Editorial

Coronary Microcirculation and Ischemic Heart Disease, Today

Abstract: This article summarizes several contributions on the coronary microcirculation. Many of the participant authors belong to the Working Group on Coronary Pathophysiology and Microcirculation of European Society of Cardiology. These contributions explored a variety of topics pertaining to coronary microvascular physiology and pathophysiology. The latest methodologies that are being used to investigate the coronary microvasculature, including myocardial contrast echocardiography, fractional flow reserve and and instantaneous wave-free ratio, are discussed. Advances in the mechanisms of dysfunction of the coronary microcirculation – for example, enhanced arginase activity and production of free radicals by dyslipidemia or hyperhomocysteinemia and its myogenic and flow-dependent responses—are reported. The articles touched on the relation of the microcirculation to clinically important conditions, such as the coronary no reflow phenomenon and offered recommendations for future research in important areas, such as angiogenesis and restoration of the microvascular network. This research is providing new ways to explore abnormalities of myocardial perfusion and its relationship with post infarction myocardial damage, an area of inquiry that until recently has been limited to examination of coronary pressure-flow relationships using doppler wire-based measures.

Keywords: Microcirculation, no reflow, vasospastic angina, myocardium, angiogenesis, dyslipidemia.

THE MICROCIRCULATION AND THE HEART

The coronary microcirculation has the significant function of maintaining the proper balance between oxygen supply and oxygen demands. To accomplish this task the resistance vessels of the heart integrate the input from many intrinsic vasodilator and vasoconstrictor signals. The goal is to discuss the innumerable outside inputs in the context of their actions on coronary blood flow and coronary resistance vessels. Many pathophysiological disturbances may alter the regulatory processes within the coronary microcirculation. Many are the clinical conditions that can be associated with microcirculatory disorders including ischemic heart disease.

RECENT PHYSIOLOGICAL FINDINGS AND CLINICAL ASPECTS OF THE CORONARY MICROCIRCULATION

We refer the reader first to the papers by Axel R. Pries et al. [1] and Lucian Calmac et al. [2] for a detailed discourse on regulation of microcirculation in patients with stable coronary artery disease. It has become increasingly apparent that microvascular dysfunction can aggravate tissue hypoxia and maintain a compromised state even after recanalization of the epicardial vessels. Single-photon emission computed tomography performed six months after Percutaneous Coronary Intervention (PCI) in normocholesterolemic patients shows reversible perfusion defects in 3% of patients treated with pravastatin and in 29% of those with placebo [3]. These data support the hypothesis of a protective vascular action of statins on an otherwise compromised coronary microcirculation.

Generally, small arterioles respond differently than larger arterioles and small arteries. However, there are neural interactions between small and large arteries, and arterioles which may account for some similarities in the development of coronary tone abnormalities in both the epicardial and endocardial segments. The epicardial and intramyocardial coronary arteries are densely innervated by postganglionic sympathetic and parasympathetic nerve fibers. Therefore, norepinephrine and acetylcholine released from these fibers interact with coronary adrenergic and muscarinic receptors to control coronary vascular resistance. The paper by Edina Cenko et al. clearly shows that the microcirculation is still the major culprit in patients having vasotonic angina or diffuse coronary epicardial artery spasm [4]. The primary cause of coronary vasospasm is coronary hyperreactivity that is commonly due to a deficiency in endothelial nitric oxide. Oxygen-derived free radicals scavenge and rapidly inactivate nitric oxide, thereby promoting coronary endothelial dysfunction and constriction of both the large and small coronary arteries even in myocardial sites remote from the ischemic region [5]. Further mechanisms that contribute to the regulation of coronary blood flow include the metabolic activity of the myocardium. The papers by Akos Koller et al. [6] and Teresa Padro et al. [7] show that hyperhomocysteinemia and dyslipidemia may affect myocardial cellular function of the resistive vessels. The pathogenic mechanisms underlying the relationship between microvascular dysfunction and dyslipidemia involve an enhanced arginase activity and production of free radicals with recruitment and accumulation of leukocytes through their diffusion in the post-capillary venules. Hyperhomocysteinemia dependent mechanisms seem to preferentially modulate tone in small arteries by increasing the uptake of glucose and lactate and decreasing the uptake of free fatty acid by the heart. Metabolic control mechanisms seem the most important, because they link flow to metabolism and are involved in ischemic vasodilation.

