Diabetes has profound effects on the vasculature, and the major complications of diabetes, accounting for increases in both morbidity and mortality, are diseases of the vasculature. In recent years, a number of techniques have been developed that provide direct in vivo assessments of vascular health in humans. These techniques include measurements of atherosclerotic burden, such as calculations of coronary calcium scores using computed tomography and high-resolution ultrasound measurements of the intima-media thickness of the carotid arteries. Tests of the dynamic properties of the vasculature have most prominently assessed endothelium-dependent vasodilation, using brachial artery ultrasound or more invasive measures such as thermodilution, dye dilution, or plethysmography.

Another set of tools has been developed to assess the dynamic physical properties of the vascular tree. Although generally categorized as measures of “stiffness,” these techniques can in fact provide information on a number of specific physical properties, including distensibility, elasticity, and resistance to deformation. These parameters are different aspects of the interrelated features of vessel wall thickness, change in wall thickness, and vessel diameter in response to force and the rates of these changes as well as the rate of return to the nondeformed state. Abnormalities in these parameters can be demonstrated in tissues from diabetic subjects (1–3), and they can also be demonstrated in vivo. The most rigorous measurements of these features necessarily include a measurement of the distending force (i.e., blood pressure), ideally at the site of measurement. This can be achieved in the research setting with invasive techniques that place pressure transducers at relevant sites, typically accompanied by imaging techniques (ultrasound or magnetic resonance imaging) that allow the change in thickness and shape of a vessel over the course of the cardiac cycle to be assessed (4–6).

The progress of the pulse wave through the walls of the blood vessels is affected by the mechanical properties of the vessels. The phenomenon of pulse-wave augmentation results from reflections of the pulse wave at distal sites (such as bifurcations), such that the forward wave and reflected wave superimpose (7). This combination of waves produces the typical arterial pulse wave, and due to both progressive reductions in force along the vascular tree and differences in wave summation, the arterial pulse wave differs at different sites along the vascular tree. The pulse-wave velocity and the amplitude of reflected waves are increased in stiffer arteries, and conversely, these features are reduced with increased arterial compliance (8). These features are dependent on a number of hemodynamic variables, including heart rate and pulse pressure (i.e., the distending force) (9).

Therefore, measures of augmentation are generally corrected for pulse pressure and expressed as an “augmentation index.” These measures are also affected by vasoactive medications (10–12) and by insulin (13) and are sensitive to inhibition of nitric oxide synthase (6,14). The application of these measurements in concert with vasodilators has been proposed as an alternative approach for the measurement of vascular function (15) beyond their capacity to assess mechanical properties.

Noninvasive techniques for assessing arterial stiffness have been developed, taking advantage of these features of the peripheral arterial pulse wave. Currently the two most important of these are applanation tonometry and peripheral measurements of pulse-wave velocity (16,17). The measurement of pulse-wave velocity is deceptively simple. At its core, the arrival of the pulse wave at two different arterial sites is timed, and from estimates of the length of blood vessels between these sites (usually by measuring the distances at overlying skin sites), the velocity of this wave is calculated (7,18,19). Subtleties come in achieving precision in the timing of the measurements and in correctly estimating the intervening distances. Although clearly less informative regarding the nuances of the various physical properties of interest, this simple measure does provide a reliable integrated measure of arterial stiffness; at a given pressure, the stiffer the vessel, the less time it takes for the pulse wave to travel the length of the vessel.

Applanation tonometry involves the measurement of the change in shape over time (i.e., the arterial wave form) at the radial artery using a pressure transducer attached to the skin overlying the pulse at this site (17,20,21). This technique was developed to allow derivation of central arterial (i.e., aortic) waveforms from peripheral measurements. The fact that changes in shape over time in these two vessels are related is intuitively evident, but the mathematical relationship is complicated. This relationship is called a transfer function, and the application of this technique involves performing peripheral measurements, then applying the transfer function to these measurements to derive the central vessel dynamics, from which various parameters of interest (e.g., the augmentation index) are then calculated. A key assumption in this process is that the transfer function, as derived in an index population, is valid in its application to a given study population. Most typically, the transfer function has been derived in healthy or hypertensive subjects and can be reasonably applied to similar populations without the need for local validation. In this issue of Diabetes Care, Hope et al. (22) have asked the important question of whether it is valid to apply the supplied generalized transfer function to a diabetic study population. The relevance of this question is clear: the pathogenic effects of diabetes on blood vessels and other tissues include
changes in connective tissue composition through, among other mechanisms, increased collagen cross-linking and other physical consequences of advanced glycosylation end product binding. This change in physical properties is the reason for the interest in applying these techniques but may also alter the assumed relationship of the behavior of central versus peripheral sites. Hope et al. (22) found that the generalized transfer function (supplied by the manufacturer of the device) did not adequately describe this relationship between peripheral and central arterial waveforms, specifically in diabetic subjects. In other words, the derived central measures did not agree with those directly measured. The authors also undertook the derivation of a diabetes-specific transfer function from their data. Although the validity and generalizability of this "diabetic transfer function" remains to be demonstrated through its application to an independent population, this effort provides hope for the valid use of application tonometry in diabetic subject populations. One feature not presented by Hope et al. is the methodology applied in the derivation of the "diabetic transfer function." These approaches are not standardized, and so future studies need to include descriptions of the method used so as to allow critical evaluations and rational comparisons within the literature.

Interestingly, another recent report (23) using a device from another manufacturer also found discrepancies between centrally measured and waveform-derived values for blood pressure in a nondiabetic population, although validation studies (24,25) in other nondiabetic populations have not raised these concerns. This finding, together with the work of Hope et al., specifically brings to light the need for more detailed technical and validation studies in subjects with diabetes and perhaps in other specific populations of interest. Ideally, this will then allow interpretable epidemiologic or intervention studies using these techniques in diabetic subjects.

Various techniques of vascular assessment are beginning to be applied in studies (26–34) of subjects with diabetes. The current results should provide the impetus to undertake a more thorough evaluation of the applicability and validity of such methods, specifically in diabetic study populations. These key groundwork components must be in place to allow the broader application of these techniques to the study of vascular disease, which is clearly of interest to the diabetes community.

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