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Update: Systemic diseases and the cardiovascular system (V)

Retinal Vascular Signs: A Window to the Heart?

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ABSTRACT

There is increasing recognition that coronary microvascular dysfunction also plays an important role in coronary heart disease. Little is known about this aspect of coronary heart disease due to difficulties in studying the coronary microcirculation directly. The retina is a unique site where the microcirculation can be imaged directly, providing an opportunity to study *in vivo* the structure and pathology of the human circulation and the possibility of detecting changes in microvasculature relating to the development of cardiovascular disease. This review covers the recent progress in research linking retinal vascular signs to coronary heart disease, and finds accumulating evidence that retinal vascular signs may provide a window into the health of the coronary microvasculature. The most widely studied signs, arteriolar narrowing, and more recently, venular dilation, are likely associated with increased risk of coronary heart disease in women, independent of traditional risk factors. Attempts to improve coronary heart disease risk prediction by incorporating retinal vessel caliber size into risk prediction scores complementing traditional algorithms such as the Framingham risk scores have so far been disappointing. Research is ongoing into the predictive utility of other retinal vascular signs. Retinal photography provides long-lasting records that enable monitoring of longitudinal changes in these retinal signs and vascular health.

Manifestaciones vasculares retinianas: ¿reflejan el estado del corazón?

Palabras clave:
Cardiopatía coronaria
Síndrome metabólico
Pruebas de imagen
Microvasculatura

RESUMEN

La importancia de la disfunción microvascular en la cardiopatía coronaria está cobrando cada vez más peso. Se sabe poco sobre este aspecto de la cardiopatía coronaria debido a las dificultades para estudiar la microcirculación coronaria directamente. La retina es el único sitio donde se puede obtener imágenes de los capilares directamente, lo que nos da la oportunidad de estudiar *in vivo* la estructura y la patología de la circulación humana, así como la posibilidad de detectar cambios microvasculares relacionados con el desarrollo de enfermedades cardiovasculares. Esta revisión abarca los últimos avances en investigación, que vinculan las manifestaciones vasculares retinianas con la cardiopatía coronaria, y pone de manifiesto la abundante evidencia científica encontrada de que las manifestaciones vasculares retinianas pueden reflejar el estado de la microvasculatura coronaria. Es probable que las manifestaciones más estudiadas, el estrechamiento de las arteriolas y, más recientemente, la dilatación de las vénulas, estén relacionadas, independientemente de los factores de riesgo tradicionales, con un elevado riesgo de cardiopatía coronaria en las mujeres. Hasta ahora se han visto frustrados los intentos por mejorar la predicción del riesgo de cardiopatía coronaria, que se centraban en la incorporación, como complemento de algoritmos tradicionales como el de Framingham, del caliber de los vasos de la retina a los sistemas de puntuación de predicción del riesgo. Sin embargo, actualmente se están realizando investigaciones sobre el valor predictivo de otras manifestaciones vasculares de la retina. Las fotografías de la retina nos ofrecen registros duraderos que permiten controlar los cambios longitudinales de estas manifestaciones y de la salud vascular.

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death worldwide. While the majority of CHD is attributable to coronary artery disease in the epicardial coronary arteries, there is increasing recognition that coronary microvascular dysfunction also plays an important role in CHD.[1,2] Little is known about this

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Abbreviations

ARIC: Atherosclerosis Risk in Communities study
AVR: arteriole to venule ratio
BDES: Beaver Dam Eye Study
BMES: Blue Mountains Eye Study
BP: blood pressure
CHD: coronary heart disease
RVO: retinal vein occlusion

aspect of CHD due to difficulties in studying the coronary microcirculation directly.

ROLE OF SMALL VESSEL DISEASE IN CORONARY HEART DISEASE

There is a subgroup of patients who present with angina-like chest pains, but when they undergo coronary catheterization and angiography are found to have minimal atherosclerotic plaques, a condition commonly known as cardiac syndrome X.[1,2] It is believed that this group of patients has coronary microvascular dysfunction, based on electrocardiographic evidence of ST-segment depression during spontaneous or stress-induced chest pain, as well as reversible stress-induced defects in myocardial perfusion.[3] However, confirming the diagnosis of microvascular dysfunction is difficult due to the lack of noninvasive modalities to image the coronary microcirculation. The microvasculature changes that underlie angina attacks are also unclear, and may be related to focal ischemia in small myocardial regions caused by pre-arteriolar dysfunction.[4] This phenomenon of syndrome X appears to occur more commonly in women and in persons with diabetes.[1] Diabetes is known to have profound effects on the microvasculature, supporting a microvascular role in syndrome X.

