Diabetic Autonomic Neuropathy

AARON I. VINIK, MD, PHD[1]
RAELENE E. MASER, PHD[2]
BRAXTON D. MITCHELL, PHD[3]
ROY FREEMAN, MD[4]

ABSTRACT—Diabetic autonomic neuropathy (DAN) is a serious and common complication of diabetes. Despite its relationship to an increased risk of cardiovascular mortality and its association with multiple symptoms and impairments, the significance of DAN has not been fully appreciated. The reported prevalence of DAN varies widely depending on the cohort studied and the methods of assessment. In randomly selected cohorts of asymptomatic individuals with diabetes, ~20% had abnormal cardiovascular autonomic function. DAN frequently coexists with other peripheral neuropathies and other diabetic complications, but DAN may be isolated, frequently preceding the detection of other complications. Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure. DAN may affect many organ systems throughout the body (e.g., gastrointestinal [GI], genitourinary, and cardiovascular). GI disturbances (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence) are common, and any section of the GI tract may be affected. Gastroparesis should be suspected in individuals with erratic glucose control. Upper-GI symptoms should lead to consideration of all possible causes, including autonomic dysfunction. Whereas a radiographic gastric emptying study can definitively establish the diagnosis of gastroparesis, a reasonable approach is to exclude autonomic dysfunction and other known causes of these upper-GI symptoms. Constipation is the most common lower-GI symptom but can alternate with episodes of diarrhea. Diagnostic approaches should rule out autonomic dysfunction and the well-known causes such as neoplasia. Occasionally, anorectal manometry and other specialized tests typically performed by the gastroenterologist may be helpful. DAN is also associated with genitourinary tract disturbances including bladder and/or sexual dysfunction. Evaluation of bladder dysfunction should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder. Specialized assessment of bladder dysfunction will typically be performed by a urologist. In men, DAN may cause loss of penile erection and/or retrograde ejaculation. A complete workup for erectile dysfunction in men should include history (medical and sexual); psychological evaluation; hormone levels; measurement of nocturnal penile tumescence; tests to assess penile, pelvic, and spinal nerve function; cardiovascular autonomic function tests; and measurement of penile and brachial blood pressure. Neurovascular dysfunction resulting from DAN contributes to a wide spectrum of clinical disorders including erectile dysfunction, loss of skin integrity, and abnormal vascular reflexes. Disruption of microvascular skin blood flow and sudomotor function may be among the earliest manifestations of DAN and lead to dry skin, loss of sweating, and the development of fissures and cracks that allow microorganisms to enter. These changes ultimately contribute to the development of ulcers, gangrene, and limb loss. Various aspects of neurovascular function can be evaluated with specialized tests, but generally these have not been well standardized and have limited clinical utility. Cardiovascular autonomic neuropathy (CAN) is the most studied and clinically important form of DAN. Meta-analyses of published data demonstrate that reduced cardiovascular autonomic function as measured by heart rate variability (HRV) is strongly (i.e., relative risk is doubled) associated with an increased risk of silent myocardial ischemia and mortality. The determination of the presence of CAN is usually based on a battery of autonomic function tests rather than just on one test. Proceedings from a consensus conference in 1992 recommended that three tests (R-R variation, Valsalva maneuver, and postural blood pressure testing) be used for longitudinal testing of the cardiovascular autonomic system. Other forms of autonomic neuropathy can be evaluated with specialized tests, but these are less standardized and less available than commonly used tests of cardiovascular autonomic function, which quantify loss of HRV. Interpretability of serial HRV testing requires accurate, precise, and reproducible procedures that use established physiological maneuvers. The battery of three recommended tests for assessing CAN is readily performed in the average clinic, hospital, or diagnostic center with the use of available technology. Measurement of HRV at the time of diagnosis of type 2 diabetes and within 5 years after diagnosis of type 1 diabetes (unless an individual has symptoms suggestive of autonomic dysfunction earlier) serves to establish a baseline, with which 1-year interval tests can be compared. Regular HRV testing provides early detection and thereby promotes timely diagnostic and therapeutic interventions. HRV testing may also facilitate differential diagnosis and the attribution of symptoms (e.g., erectile dysfunction, dyspepsia, and dizziness) to autonomic dysfunction. Finally, knowledge of early autonomic dysfunction can encourage patient and physician to improve metabolic control and to use therapies such as ACE inhibitors and β-blockers, proven to be effective for patients with CAN.

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From the [1]Strelitz Diabetes Research Institutes, Eastern Virginia Medical School, Norfolk, Virginia; the [2]Department of Medical Technology, University of Delaware, Newark, Delaware; the [3]Department of Medicine, Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland; and the [4]Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Aaron I. Vinik, MD, PhD, Director, Strelitz Diabetes Research Institutes, Eastern Virginia Medical School, 855 W. Brambleton Ave., Norfolk, VA 23510. E-mail: vinikai@evms.edu.

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Abbreviations: AAN, American Academy of Neurology; ANS, autonomic nervous system; CAN, cardiovascular autonomic neuropathy; DAN, diabetic autonomic neuropathy; DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram; ED, erectile dysfunction; E:I, expiration-to-inspiration; GI, gastrointestinal; HRV, heart rate variability; MI, myocardial infarction; PSA, power spectral analysis; QSART, quantitative sudomotor axon reflex test; TST, thermoregulatory sweat test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complications of diabetes despite its significant negative impact on survival and quality of life in people with diabetes (1,2). A subtype of the peripheral polyneuropathies that accompany diabetes, DAN can involve the entire autonomic nervous system (ANS). ANS vasomotor, visceromotor, and sensory fibers innervate every organ. DAN may be either clinically evident or subclinical. It is manifested by dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal [GI],

genitourinary, sudomotor, or ocular) (3). Many organs are dually innervated, receiving fibers from the parasympathetic and sympathetic divisions of the ANS. DAN typically occurs as a system-wide disorder affecting all parts of the ANS. Indeed, because the vagus nerve (the longest of the ANS nerves) accounts for ~75% of all parasympathetic activity (4), and DAN manifests first in longer nerves, even early effects of DAN are widespread.

Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. Whereas symptoms suggestive of autonomic dysfunction may be common they may frequently be due to other causes rather than to true autonomic neuropathy. Subclinical autonomic dysfunction can, however, occur within a year of diagnosis in type 2 diabetes patients and within two years in type 1diabetes patients (5). Because of its association with a variety of adverse outcomes including cardiovascular deaths, cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of DAN. The introduction over 20 years ago of simple, noninvasive tests of cardiovascular autonomic function has supported extensive clinical and epidemiologic investigation of CAN. These data form the strongest body of evidence for the importance of detecting and monitoring impaired autonomic function in patients with diabetes (6,7).

