1 Nerve Conduction Studies

Nerve conduction studies (NCS) involve non-invasive electrical stimulation of a peripheral nerve at one site and non-invasive measurement of the evoked response at a second site along the nerve (sensory or mixed nerve conduction) or over a muscle innervated by the nerve (motor nerve conduction). Nerve conduction measurements are characterized by three key parameters: latency, conduction velocity and amplitude. Conduction velocity and latency quantify the speed of nerve impulse propagation and are altered in diseases causing demyelination. Amplitude reflects the number of functioning nerve fibers and is reduced in diseases causing axonal degeneration. Nerve conduction is a distinct procedure from needle electromyography, which involves insertion of needles into muscles to assess muscle abnormalities.

All NCS methods are based on the same underlying neurophysiological principles. However, with advances in technology, there are now two approaches to obtaining nerve conduction data. Nerve conduction using pre-configured electrode arrays is designed for testing specific nerves where array placement is based on the location of well defined anatomical landmarks. Traditional nerve conduction utilizes individual electrodes that are placed according to neuroanatomical knowledge of the examiner.

Figure 1 compares electrode placement for testing of the sural nerve. As shown, the two methods are similar except that the pre-configured electrode array combines all the electrodes and the electrodiagnostic instrumentation into a single apparatus. The traditional approach involves discrete electrodes placed over the nerve at various locations with multiple connections to the electrodiagnostic equipment. Furthermore, although all modern electrodiagnostic instruments utilize computer automation; devices adapted for pre-configured electrode arrays generally employ more extensive automation.

Nerve conduction using pre-configured electrode arrays is particularly useful for point-of-care testing where rapid and cost efficient diagnostic testing is needed for assessment of common types of nerve disease such as diabetic neuropathies.

Figure 1. Comparison of sural nerve testing using individual electrodes (left) and pre-configured electrode array (right).
of nerve disease such as diabetic neuropathies. Traditional nerve conduction is appropriate for more extensive diagnostic studies in complicated cases, and is often performed by specialists.

The NC-stat® DPNCheck™, manufactured by NeuroMetrix Inc. of Waltham, MA, was introduced in late 2011 and is a modification to an earlier product called the NC-stat® device which was discontinued in 2010 following 12 years on the market. The NC-stat was discontinued due to obsolescence of certain electronic components. There are two primary differences between NC-stat DPNCheck and the original NC-stat. The first is that the former is limited to testing the sural nerve whereas the original NC-stat also supported testing of the median, ulnar, peroneal, and tibial nerves. The second is that NC-stat DPNCheck is a single unit that combines the device and electrodes into the form of pre-configured electrode whereas the original NC-stat had a separate pre-configured electrode array that was connected to a device through a cable. The two devices use comparable hardware, software, algorithms, and pre-configured electrode geometry for testing the sural nerve and therefore, measurement of the nerve conduction velocity and amplitude are unaffected. Figure 2 shows sural nerve testing with the NC-stat DPNCheck and the original NC-stat.

The NC-stat DPNCheck device expands on the capabilities of the original NC-stat by providing real-time waveform review, cursor editing, and report generation. These capabilities are provided by connecting the device to a PC via a USB cable. Examples of the NC-stat DPNCheck waveform review and editing software application and report are shown in Figure 3.
Diabetic Peripheral Neuropathy

Diabetic neuropathies are a serious, and in some cases, disabling complication of both Type 1 and Type 2 diabetes mellitus. The most common form is diabetic peripheral neuropathy (DPN) which is a chronic distal symmetric sensorimotor polyneuropathy. It has a prevalence of about 50% among US Type 1 and 2 diabetics, and an estimated annual direct cost of over $14 billion in the US.

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A history and physical examination, including the use of office-based testing methods such as the Semmes-Weinstein monofilament and the 128-hertz tuning fork, is the current foundation of DPN assessment. However, these methods are recognized to have limited utility in key clinical populations. Reductions in vibration sense, ankle reflexes, and distal touch sense are common in healthy elderly people. For example, up to 34% of individuals 60 years and older, without evidence of neurological disease, have absent vibration sense at the big toe. As a result, abnormalities found during a physical examination cannot reliably confirm DPN in the elderly. Another group for which traditional signs of DPN have limited value, because the history and physical examination are often normal, are those with early or mild neuropathy. Another limitation of relying exclusively on the clinical examination is that diabetic patients may have abnormal findings for reasons other than DPN, such as lumbar spinal stenosis, which is common in the Medicare population.

