Why should we study the coronary microcirculation?

GIANMARIO SAMBUCETI, ANTONIO L’ABBATE, AND MARIO MARZILLI
Consiglio Nazionale delle Ricerche Institute of Clinical Physiology, 56100 Pisa, Italy

THE QUESTION we are posing to the readers is why should we study the microcirculation of the heart. First, let us define who are “we.” In this issue of the American Journal of Physiology: Heart and Circulatory Physiology, a collection of papers are included as part of a Special Call on “Emerging Concepts in the Control of the Coronary Microcirculation.” It is obvious why the coronary microcirculation should be studied from a basic perspective; even the most seminal reactions, autoregulation and metabolic dilation, are incompletely understood. Our editorial will not highlight basic problems but rather discuss the clinical importance of the coronary microcirculation. Our opinion is that the “we” who should study the coronary microcirculation are both basic scientists and clinicians, so that a much clearer understanding of the role of coronary microvessels in the etiology of ischemic heart disease may be elucidated.

Most cardiologists believe that coronary artery disease is only a disease of large vessels, and there is little microvascular involvement in this pathology. We believe otherwise! In our opinion, abnormal coronary microvascular reactions to many stimuli contribute and possibly cause cardiac pathologies. To put our view in perspective, a case history from our institute provides a useful example (2). Several years ago we were treating a patient with angina pectoris who had rapidly decreasing tolerance to exercise. Coronary angiography documented a single subocclusive stenosis of the left anterior descending coronary artery, which was characterized by a complex morphology. Because of the presence of ischemia, the lesion was thought to be significant, and an angioplasty procedure was performed. Two minutes following successful dilation of the lesion, the patient complained of chest pain while the electrocardiogram monitoring the patient showed S-T segment elevation on the anterior leads. Another angiogram was immediately performed and showed a patent, nonstenotic left coronary artery characterized by a slow antegrade flow of the contrast medium. Measurement of coronary pressure by the balloon catheter did not show significant pressure gradients along the coronary artery, indicating that the resistance to flow was located distally to the epicardial vessel, i.e., in the coronary microcirculation. Despite intracoronary administration of nitrates, the transmural anterior ischemia persisted. The patient underwent emergency bypass grafting; however, at discharge, an anterior infarction was diagnosed with a severe impairment in left ventricular function that required cardiac transplantation in the follow-up. This case history and numerous others (28) with remarkable similarity have been published in the literature. These histories have promulgated the hypothesis that, at least in some patients, the basis for myocardial ischemia could be due to abnormalities in the control of coronary resistance vessels rather than the more generally accepted view that the disease is exclusive to stenotic, epicardial coronary arteries (13).

Difficulty in the clinical evaluation of coronary microvascular function has prevented a complete identification of the role of the coronary microcirculation as a cause of ischemic heart disease. In fact, in patients in whom coronary microvascular dysfunction was initially advocated, these uncertainties led to the naming of this condition syndrome X. The difficulty of diagnosing syndrome X has led to an alternative view; namely, that it does not exist! This opposing view to syndrome X and a culprit role for the coronary microcirculation credits many of the pathophysiological manifestations to alterations in the myocardium and even psychosomatic disorders.

The goal of this review is to cite cogent literature that supports the hypothesis that coronary microvascular dysfunction can produce pathological manifestations in patients with coronary artery disease. Clearly, the potential for the coronary microcirculation to produce cardiac abnormalities exists. For example, intracoronary infusion of the potent constrictor endothelin-1 in a normal experimental animal without coronary disease can produce such severe constriction that ischemia ensues, followed by myocardial dysfunction and often fibrillation (W. Chilian, personal communication).
cations; see also Ref. 9). Thus constriction in some
circumstances has the potential to override ischemia-
induced dilation. Within the context of this editorial,
we will review some situations of ischemic heart dis-
ease in which coronary microvascular dysfunction
seems to cause the malady. We will also summarize
how current understanding of basic coronary physiol-
ogy appears to support our hypothesis for a microvas-
cular role in certain types of ischemic heart disease.

A MICROVASCULAR ROLE IN CORONARY
ARTERY DISEASE?

