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Coronary Microvascular Dysfunction

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The link between myocardial ischemia and obstructive atherosclerosis of the epicardial coronary arteries is well established, and coronary angiography has demonstrated a relationship between the severity and extent of coronary artery disease (CAD) and survival. In the past two decades, however, a number of studies have reported that abnormalities in the function and structure of the coronary microcirculation occur in many clinical conditions. In some instances these abnormalities represent epiphenomena, whereas in others they represent important markers of risk or may even contribute to the pathogenesis of myocardial ischemia, thus becoming therapeutic targets.[1]

Functional Anatomy of the Coronary Arterial System

The coronary arterial system is composed of three compartments with different functions, although the borders of each compartment cannot be clearly defined anatomically[2] (Fig. 1). The proximal compartment is represented by the large epicardial coronary arteries, which have a capacitance function and offer little resistance to coronary blood flow. The diameter of the epicardial coronary arteries ranges from approximately 500 μm to 2 to 5 mm. The intermediate compartment is represented by prearterioles, which are characterized by a measurable pressure drop along their length. These vessels are not under direct vasomotor control by diffusible myocardial metabolites because of their extramyocardial position and wall thickness. Their diameter ranges from approximately 100 to 500 μm, and their specific function is to maintain pressure at the origin of arterioles within a narrow range when coronary perfusion pressure or flow changes. The more distal compartment is represented by intramural arterioles, which are characterized by a considerable drop in pressure along their path. They have diameters of less than 100 μm, and their function is the matching of myocardial blood supply and oxygen consumption.

When flow changes, epicardial coronary arteries and proximal arterioles have an intrinsic tendency to maintain a given level of shear stress by endothelial-dependent dilatation.[3] When aortic pressure increases, distal prearterioles undergo myogenic constriction in order to maintain a constant pressure at the origin of the arterioles. Arterioles have a fundamental role in the metabolic regulation of coronary blood flow.[4] They have a high resting tone and dilate in response to the release of metabolites by the myocardium as a result of an increase in oxygen consumption. Arteriolar dilatation decreases both resistance in the overall network and pressure in distal prearterioles, which in turn induce the dilatation of myogenically sensitive vessels. Furthermore, the dilatation of distal prearterioles and arterioles results in an increase in shear stress, which triggers flow-dependent dilatation in larger prearterioles and conductance arteries. Thus, as proposed by Chilian,[5] the coronary circulation matches blood flow with oxygen requirements by coordinating the resistances within different microvascular domains, each governed by distinct regulatory mechanisms. Such integration appears advantageous because the system does not rely on a single mechanism of control.

ASSESSMENT OF CORONARY MICROCIRCULATION

Currently, no technique allows the direct visualization of coronary microcirculation in vivo in humans. Several measurements that rely on the quantification of blood flow through the coronary circulation are commonly used to describe the function of coronary microvasculature. Coronary blood flow is a measurement of the amount of flow through a given coronary vessel per unit of time and is usually expressed in milliliters per minute.[6] Techniques for measuring coronary blood flow include intracoronary thermodilution, which uses a thermal dilution curve to measure blood flow, and an intracoronary Doppler wire, which measures blood flow ultrasonographically according to the Doppler principle. Another invasive technique for assessing coronary blood flow, the Thrombolysis in Myocardial Infarction (TIMI) frame count, does not quantify the flow in milliliters per minute but is nevertheless useful for comparative purposes. It simply determines the number of cineangiographic frames, which are commonly acquired at 25 to 30 frames per second, that it takes for contrast dye to fill the epicardial vessels.[7] More recently, transthoracic Doppler echocardiography has also been used as a noninvasive means to measure coronary blood flow.[8]

Coronary blood flow, although useful for measuring flow through epicardial coronary arteries, provides only indirect information about flow through the microvasculature. Assessment of microvascular flow is complex, although several approaches have been devised. The simplest, the TIMI myocardial perfusion grade, describes the relative "blush," or intensity, of the radiopacity of myocardial tissue achieved with an epicardial coronary injection of contrast medium, and the rapidity with which this enhancement clears. The more intense the myocardial blush of the contrast medium and the faster its clearance, the better the microvascular perfusion; the TIMI myocardial perfusion grade is scored on a scale of 0 to 3, with higher scores indicating better perfusion (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).[7,9]

