Coronary spasm is involved in many clinical scenarios, such as stable angina, acute coronary syndrome, sudden cardiac death, non-ischemic cardiomyopathy, arrhythmia and syncope. In recent years, imaging tools such as computerized tomographic angiography, intravascular ultrasound or optical coherence tomography have been applied to study the coronary pathology in patients with vasospastic angina. Patients with vasospastic angina represent a heterogeneous cohort of patients with regard to the extent of concomitant coronary atherosclerosis. They share the common pathophysiological phenomenon of vascular smooth muscle hyperreactivity leading to spasm caused by various factors that may also overlap. Focal coronary spasm is related to epicardial atherosclerosis and in the presence of obstructive coronary artery disease it may be useful to treat the lesion to prevent further spasm. The aim of this article is to review structural and functional coronary artery abnormalities in patients with vasospastic angina. (Circ J 2015; 79: 1431–1438)

Key Words: Atherosclerosis; Coronary artery disease; Vasospasm

Coronary spasm is involved in many clinical scenarios, such as stable angina, acute coronary syndrome, sudden cardiac death, non-ischemic cardiomyopathy, arrhythmia and syncope. In recent years, imaging tools such as computerized tomographic angiography (CTA), intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have been applied to study the coronary pathology in patients with vasospastic angina. This may lead to identification of therapeutic targets in the future. The aim of this article is to review the structural and functional coronary artery abnormalities in patients with vasospastic angina.

Definition and Pathophysiology of Coronary Artery Spasm

According to the Guidelines of the Japanese Circulation Society, coronary spasm is defined as a transient constriction of an epicardial coronary artery >90%, leading to resting angina (and/or dyspnea) and ischemic ECG changes (Figure 1). However, spasm can also occur at the level of the coronary microcirculation, with reproduction of symptoms and ischemic ECG changes but without epicardial spasm (Figure 2), although this phenomenon cannot currently be directly visualized in humans in vivo. In some patients, spasm may even be present in the coronary epicardial arteries as well as in the microvessels. Anatomically, epicardial coronary spasm is defined as focal if it is confined within the borders of a coronary segment according to the 16 segment coronary model of the American Heart Association. Diffuse spasm is present if adjacent coronary segments are involved. Coronary spasm can occur in only one epicardial artery, but if several vessels may be involved, this is called multivessel spasm. Coronary spasm usually occurs spontaneously in an unpredictable fashion and usually leads to angina at rest but may also be asymptomatic.
striction or vasodilation. In patients with vasospastic angina there is an abnormal vasoconstrictive response. Different pathogenic mechanisms have been proposed as the underlying cause. The most common are vascular smooth muscle cell (VSMC) hyperreactivity, endothelial dysfunction, low-grade inflammation and altered autonomic nervous system response, and these may in turn be modified by genetic factors. 

VSMC Hyperreactivity

VSMC hyperreactivity is thought to be the main pathophysiological substrate for spasm and early studies of human coronary anatomy have shown that all coronary vessels, including the microvessels, have a similar wall structure that includes a layer of VSMCs. Animal studies using light and electron microscopy have provided insights into the mechanics of VSMCs during spasm. They show that radial rearrangement of the medial VSMCs, because of their

(silent ischemia). However, various other clinical presentations of patients with coronary spasm have been described, including but not limited to angina during exercise or syncope.

The 2013 Guidelines by the European Society of Cardiology for Management of Stable Angina recommend performing coronary angiography in patients with suspected coronary spasm to determine the underlying extent of coronary atherosclerosis. Moreover, intracoronary provocation testing is recommended to determine the site and mode of spasm because it can be prognostically relevant.

Pathophysiology

Coronary arteries are able to adjust the blood supply to the heart during different loading conditions by either vasoconstriction or vasodilation. In patients with vasospastic angina there is an abnormal vasoconstrictive response. Different pathogenic mechanisms have been proposed as the underlying cause. The most common are vascular smooth muscle cell (VSMC) hyperreactivity, endothelial dysfunction, low-grade inflammation and altered autonomic nervous system response, and these may in turn be modified by genetic factors.

