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Review Article

Cardiac Microvascular Disease - A Complex Diagnosis?

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ABSTRACT

Diagnosing microvascular disease in a continuously moving organ like the contracting heart is difficult. Although we have a wide range of (non)invasive diagnostic tools available it is still a challenge to reach a solid conclusion. In many patients there is also a combination of risk factors inducing several disease causing mechanisms further obscuring classification strategies. More research will be crucial going from histology to function to determine the position of microvascular disease in patients with unexplained chest pain.

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Microvascular disease represents an entity, that is being used to explain several diseases that we find difficult to classify or even diagnose. In cardiac disease we believe that microvascular disease plays a key role in the development atrial fibrillation, heart failure with preserved ejection fraction, diabetic cardiomyopathy and anginal complaints without overt obstructive epicardial arterial disease potentially even leading to myocardial infarction (MINOCA). For some conditions we have clear evidence that microvascular disease can be documented, for instance in diabetes. The impaired perfusion in diabetes of various tissues including the extremities is well documented mainly involving the legs and feet. In addition to impaired microvasculature there is impaired functional collateral formation, although there is a non-functional angiogenesis response. The outcome of a diabetic foot is well described leading to pain, ulceration, necrosis and in many cases to the amputation of toes and sometimes feet or lower leg. The ischemia in diabetic tissue is not only the consequence of morphological changes to the vessel wall, clearly the function must be impaired as well. We have less data on the effect of diabetes induced microvascular disease in the heart.

Some studies couple end organ damage to microvascular disease, without demonstrating any direct microvascular impairment [1]. End organ damage is judged by looking at neuropathy, retinopathy and albuminuria. Probably the best studied organ here is the retina. There we see a combination of occluded vessels, microaneurysms, hemorrhages, cotton-wool spots, venous bleeding, vascular loops, vascular leakage and neovascularizations [2]. Indicating the complexity of the disease as both the arterial and venous side are involved. The most important assay used to determine function of the retina is by judging the vision. There are no well documented microvascular functional assays that are being used on a routine basis. There are however very sophisticated tools to image the retinal vessels including optical coherence tomography [3]. Although they are very useful in research, they have limited value in clinical care. The morphological changes are not translated into adjusted treatment.

In general, the morphological and functional studies in brain are better established compared with the heart. So, what is microvascular disease of the brain? Also, there the field is struggling to come to solid definitions. For instance, microvascular disease or small vessel ischemic disease is associated with depression, cognitive functional loss and stroke [4]. Basically, again end organ damage without an obvious histological substrate. There are links between small vessel disease and

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brain abnormalities based on MRI imaging [5]. Grool *et al.* showed that late-life depression and cognitive impairment are both related to underlying infarcts possibly by the disruption of emotion-regulating pathways in the frontal lobe. The difficulty to match histological changes to imaging was highlighted by Yilmazer-Hanke *et al.* The group showed that postmortem ultra-high-resolution imaging improved MRI-histological matching [6].

However, the structural characterization of chronic cortical cerebral microinfarcts, miniscule microinfarcts without thinning or iron accumulation could not be detected with certainty in the MRI scans. Even in the immobilized brain it is hard to detect all aspects of microvascular disease. Yet in general the concept of microvascular disease is accepted and provides a working hypothesis for many conditions in vascular patients. The vascular changes have been well studied in the brain and kidney and provide a wide spectrum of changes well described by pathologists. Diseases of small vessels often occur in the context of vascular cell activation. Intimal hyperplasia results from the accumulation of smooth muscle cells within. Diabetic changes involve the accumulation of plasma proteins within the vessel wall, whereas amyloid vasculopathy results from the deposition of misfolded proteins in the vessel wall. Vasculitis is inflammation in the vessel wall. Vasculitis of small vessels is primarily due to the deposition of immune complexes or to the presence of cytoplasmic antibodies. Kawasaki arteritis often involves the coronaries in the very young, while giant cell arteritis often involves the cranial arteries in the elderly [7].

With respect to the heart we encounter the difficulty to use our currently available imaging techniques to determine vascular function and also morphology. Standard techniques are MRI and CT scan providing us useful data on the epicardial vessels but limited or no info on the microvasculature. It is possible to perform perfusion MRI to combine morphological assessment of the coronary tree with functional changes. CT based fractional flow reserve (FFR) is a new technology allowing us to determine flow in the epicardial section of the coronaries, useful but limited to the larger vessels. Pet scans may lack the resolution required to identify the local microvascular changes and are not available in every institute. Yet at this point these scans are the best imaging solution to detect impaired myocardial perfusion, however not coronary vasospasm. Additional diagnostic tools have been tried including non-invasive tissue volume measurements (MRI and ECHO) and doppler measurements of LAD flow.

