

ABSTRACT: Composite scores may be more sensitive and reproducible than single attributes of nerve conduction for detection of peripheral neuropathy, but this requires validation in large patient cohorts. Also, the concordance of individual attributes versus composite scores with clinical measures of severity has not been tested. Here, we study these issues in prospectively studied cohorts: diabetic patients from Rochester, Minnesota (RDNS; $n = 396$); chronic inflammatory demyelinating polyneuropathy (CIDP) patients ($n = 55$); and multifocal motor neuropathy (MMN) patients ($n = 18$). With specificity fixed at the 97.5 percentile, we found that, in generalized polyneuropathies (diabetic and CIDP), composite scores (especially ones including conduction velocity, distal latencies, and F-waves) of individual or multiple nerves tended to be more sensitive than individual attributes. By contrast, for multiple mononeuropathies, some individual attributes or composite scores of individual nerves were more sensitive than composite scores. In diabetic polyneuropathy, composite scores tended to be more reproducible than individual attributes of nerve conduction. Highly significant correlations were found between individual attributes or composite scores and neurologic impairment in diabetic polyneuropathy and in CIDP; in general, correlation coefficients were higher for composite scores. These correlations were higher for amplitudes than for conduction velocities or distal latencies. We conclude that, with the availability of microprocessors and normative databases, electromyographers may increasingly seek to express nerve conduction abnormality also as composite scores of individual or several nerves.

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INDIVIDUAL ATTRIBUTES VERSUS COMPOSITE SCORES OF NERVE CONDUCTION ABNORMALITY: SENSITIVITY, REPRODUCIBILITY, AND CONCORDANCE WITH IMPAIRMENT

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Nerve conduction studies are done to detect (or exclude), characterize, or follow disease of nerves. They may also be used to study development, aging, and the influence of anthropomorphic factors, risk

factors of disease, toxic exposures, and response to therapeutic interventions. The decision about whether an attribute of nerve conduction is declared normal or abnormal depends, first, on the choice of which level of abnormality is to be used (and this may depend on the purposes of the study) and, second, on corrections that are made for age, gender, and applicable anthropomorphic factors.^{10,18,20,24}

It has been stated that composite scores are as or more sensitive, reproducible, and indicative of severity of polyneuropathy as individual attributes of nerve conduction,^{6,21–23} but this view is mainly intuitive and has not been validated by study of large disease cohorts. We therefore examined these issues in two generalized polyneuropathies (diabetic sen-

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; DM, diabetes mellitus; EMG, electromyography; MMN, multifocal motor neuropathy with conduction block; MNCV, motor nerve conduction velocity; MNDL, motor nerve distal latency; NIS, neuropathy impairment score; NIS(LL), neuropathy impairment score of lower limbs; RDNS, Rochester Diabetic Neuropathy Study; RDNS-NS, Rochester Diabetic Neuropathy Study–Normal Subjects; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; SNDL, sensory nerve distal latency

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sory polyneuropathy and chronic inflammatory demyelinating polyneuropathy) and in a multifocal neuropathy (multifocal motor neuropathy).

MATERIALS AND METHODS

Patients Selected for Sensitivity Studies and for Correlation with Neuropathic Impairment. All identified and consenting (signed informed consent) patients with diabetes mellitus (DM; defined by National Diabetes Data criteria, and later by American Diabetes Association criteria) from Rochester, Minnesota (later Olmsted County, Minnesota), were enrolled in cross-sectional and longitudinal epidemiologic studies of diabetic complications.^{6,10} Their neuropathic findings and test results were entered into an electronic database.¹³ At first examination, 396 patient records, with and without neuropathy, were available for this study. The chronic inflammatory demyelinating polyradiculoneuropathy cohort (CIDP) and the cohort having multifocal motor neuropathy with conduction block (MMN) were patients of one of us (P.J.D.) who were entered into interactive immunotherapy treatment and who allowed their data to be used for research purposes. Predetermined and standard evaluations (described in what follows) were used for studying patients of the three cohorts. Only data from initial evaluations were used for this study.