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Figure 1. Severe multivessel epicardial spasm provoked by 100 μg intracoronary acetylcholine with reproduction of symptoms and marked ST-segment depression in a patient with recurrent angina at rest (Left). The changes resolved after intracoronary nitroglycerine injection (Right).

Figure 2. Coronary microvascular spasm in a female patient without relevant epicardial stenosis and without epicardial spasm during acetylcholine testing (ACH) but with ST-segment depression and reproduction of symptoms (Left). These changes resolved after nitroglycerine injection (Right). (Reproduced from Ong P, et al.)
Structure and Function in Coronary Spasm

Oxidative Stress Oxidative stress (ie, increased production of oxygen-reactive species) may also contribute to the development of coronary spasm. It has been shown that biomarkers for oxidative stress (eg, thioredoxin) are elevated in patients with vasospastic angina compared with patients who have non-vasospastic angina. Moreover, concentrations of the antioxidant vitamin E are reduced in patients with vasospastic angina.

In addition, cigarette smoking (a known risk factor for coronary spasm) has been identified as an important inducer of oxidative stress. Although there is still debate about whether oxidative stress is a direct cause of coronary spasm, because it is also present in various other vascular diseases, it can be regarded as a cofactor in the genesis of coronary spasm.

Low-Grade Inflammation Biomarkers of low-grade inflammation, such as high-sensitivity C-reactive protein, CD40 ligand and interleukin 6, have been shown to be elevated in patients with vasospastic angina compared with patients who have non-vasospastic angina. Moreover, concentrations of the antioxidant vitamin E are reduced in patients with vasospastic angina. In addition, cigarette smoking (a known risk factor for coronary spasm) has been identified as an important inducer of oxidative stress. Although there is still debate about whether oxidative stress is a direct cause of coronary spasm, because it is also present in various other vascular diseases, it can be regarded as a cofactor in the genesis of coronary spasm.

Genetic Factors Several genetic polymorphisms have been described as potentially involved in the predisposition for coronary spasm. Most of these mutations concern the gene encoding for NO synthase, but mutations in other mole-

Figure 3. Schematic presentation of structural changes in the spastic coronary arterial wall. (A) Connection patterns of SMCs to the IEL in the non-spastic state. (B) Connection patterns of SMCs and their direction patterns during spasm. (C) Pattern of SMCs connecting the IEL to the external elastic lamina (EEL) in the non-spastic state. (D) Re-arranged pattern of SMCs connecting the IEL to the EEL in the spastic state. (a and b indicate the connection points to the IEL and EEL, respectively.) Contraction of SMCs reduces the distance between a and b, with resultant radial rearrangement of SMCs, leading to folding of the IEL, gathering of the EEL, medial thickening and luminal narrowing. I, intima. (Reproduced with permission from Uchida Y, et al.)

own contraction, and resultant medial thickening and folding of the internal elastic lamina create a piston effect to narrow the lumen (Figure 3). The molecular pathways leading to spasm are still not fully understood, but the rho-kinase pathway has emerged as important in the genesis of spasm.

Autonomic Nervous System The relationship between the autonomic nervous system and coronary spasm is complex. An increase in both the sympathetic and parasympathetic tone is able to induce coronary spasm. An increase in sympathetic activity may cause coronary spasm through an increase in noradrenaline, the neurotransmitter of efferent sympathetic fibers, causing vasoconstriction by stimulating VSMCs. Acetylcholine, the neurotransmitter in the parasympathetic nerve fibers, causes vasodilation in normal vessels at low dosage but may also cause vasoconstriction by stimulating VSMCs. As the parasympathetic innervation derives from the adventitia of the vessel, alterations in neuronal nitric oxide (NO) synthase may play an important role in this setting, as shown by Seddon et al.