PATHOGENESIS OF DAN

Hypotheses concerning the multiple etiologies of diabetic neuropathy include a metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency (8). Several different factors have been implicated in this pathogenic process. Hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in the NAD:NADH ratio may cause direct neuronal damage and/or decreased nerve blood flow (9–11). Activation of protein kinase C induces vasoconstriction and reduces neuronal blood flow (11). Increased oxidative stress, with increased free radical production, causes vascular endothelium damage and reduces nitric oxide bioavailability (12,13). Alternately, excess nitric oxide production may result in formation of peroxynitrite and damage endothelium and neurons, a process referred to as nitrosative stress (14,15). In a subpopulation of individuals with neuropathy, immune mechanisms may also be involved (16–18). Reduction in neurotrophic growth factors (19), deficiency of essential fatty acids (20), and formation of advanced glycosylation end products (localized in endoneurial blood vessels) (21) also result in reduced endoneurial blood flow and nerve hypoxia with altered nerve function (8,11,12). The result of this multifactorial process may be activation of polyADP ribosylation depletion of ATP, resulting in cell necrosis and activation of genes involved in neuronal damage (22,23).

EPIDEMIOLOGY OF DAN

The reported prevalence of DAN varies, depending on whether studies have been carried out in the community, clinic, or tertiary referral center. The variance among prevalence studies also reflects the type and number of tests performed and the presence or absence of signs and symptoms of autonomic neuropathy. Other factors that account for the marked variability in reported prevalence rates include the lack of a standard accepted definition of DAN, different diagnostic methods, variable study selection criteria, and referral bias (24). Additional complicating factors include the wide variety of clinical syndromes and confounding variables such as age, sex, duration of diabetes, glycemic control, diabetes type, height, and other factors. Table 1 reveals the prevalence rates of CAN for several different studies, again indicating the dramatic variability from a low of 7.7% for newly diagnosed patients with type 1 diabetes, when strict criteria to define CAN were used (24), to a high of 90% in potential recipients of a pancreas transplant (25).

To address issues in comparing data from different sources, the 1988 San Antonio Conference on Diabetic Neuropathy recommended that each laboratory should standardize the objective measures using their own population norms, reporting both absolute data and the relationship of the data to the appropriate normative control population. Subsequently, a number of studies have been conducted to assess the prevalence of DAN in defined populations.

For example, in a community-based population study of diabetic neuropathy in Oxford, England, the prevalence of autonomic neuropathy as defined by one or more abnormal heart rate variability (HRV) test results was 16.7% (38). In a further study, Ziegler et al. (24) evaluated the prevalence of CAN in 1,171 diabetic patients (647 type 1 diabetic patients, 524 type 2 diabetic patients) randomly recruited from 22 diabetes centers in Germany, Austria, and Switzerland. The study found that 25.3% of patients with type 1 diabetes and 34.3% of patients with type 2 diabetes had abnormal findings in more than two of six autonomic function tests. If more strict criteria were used (i.e., abnormalities present in least three of six autonomic function tests), the prevalence of CAN was 16.8% for individuals with type 1 diabetes and 22.1% for individuals with type 2 diabetes. Another study group observed nearly an identical prevalence rate (16.6%) for individuals with insulin-dependent diabetes (39).

Additional studies suggest that the prevalence of DAN may be even more common than these studies report. For example, using a variety of simple, validated, and noninvasive tests (e.g., fall in systolic blood pressure and heart rate response after standing), Verrotti et al. (40) found that 47 of 110 diabetic children and adolescents showed one or more abnormal tests for cardiovascular autonomic dysfunction. These results, however, recapitulate that prevalence rates will vary depending on *1*) different patient cohorts studied, *2*) varied testing modalities utilized, and *3*) different criteria used to define autonomic dysfunction.

CLINICAL MANIFESTATIONS OF DAN

The metabolic disorders of diabetes lead to diffuse and widespread damage of peripheral nerves and small vessels. Clinical manifestations of autonomic dysfunction and other microvascular complications frequently occur concurrently but in inconsistent patterns (41). The ubiquitous distribution of the ANS renders virtually all organs susceptible to autonomic dysfunction. Therefore, a patient diagnosed with diabetes should be suspected of having at least subclinical disturbances of the ANS. Overt signs and symptoms of autonomic disease fall into one or more of the following categories.

Cardiovascular

- Resting tachycardia
- Exercise intolerance

Table 1—*Reported prevalence of CAN*

Author	Date of publication	Diabetes type	Subjects (*n*)	Test(s) used	% Abnormal
Sharpey-Schafer and Taylor (26)	1960		337	Valsalva maneuver	21
Ewing et al. (27)	1974	Mixed with autonomic symptoms	124	Handgrip test	18
Morley et al. (28)	1977	Adult diabetic patients	70	Valsalva maneuver	24
				Heart rate variation	11
Hilsted and Jensen (29)	1979	Insulin-treated	126	Heart rate variation	40
Mackay et al. (30)	1980		287	Heart rate variation	30
Ewing et al. (31)	1980	Mixed with autonomic symptoms	73	Valsalva maneuver	47
				Handgrip	35
				Postural BP	45
Ewing et al. (32)	1980	Mixed with autonomic symptoms	61	Valsalva maneuver	54
				Handgrip	
				Postural BP	
Hulper and Willms (33)	1980		92	Handgrip	17
Dyrberg et al. (34)	1981	Insulin-dependent	75	Heart rate variation	27
				Valsalva maneuver	17
				Lying-to-standing	0
Xueli et al. (35)	1981	Newly diagnosed non-insulin-dependent		Valsalva maneuver	80
O'Brien et al. (36)	1991	Insulin-dependent	506	At least two of the following: heart rate variation in response to 1) rest 2) single deep breath 3) Valsalva maneuver or 4) standing	17
Ziegler et al. (24)	1992	Newly diagnosed insulin-dependent	130	At least three of the following: CV of heart rate variation, low-and mid-frequency bands of spectral analysis, MCR, Valsalva maneuver, or lying-to-standing	7.7
Ziegler et al. (24)	1992	Insulin-dependent	647	Greater than two of the following: coefficient of variation of heart rate variation, low- and mid-frequency bands of spectral analysis, MCR, Valsalva maneuver, or lying-to-standing	25.3
		Non-insulin-dependent	524		34.3
Kennedy et al. (25)	1995	Insulin-dependent	290	Heart rate variation	90
				Valsalva maneuver	88
DCCT Research Group (37)	1998	Insulin-dependent primary cohort 1–5 years' duration; secondary cohort 1–15 years' duration	1,441	Heart rate variation	1.6–6.2
				Valsalva maneuver	5.5–6.3
				Postural BP	1.1
				Any abnormality	2.6–23

BP, blood pressure; MCR, mean circular resultant.