What else do we have available? Invasive procedures determining the vascular resistance and coronary flow reserve have been developed and the intramyocardial resistance can be measured. Both the noninvasive and invasive diagnostics can be combined with pharmacological challenges in order to determine functional susceptibility and impairment. Coronary spasm is inducible in many individuals. The combination of complaints and spasm could be considered clinically useful. Nothing is known on morphological changes and function of the cardiac venous system. Yet there must be venous impairment coming with microvasculature disease [2]. Reports on cardiac histopathological findings are missing. So, from the morphological site we are left in the literal darkness.

Is the clinic going to help us by focusing on symptoms: Chronic stable angina is precipitated by exercise-induced or emotional stress-induced ischemia in patients with coronary flow-limiting atherosclerotic stenosis in the epicardial vessels? Several factors contribute to an increase in myocardial oxygen demand, like heart rate, blood pressure or afterload, myocardial wall tension, cardiac hypertrophy, and increased myocardial contractility. Conversely, the major determinants of oxygen delivery include coronary flow, depending on the pressure gradient over the coronary system and the integrity of the coronary arteries, as well as on the oxygen-transport capacity of the blood [8]. Under physiological conditions, an increased oxygen demand is met by an increase in coronary blood flow as a consequence of dilatation of coronary arteries, which does not occur in patients with atherosclerotic lesions.

In a subgroup of patients, myocardial ischemia can persist or reoccur after having undergone successful complete coronary revascularization. Autopsy studies of patients with chronic stable angina suggest that coronary artery obstruction is not necessarily synonymous with myocardial ischemia. Therefore, myocardial ischemia can occur in the absence of obstructive coronary atherosclerosis. In the majority of these patients, chronic stable angina is caused by coronary microvascular dysfunction. This condition is named microvascular angina, which often pertains to women with symptoms of chronic stable angina, normal or near-normal coronary arteries, and evidence of ischemia during stress testing or during provocation testing defining impaired flow reserve, increased resistance or microvascular spasm. Microvascular angina might occur in up to 40% of patients with angina. This high percentage, however, includes patients with chronic stable angina with suspected ischemia, but without solid proof [9].

Another circumstance in which the coronary arteries might appear normal upon angiography is with vasospastic angina. Spasm related angina presents with specific characteristics as the pain is not triggered by exercise but occurs at rest. Vasospasm can be evoked by various triggers and needs specific diagnostic tests and therapies. A certain degree of coronary spasm might also be superimposed on a moderate atherosclerotic stenosis, which becomes occlusive and therefore symptomatic when the vascular smooth muscle constricts.

Gould proposed a rather simple classification [10]. The various causes and mechanisms of chronic stable angina without obstructive coronary artery disease can be grouped into three broad categories: noncardiac, cardiac nonischemic, and cardiac ischemic causes. Microvascular angina encompasses a wide spectrum of coronary pathophysiology. He suggests combined invasive regional absolute stress flow, relative stress flow, coronary flow reserve, and noninvasive qualitative subendocardial perfusion gradient on tomograms, provides correct diagnosis. In addition, it facilitates quantitative physiological classification, and direction to potential treatment. Angina without angiographic stenosis is associated with abnormal quantitative perfusion with rare exceptions.

However, microvascular dysfunction without angina is common, particularly associated with classical risk factors. Based on precision quantitative myocardial perfusion in angina with no angiographic stenosis a classification into 4 categories is proposed: 1) subendocardial ischemia due to diffuse coronary artery disease, 2) overlooked stenosis, 3) diffuse microvascular dysfunction due to risk factors or specific micro

vasculopathies, and 4) Nonischemic cardiac pain or some mix of these mechanisms, of which the majority is associated with risk factors, or (sub)clinically manifest coronary artery disease needing aggressive risk factor treatment [10].

There is an unmet need to come with a novel approach to determine the role of microvascular disorder in cardiovascular disease. Studies to compare the various approaches in a systematic and organized manner are essential to move the field forward. Protocols should be unified, exchanged and used on a multicenter base. It is unclear what the current gold standard is to determine the presence or absence of small vessel dysfunction. With respect to the treatment, there is consensus that reducing risk factors is important, yet a customized treatment is beyond the horizon for cardiac small vessel disease [11]. The cardiac field should work close with ophthalmology, neurology and nephrology to speed up the process and use the available knowledge.

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