Endothelial Dysfunction The endothelium has a very important role in the regulation of coronary vascular tone, predominantly through its ability to release several vasodilators, with NO being the most important. Endothelial dysfunction with abnormalities in NO release and its reduced bioavailability combined with hyperreactivity of VSMCs may be an important factor in developing coronary spasm. However, it is important to remember that endothelial dysfunction alone is not sufficient to explain the phenomenon of coronary spasm because it requires the activation of VSMCs.
cules responsible for modulation of vascular tone have also been suggested. It should however be mentioned that nearly all these studies have been performed in Asian patients and only recently a study in Italian patients has described genetic polymorphisms associated with coronary microvascular dysfunction.}

### Functional Changes

As mentioned, coronary spasm is a phenomenon that involves the sudden and transient vasoconstriction of a coronary blood vessel because of vascular smooth muscle hyperreactivity caused by various factors. The number of affected vessels, as well as the location of the spasm, may vary and after resolution of spasm the vessel diameter usually returns to the previous size. These functional changes can occur in patients with epicardially normal arteries, as well as in those with atherosclerotic plaques or even relevant stenosis (see later) and may also affect the microvessels. Depending on the severity, the duration and frequency coronary spasm can lead to myocardial ischemia and may also cause permanent damage to the vascular wall. Such structural alterations can be visualized using intracoronary imaging techniques such as IVUS or OCT. Microvascular changes cannot be visualized in vivo at the moment, but non-invasive techniques such as PET or myocardial contrast echocardiology during invasive vasomotor studies can provide indirect information about microvascular function.

Experimentally, various triggers have been identified to elicit coronary spasm, such as serotonin, thromboxane, histamine and acetylcholine (ACh). The latter is, together with ergonovine, frequently used for intracoronary provocation testing for coronary spasm in the clinical setting. Apart from occasional documentation of coronary spasm on computed tomography (see later), intracoronary provocation testing is currently the only possible method of visualizing coronary spasms systematically in humans.

### Structural Changes

#### Microcirculation

Early changes in or damage to the coronary vasculature in response to cardiovascular risk factors can affect the microcirculation as well as the epicardial arteries. It is well known that cardiovascular risk factors are associated with vascular inflammation, which may lead to impaired microcirculation and it is conceivable that some risk factors cause structural changes leading to permanent damage of the microcirculation.

In hypertension, for example, intima thickening and perivascular fibrosis are often seen, the latter impairing the microvasculature’s ability to dilate independently of VSMC function. An inflammatory milieu may lead to structural changes and enhance the tendency of the microcirculation to spasm. However, the exact triggers leading to a clinical presentation of coronary (microvascular) spasm are still poorly understood. Current pathophysiological concepts of coronary microvascular dysfunction have recently been reviewed elsewhere.

#### Epicardial Arteries

As mentioned earlier, coronary spasm can occur in patients with normal coronary arteries as well as in patients with atherosclerosis. Moreover, percutaneous coronary intervention can be associated with coronary spasm. However, it is still poorly understood whether coronary spasm can promote atherosclerotic alterations or whether the latter may predispose to spasm. There are several reports of structural alterations of the epicardial arteries in patients with vasospastic angina. These may be visualized invasively by coronary angiography, IVUS and OCT and non-invasively by CTA.

#### Coronary Angiography

In some patients coronary spasm may be superimposed on an atherosclerotic lesion and it is conceivable that repetitive spasm in the area of such a lesion may lead to plaque rupture and acute myocardial infarction. It is often difficult to assess the interplay of the structural and functional aspects of significant epicardial stenosis because intracoronary provocation testing for the assessment of coronary spasm is usually not performed in the presence of a relevant stenosis. However, occasionally, spontaneous attacks of epicardial spasm can be observed during diagnostic coronary angiography, illustrating the role of coronary spasm superimposed on a relevant coronary stenosis. In such cases it may be useful to perform percutaneous coronary intervention to reduce the tendency of the vessel to spasm.

#### Coronary Computed Tomographic Angiography

CTA is useful for the detection of coronary artery calcium burden, as well as for the detection of relevant epicardial stenosis. Several reports have highlighted the usefulness of CTA in the evaluation of patients with vasospastic angina. In some cases, CTA showed a relevant stenosis that was later...
spastic coronary artery in patients with positive ACh test had a diffuse thickened intima in the entire artery compared with an age- and sex-matched control group with atypical chest pain and negative ACh test. The plaque composition, however, in the 2 groups was identical.

These findings underscore the fact that focal coronary spasm is associated with epicardial atherosclerosis. Our own experience is that stenotic lesions with superimposed spasm are uniformly eccentric with a free arc of normal-appearing coronary wall. Spasm occurs by contraction of the portion of the wall unaffected by the eccentric plaque.