CORONARY NO-REFLOW

Many of the well-accepted risk factors for no-reflow are the traditional cardiovascular risk factors, such as hypertension, smoking, dyslipidemia, diabetes, and other inflammatory processes. The most important seems to be hypercholesterolemia [8]. As such, in individuals with hyperlipidemia, intensive statin therapy before PCI is beneficial in reducing no-reflow. In a meta-analysis of 7 studies that examined 3,086 patients treated with statins before PCI, there was a complete prevention of no-reflow in 4.2% of patients treated with high dose statins, compared with control patients receiving placebo, usual care, or lower dose statin therapy [9]. Coronary no-reflow phenomenon occurs when cardiac tissue fails to perfuse normally despite opening of the occluded vessel. The paper by Marialuisa Scarpone et al. [10] demonstrates that often after prolonged occlusion the cardiac tissue did not recuperate normal perfusion despite opening of the large epicardial coronary arteries, indicating that prolonged ischemia leads to damage of the microvasculature and precludes normal perfusion. The mechanism by which prolonged occlusion triggers the damage to the microcirculation is still unclear. Some recent work has suggested a role for the endothelial glyocalyx. The Endothelial Glyocalyx (EG) is an uneven soft polysaccharide coating over the vascular wall toward the vessel lumen. Changes in the glyocalyx lead to the alteration of the transendothelial permeability, thereby causing the swelling of the endothelial cells, which is one of the regulatory factors for functional capillary density. Rapid development of myocardial tissue edema may facilitate the impact of vasoactive peptides such as endothelin and angiotensin on the microcirculation, which, in turn, may deteriorate vessel diameter and flow, leading to the no reflow as illustrated by Evangelos Oikonomou et al. [11].
MEASUREMENTS OF THE CORONARY MICROCIRCULATION

Although the focus of this special issue of *Current Pharmaceutical Design* is on the regulatory mechanisms of the microcirculation and their translation to targets in clinical practice, it is important as well to highlight some methods that may be able to assess the distribution and regulation of resistance vessels across the wall of the left ventricle in clinical practice [12]. A number of noninvasive modalities are able to accurately assess microvascular dysfunction as shown by the paper by Danijela Trifunovic et al. [13]; however, these are not readily available in the catheterization laboratory and can be challenging to use in acutely ill patients, as those presenting with no reflow after PCI. For these reasons, there has been long-standing interest in developing invasive methods for assessing microvascular function in the catheterization laboratory. A number of Doppler wire-based measures are described by the paper of Sasko Kedev et al. [14]. The findings from this study confirm those of previous studies showing that Fractional Flow Reserve (FFR) and instantaneous wave Free Ratio (iFR) measured at the time of catheterization correlate with evidence of microvascular dysfunction on noninvasive imaging.

FUTURE DIRECTIONS

With this background in mind, it is interesting to read the reports by Davor Milicic et al. [15] and Zorana Vasiljevic et al. [16]. These papers focused on the role of microcirculation in congestive heart failure. Still, there is no solid proof to directly correlate coronary microvascular dysfunction to heart failure in human patients to date, which is probably due to the lack of proper models and the need for more advanced finer techniques. Much more importantly, there is no single drug regimen that could effectively reverse cardiac dysfunction after myocardial infarction. The paper by Lina Badimon et al. [17] offers an overview of the relationship between angiogenesis and the coronary microcirculation. The restoration of the microvascular network, which has been damaged during ischemia as well as upon reperfusion, appears a promising approach to refrain the deleterious effects of coronary obstruction. Monocytes can trans-differentiate into endothelial cell-like promoting angiogenesis. In rodents, both growth factors and cell therapy can induce angiogenesis. However, uncertainties and controversies still remain. In this regard, the most common questions are: what type of cells can be primarily regenerated by angiogenesis: myocytes or endothelial cells? Are these cells able to strengthen cardiac performance? The answers to these questions may largely addresses our difficulty in understanding the mechanisms underlying the restoration of the microvascular network as well as myocardium after myocardial infarction. Human trials performed to stimulate angiogenesis in patients undergoing primary PCI have mostly failed. Investigating thoroughly the potential of different subsets of monocytes/macrophages in angiogenesis promotion, as well as the study of their receptors are needed to develop and optimize future therapies aimed to restore myocardial function after ischemia.

In summary in this issue of *Current Pharmaceutical Design*, we summarized several aspects of control mechanisms that govern the level and the size of the coronary microcirculation: endothelial and myogenic control mechanisms in the coronary microcirculation and the translation in their clinical counterparts.

REFERENCES


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