A more direct and precise quantification of microvascular function is based on the measurement of myocardial blood flow by positron-emission tomography, which allows the calculation of the quantity of blood flow per unit of mass (expressed as milliliters per minute per gram of tissue).[6] Cardiovascular magnetic resonance imaging (MRI) or transthoracic echocardiography with the intravenous infusion of contrast material can also be used for the quantification of myocardial blood flow.[10,11]

Coronary flow reserve is the magnitude of the increase in coronary flow that can be achieved in going from basal coronary perfusion to maximal coronary vasodilation; since flow resistance is primarily determined by the microvasculature, coronary flow reserve is a measurement of the ability of the microvasculature to respond to a stimulus and therefore presumably of the function of the small vessels. Coronary flow reserve is determined by measuring coronary or myocardial blood flow and taking measurements both at rest (basal flow) and with maximal hyperemia, which is achieved

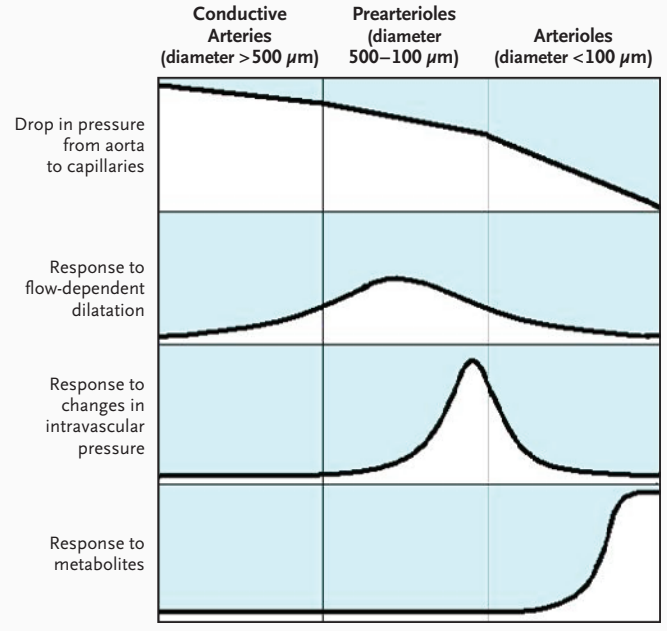

Figure 1. Functional Anatomy of the Coronary Arterial System.

Conductive arteries, prearterioles, and arterioles make up the functional subdivisions of the coronary arterial system. The drop in pressure along conductive arteries is negligible, appreciable through prearterioles, and largest through the arterioles. Conductive arteries are responsive to flow-dependent dilatation, and proximal prearterioles are even more responsive. Distal prearterioles are more responsive than the other types of vessels to changes in intravascular pressure and are mainly responsible for autoregulation of coronary blood flow. Arterioles are responsive to changes in the intramyocardial concentration of metabolites and are mainly responsible for the metabolic regulation of coronary blood flow. Prearterioles, by definition, are not exposed to myocardial metabolites because of their extramyocardial position and their wall thickness.

with an intracoronary or intravenous infusion of adenosine or an intravenous infusion of dipyridamole. Coronary flow reserve is then expressed as the ratio of blood flow during hyperemia to blood flow at rest. In patients with CAD, the extent of the reduction in coronary flow reserve is directly related to the severity of stenosis, whereas in persons with angiographically normal arteries it is a marker of microvascular dysfunction.[6] A coronary flow reserve of less than 2.0 is often considered abnormal. In healthy persons, however, coronary flow reserve varies according to age and sex.[6] Therefore, it is essential to compare data on coronary flow reserve in patients with data obtained in age-matched and sex-matched control subjects. The assessment of microvascular dysfunction in myocardial regions subtended by stenotic coronary arteries is complex because the evaluation of microvascular function in such cases depends on the clinical context.

CLASSIFICATION OF CORONARY MICROVASCULAR DYSFUNCTION

On the basis of the clinical settings in which it occurs, coronary microvascular dysfunction can be classified into four types: dysfunction occurring in the absence of CAD and myocardial diseases, dysfunction in the presence of myocardial diseases, dysfunction in the presence of obstructive epicardial CAD, and iatrogenic dysfunction (Table 1). Coronary microvascular dysfunction may be sustained by several pathogenetic mechanisms, as summarized in Table 2. The importance of these mechanisms appears to vary in different clinical settings, although several of them may coexist in the same condition.