It is well known that stable coronary disease is char-
acterized by the appearance of symptoms during effort.
The pathophysiology of this condition has been accu-
ately characterized by a number of experimental and
clinical studies. In animal experiments, it is well known
that the severity of epicardial obstruction, usually ob-
tained by external constriction of an otherwise normal
coronary artery, is strictly correlated with the degree of
impairment in maximal flow capacity, which is the in-
crease in flow obtained with pharmacological vasodila-
tion (5). Because autoregulation and metabolic regulation
of blood flow maintain constant rates of myocardial per-
fusion under baseline conditions, the degree of epicardial
stenosis is also correlated with the reduction in the ratio
between maximal and baseline blood flow, i.e., in coro-
nary reserve. This concept has been accurately docu-
mented in a number of experiments and to date repre-
sents an intuitive explanation of the occurrence of ischemia on effort in patients with coronary artery dis-
ease. Nevertheless, this clinical convention (a stenosis is
the only culprit in lessening reserve) is challenged by a
large number of observations. First, the tolerance to ef-
fort markedly varies over time according to the presence
of various, often unpredictable, factors. Second, when
tested in the clinical setting, the relationship between
stenosis severity and coronary flow reserve is character-
ized by large scatter (25, 26). This variance has been
attributed to the presence of diffuse atherosclerosis,
which might prevent a correct angiographic estimation
of stenosis severity (1). Third, in regions perfused by non-
stenotic vessels in patients, several studies documented
an abnormal flow response to many vasodilators: seroto-
nin (4), acetylcholine (15, 29), dipyridamole (17, 24), or
atrial pacing (15, 17). From a clinical standpoint, these
findings strongly suggest the presence of a microvascular
abnormality in patients with coronary artery disease and
point to an important clinical implication; that is to say,
it calls into question the definition of critical stenosis
(refer to the case from our institute described previously).
This phenomenon might explain the limited sensitivity
of myocardial perfusion scintigraphy in the detection of
single vessel coronary artery disease (17).

A major question is whether endothelial dysfunction,
in the absence of coronary disease, could cause im-
proper regulation of coronary resistance vessels to such
an extent that ischemia could result. To this end,
several basic observations provide insight into this
possibility. It is well known that stimuli most active on
distal vascular segments, such as oxygen consumption,

ischemia, or adenosine, primarily exert their vasodila-
tion independently from the endothelium. However,
distal vasodilation also affects proximal tone: it lowers
the distal microvascular resistance and increases
shear stress in the more proximal segments. This in-
crease in shear stress causes flow-dependent dilation of
these segments (6, 8, 14, 20, 21). This pathway offers
some theoretical benefits during changes in flow. Dil-
ation of the proximal segment would allow better trans-
mission of pressure into the microcirculation to facil-
titate water and solute exchange. Also, this mechanism
would prevent excessive dilation of the distal segment
(3), thus preserving vasodilator reserve of small coro-
nary arterioles. Importantly, atherosclerosis impairs
endothelial production of nitric oxide and other endo-
thelial-dependent dilators in response to shear stress
(6, 8). From the preceding discussion, it is not unrea-
sonable to propose that coronary atherosclerosis might
hamper the regulation of vasomotor tone and thus
myocardial perfusion via mechanisms besides the hy-
draulics of epicardial obstruction.

In agreement with the hypothesis based on basic
observations, some observations in the literature chal-
lenge the current dogma of coronary disease: that large
evessel disease is a prerequisite. Recently, Sambuceti
et al. (18) observed that, in patients with single vessel
coronary artery disease, progressive increases in heart
rate were associated with paradoxical increases in coro-
nary resistance leading to angina and S-T segment
depression. Intracoronary administration of adenosine
markedly decreased coronary resistance in all patients
and eliminated, in some cases, the electrocardiographic
signs of ischemia.

