Retinal microvascular damage and nocturnal hypertension: Therapeutic targets to bear in mind

Repercussão microvascular retineana e hipertensão noturna – alvos terapêuticos a não esquecer

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Assessing the severity of hypertension entails study of damage to target organs, including the retina. Fundoscopy is an important test for this purpose, providing easy direct observation in vivo of the retinal microvasculature, which anatomically and physiologically bears close similarities to cerebral, coronary and renal microvasculature.\(^1,2\) The relationship between alterations in the retinal vasculature, assessed qualitatively by fundoscopy using the Keith-Wagener-Barker or Scheie classification systems, and current or previous high blood pressure (BP) has been amply demonstrated, as has their prognostic value for cardiovascular and renal morbidity and mortality, especially in the case of exudative retinopathy.\(^1,3\) However, the predictive value of less severe alterations such as arteriolar narrowing, widening of the light reflex and arteriovenous nicking is more uncertain, given the subjective nature of their assessment.\(^2,4\) Recent studies using semi-automated computer-based retinal imaging programs applied to high-definition digital photographs and laser Doppler flowmetry, among other techniques, have provided detailed data, not only qualitative but, importantly, quantitative, on a range of parameters of the retinal vasculature including arteriolar wall-to-lumen ratio, caliber, tortuosity, vasomotricity, and branching patterns and relative diameters of arterioles and venules.\(^2,3,5\) These, in a more robust fashion than the subjective assessments of older methods, have established or confirmed significant associations between the early structural and functional alterations of the initial stages of hypertension and coronary artery disease, heart failure, stroke, cognitive dysfunction, microalbuminuria and renal dysfunction, left ventricular hypertrophy, and increased carotid intima-media thickness and arterial stiffness.\(^2,3\) Some studies have shown the value of these new techniques for predicting the development or worsening of hypertension,\(^2,3,6\) and genetic studies have identified loci and polymorphisms that are associated with both changes in arteriolar caliber and regulation or elevation of BP.\(^7,8\)

Interestingly, some authors have described an association between increased venule caliber and the incidence

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**DOI of original article:** [http://dx.doi.org/10.1016/j.repce.2017.06.014](http://dx.doi.org/10.1016/j.repce.2017.06.014)

Please cite this article as: Nogueira JB. Repercussão microvascular retineana e hipertensão noturna – alvos terapêuticos a não esquecer. Rev Port Cardiol. 2018;37:175–177.

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of hypertension and risk of stroke, especially lacunar stroke.\textsuperscript{2,3,6}

Ambulatory blood pressure monitoring (ABPM) has shown the significance of certain abnormalities in the 24-hour circadian profile with regard to target organ damage and cerebral, cardiovascular and renal morbidity and mortality, as seen in both studies of hypertensives and population studies.\textsuperscript{1} Of these abnormalities, non-dipping and nocturnal hypertension are most often independently associated with increased risk of target organ damage and worse prognosis, with various studies showing more severe cardiac, cerebral, renal and macrovascular repercussions in these patients.\textsuperscript{9-11} It should be noted that there have been few studies on the relationship between vascular abnormalities in hypertensive retinopathy and circadian patterns on ABPM, in particular nocturnal BP, and some are contradictory.\textsuperscript{12-15}

The study by Duarte et al. published in this issue of the Journal\textsuperscript{16} does in fact analyze precisely this relationship between 24-hour and nocturnal BP by ABPM and the presence and severity of hypertensive retinopathy, assessed qualitatively by fundoscopy and graded using the Scheie classification, in a group of 46 hypertensives, most of them medicated but only a third controlled.

Despite the limitations pointed out by the authors, mainly related to the small study population, the study clearly showed not only the high prevalence of retinopathy in these hypertensives but also the crucial role of nocturnal BP, especially systolic, in the presence and severity of retinopathy. There were also associations between retinopathy and age and duration of hypertension, as described elsewhere,\textsuperscript{7,13} particularly when the same classification system was used, and in which most patients were in the sclerotic stage of retinopathy (37 patients in the present study). Regarding the mean daytime and nocturnal BP levels of this patient group, unusually, mean nocturnal values were higher than daytime levels, which raises the question whether they included a large number of inverted dippers (which was not the case), or that some may have suffered from obstructive sleep apnea or other sleep disorders, which the authors do not mention. It would have been interesting to know the nocturnal BP levels of dippers and non-dippers in this group, since nocturnal BP can be high even in dippers,\textsuperscript{17} which may be why there were no differences in the presence and severity of retinopathy between dippers and non-dippers.

The small sample size is probably the reason that no association was found between the presence of retinopathy and cardiac involvement, as has been described in other studies.\textsuperscript{7} Similarly, medicated and controlled patients were no different in terms of the presence of retinopathy, although improvements in structural alterations of the retinal vasculature have been reported following BP control,\textsuperscript{3,18} particularly with drugs that act on the renin-angiotensin-aldosterone system and with calcium channel blockers, which were used in this study. Such improvements have been amply demonstrated, especially in cases of exudative retinopathy (which only one patient presented in the study by Duarte et al.) and when the assessment of retinopathy is quantitative as well as qualitative, using sophisticated and precise computer algorithms, which was not the case in the present study. The apparent lack of improvement seen in this study may thus be because BP control had not been achieved for sufficient time to take effect, or due to the methods used to assess retinopathy, or to the patients’ age and duration of hypertension, leading to a larger proportion of sclerotic lesions that are less likely to regress. If patient numbers had permitted such an analysis, it would have been interesting to assess whether there were significant differences in retinal findings or in nocturnal BP levels between non-medicated and medicated but not controlled subjects.

Furthermore, the study does not report office BP measurements, and thus cannot clarify whether some patients had masked hypertension and if so, whether retinopathy in this group was similar to that of the other hypertensives, as has been reported for other organ damage,\textsuperscript{7} or how it related to nocturnal BP.

In conclusion, despite the limitations pointed out above with regard to population size and the methodology for assessing the fundoscopy findings, the present study has the merit of demonstrating the importance of nocturnal BP in alterations in the retinal vasculature, and of calling attention to these alterations, which are frequently underestimated and are potential therapeutic targets. They may also play an important role in early assessment of the severity of hypertension, particularly with regard to cardiovascular and renal risk, as well as in monitoring the efficacy of and adherence to antihypertensive medication; when such lesions are detected but the patient has apparently normal BP levels, they may reflect inadequate control of nocturnal BP.

Further studies are awaited, with larger samples and more detailed assessment of the retinal vascular architecture,\textsuperscript{19} that could widen our understanding of hypertensive microvascular alterations, both arteriolar and venular, and their relationship with changes in circadian BP profiles, therapeutic efficacy, the possible benefits of chronotherapy, and – for example in cases of white-coat hypertension – the decision whether to initiate antihypertensive therapy.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**References**