MICROVASCULAR DYSFUNCTION WITHOUT CAD OR MYOCARDIAL DISEASES

CIGARETTE SMOKING

Cigarette smoking is a well-established risk factor for cardiovascular disease,[12] affecting both the coronary and the peripheral circulation.[13] Endothelial dysfunction has been demonstrated in the brachial[14] and coronary[15] arteries of long-term smokers. Coronary microvascular dysfunction has been demonstrated in asymptomatic smokers with no evidence of CAD, in whom coronary flow reserve was reduced by 21% as compared with the value in nonsmoking controls.[16] Short-term administration of vitamin C, an antioxidant, normalized coronary flow reserve in smokers but had no significant effect in nonsmoking control subjects, lending

Table 1. Clinical Classification of Coronary Microvascular Dysfunction.

Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases	This type represents the functional counterpart of traditional coronary risk factors (smoking, hypertension, hyperlipidemia, and diabetes and insulin-resistant states). It can be identified by noninvasive assessment of coronary flow reserve. This type is at least partly reversible, and coronary flow reserve can also be used as a surrogate end point to assess efficacy of treatments aimed at reducing the burden of risk factors.
Coronary microvascular dysfunction in the presence of myocardial diseases	This type is sustained in most instances by adverse remodeling of intramural coronary arterioles. It can be identified by invasive or noninvasive assessment of coronary flow reserve and may be severe enough to cause myocardial ischemia. It has independent prognostic value. It remains unclear whether medical treatment may reverse some cases. It is found with primary (genetic) cardiomyopathies (e.g., dilated and hypertrophic) and secondary cardiomyopathies (e.g., hypertensive and valvular).
Coronary microvascular dysfunction in the presence of obstructive CAD	This type may occur in the context of either stable CAD or acute coronary syndromes with or without ST-segment elevation and can be sustained by numerous factors. It is more difficult to identify than the first two types and may be identified through the use of an integrated approach that takes into account the clinical context with the use of a combination of invasive and noninvasive techniques. There is some early evidence that specific interventions might prevent it or limit the resultant ischemia.
Iatrogenic coronary microvascular dysfunction	This type occurs after coronary recanalization and seems to be caused primarily by vasoconstriction or distal embolization. It can be identified with the use of either invasive or noninvasive means on the basis of a reduced coronary flow reserve, which seems to revert spontaneously in the weeks after revascularization. Pharmacologic treatment has been shown to promptly restore coronary flow reserve, and it may also change the clinical outcome. The likelihood of distal embolization can be reduced by the use of appropriate devices during high-risk procedures.

support to the hypothesis that the damaging effect of smoking is explained at least in part by an increase in oxidative stress.[16]

HYPERLIPIDEMIA

Reductions in coronary flow reserve have been documented in asymptomatic subjects with hypercholesterolemia and angiographically normal coronary arteries, as have their reversibility with cholesterol-lowering strategies.[17-19] A statistically significant inverse correlation between the measurement of coronary flow reserve and levels of lipid subfractions has been demonstrated in subjects with elevated levels of total cholesterol in blood.[17,20] These data provide pathophysiologic support for a clinical strategy of treating the entire lipid profile rather than focusing on a reduction in total cholesterol alone.

DIABETES

Although much of the excess risk of CAD among patients with diabetes may be accounted for by the presence of diabetes-associated coronary risk factors such as obesity, dyslipidemia, and hypertension, a substantial proportion remains unexplained.[21] A direct deleterious effect of diabetes on vascular and, particularly, endothelial function may be its ability to increase the potential for vasoconstriction and thrombosis. There is consistent evidence that coronary flow reserve is impaired in patients with diabetes, and it may be an early marker of atherosclerosis.[22-24] A recent study showed marked coronary microvascular dysfunction in response to adenosine infusion (primarily reflecting aberrant endothelium-independent vasodilatation) and to the cold pressor test (primarily reflecting endothelium-dependent vasodilatation) in young subjects with uncomplicated diabetes.[25] Similar observations were made in subjects with type 1 or type 2 diabetes mellitus. Such observations provide further support for a key role for hyperglycemia in the pathogenesis of vascular dysfunction in diabetes.