Patients Utilized for Reproducibility Studies. Patients from the Rochester Diabetic Neuropathy Study (RDNS) with and without diabetic sensory polyneuropathy (of varying severity) were recruited for reproducibility studies and signed an additional consent form to the one for entry into the RDNS approved by our institutional review board. Nerve conduction studies were performed twice, but on different days (within a period of 2–5 days), by trained electromyographic technicians under the supervision of one of the investigators (W.J.L. or C.M.H.). These technicians were asked not to review earlier or concurrent medical information. Some of these nerve conduction reproducibility studies (of single attributes and only on a subset of these patients) have been reported previously.⁸

Nerve Conduction and Neuropathic Assessments. Attributes of nerve conduction were generally obtained on the left side of the body (except when the left side was unsuitable) using percutaneous stimulation and recording techniques as is standard for our electromyography (EMG) laboratory. Limbs were warmed if below 30°C and were maintained above this temperature using infrared lamps. We

studied motor conduction of ulnar, median, peroneal, and tibial nerves; recording amplitude of the compound muscle action potential (CMAP); conduction velocity (MNCV); and distal latency (MNDL). F-wave latencies were assessed for ulnar, median, and tibial nerves. We also studied sensory nerve conduction, determining amplitude of the sensory nerve action potential (SNAP), conduction velocity (SNCV), and distal latency (SNDL) of ulnar, median, and sural nerves. Because median neuropathy at the wrist is common in diabetic patients, we did not include median nerve attributes in these studies.

Attributes of nerve conduction were entered into the database as measured values, and percentiles and normal deviates were estimated using computer programs, taking into account the patient's age, gender, and applicable anthropomorphic characteristics. These corrections are based on a study of 330 patients from a screened cohort of more than 500 randomly selected and consenting patients from Rochester, Minnesota. The normative data are from the first randomly selected 15 men and 15 women from each hemidecade between 18 and 74 years who were without diabetes mellitus, systemic or metabolic diseases, or exposure to toxins predisposing to neuropathy, and who had a normal neurologic examination. Additional healthy subject results were provided by J. C. Stevens, MD, for estimating percentile responses at up to 90 years of age.

The neuropathy impairment score (NIS) is the sum score of standard items from the neurologic examination.¹² Muscle weakness is graded as 0 (normal) to 4 (paralyzed); reflex loss is graded from 0 (normal) to 2 (absent); and each modality of touch-pressure, joint position and motion, vibration, and pinprick sensation of the index finger and great toe is graded from 0 (normal) to 2 (absent). Abnormality is graded in a standard manner taking age, gender, body build, physical fitness, and anthropomorphic factors into account. Scores for one side are summed and added to the score of the other side. Thus, a patient with 50% weakness of toe extension (2 + 2), ankle areflexia (2 + 2), and decreased touch-pressure (1 + 1), vibration (1 + 1), and pinprick (1 + 1) sensation of the great toe would have an NIS score of 4 + 4 + 2 + 2 + 2 = 14 points. A patient with no neurologic abnormalities would have a score of 0. For diabetic polyneuropathy, we scored only the lower limbs (NIS[LL]).

Abnormality of Attributes of Nerve Conduction and of Composite Scores. The basis of abnormality for attributes of nerve conduction was a percentile value

of ≥ 97.5 or ≤ 2.5 (depending on the attribute), taking into account all applicable biographic and anthropomorphic variables.^{10,18} In developing composite scores of several attributes combined, we chose to express all abnormalities in the upper tail of the distribution (e.g., conduction velocity and amplitude values at the 2nd percentile were expressed as the 98th percentile, and so on). Next, we summed the normal deviates (*Z* scores, based on data from our normal subject cohort¹⁰) of the percentiles of the tests to be included in the composite score (e.g., 7 tests). Further details have been provided elsewhere.⁶ Because not all attributes could be measured (as it is not possible to estimate velocity and latency when amplitude is 0), the sum of the normal deviates was divided by the number of attributes that could be measured. This quotient was then multiplied by the number of components of the composite score (e.g., 7). The composite scores were regressed against age and, using the resulting regression lines, the line providing the corresponding 97.5 percentiles was obtained empirically by increasing the intercept.

Assessing Sensitivity, Reproducibility, and Concordance with Impairment. Because specificity for individual attributes and composite scores was set at the 97.5 percentile, the percentage of the cohort which is abnormal for individual attributes or for composite scores is the sensitivity for that measure and can be directly compared. For reproducibility, we used the intraclass correlation coefficient. For concordance with neuropathy impairment, we computed the correlation coefficient between NIS or NIS[LL] and individual attributes and composite scores.

RESULTS

The height of the bars in Figure 1 represents the sensitivity (percent abnormal at the 97.5 percentile) of the various individual attributes and composite scores in the three studied cohorts. From left to right, the order of the bars for individual nerves is amplitude, conduction velocity, distal latency, and the composite of the three. Bars 21–27 are composite scores of more than one nerve as listed in the legend to the figure.