Based on the significant health impact of DPN, the American Diabetes Association (ADA) recommends an annual evaluation for peripheral neuropathy as the central component of the comprehensive foot examination. However, these practice recommendations are not consistently followed leading to low rates of clinically adequate foot examinations or other preventive strategies. The lack of attention to DPN is a critical health care issue because it may lead to missed opportunities for both physicians and patients to engage in and benefit from better glycemic control and a reduction in other cardiovascular risks factors, both of which have been shown to slow the progression of DPN. Further, the lack of DPN detection limits opportunities to initiate strategies to prevent foot ulcers and other complications such as falls in the elderly.

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Risk factors for DPN have been determined through cross sectional and prospective studies. Hyperglycemia is highly correlated to the development and progression of DPN. However, glycemic exposure accounts for less than one-third of the prevalence and severity of DPN. Therefore, other factors, some of which may be modifiable, have been implicated in the development and progression of DPN. These include older age, duration of diabetes, body mass index, hyperlipidemia, hypercholesterolemia, hypertension, history of smoking, nephropathy, and retinopathy.
examinations for neuropathy. 

Kirkman and colleagues sampled rural primary care physicians and found that only 15% of patients with diabetes received a foot examination. Better results were reported in a study evaluating adherence to diabetes quality standards in five Arizona Medicare managed care plans, where 63% of patients with diabetes received an annual foot examination. In a claims and survey based analysis of Medicare beneficiaries in Montana, only 46% of patients with diabetes at high risk of foot complications received a monofilament test in the past 12 months. Moreover, only 26% of high risk patients recognized that they were at risk. The lack of attention to DPN is a critical health care issue because it may lead to missed opportunities for both physicians and patients to engage in and benefit from better glycemic control and a reduction in other cardiovascular risks factors, both of which have been shown to slow the progression of DPN. Further, the lack of DPN detection limits opportunities to initiate strategies to prevent foot ulcers and other complications such as falls in the elderly.

The reasons for poor adherence to DPN and foot examination guidelines are unclear, but may include the perception that patients will not comply with resulting recommendations, lack of physician time to carry out the examination, and questions about the accuracy of the suggested clinical methods. It is now well recognized that clinical approaches, including the monofilament test, are subject to both false negatives (low sensitivity) and false positives (low specificity). Patients with DPN are often asymptomatic and monofilament and vibration perception may appear normal despite substantial nerve fiber degeneration. As a result, conventional clinical approaches are largely insensitive to subclinical or mild neuropathy. However, even moderate and severe neuropathy may appear normal by conventional testing. In fact, some patients present with foot ulcers without a prior diagnosis of DPN. The implication of diagnostic false negatives is that patients with DPN may go undiagnosed and opportunities to initiate preventative measures and educate the patient on proper foot care are lost. Although there are no simple pharmacological solutions to DPN, diagnosed patients can be managed with better glycemic control, modification of cardiovascular risk factors, education and implementation of self foot care, and referral, when indicated, to specialists such as podiatrists or neurologists. False positives could result in patients being inappropriately diagnosed with DPN, which may cause unneeded patient distress, missed opportunities to treat the actual cause of the positive clinical findings such as lumbar spinal stenosis, and overutilization of expensive interventions including diabetic shoes and insoles, specialist referrals, and unnecessary diagnostic tests. The Medicare Part B therapeutic shoe benefit includes “peripheral neuropathy with evidence of callus formation” as one of the qualifying criteria. Therefore, false positive diagnosis of peripheral neuropathy could lead to medically unnecessary prescriptions for diabetic shoes and insoles.

Nerve conduction studies are the most objective, accurate, and reliable method for detecting DPN. DPN is associated with changes in both nerve conduction velocity and amplitude. Although conduction velocity changes may be an earlier indication of peripheral neuropathy, amplitude loss is the most clinically relevant because it is directly indicative of myelinated nerve fiber loss, which leads to loss of protective sensation and increased risk of foot ulcers. There are generally agreed upon normal limits for nerve conduction measurements used in the assessment of DPN, particularly of the sural and peroneal nerves. A particular advantage of the sural nerve is that it is unaffected by lumbosacral radiculopathies and focal entrapment of this nerve is very rare. As a result, sural nerve abnormalities are highly specific biomarkers for peripheral neuropathies such as DPN. This makes interpretation of nerve conduction studies straightforward and means that treating physicians need not have specialized neurophysiology training.

