Attilio and Francesca's friendship and support, which we will treasure for years to come.

Hiroaki Shimokawa When I started my research career in the early 1980s, my research theme was coronary artery spasm. I clearly remember being so impressed with Prof Attilio Maseri's papers and reading them many times. Japan was one of the countries where much attention was paid to the spasm from the beginning and he visited Japan many times and inspired us, especially those of us in the Japanese coronary spasm association, which I established in 2006. He will be remembered forever as a giant in the cardiology world.

(angina) at rest, typically occurring at night time.[10] Angina symptoms caused by epicardial coronary spasm are often rapidly relieved by the administration of sublingual or IV nitrates.

The most typical form of spasm presentation, with angina at rest and transient ST-segment elevation, is also known as Prinzmetal's variant angina.[11] The terms vasospastic angina and vasospastic myocardial ischaemia were coined by Maseri et al. to describe the wide spectrum of patients whose anginal symptoms are triggered by coronary spasm.[12] Patients with vasospastic angina characteristically have a preserved exercise capacity, despite the occurrence of angina at rest.

However, coronary artery spasm can also be silent (no chest pain) and associated with ischaemic ECG changes other than ST-segment elevation. Severe and prolonged coronary artery spasm can lead to life-threatening arrhythmias, MI and sudden cardiac death.[12] Coronary spasm can affect one or more coronary segments in isolation (focal spasm) or involve several adjacent segments or even the whole length of the vessel (diffuse spasm). Moreover, spasm can sometimes predominantly affect the coronary microcirculation (microvascular spasm), as originally demonstrated by Mohri et al. and discussed by Godo et al. in this issue.[13,14] Coronary microvascular spasm is often underdiagnosed because non-invasive tools to investigate microvascular abnormalities are currently lacking.

Several triggers for coronary spasm have been identified, including mental stress, exposure to cold, hyperventilation, the Valsalva manoeuvre, alcohol consumption, cocaine use, pharmacological agents with sympathomimetic or parasympathomimetic activity, allergies and increased serotonin concentration.

The molecular mechanisms of coronary spasm, however, are still incompletely understood. The rho-kinase pathway may be implicated, as suggested by the Shimokawa group, together with a variety of other mechanisms, such as non-specific smooth muscle hyperreactivity, autonomic nervous system abnormalities, endothelial dysfunction, inflammation and genetic mechanisms.[8,15] Rho-kinase hyperactivity appears to increase the sensitivity of vascular smooth cells to calcium, which in turn increases myosin light chain phosphorylation that promotes vasoconstriction.[16] Similarly, multiple pathways are involved in coronary smooth muscle cell hypercontractility, such as nitric oxide, phospholipase C and KATP channels. In this special focus issue, Nishimiya et al. discuss the diverse mechanisms implicated in coronary artery spasm.[17]

Ethnic variations have been suggested to play a role in coronary artery spasm in different populations. In this issue, Ong et al. provide further insight into the importance of sex and ethnicity in the development of coronary artery spasm.[18]

Criteria for the diagnosis of vasospastic angina were proposed in 2017 by the Coronary Vasomotor Disorders International Study (COVADIS) Group.[19] According to the COVADIS criteria, the presence of angina at rest and transient ischaemic ECG changes, such as ST-segment elevation or depression, are suggestive of coronary artery spasm. A definitive diagnosis of vasospastic angina, however, requires the documentation of coronary spasm at angiography. Provocative spasm testing requires the administration of a provocative stimulus – intracoronary acetylcholine or, alternatively, intracoronary or IV ergonovine – in the catheterisation laboratory during coronary angiography. Patients must be carefully monitored during the procedure. Symptoms, ECG changes and angiographic documentation of coronary artery spasm are all key elements for the objective diagnosis of spasm. COVADIS criteria for the diagnosis of spasm include: reproduction of the patient's usual chest pain; ischaemic ECG changes; and 90% diameter reduction due to vasoconstriction on angiography.[19,20]

Regarding treatment, little progress has been made in the past 3 decades regarding pharmacological approaches. In this issue of *European Cardiology Review*, Lanza and Shimokawa take us through the different therapeutic options available for the management of patients with coronary spasm.[21] Sublingual nitrates (tablets or spray) remain the main treatment to relieve episodes of coronary spasm. Smoking cessation, in particular, and avoiding triggers are helpful preventive measures. Studies, mainly from Japan, have guided the treatment of coronary spasm over the years and informed international guidelines.[20]

For the prevention of recurrent chest pain episodes, long-acting calcium-channel blockers (CCBs), such as diltiazem, amlodipine and verapamil, are useful agents, as several studies have documented. Non-dihydropyridine CCBs (e.g. diltiazem and verapamil) rather than

dihydropyridine CCBs (e.g. amlodipine or nifedipine) can achieve a marked reduction in recurrent symptoms. Oral nitrates and nicorandil – a potassium-channel activator – are also good alternative vasodilator therapies, but the development of nitrate tolerance represents a limitation for the long-term use of oral nitrates in vasospastic angina.

Nicorandil is recommended in patients who do not respond to conventional treatment, but caution is advised because there have been reports of gastrointestinal ulceration.[22] Clinical and angiographic studies from Japan have shown that fasudil, a rho-kinase inhibitor, blocks coronary artery spasm induced by acetylcholine.[15,16] The myosin-binding substrate promotes vasodilation by dephosphorylating the myosin head and causing detachment of the myosin–actin crosslink. Rho-kinase inhibits this process, thus generating a vasoconstrictive state. Rho-kinase inhibitors, such as fasudil, can therefore promote vasodilatation. This agent, which is currently available only in Japan, is used intravenously for management of acute episodes of coronary vasospasm.

For coronary artery spasm patients who have survived a cardiac arrest or have recurrent ventricular tachycardia associated with coronary spasm, ICD implantation should be considered.

The articles in this special focus issue have been written by several of Maseri's collaborators and we hope they will bring at least some of his great scientific achievements to the attention of *European Cardiology Review*'s large readership. ❑

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