For diabetic sensory polyneuropathy, composite scores tended to be more sensitive (the percent of cases with values greater than the 97.5 percentile, based on study of normal subjects) than were individual attributes. There were eight composite scores, each of which was more sensitive than the single attribute of nerve conduction with the highest sen-

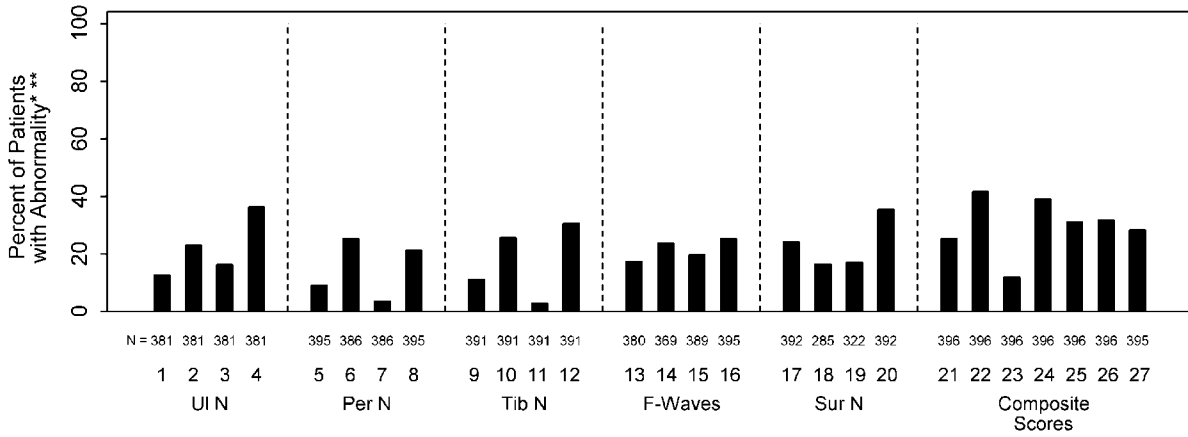
sitivity (tibial MNCV, 25.6%, bar 10). From high to low, these composite scores were: (1) Σ motor nerve conduction velocity (MNCV) of ulnar, peroneal, and tibial nerves (41.7%, bar 22); (2) Σ MNCV of ulnar, peroneal, and tibial nerves and sural SNCV (39.1%, bar 24); (3) Σ motor amplitude, conduction velocity, and distal latency of ulnar nerve (36.2%, bar 4); (4) Σ sural SNAP amplitude, conduction velocity, and latency (35.5%, bar 20); and four other composite scores. The sensitivity of each of the first seven composite scores was significantly higher than was the sensitivity of the single attribute of nerve conduction with the highest sensitivity (all seven $P \leq 0.02$, sign test). Considering individual attributes as a group and composite scores as a group, sensitivity was higher for composite scores (median 30.9%; range 11.9–41.7%) than for individual attributes (median 17.1%; range 2.8–25.6%).

In CIDP, an individual attribute, median nerve F-wave, was most sensitive, but it was evaluated in less than 50% of cases (and therefore is not shown in Fig. 1). Setting aside this single attribute, the next three highest sensitivities were: (1) Σ ulnar, peroneal, and tibial MNCV (92.6%, bar 22); (2) Σ ulnar, peroneal, and tibial MNCV and sural SNCV (92.6%, bar 24); and (3) Σ ulnar, peroneal, and tibial MNCV and ulnar, peroneal, and tibial MNDL (92.6%, bar 25). None of these three composite scores had sensitivities that were significantly higher ($P = 0.05$, sign test) than the individual attributes with the highest sensitivity (ulnar MNCV, 92.3%, bar 2). However, the median value of the sensitivity of 12 composite scores (85.3%; range 57.1–92.6%) was higher than the median value of 14 individual attributes (67.7%; range 25.8–92.3%).