Analogous evidence supporting a parallel role of microvascular disease in some angina cases comes from the role of microvascular disease in some subtypes of stroke. Lacunar stroke, accounting for a quarter of ischemic stroke cases,[5,6] is known from magnetic resonance imaging and autopsy studies to be a disease of small cerebral penetrating arteries, although exact underlying small vessel pathologies are still uncertain.[7–9] Recently, there has been renewed interest in studying the microvascular aspects of acute stroke, in an attempt to better understand various causes of acute stroke and thus better target therapies and improve rehabilitation outcomes. It may be that cardiac syndrome X is the cardiac equivalent of lacunar stroke.

RETINAL IMAGING AND RETINAL VASCULAR SIGNS

The retina is a unique site where the microcirculation can be imaged directly, providing an opportunity to study *in vivo* the structure and pathology of the human circulation and the possibility of detecting changes in the microvasculature relating to the development of cardiovascular disease.[10–12] Further, the retinal vasculature can be viewed directly not only by ophthalmoscopy but also photography, enabling lasting records over a series of time points. These photographic records can be magnified and studied in detail at a later time. Recent technological advances in high resolution digital photography and image processing software programs[13–15] have enabled quantitative and reproducible measurement of various changes in the retinal vasculature, termed retinal vascular signs in this review. Figure 1 shows the application of an image software program to measure retinal arteriolar and venular caliber.

An important observation from initial studies is that various retinal vascular signs, including isolated microaneurysms and hemorrhages, focal arteriolar narrowing, and arterio-venous nicking, are relatively common in the adult population, and are detectable from retinal photographs in 2% to 14% of the nondiabetic population of adults aged over 40 years,[16–19] with new signs developing in 6% to 10% of people every 5 years.[20–22] Figure 2 provides some examples of these signs, which if severe can be detected on dilated ophthalmoscopy.

Histopathological studies have demonstrated that these retinal signs reflect vascular damage from aging, hypertension, and other processes.[12,23,24] Pathological studies have further suggested that retinal signs are closely related to microvascular pathologies of other organs (eg, in persons with hypertension, the retinal arteriole narrows and its media thickens and develops scleroses).[12] Similar sclerotic changes have been observed in intramyocardial small arterioles, which in the presence of hypertension show luminal narrowing as in the retina.[25,26] Increased media to lumen ratio of arteries in subcutaneous fat independently predicts risk of cardiovascular disease events including myocardial infarction.[27,28] Biopsies of these subcutaneous small arteries (usually obtained from gluteal biopsies) indicate that vascular remodeling is one of the first manifestations of target organ damage, occurring before proteinuria or cardiac hypertrophy, and that it is a reversible, dynamic process.[29,30] Of clinical importance, the magnitude of remodeling of small arteries has prognostic significance over a 10-year period, with worse prognosis for hypertensive subjects with greater magnitude of remodeling.[27] Arterioles have a similar structure to small arteries but less elastic and muscular fibers. The retinal vessels offer access to study these small arterial and arteriolar changes noninvasively.

Our group and other investigators have recently applied retinal microvascular imaging to study microvascular pathologies among acute stroke patients.[31,32] Findings from these studies showed a distinct range of retinal vascular signs more frequently associated with acute lacunar stroke compared to other ischemic stroke subtypes, supporting the view of predominantly localized arteriolar pathologies in the pathogenesis of lacunar stroke, and also suggesting a potential for retinal imaging to be used in studying small vessel disease.[31,32]

Analogous to the link between the retina and the brain, there are indications that retinal vascular changes parallel pathological changes in both the coronary micro- and macro-circulation.[33] In a study of 234 participants free from CHD, retinal arteriolar narrowing was strongly associated with reduced myocardial perfusion measures on cardiac magnetic resonance imaging.[33] In other studies, retinopathy lesions were correlated with coronary artery calcification (measured on cardiac computed tomography scanning) in a dose response manner, with more severe lesions associated with worse coronary artery disease on angiography.[34,35] Thus there are suggestive anatomical, physiological and pathological reasons to believe that changes in the retinal microvasculature may be useful indicators of the vascular structural pathologies of the coronary micro-circulation,[36] and that noninvasive retinal assessment may assist CHD risk stratification.[36]

Different Retinal Vascular Signs Are Associated With Different Coronary Heart Disease Risk Factors

A number of studies have reported that retinal vascular signs are associated with chronic elevation of blood pressure (BP)[14,37–39] and systemic markers of inflammation and endothelial dysfunction.[39–42] Studies have demonstrated that narrower retinal arterioles are strongly correlated with elevated ambient BP, and less strongly with prior BP levels.[43] A consistent gradient of