MICROVASCULAR ANGINA

Patients without evidence of obstructive atherosclerotic plaques and myocardial disease may present with angina-like chest pain, a condition commonly known as syndrome X. The hypothesis that such chest pain is ischemic in origin was based on the presence of ST-segment depression during spontaneous or stress-induced chest pain in affected patients, as well as on the evidence of reversible stress-induced defects in myocardial perfusion.[26] Furthermore, some studies have provided evidence of reduced endothelium-dependent and endothelium-independent coronary vasodilatation,[27] as well as metabolic evidence of myocardial ischemia, in such patients.[28] Other studies, however, failed to find evidence of abnormal myocardial blood flow or coronary flow reserve or metabolic or functional evidence of ischemia during stress.[29-31] However, in a subgroup of patients with syndrome X characterized by reduced coronary flow reserve and metabolic evidence of myocardial ischemia, coronary microvascular dysfunction is the probable cause of the angina. On the basis of these findings, the appropriate diagnosis is microvascular angina.[32] Maseri et al.[33] proposed that these patients have focal ischemia in small myocardial regions scattered throughout the myocardium caused by prearteriolar dysfunction. The presence of such defects might explain the paradox of angina and ST-segment depression or even ST-segment elevation in the absence of wall-motion changes in these patients. Other pathogenic mechanisms of coronary microvascular dysfunction may have a role in patients without associated risk factors.[34,35]

Table 2. Pathogenetic Mechanisms of Coronary Microvascular Dysfunction.

Alterations	Causes
Structural	
Luminal obstruction	Microembolization in acute coronary syndromes or after recanalization
Vascular-wall infiltration	Infiltrative heart disease (e.g., Anderson–Fabry cardiomyopathy)
Vascular remodeling	Hypertrophic cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth-muscle cell	Hypertrophic cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stenosis

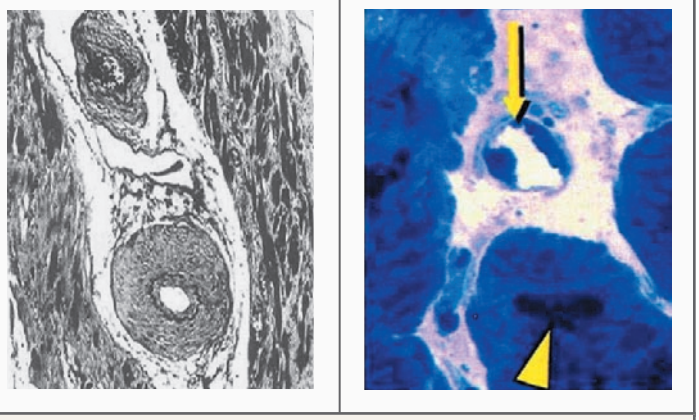

Figure 2. Coronary Microvascular Dysfunction in Myocardial Diseases.

Panel A shows a single large abnormal intramural coronary artery in an interstitial space of the left ventricular free wall in a patient with hypertrophic cardiomyopathy. The thickening of the wall is due primarily to the proliferation of medial components, although the intima is also mildly thickened. The internal elastic membrane is well defined. (Reproduced from Maron et al.,[44] with the permission of the publisher.) Panel B shows interstitial capillaries of the myocardium with small-to-medium-sized glycosphingolipid inclusions in the endothelium (arrow) and globotriaosylceramide inclusions in the cardiomyocytes (arrowhead) in a patient with Anderson–Fabry disease (methylene blue–azure II stain). (Reproduced from Eng et al.,[45] with the permission of the publisher.)

MICROVASCULAR DYSFUNCTION WITH MYOCARDIAL DISEASES

PRIMARY (GENETIC) CARDIOMYOPATHIES

Hypertrophic Cardiomyopathy

Symptoms and signs of myocardial ischemia are often found in patients with hypertrophic cardiomyopathy, despite the presence of angiographically normal coronary arteries. Myocardial ischemia can contribute to some of the severe complications of hypertrophic cardiomyopathy, including ventricular arrhythmias, sudden death, progressive left ventricular remodeling, and systolic dysfunction.[36-39] In the past 15 years a number of studies[40-43] have demonstrated that coronary flow reserve is severely blunted not only in the hypertrophied septum but also in the less hypertrophied left ventricular free wall. These findings are in line with the evidence of widespread remodeling of intramural arterioles at autopsy in patients with hypertrophic cardiomyopathy (Fig. 2A).[44] Furthermore, the severity of coronary microvascular dysfunction in affected patients has been found to be an independent predictor of long-term clinical deterioration and death from cardiovascular causes.[46,47]