- Orthostatic hypotension
- Silent myocardial ischemia

GI
- Esophageal dysmotility
- Gastroparesis diabeticorum
- Constipation
- Diarrhea
- Fecal incontinence

Genitourinary
- Neurogenic bladder (diabetic cystopathy)
- Erectile dysfunction
- Retrograde ejaculation
- Female sexual dysfunction (e.g., loss of vaginal lubrication)

Metabolic
- Hypoglycemia unawareness
- Hypoglycemia-associated autonomic failure

Sudomotor
- Anhidrosis
- Heat intolerance
- Gustatory sweating
- Dry skin

Pupillary
- Pupillomotor function impairment (e.g., decreased diameter of dark-adapted pupil)
- Argyll-Robertson pupil

The differential diagnosis of DAN involves excluding the following conditions:

- Pure autonomic failure (formerly called idiopathic orthostatic hypotension)
- Multiple system atrophy with auto-

nomic failure (formerly called Shy-Drager syndrome)
- Addison's disease and hypopituitarism
- Pheochromocytoma
- Hypovolemia
- Medications, with anticholinergic or sympatholytic effects (insulin, vasodilators, sympathetic blockers)
- Peripheral autonomic neuropathies (e.g., amyloid neuropathy, idiopathic autonomic neuropathy)

DAN is typically assessed by focusing on symptoms or dysfunction attributable to a specific organ system. CAN is the most prominent focus because of the life-threatening consequences of this complication and the availability of direct tests of cardiovascular autonomic function. However, neuropathies involving other organ systems should also be considered in the optimal care of patients with diabetes.

CAN

Perhaps one of the most overlooked of all serious complications of diabetes is CAN (42). CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics (43). Reduced heart rate variation is the earliest indicator of CAN (44).

In a review of several epidemiological studies among individuals diagnosed with diabetes, it was shown that the 5-year mortality rate from this serious complication is five times higher for individuals with CAN than for individuals without cardiovascular autonomic involvement (4).

In this report, the clinical manifestations (e.g., exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension, and increased risk of mortality) of the presence of CAN will be discussed. It will also be shown that autonomic dysfunction can affect daily activities of individuals with diabetes and may invoke potentially life-threatening outcomes. Advances in technology, built on decades of research and clinical testing, now make it possible to objectively identify early stages of CAN with the use of careful measurement of autonomic function.

Clinical manifestations of CAN

Exercise intolerance. Autonomic dysfunction can impair exercise tolerance (45). In a study of individuals with and without CAN, Kahn et al. (46) showed a reduced response in heart rate and blood pressure during exercise in individuals with CAN. Roy et al. (47) demonstrated a decreased cardiac output in response to exercise in individuals with CAN. The severity of CAN has also been shown to correlate inversely with an increase in heart rate at any time during exercise and with the maximal increase in heart rate. It should also be noted that decreased ejection fraction, systolic dysfunction, and diastolic filling limit exercise tolerance (1). Given the potential for impaired exercise tolerance, it has been suggested that diabetic patients who are likely to have CAN have cardiac stress testing before undertaking an exercise program (45).

Intraoperative cardiovascular lability. Hemodynamic changes occur during surgery for individuals with and without diabetes. Burgos et al. (48) found that vasopressor support was needed more often in diabetic individuals with autonomic dysfunction than in those without. The normal autonomic response of vasoconstriction and tachycardia did not completely compensate for the vasodilating effects of anesthesia. Kitamura et al. (49) also recently demonstrated an association between CAN and more severe intraoperative hypothermia. Complications arising from intraoperative hypothermia include decreased drug metabolism and impaired wound healing. Sobotka et al. (50) showed that some diabetic patients with autonomic neuropathy have a reduced hypoxic-induced ventilatory drive. These data suggest that preoperative cardiovascular autonomic screening may provide useful information for anesthesiologists planning the anesthetic management of diabetic patients and identify those at greater risk for intraoperative complications.

Orthostatic hypotension. Orthostatic hypotension is defined as a fall in blood pressure (i.e., >20 mmHg for systolic or >10 mmHg for diastolic blood pressure) in response to postural change, from supine to standing (51). In patients with diabetes, orthostatic hypotension is usually due to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature (52). In addition, there is a decrease in cutaneous, splanchnic, and total vascular resistance that occurs in the pathogenesis of this disorder.

Normally, in response to postural change there is an increase in plasma norepinephrine. For individuals with orthostatic hypotension, there may be a reduction in this response relative to the fall in blood pressure (53). Diminished cardiac acceleration and cardiac output, particularly in association with exercise, may also be important in the presentation of this disorder (53,54). Less frequently, there is a rise in norepinephrine that may be due to low blood volume or reduced red cell mass (55,56). Frequently, there are fluctuations in the degree of orthostatic hypotension. This may reflect postprandial blood pooling, the hypotensive role of insulin, and changing patterns of fluid retention due to renal failure or congestive heart failure (57–59).

Patients with orthostatic hypotension typically present with lightheadedness and presyncopal symptoms. Symptoms such as dizziness, weakness, fatigue, visual blurring, and neck pain also may be due to orthostatic hypotension. Many patients, however, remain asymptomatic despite significant falls in blood pressure (60). If the cause of orthostatic hypotension is CAN, treatment goals should not only consist of therapies to increase the standing blood pressure, balanced against preventing hypertension in the supine position (61), but should also provide education to patients so that they avoid situations (e.g., vasodilation from hot showers) that result in the creation of symptoms (i.e., syncopal episodes). Such symptoms can result in injuries from falling. Cardiovascular autonomic function testing may help differentiate CAN from other causes of weakness, lightheadedness, dizziness, or fatigue and promote appropriate therapeutic intervention (62).

Silent myocardial ischemia/cardiac denervation syndrome. The cause of silent myocardial ischemia in diabetic patients is controversial. It is clear, however, that a reduced appreciation for ischemic pain can impair timely recognition of myocardial ischemia or infarction and thereby delay appropriate therapy. Table 2 and Fig. 1*A* summarize the results of 12 cross-sectional studies, comparing the presence of silent myocardial ischemia, generally measured by exercise stress testing between diabetic individuals with and without CAN.