Optical Coherence Tomography

In an early study from Morikawa et al using OCT in patients with vasospastic angina the coronary artery segments involved in spasm were characterized by diffuse intimal thickening without lipid or calcium content, findings similar to those reported from IVUS-based studies. Tanaka et al described patients with vasospastic angina as having a larger media thickness, intimal bump at rest and intimal gathering during spasm (Figure 6). Moreover, Park et al showed that in patients with vasospasm-induced acute coronary syndrome, intimal tear, intimal erosion, and microthrombi are major abnormal morphologic findings of OCT compared with patients with chronic stable variant angina.

Intravascular Ultrasound

IVUS is a useful technology to evaluate coronary plaques in vivo. Combined with virtual histology (VH-IVUS), it is possible to study the plaque composition in an epicardial artery. Early studies in patients with vasospastic angina and angiographically normal coronary arteries have shown that spastic arteries show significant intimal thickening. Hong et al reported the IVUS findings of patients with focal coronary spasm, showing atherosclerotic lesions at all coronary spasm sites with a high incidence of negative arterial remodeling compared with proximal and distal sites. Similar results were shown by Saito et al in a Japanese IVUS study in which patients with focal spasm had atherosclerotic lesions in 100% of cases but calcification of the lesions was uncommon. A Japanese VH-IVUS study from 2013 showed that the vasospastic coronary artery in patients with positive ACh test had a diffuse thickened intima in the entire artery compared with an age- and sex-matched control group with atypical chest pain and negative ACh test. The plaque composition, however, in the 2 groups was identical. These findings underscore the fact that focal coronary spasm is associated with epicardial atherosclerosis. Our own experience is that stenotic lesions with superimposed spasm are uniformly eccentric with a free arc of normal-appearing coronary wall. Spasm occurs by contraction of the portion of the wall unaffected by the eccentric plaque.

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Overall, intracoronary imaging techniques have shown that focal coronary spasm is associated with non-calcified epicardial lesions. Moreover, both intimal and media thickening are
frequently found in patients with vasospastic angina.

**Knowledge Gaps**

**Sex**

In the USA, functional coronary vasomotor abnormalities have been studied most often in women, with a focus on microvascular dysfunction, whereas in Asia, especially in Japan, coronary artery spasm is a male disease with an epicardial location. Recently, reports from Japan have highlighted sex differences among patients with vasospastic angina and we have reported that coronary microvascular spasm is indeed more prevalent in German women and epicardial spasm is more prevalent in German men. This underscores the need for further investigations on sex differences in patients with vasospastic angina.

**Relationship Between Epicardial and Microvascular Disorders**

The relationship between epicardial and microvascular vasomotor abnormalities is poorly understood. Clinical observations suggest that a subgroup of patients may have a common pathophysiological background leading to microvascular dysfunction at low doses of ACh provocation and epicardial spasm at higher doses. Moreover, some studies have suggested that patients with coronary microvascular dysfunction have increased epicardial plaque vulnerability on IVUS (ie, thin-cap fibroatheroma), but these results need further confirmation as data from large follow-up studies are lacking.

**Racial Differences**

It has been suggested that coronary spasm is more prevalent among Asians than in white populations, but our prior evaluation of 921 consecutive white patients with angina pectoris and unobstructed coronary arteries showed epicardial or microvascular spasm in a similarly high proportion of 57% of the patients. This has been supported by previous studies of European patients showing a similar frequency of coronary spasm compared with Japanese studies. These findings indicate that coronary artery spasm may play an important role in angina pectoris patients without significant differences between ethnic groups.

**Conclusions**

Patients with vasospastic angina represent a heterogeneous cohort of patients with regard to the extent of concomitant coronary atherosclerosis. They share the common pathophysiological phenomenon of VSMC hyperreactivity leading to spasm caused by various factors that may also overlap. Focal coronary spasm is related to epicardial atherosclerosis and in the presence of obstructive coronary artery disease it may be useful to treat the lesion to prevent further spasm. Investigative...
tions in patients with unexplained chest pain should not only integrate fractional flow reserve, OCT and IVUS if indicated, but should also incorporate assessment of functional vasomotor disorders using, for example, intracoronary provocation testing for the detection of coronary spasm.

Disclosures
No conflicts to disclose.

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