# Cardiovascular Autonomic Neuropathy

## Where have we been and where are we going?

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In this issue of *Diabetes Care*, there are two articles addressing the diagnosis of cardiovascular autonomic neuropathy. In the article by Hartwig et al. (1), the authors evaluate tests for the analysis of vasomotor autonomic function and compare these with well-established cardiovascular autonomic tests. They demonstrate that cardiovascular autonomic tests and their two vasomotor tests are valid and reliable tests to identify diabetic autonomic neuropathy, and show that the sensitivity and specificity of these tests are reasonably acceptable for clinical evaluation. In the study by McDaid et al. (2), the authors look at vasoconstrictor responses and compare these with cardiac autonomic function tests. No differences in cardiac autonomic function in recently diagnosed type II diabetic subjects were found, but differences in vasoconstrictor responses were found. The summation of these two studies indicates that it is important not only to look at cardiovascular autonomic tests, but also peripheral vascular autonomic function in the diabetic population. Both of these studies are very interesting, and are valuable contributions to autonomic nervous system testing.

In general, when we consider cardiovascular autonomic nervous system tests, we now have clinical tools to independently evaluate sympathetic and parasympathetic function. Independent consideration is important as the clinical ramifications vary. Parasympathetic tests have been defined by heart rate variability (sinus arrhythmia) to deep breathing, first by Wheeler and Watkins (3), and refined by Ewing et al. (4) and Weinberg and Pfeifer (5). Analysis of heart rate variability can be done by at least six different methods. They include *1*) the high frequency band of spectral analysis, 2) coefficient of variation (CV), 3) the root mean squared successive differences, 4) Max-Min difference, 5) E:I ratio, and 6) mean circular resultant. In a recent study by Ziegler et al. (6), it was shown that all of these methods were related to and declined with age, which is an important consideration of any neural test. However, only the mean circular resultant, the high frequency band of spectral analysis, and the CV were not confounded by the ambient heart rate at the time of testing. When Ziegler et al. (6) looked at reproducibility, they found that the mean circular resultant gave the best reproducibility; slightly better than the reproducibility provided by the CV and the high frequency band of spectral analysis. In view of these results, it would seem prudent for future studies to use one of these methods of analysis of heart rate variability (mean circular resultant, high frequency band of spectral analysis, or CV). Methods such as the change in heart rate during deep breathing, which is basically Max-Min difference, in our opinion, should not be used. Of particular concern is the inclusion of several of these analyses in a single study as separate tests, when in fact, they are just different analyses of the same data.

Sympathetic function is somewhat more difficult to isolate from concomitant physiological mechanisms, although a number of tests have been suggested. The Valsalva maneuver is a very complex test, assessing baroreceptor sensitivity, cardiac function, sympathetic and parasympathetic pathways, and vascular responsiveness. Therefore, it is a generalized cardiovascular autonomic test that requires a greater degree of autonomic impairment before abnormalities are demonstrable (7). It should be viewed as a separate autonomic neuropathy test. Postural testing is fraught with great variability (6) and, therefore, has required more impairment before consistent abnormality can be documented. The two studies in this issue of *Diabetes Care* offer reliable and valid methods for measuring sympathetic activity. One method is supported by a normal range derived from a substantial number of tests in nondiabetic individuals (1). In addition, a new method using meta-iodobenzylguanidine scintigraphy to assess myocardial sympathetic innervation has been shown to be a more sensitive and specific indicator of abnormal innervation than the standard reflex tests.

We believe that a more compre-

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CV, coefficient of variation; DCCT, Diabetes Control and Complications Trial.

hensive evaluation consisting of one parasympathetic test (such as heart rate variability) with standardized analysis (such as mean circular resultant, CV, or high frequency band of spectral analysis), a vascular sympathetic index (such as one of the two described in the current issue of *Diabetes Care*), a Valsalva ratio and, perhaps in the near future, scanning for myocardial innervation would constitute a valuable surveillance battery of cardiovascular autonomic function tests. With this battery, a clearer understanding of the natural history and mechanism of autonomic neuropathy may be developed. Future studies should clearly focus on clinical outcomes and pathophysiological correlations using these tools.

Current evidence indicates that diabetic neuropathy first is manifested in biochemical aberrations that eventually result in structural abnormalities. The degree of biochemical (potentially reversible) and structural (permanent) aberration is believed to shift toward structural abnormality with duration and degree of hyperglycemia. Reversibility of abnormal nerve function can only be reasonably expected as a result of the reversal of the biochemical aberrations. It is unreasonable to expect cardiovascular autonomic dysfunction resulting from structural nerve damage to improve with intervention therapy. This may explain why only very small changes in nerve conduction velocity have been observed with improved glucose control (8) and experimental therapy such as aldose reductase inhibitors. Even with strict, tight glucose control, there is very little improvement in nerve conduction velocity, but there is a lack of deterioration (albeit small) over 5 years, as demonstrated by the Diabetes Control and Complications Trial (DCCT). Similarly, it is reasonable to expect only a small degree of improvement in cardiovascular autonomic function, but in future studies, we should anticipate preventing deterioration rather than expecting improvement. This concept is analogous to the expectations for retinopathy and/or nephropathy, as tight glucose control seldom reverses impairment but prevents further deterioration.

In conclusion, cardiovascular autonomic tests have been refined to such a degree that it is reasonable to use these as bedside tests. The next step is to develop models using these tests to predict clinical outcomes and pathophysiological correlations. Trials like the DCCT, the Framingham Study, and others clearly have the database to answer some of these questions.

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