Dilated Cardiomyopathy

Severely reduced coronary flow reserve has been demonstrated in patients with dilated cardiomyopathy.[48-52] In one study, the microvascular function of the systemic (as measured in the forearm) and coronary circulations was evaluated in the same subjects. In contrast to the findings in healthy volunteers, no correlation between systemic and coronary microvascular function was observed in patients with dilated cardiomyopathy, indicating that the endothelial function in the peripheral circulation cannot necessarily be extrapolated to the coronary circulation.[53] As in patients with hypertrophic cardiomyopathy, in patients with dilated cardiomyopathy, the degree of coronary microvascular dysfunction has been shown to be an independent predictor of cardiac events and is associated with an increased relative risk of death and further progression of heart failure.[54]

SECONDARY CARDIOMYOPATHIES

Arterial Hypertension

Abnormal coronary flow reserve has been demonstrated in patients with essential hypertension, despite the presence of angiographically normal coronary arteries and the absence of left ventricular hypertrophy.[55,56] This observation has often been attributed both to the remodeling of vascular and extravascular structures and to coronary hemodynamics.[57] The former includes remodeling of intramural arterioles and interstitial fibrosis, which leads to a decreased density of vessels in the coronary microvasculature, whereas the latter is characterized by increased extravascular compressive forces with elevated systolic and diastolic wall stress and impaired relaxation. Coronary microvascular dysfunction in patients with hypertension is not necessarily related to the presence or degree of left ventricular hypertrophy.[58] In some patients, the abnormalities of coronary flow reserve are regionally heterogeneous, although the entire myocardium is affected in others.[59] Regional coronary microvascular dysfunction may predispose patients to abnormal patterns of myocardial electrical depolarization or repolarization or to regional myocardial ischemia during conditions in which a high flow is necessary.

Aortic Stenosis

The development of left ventricular hypertrophy in patients with aortic stenosis is an adaptive response, in that it may reduce wall stress in the left

ventricle.[60] Some of the changes associated with the hypertrophic process also affect the coronary circulation, and patients with aortic stenosis have a reduced coronary flow reserve, despite the presence of angiographically normal coronary arteries.[61] A series of unfavorable hemodynamic changes that include high left ventricular pressure, low coronary perfusion pressure as compared with intracavitary pressure, and increased extravascular compressive forces lead to a reduction in coronary flow reserve and increased minimal coronary resistance.[62,63] Characteristic pathological changes that contribute to impaired microvascular function are perimyocytic fibrosis and a reduction in the number of resistance vessels per unit of weight.[64] In one study, the severity of coronary microvascular dysfunction was related to the aortic-valve area, imposed hemodynamic load, and diastolic perfusion time, rather than to left ventricular mass.[65] Reduced extravascular compression and increased diastolic perfusion time have been proposed as the main mechanisms for improvement in myocardial blood flow and coronary flow reserve after aortic-valve replacement.[66]

Infiltrative Heart Disease

Anderson–Fabry disease is an X-linked deficiency of lysosomal α-galactosidase A. This enzyme deficiency results in multiorgan damage from glycosphingolipid deposition and leads to renal, cardiac, and cerebrovascular disease and premature death.[67] Patients with this disease often have angina, despite the presence of angiographically normal coronary arteries. A recent study demonstrated that coronary flow reserve is severely blunted in these patients.[68] The cardiomyopathy of Anderson–Fabry disease is characterized by glycosphingolipid deposition in myocytes, conduction tissue, vascular endothelium, and valvular tissue (Fig. 2B). This is accompanied by secondary changes such as myocyte hypertrophy and fibrosis. Endothelial deposits may lead to endothelial dysfunction, and perivascular fibrosis may contribute to increased microvascular resistance.[69]

MICROVASCULAR DYSFUNCTION WITH OBSTRUCTIVE CAD

STABLE CAD

Studies of patients with single-vessel CAD and normal left ventricular function have documented the presence of abnormal coronary flow reserve in regions subtended by angiographically normal coronary arteries.[70,71] In patients with stable angina, coronary microvascular dysfunction distal to coronary stenosis has an important role in determining the ischemic threshold. This was first demonstrated by Pupita et al.,[72] who observed marked variability of the ischemic threshold in patients with a single total coronary occlusion and no previous myocardial infarction. In the absence of dynamic epicardial coronary artery stenoses, such variability could only be explained by coronary microvascular dysfunction, including that in the collateral circulation.