Of the 12 studies, 5 showed a statistically significant increased frequency of silent myocardial ischemia in individuals

Table 2—*Studies of CAN and silent myocardial ischemia*

Reference	Tests of autonomic function	Definition of CAN	% SMI^+/CAN^+	% SMI^+/CAN^-	Notes
Niakan et al. (63)	1. Valsalva maneuver	Abnormal Valsalva ratio	20% (5/25)	4% (2/48)*	All subjects had symptomatic peripheral neuropathy. Outcome was silent myocardial infarction
Hume et al. (64)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio	At least two of three were abnormal	36% (5/14)	20% (9/46)	Asymptomatic middle-aged men, no symptoms or signs of heart disease
Murray et al. (65)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. BP response to standing 5. BP response to handgrip	At least two of the first three tests = mild CAN	72% (13/18)	42% (5/12)	Patients with known or suspect CAD
Langer et al. (66)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. sBP response to standing 5. dBP response to handgrip	At least two of the tests were abnormal	38% (8/21)	5% (2/37)†	Men only, no clinical evidence of CAD
O'Sullivan et al. (67)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. sBP response to standing 5. dBP response to handgrip	At least two abnormal parasympathetic function tests	65% (11/17)	4% (1/24)‡	Men >40 years old. One-half of patients with known or suspected CAD
Koistinen et al. (68)	1. HRV during deep breathing 2. 30:15 ratio 3. BP response to standing	Both HRV during deep breathing and 30:15 ratio were abnormal	38% (3/8)	38% (11/29)	Patients with known CAD
Hartmann et al. (69)	1. HRV at rest over 5 min 2. HRV during deep breathing	Authors did not indicate whether only one or both tests were abnormal	82% (9/11)	40% (4/10)	CAD confirmed by coronary angiography
Jermendy et al. (70)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. BP response to standing	Results of parasympathetic tests (1,2,3) were scored 0 = normal, 1 = borderline, 2 = abnormal. Those with a score of 0–1 = without CAN, score of 2–3 = early CAN, and score of 4–6 = definitive CAN.	30% (11/37)	0% (0/26)†	Diabetic subjects with lack of symptoms of angina pectoris and ≥1 additional CVD risk factor
Zarich et al. (71)	1. HRV during deep breathing 2. Valsalva maneuver 3. sBP response to standing 4. dBP response to handgrip	Two or more abnormal test results were classified as moderate to severe	100% (10/10)	67% (10/15)	Subjects with known CAD
MiSAD Group (72)	1. HRV during deep breathing 2. HRV from lying to standing 3. Orthostatic hypotension	Autonomic neuropathy score ≥3	7% (13/175)	6% (46/750)	Asymptomatic men and women aged 40–65 years with no prior history of CAD
Jalal et al. (73)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. BP response to standing 5. BP response to handgrip	Normal = all tests normal or one borderline; Early = one of the three heart rate tests abnormal or two borderline; Definite = ≥two heart rate tests abnormal; severe = ≥two heart rate tests abnormal plus one or both BP tests abnormal	40% (12/30)	10% (3/30)†	Subjects with history of CAD were excluded. CAN^- subjects age- and sex-matched to CAN^+ subjects
Valensi et al. (74)	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio	Not indicated	30% (10/33)	36% (15/42)	Subjects asymptomatic for CAD, but had diabetes and ≥2 additional CVD risk factors
Total§			110/399	108/1,069	

BP, blood pressure; CAD, coronary artery disease; dBP, diastolic blood pressure; sBP, systolic blood pressure; SMI, silent myocardial ischemia. *$P < 0.05$; †$P < 0.001$; §Mantel-Haenszel estimate for the pooled rate ratio for silent myocardial ischemia = 1.96 (95% CI: 1.53–2.51, $P < 0.001$).

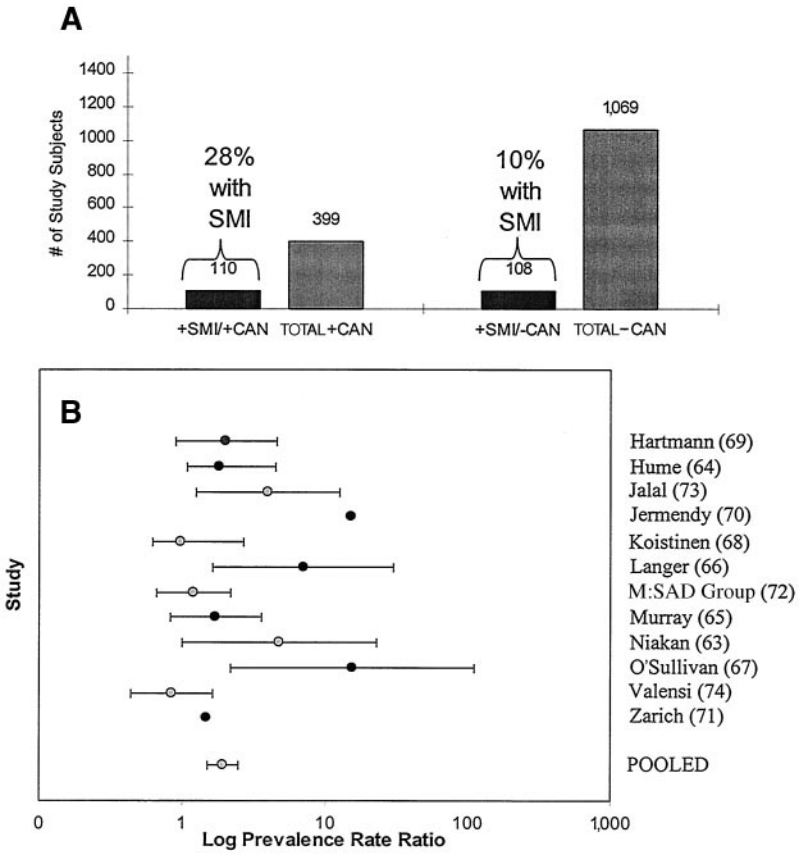

Figure 1— *Association of CAN and silent myocardial infarction (SMI) in 12 studies.* A*: +CAN, CAN present; −CAN, no CAN found; +SMI, SMI present.* B*: Prevalence rate ratios and 95% CIs for association between CAN and SMI from the 12 studies.*

with CAN compared with individuals without CAN. The point estimates for the prevalence rate ratios in these 12 studies ranged from 0.85 to 15.53 (Fig. 1*B*). The prevalence rate ratio was >1 in 10 of the 12 studies, and in 4 of these, the lower limit of the 95% CI was >1. Via meta-analysis, the Mantel-Haenszel estimate for the pooled prevalence rate risk for silent myocardial ischemia was 1.96, with a 95% CI of 1.53–2.51 ($P < 0.001$; $n =$ 1,468 total subjects). These data demonstrate a consistent association between CAN and the presence of silent myocardial ischemia.