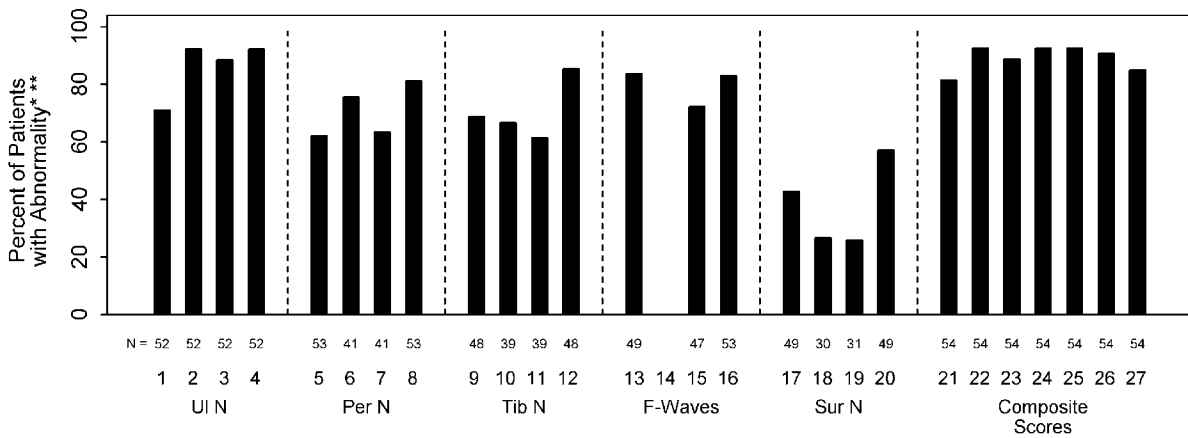
For multifocal motor neuropathy (MMN), the sensitivity of an individual attribute (ulnar MNFV, 85.7%) was highest. Composite scores of ulnar and median nerves were higher than were the individual attributes of these nerves (Fig. 1). The sensitivities of composite scores of multiple nerves were generally lower than those mentioned earlier.

Reproducibility. The reproducibility (intraclass correlation coefficients) of certain composite scores of multiple nerves and of certain individual nerves was higher than was the reproducibility of individual attributes (Fig. 2). The order from high to low was: (1) Σ MNCV and MNDL of ulnar, peroneal, and tibial nerves and SNCV and SNDL of sural nerve (0.97, bar 26); (2) Σ peroneal CMAP, MNCV, and MNDL (0.96, bar 8); (3) peroneal CMAP, MNCV, and MNDL and sural SNAP amplitude and SNDL

Diabetic Patients (RDNS)



Chronic Inflammatory Polyradiculoneuropathy (CIDP)



Multifocal Motor Neuropathy (MMN)