Nerve conduction data can enhance the DPN diagnostic process in several ways. Nerve conduction changes are among the earliest evidence of DPN and are therefore a
A recent study by Hsu and colleagues prospectively investigated the relationship between the presence of neuropathy as assessed by nerve conduction and future mortality in patients with type 2 diabetes. The presence of neuropathy increased the risk of diabetes-related mortality more than 10-fold when corrected for other risk factors.

Despite the diagnostic benefits of NCS in evaluation of DPN, they are not widely utilized due to availability, complexity and cost. The routine referral of diabetic patients for comprehensive traditional nerve conduction studies is not practical, would be highly inconvenient to both patients and their providers, and would impose a high cost on patients and payers, including Medicare, which cannot be justified. Furthermore, such an approach would not be an effective use of limited specialist resources.

3 Guidelines

The ADA diabetic neuropathy guideline was established in 2005 by US and international experts in both endocrinology and neurology. The guideline defines DPN as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.” The guideline further states “Confirmation [of DPN] can be established with quantitative electrophysiology [nerve conduction], sensory, and autonomic function testing.” A more recent guideline established by many of the same diabetic neuropathy experts was developed during a joint meeting of the 19th annual Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes (NEURODIAB) and the 8th International Symposium on Diabetic Neuropathy in Toronto, Canada in 2009. This updated guideline confirms the importance of nerve conduction testing in evaluating DPN, by stating “We suggest a reliable objective and quantitative measure (i.e., NC [nerve conduction] abnormality) as the minimal criteria for the diagnosis of DSPN [DPN]. When NC values have not been assessed, it is not possible to provide a confirmed diagnosis of DSPN — only a possible or probable diagnosis.” (emphasis added) A similar position is held by US neurology and physical medicine & rehabilitation professional societies. An evidence-based definition of peripheral neuropathy published by the American Academy of Neurology (AAN), the American Academy of Physical Medicine and Rehabilitation (AAPM&R), and the American Association of Electrodiagnostic and Neuromuscular Medicine (AANEM) states that “The combination of neuropathic symptoms,
signs, and abnormal electrodiagnostic studies provides the most accurate diagnosis of distal symmetrical polyneuropathy." Consistent with these guidelines, wider use of nerve conduction testing in the assessment and confirmation of DPN has been suggested to have the potential to improve outcomes by accurately detecting and staging DPN at an earlier point in the disease process when clinical evidence is equivocal.30,44

4 Research on Pre-configured Electrode Arrays

Diagnostic devices are generally evaluated with respect to their technical and diagnostic performance. This review is focused on published peer-reviewed studies that evaluated the ability of pre-configured electrode arrays to accurately measure sural and/or peroneal nerve conduction because these nerves are considered the most sensitive and specific biomarkers for DPN.25,31 The analysis of diagnostic performance is focused on studies that evaluated patients with suspected peripheral neuropathies, primarily DPN. Although all of these studies were performed using the NC-stat, the results are applicable to NC-stat DPNCheck because it uses the same hardware, software, algorithms, and pre-configured electrode geometry for testing the sural nerve. Therefore, measurement of the nerve conduction velocity and amplitude are unaffected.

Technical performance studies have established that measurement of nerve conduction with pre-configured electrode arrays are valid and reliable when compared to the same measurements obtained in a neurophysiology laboratory as a reference standard. Unlike blood analytes, such as glucose, where definitive gold standard laboratory values exist, nerve conduction parameter values may vary according to a number of procedural and technical factors, including recording electrode location and configuration, temperature, instrumentation settings, and waveform features. Therefore measurements obtained in high quality neurophysiology laboratories are subject to variability.45 Nevertheless, they remain the best standard against which to compare alternative means of measuring nerve conduction. The pre-configured electrode results may be benchmarked against inter-examiner reproducibility studies in which the nerve conduction measurements were performed using traditional laboratory methods. These studies suggest that correlation coefficients greater than about 0.8 are indicative of strong technical performance by the pre-configured electrode array method.46

Perkins and colleagues assessed the technical performance of the NC-stat in the measurement of sural nerve