There are several additional published studies that have examined the relationship between autonomic dysfunction and silent myocardial ischemia in diabetic individuals but that are not included in the meta-analysis because the raw numbers of case and control subjects among individuals with and without cardiovascular autonomic dysfunction were not presented (75–78). However, virtually all of these studies also provide evidence for an association. For example, Ambepityia et al. (75) measured the anginal perceptual threshold (i.e., the time from onset of 0.1 mV ST depression to the onset of angina pectoris during exercise) in individuals with and without diabetes. The influence of autonomic function was assessed via heart rate variation during deep breathing (beats/min), Valsalva maneuver, 30:15 ratio, and blood pressure response to standing. The perception of angina was severely impaired in the diabetic patients, allowing these individuals to exercise longer after the onset of myocardial ischemia. The delay in perception of angina was associated with the presence of cardiovascular autonomic dysfunction. The investigators suggested that the neuropathic damage to the myocardial sensory afferent fibers in the autonomic nerve supply reduced the diabetic individual's sensitivity to regional ischemia by interrupting pain transmission (75). A study by Marchant et al. (76) examined 22 diabetic and 30 nondiabetic individuals who had similar left ventricular function and severity of coronary artery disease as assessed by coronary angiography and ventriculography. The following autonomic function tests were included: heart rate variation during deep breathing (beats/min), 30:15 ratio, Valsalva maneuver, blood pressure response to standing, and blood pressure response to sustained handgrip. All 52 individuals manifested ischemia during exercise. A total of 16 individuals did not experience angina, and 10 of these had diabetes. Comparing the silent ischemia group ($n = 16$) with the group who did experience angina ($n = 36$) revealed impaired autonomic function in the silent ischemia group, with statistically lower 30:15 ratios. In subgroup analysis, the impaired autonomic function was found to be confined to just the diabetic individuals and not seen in the nondiabetic individuals with silent myocardial ischemia, thus indicating that subclinical autonomic neuropathy is associated with silent ischemia in individuals with diabetes (76). Hikita et al. (77), using 24-h ambulatory electrocardiographic recordings, demonstrated that HRV is reduced in diabetic patients with silent ischemia when compared with nondiabetic individuals with silent or painful ischemia. Some investigators, however, have questioned whether the association between CAN and silent myocardial ischemia is a causal one (79), suggesting instead that underlying coronary artery disease might be a cause of both autonomic dysfunction and silent myocardial ischemia (80).

The presence of CAN does not exclude painful myocardial infarction (MI) among individuals with diabetes (81). Chest pain in any location in a patient with diabetes should be considered to be of myocardial origin until proven otherwise; but, of equal importance, unexplained fatigue, confusion, tiredness, edema, hemoptysis, nausea and vomiting, diaphoresis, arrhythmias, cough, or dyspnea should alert the clinician to the possibility of silent MI (1).

Increased risk of mortality

Table 3 summarizes investigations that have examined the association of autonomic dysfunction and mortality. These studies have consistently provided evidence for an increased mortality risk among diabetic individuals with CAN compared with individuals without CAN (Table 3).

Table 3—*Studies of CAN and mortality*

Reference	Follow-up (years)	Tests of autonomic function	Definition of CAN	% Mortality/ CAN^+	% Mortality/ CAN^-	Notes
Ewing et al. (31)	5	1. Valsalva maneuver 2. Handgrip 3. Postural fall in BP		53% (21/40)	15% (5/33)†	Subjects who complained of symptoms suggestive of autonomic neuropathy comprised the study cohort. CAN^+ subjects had more complications at baseline. Half of the deaths for the CAN^+ subjects were attributed to renal failure.
Sampson et al. (82)	10–15	1. HRV during deep breathing 2. Valsalva maneuver 3. Heart rate and sBP response to standing	Based on HRV and the presence or absence of symptomatic autonomic neuropathy	27% (20/73)	11% (4/38)	Mortality in asymptomatic individuals with an isolated abnormality in autonomic function tests was not increased. Excess mortality was restricted to those with symptomatic CAN (18/49 vs. 4/38).
O'Brien et al. (36)	5	HRV in response to 1. supine rest 2. single deep breath 3. Valsalva maneuver 4. standing for 60 s	Two or more of the four tests were abnormal	27% (23/84)	8% (7/84)†	Those with CAN had greater prevalence of other complications, but in multivariate analysis, CAN was the most important predictor of mortality.
Ewing et al. (83)	3	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. BP response to standing 5. BP response to handgrip	Normal = all tests normal or one borderline; early = one of the three heart rate tests abnormal or two borderline; definite = two or more of the heart rate tests abnormal; severe = at least two of the heart rate tests abnormal and one or both of the BP tests abnormal or both borderline	31% (10/32)	8% (3/39)*	Included men <60 years old. CAN^+ subjects who died ($n = 10$) had longer QT intervals than those who did not.
Jermendy et al. (84)	5	1. HRV during deep breathing 2. Valsalva maneuver 3. 30:15 ratio 4. sBP response to standing	Results of parasympathetic tests (1,2,3) were scored 0 = normal, 1 = borderline, 2 = abnormal. Those with a score of 0–1 = without CAN; score of 2–3 = early CAN; score of 4–6 = definitive CAN.	40% (12/30)	4% (1/23)†	No patients had an abnormal sBP response to standing. Deceased subjects were older and had more complications at baseline.
Rathmann et al. (85)	8	1. Coefficient of variation of R-R intervals with normal respiration 2. Coefficient of variation of R-R intervals with deep respiration	Both tests abnormal	23% (8/35)	3% (1/35)*	Subjects with advanced renal disease, proliferative retinopathy, and CVD were excluded.
Hathaway et al. (86)	2–5 (case-control study)	1. HRV during deep 2. Valsalva maneuver	Both tests abnormal	31% (4/13)	0% (0/16)*	Case-control study of transplant recipients (pancreas-kidney or kidney alone). Case subjects ($n = 4$) died of sudden cardiac death within 3.5 years posttransplant. Control subjects survived 2–5 years posttransplant.

Continued on following page

Table 3—Continued

	Follow-up (years)	Tests of autonomic function	Definition of CAN	% Mortality/ CAN^+	% Mortality/ CAN^-	Notes
Orchard et al. (87)	2	1. HRV during deep breathing	Abnormal E:I ratio	9% (8/88)	2% (9/399)†	Relative risk decreased from 4.03 to 1.37 after controling for duration, renal disease, hypertension, and coronary heart disease.
Sawicki et al. (88)	5–13	1. R-R variation between supine and standing position	$R\text{-}R_{supine}/R\text{-}R_{standing} < 1.03$	62% (16/26)	29% (17/59)†	All subjects with overt diabetic nephropathy
Navarro et al. (89)	1–11.5	1. HRV during deep breathing 2. Valsalva maneuver	Both tests abnormal	28% (101/359)	5% (6/128)‡	All subjects were candidates for pancreas transplantation.
Toyry et al. (90)	10	1. HRV during deep breathing 2. sBP decrease during standing	Parasympathetic neuropathy = abnormal E:I ratio	50% (3/6)	17% (20/116)	Mortality rates for CVD mortality only. Subjects were newly diagnosed with diabetes. In multivariate analysis, sympathetic CAN^+ at 5-year, follow-up predicted CVD mortality at 10-year, follow-up even after adjusting for conventional CVD risk factors.
Sawicki et al. (91)	15–16	1. R-R variation between supine and standing position	$R\text{-}R_{supine}/R\text{-}R_{standing} < 1.03$	69% (58/84)	76% (100/132)	Consecutive patients (31% male) enrolled over a 2-year period for improvement in metabolic control.
Veglio et al. (92)	5	1. Heart rate (resting) 2. HRV during deep breathing 3. BP response to standing	Two or more of the tests abnormal	13% (10/75)	4% (10/241)†	QTc prolongation was associated with increased mortality risk.
Gerritsen et al. (93)	0.5–9.2	1. E:I difference		Not available	Not available	Relative risk = 2.25 (1.13–4.45); diabetic subjects (n = 159) identified through a population survey
Chen et al. (94)	7.7	HRV in response to 1. single deep breath 2. six consecutive breaths 3. supine to standing 4. Valsalva maneuver BP change sitting to standing	Unique diagnostic criteria defined by scoring 3 or more	29% (106/371)	12% (29/241)‡	CAN^+ associated with increased mortality even in the absence of postural hypotension
Total§				400/1,316	212/1,584	