Coronary microvascular dysfunction distal to a critical coronary stenosis may be caused by two mechanisms: inappropriate subepicardial prearteriolar dilatation in the presence of increased myocardial oxygen consumption and prearteriolar and arteriolar constriction.

In the presence of a critical stenosis, transmural myocardial perfusion is redistributed toward the subepicardial layers of the left ventricle. In classic experiments, Feigl[73] demonstrated the occurrence of selective sympathetically mediated constriction of subepicardial vessels during exercise, which should favor subendocardial perfusion. In patients with CAD this compensatory mechanism appears to be dysfunctional, as suggested by the observation that the blockade of A_1 adenosine receptors improves the ischemic threshold during exercise.[74] This is probably due to selective subepicardial vasoconstriction caused by prejunctional inhibition of A_1 adenosine receptors, resulting in enhanced catecholamine release from perivascular sympathetic nerves.[75,76]

The role of prearteriolar and arteriolar constriction in determining the ischemic threshold has been elucidated very recently. Indeed, studies in humans have shown increased microvascular resistance during atrial pacing, thus suggesting the presence of microvascular constriction during tachycardia.[77] This paradoxical microvascular prearteriolar constriction causing capillary derecruitment appears to result in the maintenance of a perfusion pressure sufficiently high to ensure nutrient exchange through the capillary network in the rest of the underperfused myocardium.[78] Yet, in a subgroup of patients with stable CAD, the potentially protective mechanism of capillary derecruitment can further worsen the severity of stress-induced myocardial ischemia, probably as a result of ath-

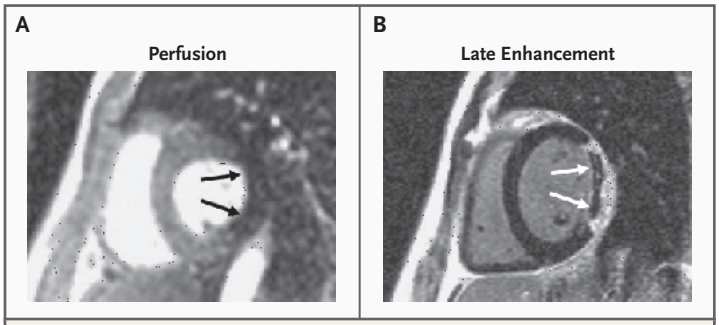

Figure 3. MRI Scans Showing Coronary Microvascular Dysfunction in a Patient with Coronary Artery Disease.

The patient presented with chest pain and ST-segment elevation in electrocardiographic leads II, III, aVF, V_5, and V_6. Despite successful recanalization of the circumflex coronary artery, the flow down the artery is sluggish. Perfusion MRI performed while the patient was at rest (Panel A) shows a defect in the lateral wall (arrows). Late enhancement imaging (Panel B) shows transmural infarction of the lateral wall, with an avascular central core, which represents an area of microvascular obstruction (arrows). (Images courtesy of Prof. D. Pennell and Dr. J. Moon, National Heart and Lung Institute, Imperial College, London.)

erosclerosis-related coronary microvascular dysfunction.

ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

In patients with acute coronary syndromes without ST-segment elevation, coronary microvascular dysfunction distal to the critical stenosis plays an important role in determining the severity of myocardial ischemia, not only through the mechanisms operating in stable CAD but also through other mechanisms operating specifically in patients with unstable disease. Marzilli et al.[79] found that in patients with unstable angina, episodes of transient myocardial ischemia at rest are associated with a brisk increase in coronary microvascular resistance and that this increase is prevented by the administration of antiplatelet drugs. Furthermore, the degree of coronary microvascular dysfunction is proportional to systemic levels of C-reactive protein, a prototypical marker of inflammation independent of traditional coronary risk factors, thus suggesting that the impairment caused by inflammation is independent of that caused by risk factors.[80]

ACUTE MYOCARDIAL INFARCTION WITH ST-SEGMENT ELEVATION

In patients with acute myocardial infarction, a reduction of baseline flow severe enough to impair regional wall motion in remote, normally contracting myocardium subtended by angiographically normal coronary arteries has been observed very early after the infarction. Both coronary microvascular dysfunction and the impairment of regional wall motion are relieved by alpha-blockers, thus suggesting that enhanced sympathetic activation is likely to contribute to these abnormal findings.[81] Myocardial ischemia reflexively increases cardiac sympathetic nerve activity by stimulating cardiac ventricular and coronary nerve–ending receptors.[82]