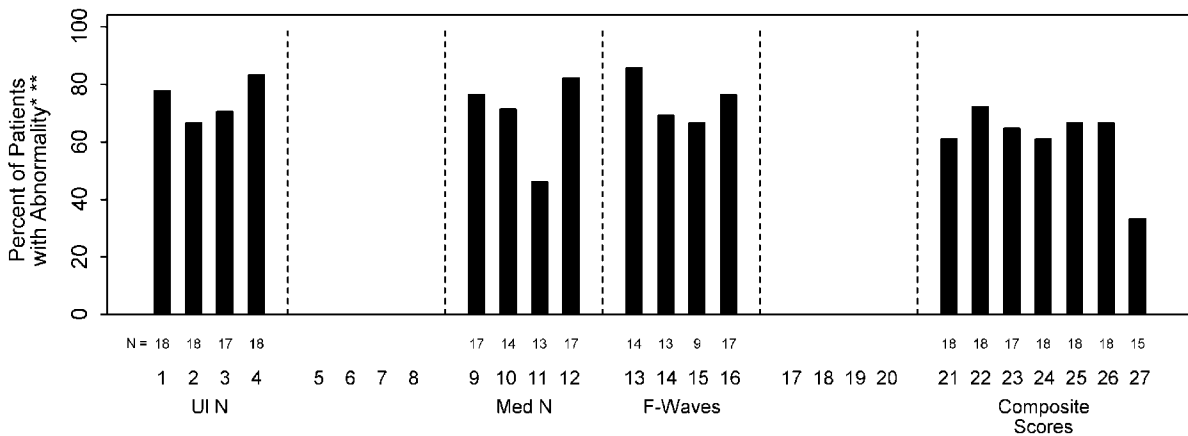


FIGURE 1. The sensitivity of individual attributes (bars 1–3, 5–7, 9–11, 13–15, and 17–19), composite scores of individual nerves (bars 4, 8, 12, and 20), and composite scores of multiple nerves (bars 16 and 21–27). For each of the three disease cohorts, and for ulnar, peroneal, and tibial nerves, the bars from left to right represent CMAP amplitude, motor conduction velocity (MNCV), and distal motor latency (MNDL). Bars 4, 8, and 12 are composite scores of CMAP, MNCV, and MNDL for ulnar, peroneal, and tibial nerves. The other bars are: 13 = ulnar (Ul) motor nerve F-wave (MNFV) ≥ 97.5 percentile; 14 = median (Med) MNFV ≥ 97.5 percentile; 15 = tibial (Tib) MNFV ≥ 97.5 percentile; 16 = MNFV composite score of 13, 14, and 15; 17 = sural (Sur) SNAP amplitude ≤ 2.5 percentile; 18 = Sur sensory SNCV ≥ 2.5 percentile; 19 = Sur sensory nerve distal latency (SNDL) ≥ 97.5 percentile; 20 = Sur composite score of 17, 18, and 19; 21 = Σ CMAP of Ul, Per, and Tib nerves ≥ 97.5 percentile; 22 = Σ MNCV of Ul, Per, and Tib nerves ≥ 97.5 percentile; 23 = Σ MNDL of Ul, Per, and Tib nerves ≥ 97.5 percentile;

Diabetic Patients, Reproducibility

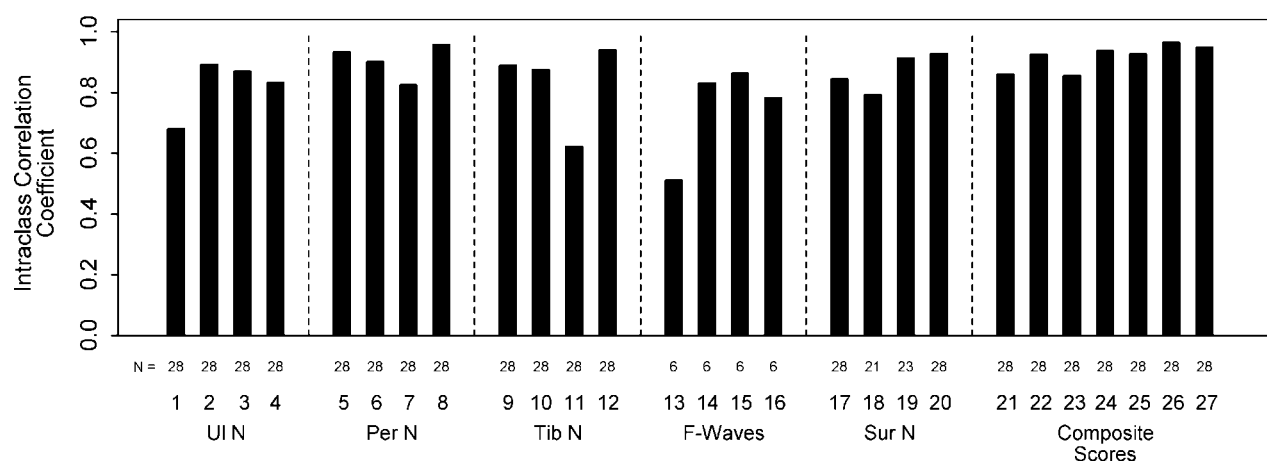


FIGURE 2. Intra-class correlation coefficients of the individual attributes and composite scores of nerve conduction of 25 patients without and with varying severities of diabetic sensory polyneuropathy as described in the text. The identity of the bars is given in the legend to Figure 1.

(0.95, bar 27); and (4) tibial CMAP, MNCV, and MNDL (0.94, bar 12). The highest reproducibility of an individual attribute was the peroneal nerve CMAP (0.93, bar 5).

Correlation with Clinical Impairment. The correlation coefficients of individual attributes of nerve conduction or composite scores and neuropathic impairment for the three cohorts studied are shown in Figure 3. The height of the bar indicates the correlation coefficient. An asterisk above the bar indicates statistical significance ($P < 0.05$).

For the diabetic cohort, all individual attributes of nerve conduction and all composite scores were significantly associated with severity of neuropathy. Considering individual attributes and composite scores, the order of correlation coefficients from high to low was: (1) Σ ulnar, peroneal, and tibial CMAP (29.4%, bar 21); (2) Σ peroneal CMAP, MNCV, and MNDL and sural SNAP and SNDL (28.0%, bar 27); and (3) Σ peroneal CMAP, MNCV, and MNDL (25.9%, bar 8).

For chronic inflammatory demyelinating polyneuropathy, seven composite scores were significantly associated with neuropathic impairment, whereas five were not. For individual nerve conduction attributes, 3 were significantly associated and 12 were not.

