Pulse Pressure and Diabetic Eye Disease

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Diabetic retinopathy is an important complication of diabetes mellitus, and understanding its determinants, particularly those that are modifiable, is essential to efforts to reduce the likelihood of its occurrence. Previous studies have indicated that the adequacy of diabetic control, usually determined as hemoglobin A1c percentage, and blood pressure are 2 such determinants, both of which are amenable to treatment.[1] However, incident diabetic eye disease is not always related to systolic blood pressure (SBP),[2] and the potential importance of other components of blood pressure (ie, diastolic blood pressure [DBP] and pulse pressure [PP]) is not clear. In this issue of the *Journal of the American Heart Association* (*JAHA*),[3] Yamamoto et al have examined the role of PP in the incidence of treatment-required diabetic eye disease among Japanese patients from a national health insurance–claim database. More important, patients with preexisting treatment-required diabetic eye disease were excluded and brachial blood pressures were taken in accordance with the guidelines of the Japanese Society of Hypertension. The incidence of treatment-required diabetic eye disease during a median surveillance period of ≈5 years was dependent on age, blood pressure, diabetic control, and low-density lipoprotein cholesterol level. When various components of blood pressure were considered individually, PP was a superior predictor to SBP; and when both were included in multivariate analyses, PP, but not SBP, remained a significant determinant. When considered in isolation, DBP was not a significant predictor. Whether the relationship between PP and eye disease is causal or not cannot be established by this observational study, although several potentially confounding factors (ie, those that may affect both PP and eye disease) were included in the multivariate analyses (eg, age, sex, and diabetic control). Even with an intervention study, this question would not be easily amenable to investigation because of the current absence of treatment, which will selectively affect PP.

In considering whether the observed relationship with brachial-determined PP is causally related to the incidence of subsequent eye disease, it is necessary to consider the relationship between peripheral and retinal pressures. Although simultaneous measures of brachial and retinal pressures are not available, experimental studies have examined the relationship between aortic and retinal vessels. In a study in dogs[4] using micropuncture in retinal arterioles (which are devoid of elastic lamellae) and veins, there was a close linear relationship between aortic and retinal mean arterial blood pressure (r=0.99, P<0.01), given by the following equation: retinal mean arterial blood pressure=0.74×(brachial mean arterial blood pressure+4.7). More important, there was also a close correlation between both SBP and DBP measured at these 2 sites (r>0.97 for both), whereas for PP, the correlation was not as tight (r>0.89). In humans, the situation will be altered by any nonlinearity in the relationship between brachial and aortic SBP and PP. In addition, the retinal arteriolar pressures will be posture dependent. Retinal vein pressure and transmural pressure are closely dependent on intraocular pressure.

In primary prevention of cardiovascular end points, the Prospective Studies Collaboration, in 1 million adults,[5] reported monotonic relationships for both SBP and DBP with cardiovascular outcomes. However, this conclusion is likely not valid in at least some cases of secondary prevention. This is most evident in the case of coronary artery disease. Several studies have now demonstrated that a low DBP is associated with a worse outcome in these patients.[6,7] A previous study provided evidence that stiffened large arteries, the primary cause of elevated PP and low DBP in older populations, are related to decreased myocardial perfusion with exercise in patients with coronary artery disease.[8] These findings, in relation to cardiac disease, are explicable in the light of the dual components of elevated PP (ie, increased afterload [and left ventricular hypertrophy] attributable to elevated SBP and reduced myocardial perfusion attributable to lower DBP). Such

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a contribution from the lower diastolic component of elevated PP will not apply to the retinal circulation. The closest analogous situation to that of eye disease would be cerebrovascular disease, albeit that this is in part attributable to artery, and not arteriolar, disease. PP was predictive of composite cardiovascular end points but not stroke in the study of Benetos et al,[9] whereas in another study, there was an association of PP with stroke, but this was not independent of SBP.[10] In a recently published substudy of SPRINT (Systolic Blood Pressure Intervention Trial; a comparison of standard and more aggressive SBP lowering), the relation between stroke and DBP in an at-risk (although not diabetic) population was examined.[11] Interestingly, the authors of this study found an association with low DBP only in the "usual" treatment arm (ie, those with a higher SBP and, thus, PP). Studies examining a possible relation between PP and dementia have given conflicting results.[12,13] In the study of Peters et al,[13] there was an inverse relation between DBP at baseline and subsequent dementia.

If the PP relationship with diabetic retinal disease is causal, then what might be the mechanism? One possibility is an alteration in small-vessel properties by increased cyclical wall stress. The relevant arterial vessels to be considered are arterioles. The consequences of enhanced cyclical vascular wall strain have been studied experimentally, examining several end points, usually by studying vascular smooth muscle cells placed on deformable substrates, as reviewed by Haga et al.[14] Such studies have shown effects on receptor tyrosine kinases, ion channels, vascular smooth muscle cell signaling pathways, and gene expression as well as on vascular smooth muscle cell function. Different effects are observed between cyclical and step deformation. Arterial PP has also been related to other microvascular disease in diabetic subjects. Thus, proteinuria in subjects with established diabetes mellitus has been shown to be more likely in the presence of increased PP.[15] It, of course, remains possible that the demonstrated association of PP and incident diabetic retinal disease is not causal but is related to other, unidentified, common factors. The study of Yamamoto et al accounted for several candidates, such as age and sex, but did not find any accounted for the observed relationship with PP. One possibly important omission is the absence of any data on renal function.

If the relationship between PP and eye disease in diabetes mellitus is causal, what does this mean for the management of blood pressure in diabetic subjects? First, the good control of SBP is paramount for the prevention of vascular disease in patients with diabetes mellitus. A substantial fraction of patients with type 2 diabetes mellitus will have coexistent coronary artery disease; and in these patients, it is prudent to avoid low DBPs. Although the threshold DBP is not clearly established, it seems prudent to avoid a DBP of <65 mm Hg, if possible. Because such patients also require good control of SBP, this would require a reduction in PP. Prevention of microvascular disease also requires good control of SBP, and the findings of Yamamoto et al imply that in this group, it would be best to avoid an excessively low DBP to have a lower PP. The increasing implication for a role of PP in vascular disease, including in subjects with diabetes mellitus, could be better evaluated and, if indicated, treated by the availability of therapeutic agents that primarily target large-artery stiffening, the underlying pathological feature. Although attempts to develop such agents have been undertaken, and have initially seemed promising, they have not, to date, led to available treatments.[16] Among currently available antihypertensive therapies, there have been only a limited number of studies in which the efficacy of various therapies has been compared, with somewhat inconsistent results; however, β blockers have generally been shown to have less beneficial effects on PP than other classes. In the only study of multiple agents, Cushman et al found hydrochlorothiazide the most, and atenolol the least, effective agent in lowering PP in older hypertensive subjects.[17]

The study of Yamamoto et al[3] provides further evidence that PP may mediate some of the adverse consequences of elevated blood pressure and that these include microvascular disease, albeit likely from a different mechanism that pertains to larger vessels. Further evidence of specific damage attributable to PP may help in deciding to what extent PP per se should be a therapeutic target.[18]

Disclosures

None.

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