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Figure 5. Perkins et al. 2006 (Figure 1).47 Comparison of sural nerve amplitude measured by NC-stat (Y-axis) and neurophysiology laboratory (X-axis) in 72 diabetic patients.
amplitude in a prospective study of 72 consecutive patients with diabetes presenting to diabetes or neuropathy outpatient clinics. Patients were enrolled if they were at least 18 years of age and had a diagnosis of diabetes (Type 1 or 2), but were excluded if anatomical changes such as limb deformity, open skin lesions, injuries, or amputation precluded appropriate placement of nerve conduction equipment. The mean age was 56±11 years with 89% having Type 2 diabetes. Independent, masked observers performed both the NC-stat and a traditional nerve conduction assessment during the same visit. As shown in Figure 5, the NC-stat and traditional laboratory measurements of sural nerve amplitude were highly correlated (Spearman correlation coefficient was 0.95). The authors concluded, “Measurements of the amplitude potential obtained using a point-of-care device agree with measurements obtained by using the conventional method performed by electromyography technicians …” In a follow-up publication, the authors reported on the peroneal nerve. The correlation coefficient between the NC-stat and traditional methods was 0.83, 0.86, and 0.83 for the peroneal motor latency, F-wave latency, and motor amplitude respectively.

In addition to determining the correlation of sural nerve amplitude measured by NC-stat and traditional methods, Perkins and colleagues prospectively evaluated the diagnostic accuracy of the NC-stat. As described above, the study consisted of 72 consecutive diabetic subjects presenting to diabetes or neuropathy outpatient clinics. The primary outcome measure was diabetic sensorimotor polyneuropathy (i.e., DPN) according to the American Academy of Neurology classification, which requires the presence of one or more neuropathic symptoms or signs and abnormalities of three or more nerve conduction parameters in two or more nerves. The prevalence of signs and/or symptoms of DPN in the study cohort was not reported, however the prevalence of DPN according to the AAN criteria was reported to be 69% indicating a moderately high pre-test probability of DPN. An abnormal NC-stat test was defined as low sural nerve amplitude using conventional criteria (≤6 µV). The sensitivity and specificity of the NC-stat were 0.92 and 0.82, respectively. The authors concluded, “… abnormality of the sural nerve amplitude potential as measured by the point-of-care device [NC-stat] detects the presence of polyneuropathy (as determined by clinical and diffuse electrophysiologic criteria interpreted by a specialized neurologist) with acceptable sensitivity and specificity.”

Jabre and colleagues evaluated the technical performance of peroneal and posterior tibial distal motor latency, amplitude and F-wave latency measurements by the NC-stat using laboratory methods as the reference standard. The study cohort was 60 patients with lower extremity symptoms and/or physical findings suggestive of neuropathy referred to a neurophysiology laboratory for lower extremity nerve studies. The mean age of the study cohort was 54.3±16.3 years (range 17 to 83, 17.2% over 69). Both the NC-stat and traditional nerve conduction were performed by the same technician. Correlation between the two measures was assessed with the Spearman correlation coefficient. The authors reported correlation coefficients of 0.70, 0.91, and 0.86 for the peroneal motor latency, F-wave latency, and motor amplitude respectively. The authors concluded “Our study indicates that the technology used by the NC-stat for recording and analyzing NCS in the peroneal and posterior tibial nerves compares favorably with that obtained with traditional EMG equipment.”

Schmidt and colleagues evaluated the technical performance of peroneal and sural nerve conduction measurements with the NC-stat in a study assessing the performance of a now commercially discontinued computerized interpretation algorithm for lumbosacral radiculopathy. The study cohort consisted of 50 subjects (86% over 50 years of age) referred to a neurophysiology laboratory with complaints of predominantly unilateral leg pain, numbness, or weakness for 20 days or more. An additional 25 asymptomatic subjects were evaluated. The authors reported Pearson correlations of 0.90-0.92 for the peroneal F-wave latency. The authors concluded, “Overall, we found that the NC-stat device was able to accurately collect raw nerve conduction data.”

Kong and colleagues evaluated repeatability of nerve conduction measurements using pre-configured electrode...
arrays and computerized data acquisition and analysis (ADVANCE™ NCS/EMG device) in 29 subjects, 25 (86%) of which had symptoms suggestive of neuropathies, including 9 (31%) with neuropathic pain. The age range was 22-77 years with mean 50 years. The median, ulnar, deep peroneal, posterior tibial, and sural nerves were evaluated bilaterally at two test sessions 3-7 days apart. Within each session, nerves were tested twice within 10 minutes. The primary outcome measure was the between-session-test variance which quantifies the total variation between test sessions. The sural conduction velocity and amplitude had coefficients of variation of 4.5% and 30.8% respectively. The peroneal F-wave latency had a coefficient of variation of 5.0%. These results compare favorably to repeatability studies using laboratory methods. For example, Bird and colleagues measured coefficients of variation for nerve conduction measurements of the sural and peroneal nerves, in a laboratory, as part of a phase III clinical trial of a DPN therapeutic drug.52 They reported 11.9% and 53.4% for sural nerve conduction velocity and amplitude, and 10.8% for peroneal F-wave latency.