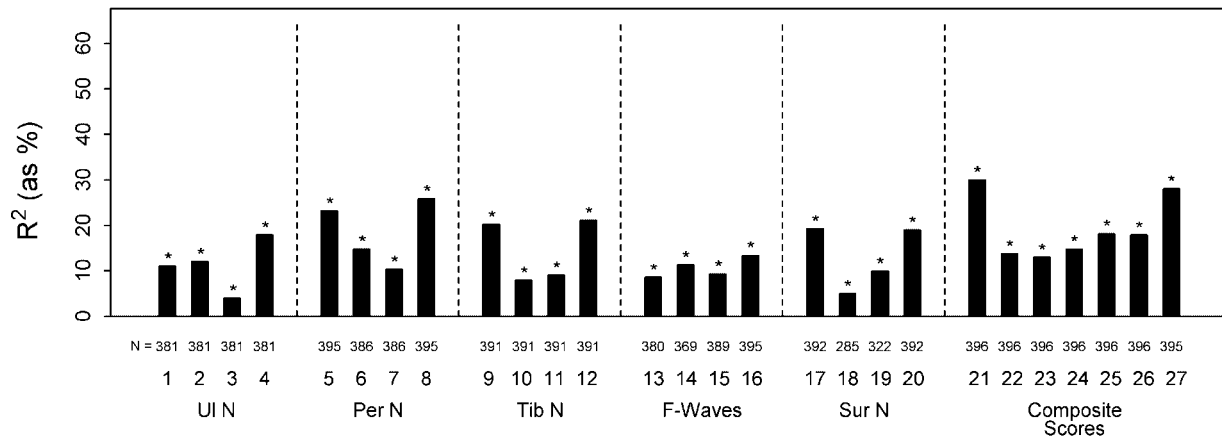
For multifocal motor neuropathy, none of the individual attributes of nerve conduction or composite scores were significantly associated with neuropathic impairment.

DISCUSSION

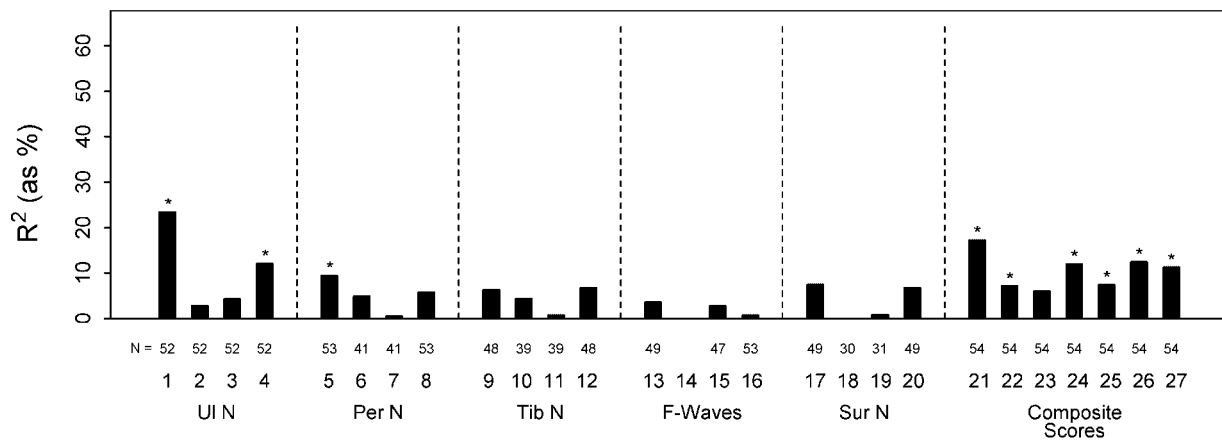
Tests of nerve conduction are used extensively in medical practice, epidemiologic surveys, and clinical research. If properly done and correctly interpreted, the test results provide sensitive, reproducible, and characterizing information about pathophysiologic alterations of nerves.¹ An important feature of these tests is that results cannot be willed by the patient, but the results do not correlate closely with overall neuropathic impairment, may correlate only weakly or not at all with symptoms, and do not inform about small-fiber (sensory or autonomic) symptoms or impairments.⁵ The nerves, the attributes of nerve conduction, and the specific alterations that are best for the detection and characterization of various peripheral nerve diseases have also been studied, for example, in Guillain-Barré syndrome^{3,19} and diabetic neuropathy.^{2,8,16,25}