BP, blood pressure; CVD, cardiovascular disease; E:I difference = mean expiration to inspiration difference in R-R intervals over six consecutive breaths; R-R interval, time interval between successive ECG R-waves; sBP, systolic blood pressure. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$; §Mantel-Haenszel estimate for the pooled relative risk for mortality = 2.14 (95% CI 1.83–2.51, $P < 0.0001$). Adapted from Maser et al. (94a).

Ewing et al. (31) reported a 2.5-year mortality rate of 27.5% that increased to 53% after 5 years in diabetic patients with abnormal autonomic function tests compared with a mortality rate of only 15% over the 5-year period among diabetic patients with normal autonomic function test results. It should be noted that half of the deaths in individuals with abnormal autonomic function tests were from renal failure, and 29% were from sudden death. This study also revealed that symptoms of autonomic neuropathy, especially postural hypotension, and gastric symptoms in the presence of abnormal autonomic function tests carried a particularly poor prognosis.

A study by O'Brien (36) reported 5-year mortality rates of 27% in patients having asymptomatic autonomic neuropathy compared with an 8% mortality rate in diabetic subjects with normal autonomic function tests. Among individuals who died, there was no difference in duration of diabetes between those with and without autonomic neuropathy. As was true for the study performed by Ewing et al. (31); a significant number of the deaths (10/23) of the neuropathic patients were attributable to renal failure. O'Brien et al.,

Table 4—*Discriminant analysis of 5-year survival in type 1 diabetic patients*

Variable	Change in Rao's V	Significance
Autonomic neuropathy	44.8	0.0001
Systolic blood pressure	18.1	0.0001
Foot disease	13.4	0.0002
BMI	3.1	0.08
Peripheral sensorimotor neuropathy	3.5	0.06
Proteinuria	2.6	0.1
Macrovascular disease	1.9	0.2
Duration of diabetes	—	—
Retinopathy	—	—
Smoking	—	—

Duration of diabetes, retinopathy, and smoking were not found to be significant predictors of death. Adapted from O'Brien et al. (36).

however, compared the relative importance of various factors associated with mortality by discriminate analysis of survivors and nonsurvivors using Rao's stepwise selection method and revealed that autonomic neuropathy was more of an independent predictive factor than systolic blood pressure, foot disease, BMI, sensory neuropathy, proteinuria, and macrovascular disease (36) (Table 4).

Rathmann et al. (85) reported the results of a study designed to assess the risk of mortality due to CAN among patients with CAN but without a clinical manifestation of severe complications (proteinuria, proliferative retinopathy, coronary artery disease, or stroke) 8 years after their first clinical examination. The mortality of diabetic patients with CAN increased steadily over the 8-year period (6% after 2 years, 14% after 4 years, 17% after 6 years, and 23% after 8 years) compared with an age-, sex-, and duration of diabetes–matched control group where there was one death. Autonomic dysfunction was found to be an independent risk factor with poor prognosis. Some autonomic neuropathic symptoms (orthostatic hypotension, gastroparesis, gustatory sweating, and erectile impotence) were found more frequently among subjects who died (85).

Two separate population-based studies have also examined the association of CAN and mortality. Orchard et al. (87) studied a population-based sample of individuals with type 1 diabetes. Individuals for this study were identified through a hospital-based registry system and were considered to be representative of all type 1 diabetic patients residing in Allegheny County, Pennsylvania. Initial analyses based on a 2-year follow-up of 487 subjects revealed a fourfold higher mortality rate in individuals with CAN at baseline compared with individuals without. However, after adjusting for baseline differences between individuals with and without CAN for markers related to renal and cardiovascular disease, the relative risk decreased from 4.03 to 1.37 and was no longer statistically significant.

Another population-based study (the Hoorn study) examined 159 individuals with type 2 diabetes (85 had newly diagnosed diabetes) who were followed for an average of nearly 8 years. All-cause as well as cardiovascular mortality were found to be associated with impaired autonomic function in this study. In addition, the investigators suggested that cardiovascular autonomic dysfunction in individuals already at high risk (e.g., those with diabetes, high blood pressure, or a history of cardiovascular disease) may be particularly hazardous (93).

Meta-analysis of the relationship between CAN and mortality

As noted above, the relationship of CAN and mortality in diabetic individuals has been evaluated in a number of studies on an individual basis. Analysis of each of these studies as a single entity, however, only includes a limited number of subjects. Thus, in this section, results were pooled from a number of studies into a meta-analysis for the purpose of obtaining more precise estimates. Studies were included in this meta-analysis if they were based on diabetic individuals, included a baseline assessment of HRV, and included a mortality follow-up (94a).

Table 3 and Fig. 2*A* summarize the results from 15 different studies that have included a follow-up of mortality. The follow-up intervals in these studies ranged from 1 to 16 years. In all 15 studies, the baseline assessment for cardiovascular autonomic function was made on the basis of one or more of the tests described by Ewing et al. (95). Total mortality rates were higher in subjects with CAN at baseline than in subjects whose baseline assessment was normal, with statistically significant differences in 11 of the studies. The study-specific relative risks ranged from 0.91 for the study by Sawicki et al. (91) to 9.20 for the study by Jermendy et al. (84). Figure 2*B* shows the relative risks and 95% CIs for each study, as well as the pooled risk estimate estimated by the Mantel-Haenszel procedure. The pooled estimate of the relative risk, based on 2,900 total subjects, was 2.14, with a 95% CI of 1.83–2.51 ($P < 0.0001$).