In patients with acute coronary syndromes with ST-segment elevation, coronary microvascular dysfunction in the territory of a recanalized infarct-related artery is responsible for the inability of a previously ischemic region to be reperfused ("no-reflow" phenomenon).[83] This phenomenon is characterized by the lack of microvascular integrity and patency despite the successful reopening of the infarct-related artery (Fig. 3). It appears to be the result of pathologic changes that begin during ischemia[84] and are aggravated during reperfusion.[85] Extensively studied in both the experimental and clinical settings, this concept recognizes a multifactorial pathogenesis. Galiuto[86] has recently proposed that this phenomenon can be classified into structural and functional forms, on the basis of the observation that the two forms differ with respect to pathogenesis, time course, clinical implications, and possible therapeutic strategies. In the structural type of no-reflow phenomenon, the cellular components of the walls of microvessels well confined within necrotic myocardium exhibit irreversible damage, whereas in the functional form, the patency of anatomically intact microvessels is compromised by the loss of endothelium-mediated vasomotion, alteration of sympathetic innervation, and external compression owing to interstitial edema and the plugging of platelets and neutrophils. The clinical relevance of the no-reflow phenomenon has been demonstrated by several studies correlating the microvascular damage with cardiac remodeling and with clinical outcome.[87,88]

IATROGENIC CORONARY MICROVASCULAR DYSFUNCTION

Coronary vasoconstriction has been demonstrated after successful percutaneous coronary angioplasty. The vasoconstriction occurs both at the site of dilatation and distal to it. In one report, coronary flow reserve in the region subtended by the dilated artery was still depressed 1 week after suc-

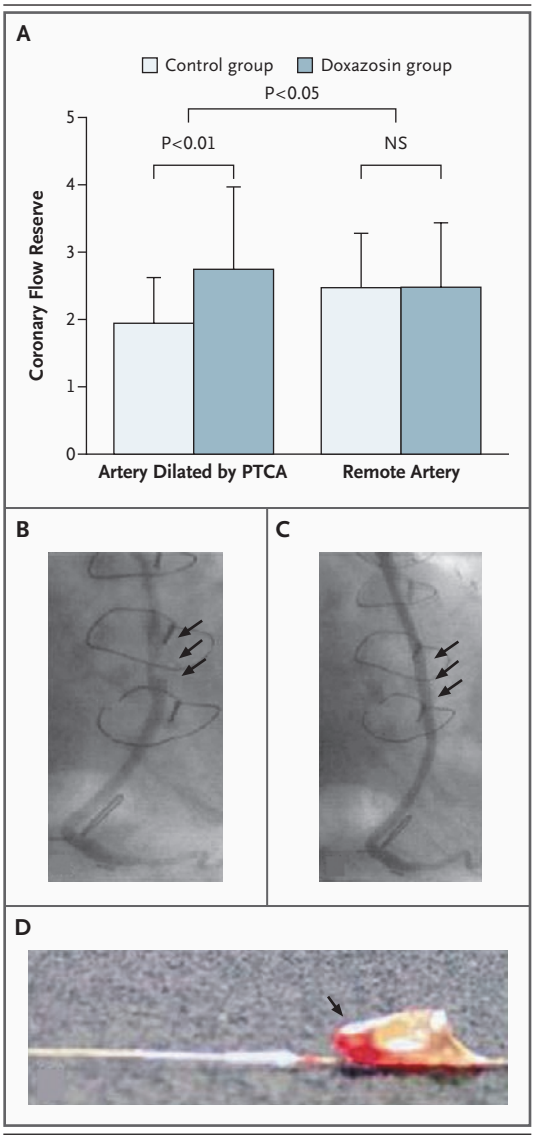

Figure 4. Iatrogenic Coronary Microvascular Dysfunction after Percutaneous Transluminal Coronary Angioplasty (PTCA).