The issue studied here was whether individual attributes of nerve conduction studies or composite scores are more sensitive (at a defined level of specificity) for detection of neuropathy. We also sought to determine which is more reproducible and which correlates best with neuropathic abnormality. We have advocated the use of composite scores for epidemiologic surveys and controlled trials because they provide a single and perhaps more global representation of severity of peripheral neuropathy.⁶ If such composite scores are as or more sensitive and reproducible than the best individual attributes of nerve conduction and also correlate as well or better with overall neuropathic impairment than individual

Diabetic Patients (RDNS), Correlation with NIS(LL)



Chronic Inflammatory Polyradiculoneuropathy (CIDP), Correlation with NIS



Multifocal Motor Neuropathy (MMN), Correlation with NIS

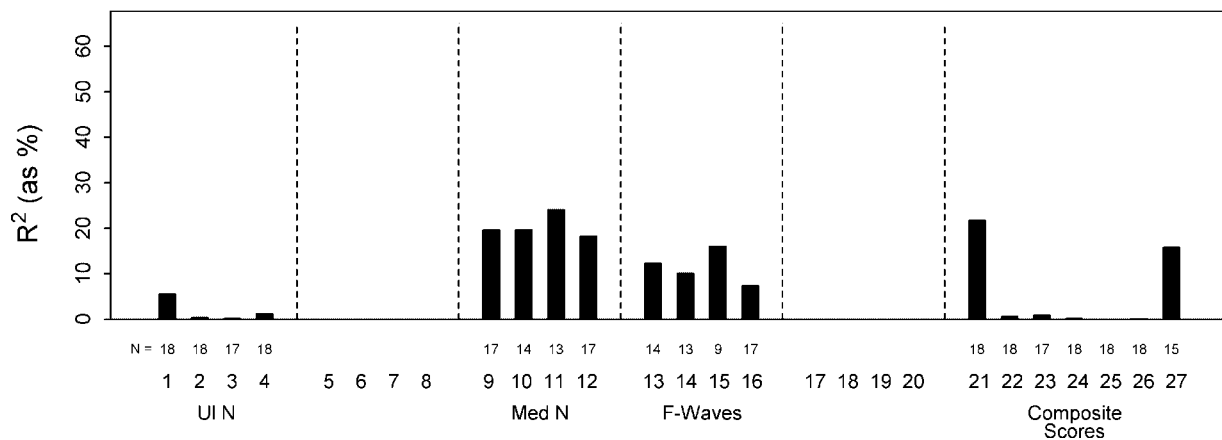


FIGURE 3. Correlation coefficients of various individual attributes or composite scores of nerve conduction and clinical impairment. In the RDNS, clinical impairment was assessed using NIS(LL), whereas, in CIDP and MMN, it was assessed with NIS. The height of the bar represents the correlation coefficient. Statistical significance ($P < 0.05$) is indicated by an asterisk above the bar. The identity of the bars is given in the legend to Figure 1. The findings are discussed in the Results section.

attributes, composite scores should increasingly find a place in medical practice and research.

The precedence for using composite scores for overall abnormalities of nerve conduction studies followed the use of composite scores for overall neuropathic impairment. Tallying a representative and standard set of items from the neurologic examination (as done in NIS, NIS[LL], or NIS [legs]) allows calculation of an overall sum score of neuropathic impairment.^{12,13} Likewise sum scores of neuropathic symptoms, and subsets of motor, sensory (further separable into positive and negative neuropathic sensory symptoms), and autonomic symptoms have been introduced and are being used in epidemiologic surveys and controlled trials.¹³ Composite scores of attributes of nerve conduction have therefore been introduced.^{4,6,9,14,17,21-23} Expressing attributes of nerve conduction as percentiles and normal deviates based on study of these attributes in large normative populations has facilitated the development of such composite scores. Choice of attributes of nerve conduction selected for composite scores depends on the use to be made of the composite score; for example, detection of abnormality, correlation with clinical abnormality, or both. It may also be possible to combine composite scores of clinical impairment and attributes of nerve conduction, for example, NIS(LL) + 7 (or another number) tests.⁶

Here we have shown that, in generalized peripheral neuropathy, composite scores tend to be more sensitive and reproducible, and correlate better with neuropathic impairment than do individual attributes of nerve conduction, a view previously expressed,²¹ but needing confirmation by actual evaluation of large patient cohorts.¹¹ The improved sensitivity with the use of some composite scores compared with individual attributes can be large; for example, in diabetic neuropathy from 41.7% (composite score, bar 22, Fig. 1, the best case) to 2.8% (individual attribute, bar 11, Fig. 1, the worst case). It is important to note, however, that there was overlap between sensitivities of composite scores and of individual attributes.