Association of CAN with major cardiovascular events

The relationship between CAN and major cardiovascular events has been assessed in two prospective studies. Specifically, the relationship between baseline CAN and the subsequent incidence of a fatal or nonfatal cardiovascular event, defined as an MI, heart failure, resuscitation from ventricular tachycardia or fibrillation, angina, or the need for coronary revascularization, was examined (64,74). The relative risks associated with CAN in these studies were 2.2 and 3.4, respectively, with the latter result just achieving statistical significance ($P < 0.05$). It would appear, therefore, that there is an association between CAN and major cardiovascular events, but given the small number of events that occurred in each of these studies, more follow-up studies are required.

Potential reasons for the increased mortality rate associated with CAN

Despite the increased association with mortality, the causative relationship between CAN and the increased risk of mortality has not been conclusively established. Several mechanisms have been suggested including a relationship with autonomic control of respiratory function. Page and Watkins (96) reported 12 cardiorespiratory arrests in eight diabetic individuals with severe autonomic neuropathy and suggested that diabetic individuals with CAN have impaired respiratory responses to conditions of hypoxia and may be particularly suscep-

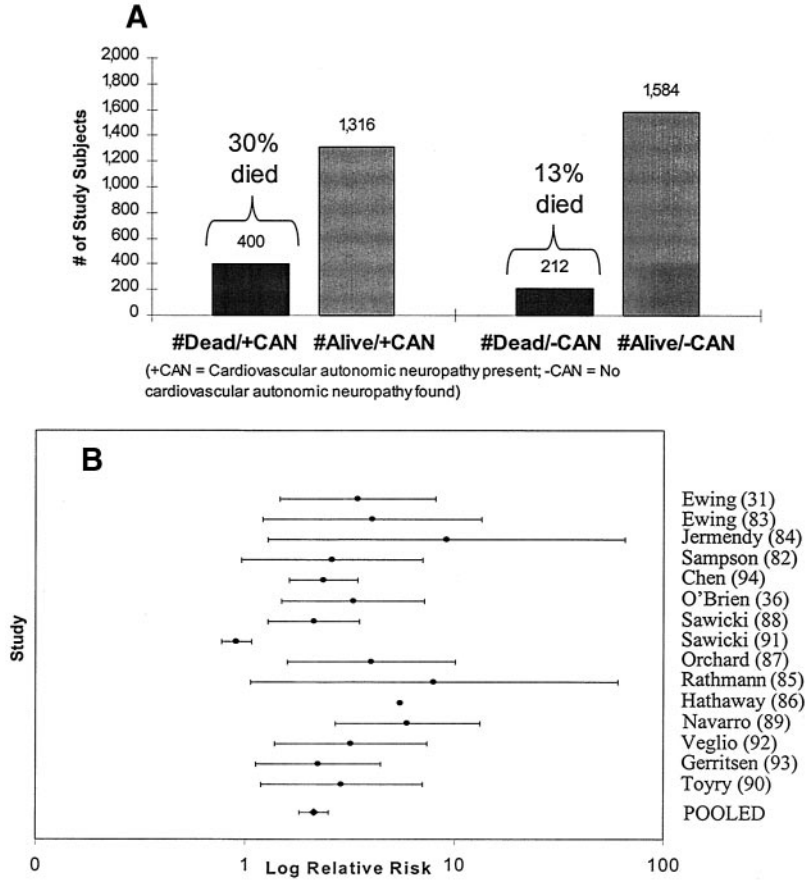

Figure 2—*Relative risks and 95% CIs for association between CAN and mortality in 15 studies. A: Association of CAN and mortality in 15 studies. +CAN, CAN present; −CAN, no CAN found. B: Log relative risks from the 15 studies.*

tible to medications that depress the respiration system. An impaired ability to recognize hypoglycemia and impaired recovery from hypoglycemic episodes due to defective endocrine counterregulatory mechanisms are also potential reasons for death (36). Other investigators have noted explanations for the high mortality rate as an interaction with other concomitant disorders that also carry high risks of mortality. Clarke et al. (7) speculated that the increased mortality found for patients with clinical symptoms of autonomic neuropathy were due to both a direct effect of the autonomic neuropathy itself and an indirect, but parallel, association with accelerating microvascular complications. O'Brien et al. (36) suggested that the high rate of mortality due to end-stage renal disease among diabetic patients with autonomic neuropathy may have been due to the parallel development of late-stage neuropathy and nephropathy. The presence of autonomic neuropathy may accelerate the rate of progression of diabetic glomerulopathy by mechanisms not completely understood (36). A consequential increase in cardiovascular risk experienced by individuals with nephropathy has also been noted. In one study of type 1 diabetic individuals, hypertension along with LDL and HDL cholesterol concentrations were found to be independent correlates of CAN (97). These results suggested that a disturbed cardiovascular risk profile seen in individuals with nephropathy might lead to both cardiovascular disease and CAN. Other investigators have also shown independent associations of autonomic dysfunction with markers of cardiovascular risk (e.g., elevated blood pressure [98], body weight, glycosylated hemoglobin, and overt albuminuria [99]). Long-term follow-up studies are needed to distinguish the exact roles of cardiovascular risk factors, nephropathy, and CAN in the etiology of cardiovascular disease. Nonetheless, CAN cosegregates with indexes of macrovascular risk, which may contribute to the marked increase in cardiovascular mortality. Diabetic patients with CAN are predisposed to a lack of the normal nighttime decrease in blood pressure because of an increased prevalence of sympathetic activity (100). A disturbed circadian pattern of sympathovagal activity with prevalent nocturnal sympathetic activity combined with higher blood pressure values during the night and increased left ventricular hypertrophy could represent another important link between CAN and an increased risk of mortality.

CAN and sudden death

A number of researchers have reported sudden unexpected deaths among subjects identified with autonomic neuropathy (31,82,85). One potential cause of sudden death may be explained by severe but asymptomatic ischemia, eventually inducing lethal arrhythmias (85). An autonomic imbalance resulting in QT prolongation may also predispose individuals to life-threatening cardiac arrhythmias and sudden death (101). Results from the EURODIAB IDDM Complications Study showed that male patients with impaired HRV had a higher corrected QT prolongation than males without this complication (102). Imaging of myocardial sympathetic innervation with various radiotracers (e.g., metaiodobenzylguanidine) has shown that predisposition to arrhythmias and an association with mortality may also be related to intracardiac sympathetic imbalance (103,104).

The significance of CAN as an independent cause of sudden death has, however, been recently questioned (105). In the Rochester Diabetic Neuropathy Study, the investigators found that all case subjects (individuals with and without diabetes) with sudden death had severe coronary artery disease or left ventricular dysfunction. Therefore, they suggested that although CAN could be a contributing factor, it was not a significant independent cause of sudden death. Heart failure is, however, common in individuals with diabetes, identified by the presence of neuropathy, even in individuals without evidence of coronary artery disease or left ventricular dysfunction (106). The association of cardiovascular autonomic dysfunction in the absence of coronary disease and cardiomyopathy requires further study.

