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The metabolic-microvascular dysregulation syndrome☆

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Introduction

The McDonald Lecture honours Donald Arthur McDonald (1917-1973), a British physiologist who established the modern approach to the study of arterial haemodynamics over a 20-year period from 1953-1973. His work established the logic of using Fourier analysis to break down pressure and flow waves, and developed the general concept of vascular impedance.[1] His classic book on blood flow in arteries was published in 1960,[2] and has remained a basic treatise in this field for more than 50 years.[3] Linking with engineers and with physicians, he influenced many young physicians and physiologists. He directed work into the clinical sphere while continuing in basic physiology and haemodynamics.[1] Donald McDonald thus is an intellectual godfather of the ARTERY society, and I am honoured to present the 2017 McDonald Lecture.

ARTERY's goal is to promote the advancement of knowledge and dissemination of information concerning the pathophysiology, pharmacology, epidemiology, detection, investigation and treatment of arterial structure and function. Thus its goal is to further the understanding of human diseases from the point of view of large artery structure and function. As a clinical scientist, I submit that understanding human disease is impossible without crossing borders, notably that from large arteries to the microcirculation. Indeed, the society's journal, *Artery Research*, publishes papers not only in the classic domain of arterial structure and function and its interaction with various organs such as the heart, kidney and brain, but has on occasion published papers that focus entirely on the microcirculation.[4,5]

The microcirculation is widely taken to encompass vessels <150 μm in diameter. It therefore includes arterioles, capillaries, and venules. A definition based on arterial vessel physiology rather than diameter or structure has also

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been proposed, depending on the response of the isolated vessel to increased internal pressure. By this definition, all vessels that respond to increasing pressure with a myogenic reduction in lumen diameter are considered part of the microcirculation, including the smallest arteries and arterioles in addition to capillaries and venules. A primary function of the microcirculation is *metabolic*, to optimize the delivery of nutrients and removal of waste products in response to variations in demand. A second important function is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries that otherwise would impair capillary exchange. Finally, it is at the level of the microcirculation that a substantial proportion of the drop in hydrostatic pressure occurs. The microcirculation is, therefore, extremely important in determining the overall peripheral resistance. In normal conditions, systemic, regional, and local metabolic and myogenic autoregulatory mechanisms ensure adequate progress of these microcirculatory functions. In pathological conditions, however, the loss of such mechanisms results in the development of microvascular dysfunction.[6]

At the ARTERY14 meeting, in 2014, Alun Hughes elegantly considered the design of the circulation (large and small vessels) from the point of view of optimality and cost minimization.[7] In this McDonald Lecture, I shall take this one step further and develop *the concept that microvascular and metabolic physiology are inextricably linked*. Indeed, I shall postulate that dysfunction of the one causes dysfunction of the other, justifying the concept of a 'Metabolic-Microvascular Dysregulation Syndrome'.

Microvascular consequences of metabolic dysregulation

Diabetic retinopathy is the classic example of the link between metabolism and microvessels. In diabetic retinopathy, metabolic dysregulation (hyperglycaemia) causes many microvascular changes, such as microaneurysms, haemorrhages, and hard and soft exudates.[8] There is convincing evidence that the link is causal; thus, reduction of hyperglycaemia reduces onset and progression of retinopathy.[9,10]

Diabetic nephropathy is a second example. Morphologically, diabetic nephropathy is less exclusively microvascular than is diabetic retinopathy, and is characterized by arteriolar hyalinosis but most typically by glomerular basement membrane thickening and mesangial expansion.[11] Nevertheless, microvascular endothelial dysfunction has been shown to be a core feature of diabetic nephropathy. Functionally, there is first an increase in glomerular filtration rate (hyperfiltration), followed by a steady decrease over time. In parallel, urinary albumin excretion increases from normal (<30 mg/24h) to microalbuminuria (30-300 mg/24h) and macroalbuminuria (>300 mg/24h).[12] It is in the urinary leakage of albumin that microvascular endothelial dysfunction is especially important. A key observation, in the 1980s and 1990s, was that in type 2 diabetes, type 1 diabetes and in the general population even a slight increase in urinary albumin excretion (microalbuminuria) was associated with a large increase in risk of cardiovascular events.[13-15] This association has in many studies been shown to be independent of conventional risk factors and persists over many years.[16] From renal physiology it follows that excess albuminuria must be explained by excess permeation across the glomerular capillary wall (itself dependent on glomerular pressure, permeability and surface area) and/or impaired renal tubular reabsorption.[17] Cell types involved include podocytes, microvascular (arteriolar and glomerular) endothelial cells, mesangial cells and tubular cells. Of these, endothelial cells, if dysfunctional not only in the kidney but also elsewhere, could potentially explain the link between microalbuminuria and cardiovascular disease (i.e., atherothrombosis).

In late 1980s, we set out to investigate this concept with then available markers of microvascular endothelial dysfunction, such as plasma levels of von Willebrand factor and, later, of adhesion molecules (sVCAM-1, sICAM-1, sE-selectin). We found that levels of such biomarkers were strongly associated with onset and progression of microalbuminuria in type 1 and type 2 diabetes as well as in the general population,[18-20] as reviewed elsewhere.[21] It took many years to develop more direct methods to investigate microvascular endothelial function at the population level.[22] Studies using such methods further supported the concept of microalbuminuria as a marker of microvascular endothelial dysfunction. In the Maastricht Study,[23] albuminuria was associated with capillary density (assessed in skin),[24] heat-induced microvascular dilation (also assessed in skin), and flicker-light-induced arteriolar dilation (assessed in the retina) (Martens et al, unpublished observations).

Taken together, these findings establish that relatively severe hyperglycaemia, as in diabetes, can cause microvascular disease (retinopathy and albuminuria). We recently showed that less severe hyperglycaemia (prediabetes) is also associated with microvascular dysfunction. The association between glycaemia and microvascular dysfunction in fact appears not to have a threshold and can be demonstrated in skin[25,26], retina[25,26] and brain, in the latter as white matter hyperintensities (Van Agtmaal et al, unpublished observations), which are thought to represent cerebral small vessel disease.

Microvascular dysfunction demonstrated with such methods is clinically relevant. For example, biomarkers of microvascular dysfunction are associated with depression both cross-sectionally and longitudinally;[27,28] microalbuminuria is associated not only with myocardial infarction and stroke but also with depression[27,28] and impairment of cognitive function;[29] and white matter hyperintensities predict stroke, dementia, depression and mortality (Rensma et al, unpublished observations).

Taken together, there is a continuous, presumably causal, association between glycaemia and microvascular dysfunction, which does not have a clear threshold, and which predisposes to clinical disease.

Metabolic consequences of microvascular dysregulation

Observations over the past 25 years have convincingly shown that microvascular dysregulation impairs normal