Why are some composite attributes more sensitive than individual attributes? It seems likely that the addition of almost-abnormal individual attributes could result in abnormality of a composite score. This was clearly evident in our previous study of quantitative sensation testing in patients with diabetes mellitus.⁷ In that study we found that a preponderance of normal vibratory thresholds of the diabetic cohort fell between the 50 and 97.5 percen-

tile, suggesting that some patients' values had previously shifted from values of <50 to ≥ 50 — an indication of a subtle abnormality. By adding normal deviate values, a preponderance falling between the 50 and 97.5 percentile, as one does in determining composite scores, it is likely that composite scores ≥ 97.5 result. A further reason might be that very high normal deviates of certain abnormal attributes would raise the mean value of composite scores.

An important insight to come from this study is that several composite scores made up of conduction velocities, distal latencies, and F-waves provided the most sensitive and reproducible indicators of diabetic polyneuropathy and chronic inflammatory demyelinating polyneuropathy. Kimura emphasized the importance of reproducibility in nerve conduction studies, and in this context he has found measurement of F-wave latency to be especially meritorious.¹⁵ In contrast to composite scores of nerve conduction, composite scores of CMAP and SNAP amplitudes correlated better with neuropathic impairment.

Knowing that sensory fibers are involved to a greater extent than motor fibers in diabetic polyneuropathy, why were distal sensory nerve conduction parameters not altered to a greater extent than motor ones? Other investigators have come to the same conclusion that we have.¹⁶ An obvious reason is that the preponderance of diabetic patients in cross-sectional cohorts have type 2 diabetes mellitus and are old. Nerve conduction abnormality of the sural nerve no longer scales abnormality when the potential falls to zero, whereas motor nerve conduction attributes scale abnormality into old age. A second reason may be that phase cancellations are more likely (for various reasons) to decrease the SNAP to a greater degree than the CMAP.

The reason that the sensitivity of the composite score of the ulnar nerve was higher than that of the peroneal and tibial nerves in diabetic polyneuropathy is not easily explained, assuming that diabetic polyneuropathy is length-dependent and lower limb predominant. It should be noted, however, that only the composite score was higher for the ulnar nerve—the sensitivity levels of individual attributes of the ulnar nerve were generally lower than the attributes of peroneal and tibial nerves. Also, some involvement of upper limb nerves is known to occur in diabetic polyneuropathy. Conceivably, other mechanisms might also be involved; for example, ulnar neuropathy from repeated injury at the elbow might have gone unrecognized in some of our patients.

It may be that the insights obtained from the study of diabetic polyneuropathy and CIDP can be extrapolated to other varieties of generalized polyneuropathies, but our studies of MMN show that they may not apply to all neuropathies. However, even in MMN, composite scores of individual affected nerves performed well. Nevertheless, even composite scores of individual nerves in MMN did not correlate with neuropathic impairment. This may have been due to the small number of cases studied and the small contribution of the CMAP from small muscles used in nerve conduction testing.

We have not directly tested the idea that composite scores are more representative of neuropathy than individual attributes, but have assumed it. We infer that a polyneuropathy is the sum of all neuropathic symptoms, impairments, and dysfunctions, and therefore that summations of the nerve conduction components are more representative than individual components.

Because some composite scores are more sensitive, less variable, more representative, and correlate better with neuropathic impairment than individual attributes, we suspect that they will find an increasing role in epidemiologic surveys, controlled trials of therapeutic interventions, and clinical practice.

Recognizing that composite scores have certain advantages over individual attributes, what is required for their use? There are perhaps three fundamental requirements: (1) an adequate normative database so that attributes of nerve conduction can be expressed as percentile values and normal deviates (Z scores) and as corrected for attribute, age, gender, height, weight, and body mass index (which ever apply); (2) a microprocessor and the software necessary to automatically determine percentile and Z scores and calculate composite scores; and (3) physicians who can interpret the results. In our opinion, the greatest impediment to increased use of composite scores may be availability of adequate normative data for certain ethnic populations and geographic regions. Our normative data are for individuals of northern European extraction and for those 18–90 years of age. It is not known whether these normative values apply to persons of different ethnicity or geographic and nutritional status. The availability of microprocessors should not be limiting because of their increasingly low cost. Finally, the concepts of percentiles, Z scores, and composite scores are not difficult to understand and, in all instances, results could be generated by microprocessors in readily understood form. Whether electro-

myographers will choose to use composite scores will perhaps depend on imponderables not studied herein.

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