As part of the Pittsburgh Epidemiology of Diabetes Complications Study (EDC), Pambianco and colleagues presented data comparing monofilament and vibration perception testing to nerve conduction measurements made with the NC-stat device.53 The authors noted, “…as the NC-stat is based upon the same underlying physiology as traditional nerve conduction, we further sought to examine the association of the other neuropathy measures (and DSP) with this test representing the “Gold Standard”.” The study cohort consisted of 195 subjects with long standing Type 1 diabetes. The mean age was 41.4±6.5 years and 46.2±7.2 years for those without and with clinically defined DPN, respectively. The corresponding diabetes duration was 33.6±5.2 and 38.3±7.2. The prevalence of clinical DPN was 41.5%.54 The NC-stat sural amplitude was defined as abnormal using conventional criteria (i.e., <6 uV). Monofilament testing had a sensitivity of 0.15 and a specificity of 1.00 for an abnormal NC-stat sural amplitude. The interpretation of this data is that all (100%) subjects with an abnormal monofilament test were also abnormal by the NC-stat. However, the monofilament test missed 85% of abnormal NC-stat sural amplitudes. These results indicate that the NC-stat has very high sensitivity for advanced neuropathy, as indicated by an abnormal monofilament test, but as expected also detects mild disease. Another interesting finding reported by Pambianco and colleagues was that vibration perception assessment had a sensitivity of 0.88 and a specificity of 0.30. The interpretation of these data is that most patients with an abnormal NC-stat test also have abnormal vibration. However, 70% of patients with abnormal vibration lack objective confirmation of neuropathy as indicated by a normal sural nerve amplitude measured by the NC-stat. This result is consistent with the recognized lack of specificity of vibration assessment, particularly in older populations.15

In Shepherd 2010,55 a prospective diagnostic before-and-after study design was used to evaluate the impact of NC-stat testing on physician diagnostic reasoning and patient management in a primary care setting. In this study, a clinical diagnosis was made from the symptoms and physical examination, and then NC-stat testing was conducted when deemed medically appropriate during the course of routine clinical care. The key study outcomes were how often the NC-stat test confirmed the physician’s pretest diagnosis, how often the NC-stat test changed the physician’s pre-test diagnosis, which was defined as a complete change from the suspected pretest diagnosis to another diagnosis, how often the NC-stat test expanded the pretest diagnosis by adding a previously unsuspected diagnosis, and how often the plan of care was altered by the NC-stat test which was defined as ordering a diagnostic test, implementing a change in therapy, or initiating a referral because of the test results. The study design was prospective because the pretest diagnosis and treatment plan were noted by the participating physicians before the NC-stat test was performed. The study cohort consisted of 100 tests from 85 distinct patients. The mean age was 60.0±16.8, with 53% 65 years or older. Some of the patients did not have diabetes. Among the 100 tests, the pretest diagnosis was carpal tunnel syndrome in 34%, and in another 49% it was peripheral neuropathy due to diabetes and/or other causes. The pretest diagnosis of peripheral neuropathy was confirmed by NC-stat testing in 26 (53.1%) tests. The pretest diagnosis was changed by
In summary, sural and peroneal nerve conduction measurements using pre-configured electrode arrays have consistently demonstrated high technical performance in diverse patient populations as assessed by correlations to the same parameters measured with traditional methods in neurophysiology laboratories. Reported correlations were typically 0.80 - 0.95.

Conclusion

Diabetic peripheral neuropathy (DPN) is a common and challenging complication of diabetes. Diagnostic assessment of DPN is particularly difficult in the elderly due to the equivocal nature of clinical findings in this population. Evidence based and consensus guidelines by experts in endocrinology and neurology note the limitations of clinical diagnoses of DPN and recommend confirmation by nerve conduction measurements in order to maximize diagnostic accuracy. Nerve conduction studies using pre-configured electrode arrays provides physicians treating elderly patients with an efficient, cost-effective, and convenient way to increase the diagnostic certainty and quality of DPN diagnosis at the point of care, which could lead to more optimal individualized patient management.

References