The hypothesis of an abnormal microvascular func-
tion has been corroborated by the measurement of coronary reserve following revascularization. After coro-
nary angioplasty, Wilson et al. (27) showed that an
abnormally low coronary flow reserve can persist fol-
lowing angioplasty in a significant fraction of patients.
More recent studies (7) showed that even the optimi-
ization of revascularization by stent deployment does
not always result in the restoration of a normal vaso-
dilating capability. Although it is well known that
coronary angioplasty might per se affect microvascular
function, abnormal recovery of coronary-vasodilating
capability following revascularization is more fre-
quently observed in those patients who have evidence
of an improper coronary microvascular function already
before the procedure. In fact, preliminary data ob-
tained in our institute indicate that patients with low
values of coronary reserve following revascularization
show high minimal resistance also before angioplasty
as measured by monitoring of coronary blood flow and
distal coronary pressure following administration of
adenosine (12). These data indicate that regulation of
coronary microvascular function might be profoundly
altered in patients with coronary artery disease and
that this disorder might contribute to the precipitation
of ischemia in these patients.
The study of coronary microvascular function in patients with acute coronary syndromes is particularly difficult because of their unpredictable presentation. Only recently the study of microvascular resistance has been possible in patients with unstable angina by the continuous monitoring of coronary blood flow and transstenotic pressure gradient. With this methodology, it has been possible to separate the contribution of atherosclerotic plaque and distal coronary microcirculation during transient ischemia in patients with unstable angina. Marzilli and co-workers (11) documented that transient ischemia was associated with a marked increase in coronary microvascular resistance in patients with unstable angina. Importantly, adenosine caused dramatic dilation of the coronary microcirculation. Furthermore, preliminary data (19) indicate that the beneficial effect of the glycoprotein IIB/IIIa antagonists might also be due to the effect of this molecule on microvascular function. In fact, in patients with unstable angina, administration of abciximab induced an early reduction in baseline and minimal resistance at the level of coronary microvasculature without any significant effect at the level of coronary plaque.

A MICROVASCULAR ROLE IN MYOCARDIAL INFARCTION?

Traditionally, myocardial infarction is thought to be exclusively related to large vessel disease (critical stenosis, spasm, or thrombus). However, as we mentioned in our first case report, there may be the possibility that inappropriate microvascular constriction may cause myocardial infarction. Several studies suggest the presence of a coronary microvascular involvement in patients with acute myocardial infarction. In this setting, of course, the study of a pathophysiological role for this vascular compartment is particularly difficult because patients undergo diagnostic evaluation after the precipitation of ischemia. Under this condition, ischemia and reperfusion can affect per se coronary microvascular function, and this has been extensively documented both in the clinical setting and in experimental models (22). However, some observations suggest a peculiarity of the clinical model of myocardial infarction with respect to microvascular function. In fact, Uren and co-workers (23) studied, by positron emission tomography, a group of patients with acute myocardial infarction and single vessel disease, paying attention to myocardial regions remote to infarction and supplied by nonstenotic coronary arteries (23). Using this methodology, these authors documented that microvascular response to dipyridamole is particularly impaired soon after the episode and shows a progressive improvement over time. The mechanisms of these phenomena have not been conclusively investigated; however, they strongly suggest the presence of a microvascular abnormality at least in the early days following acute infarction. In agreement with this hypothesis, Neumann and co-workers (16) documented that the administration abciximab can improve microvascular function following primary angioplasty for acute myocardial infarction. Moreover, Marzilli and co-workers (10) treated the ischemic myocardium with adenosine before primary percutaneous transluminal coronary angioplasty for acute myocardial infarction, and they observed a marked beneficial effect of this maneuver on mortality in a small group of patients. The result of this pilot study strongly suggests that administration of drugs that “target” the coronary microcirculation of the ischemic myocardium can improve the results of therapies in the setting of acute ischemic syndromes.

In summary, from the above discourse, we can summarize three important concepts. First, paradoxical coronary microvascular constriction occurs in some patients during increases in oxygen consumption and during attacks of unstable angina. Second, dilation of the microcirculation reduces the severity of ischemia in many patients with the above symptoms. Finally, interventions aimed at treating the coronary microvasculature can improve outcomes of many patients with coronary artery disease. Thus the answer to why should we study the coronary microcirculation hopefully has become even more obvious: to further our understanding of both coronary physiology and the pathophysiology of ischemic heart disease.

REFERENCES

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