Panel A shows the mean (±SD) value of coronary flow reserve in patients 5 days after PTCA. Coronary flow reserve was measured both in the territory subtended by the artery that was dilated by PTCA and in territories subtended by an angiographically normal artery (remote artery). Before the procedure, the patients were randomly assigned to receive the α-adrenergic receptor antagonist doxazosin (4 mg daily) or matching placebo, starting 11 days before PTCA. There was no significant difference in the coronary flow reserve of the remote territories between the two groups (NS). By contrast, the coronary flow reserve in the territory subtended by the dilated artery was higher in the group pretreated with the α-adrenergic receptor antagonist than in the placebo group ($P<0.01$). In the placebo group, coronary flow reserve was significantly depressed in the territory subtended by the artery undergoing PTCA, as compared with the remote territories ($P<0.05$).[91] Panel B shows a coronary angiogram obtained in a 76-year-old patient with an acute coronary syndrome treated for an ulcerated lesion in a saphenous-vein graft to the lower circumflex–marginal branch (arrows). A stent was then placed in the lesion, with an excellent final result and good distal flow (Panel C, arrows), after distal positioning of a filter basket similar to that shown in Panel D (arrow). No elevation in creatine kinase or creatine kinase MB fraction was noted after the procedure. In the absence of such protective devices, the implantation of a stent in high-risk lesions may cause dislodgment of the plaque or thrombotic material into the microcirculation, which may result in microinfarcts and elevations of the indexes of tissue necrosis. (Panels B, C, and D are reprinted from Kornowski et al.,[92] with the permission of the publisher.)

cessful percutaneous coronary angioplasty.[89] Gregorini et al.[90] have related epicardial coronary vasoconstriction that has been reported soon after percutaneous coronary angioplasty to α-adrenergic activation that can be reversed by α-adrenergic receptor antagonists given before the procedure (Fig. 4). This reversible α-adrenergic receptor–mediated constriction of coronary microvessels may account for the delayed improvement of exercise-induced myocardial ischemia after successful percutaneous coronary angioplasty.[93] A delayed recovery of coronary microvascular function similar to that of percutaneous coronary angioplasty has been demonstrated after bypass surgery.[94]

In addition to vasoconstriction, embolization of the coronary microcirculation can contribute to coronary microvascular dysfunction in patients undergoing percutaneous interventions and coronary bypass surgery. Plaque rupture may follow percutaneous coronary interventions. The material that is washed out of the plaque can be dislodged into the microcirculation[95] and may cause microinfarcts, resulting in increased levels of the markers of tissue necrosis with an effect on long-term mortality (Fig. 4).[96]

CONCLUSIONS

Coronary microvascular dysfunction in the absence of obstructive CAD is the functional counterpart of traditional coronary risk factors. Since this type of dysfunction is at least partly reversible, its assessment might be used to guide interventions aimed at reducing the burden of risk factors. In a subgroup of patients, coronary microvascular dysfunc-

tion caused by traditional coronary risk factors or by yet unknown mechanisms is severe enough to cause myocardial ischemia.[35]

Coronary microvascular dysfunction in the presence of myocardial diseases can be identified in patients with primary or secondary cardiomyopathies, and the assessment of this condition can be useful in risk stratification.[46,54] So far, coronary microvascular dysfunction has not been used as a surrogate for the efficacy of treatment in these patients because the pathogenetic mechanisms involved are still unclear.

The complexity of the assessment of coronary microvascular dysfunction is increased by the presence of obstructive CAD. In patients with stable CAD, coronary microvascular dysfunction should be suspected in those whose symptoms are worse than anticipated on the basis of the severity and extent of angiographic findings.[72] In such patients, coronary microvascular dysfunction might represent a new therapeutic target.[74,75] In patients with acute myocardial infarction, coronary microvascular dysfunction is responsible for the no-reflow phenomenon, which is known to be associated with a worse outcome than in patients without the no-reflow phenomenon.[87,88] The phenomenon is an important but still elusive therapeutic target. Limitation of distal embolization[97] and interventions aimed at reducing microvascular obstruction and vasoconstriction[98] might have a beneficial effect on ventricular remodeling and prognosis.

Iatrogenic coronary microvascular dysfunction after percutaneous interventions seems to revert spontaneously in the weeks after revascularization. Although pharmacologic treatment has been shown to promptly restore coronary flow reserve, its effect on the clinical outcome remains to be determined. Coronary microvascular dysfunction caused by distal embolization is an important therapeutic target. In this setting, the main goal is the prevention of the dysfunction in high-risk procedures.[99]

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