Increased mortality after an MI

Mortality rates after an MI are also higher for diabetic patients than for nondiabetic patients (107). This may be due to autonomic insufficiency, increasing the tendency for development of ventricular arrhythmia and cardiovascular events after infarction. Fava et al. (108) showed that the presence of autonomic neuropathy contributed to a poor outcome in a study of 196 post-MI diabetic patients. In another study, Katz et al. (109) showed that a simple bedside test that measured 1-min HRV during deep breathing was a good predictor of all-cause mortality for 185 patients (17.8% with diabetes) after a first MI. These investigators also suggested that cardiovascular autonomic function testing provided a predictive value that could be used to identify a subgroup of patients after an MI who are a high risk for cardiovascular death (109).

Dysfunction of the ANS is associated with increased risk of mortality in individuals with diabetes. It is true, however, that at least some of the association between CAN and mortality appears to be due to an increased prevalence of other complications in individuals with CAN. Though the exact pathogenic mechanism is unclear, it is realized that some deaths may be avoidable through early identification of these higher-risk patients and by slowing, with therapy, the progression of autonomic dysfunction and its associated conditions. In addition, it would appear that autonomic function testing is a valuable tool in identifying a subgroup of post-MI patients who are at high risk for death.

Association of cerebrovascular disease and CAN

The frequency of ischemic cerebrovascular events is increased in individuals with type 2 diabetes. The impact of autonomic dysfunction on the risk of the development of strokes was examined by Toyry et al. (110), who followed a group of 133 type 2 diabetic patients for 10 years. During the study period, 19 individuals had one or more strokes. Abnormalities of parasympathetic and sympathetic autonomic function were found to be independent predictors of stroke in this cohort (110).

Progression of CAN

Results of the cardiovascular autonomic function tests that are mediated mainly by the parasympathetic nervous system (e.g., heart rate response to deep breathing) are typically abnormal before those responses that are mediated by the sympathetic nerves. Although one might speculate then that parasympathetic damage occurs before sympathetic damage, this may not always be true. The increased frequency of abnormalities detected via tests of the parasympathetic system may merely be a reflection of the test (e.g., sensitivity) and not of the natural history of nerve fiber damage (111). Thus, it may be better to describe the natural history of autonomic dysfunction as developing from early to more severe involvement rather than to anticipate a sequence of parasympathetic to sympathetic damage (111).

Although much remains to be learned about the natural history of CAN, previous reports can be coalesced into a few observations that provide some insight with regard to progression of autonomic dysfunction:

- It can be detected at the time of diagnosis (24,44,112).
- Neither age nor type of diabetes are limiting factors in its emergence, being found in young individuals with newly diagnosed type 1 diabetes and older individuals newly diagnosed with type 2 diabetes (5,24,40,44,113,114).
- Poor glycemic control plays a central role in development and progression (44,115–117).
- Intensive therapy can slow the progression and delay the appearance of abnormal autonomic function tests (37).
- Subclinical autonomic neuropathy can be detected early using autonomic function tests (26,41,44).
- Autonomic features that are associated with sympathetic nervous system dysfunction (e.g., orthostatic hypotension) are relatively late complications of diabetes (31,41,116,118–120).
- There is an association between CAN and diabetic nephropathy that contributes to high mortality rates (31,44,82).

Even with consensus regarding these general observations, much remains unclear:

- Some individuals with symptoms associated with autonomic neuropathy die suddenly and unexpectedly (31,44,82).
- Clinical signs and symptoms of autonomic dysfunction do not always progress. This underscores the need for performance of quantitative autonomic function tests to identify individuals at risk for premature death (121).
- Type 1 and type 2 diabetes may have different progression paths.
- The relationship between autonomic damage and duration of diabetes is not clear although numerous studies support an association (116).
- Prevalence and mortality rates may be higher among individuals with type 2 diabetes, potentially due in part to longer duration of glycemic abnormalities before diagnosis.

OTHER AUTONOMIC NEUROPATHIES

GI autonomic neuropathy

GI symptoms are relatively common among patients with diabetes and often reflect diabetic GI autonomic neuropathy (7,122). It should be noted, however, that although GI symptoms are common, symptoms may be more likely due to other factors than to autonomic dysfunction. GI manifestations of DAN are diverse, and symptoms and pathogenic mechanisms have been categorized according to which section of the GI tract is affected:

- Esophageal enteropathy (disordered peristalsis, abnormal lower esophageal sphincter function)
- Gastroparesis diabeticorum (nonobstructive impairment of gastric propulsive activity; brady/tachygastria, pylorospasm)
- Diarrhea (impaired motility of the small bowel [bacterial overgrowth syndrome], increased motility and secretory activity [pseudocholeretic diarrhea])
- Constipation (dysfunction of intrinsic and extrinsic intestinal neurons, decreased or absent gastrocolic reflex)
- Fecal incontinence (abnormal internal anal sphincter tone, impaired rectal sensation, abnormal external sphincter)
- Gallbladder atony and enlargement

Esophageal dysfunction results at least in part from vagal neuropathy (123); symptoms include heartburn and dysphagia for solids. Via the use of radioisotopic techniques that quantify gastric emptying, it appears that ~50% of patients with longstanding diabetes have delayed gastric emptying (gastroparesis)

(124). Gastric emptying largely depends on vagus nerve function, which can be severely disrupted in diabetes. Gastroparesis in diabetes is usually clinically silent, although severe diabetic gastroparesis is one of the most debilitating of all diabetic GI complications. Major clinical features of this disorder are early satiety, anorexia, nausea, vomiting, epigastric discomfort, and bloating. Episodes of nausea or vomiting may last days to months or occur in cycles (125).

Diarrhea is evident in 20% of diabetic patients, particularly those with known DAN (1). Diarrhea is typically intermittent, but bowel movements may occur 20 or more times per day with urgency, and the stools are often watery. Bacterial overgrowth due to stasis of the bowel may contribute to diarrhea, in which case broad-spectrum antibiotics (e.g., tetracycline and metronidazole) are useful. Individuals with constipation may have less than three bowel movements per week, and these may alternate with diarrhea. Treatment of diarrhea with or without constipation should always involve the use of a prokinetic agent rather than constipating agents that create vicious cycles of constipation and diarrhea (1). Fecal incontinence due to poor sphincter tone (126) is common for individuals with diabetes (127) and may be associated with severe paroxysmal diarrhea or constitute an independent disorder of anorectal dysfunction.

Genitourinary autonomic neuropathy

The neurogenic bladder, also called cystopathy, may be due to DAN (62). An examination of the neuroanatomy of the genitourinary system provides an insight into the extent to which autonomic fibers are involved with its proper control. Serving as a receptacle for the storage and appropriate evacuation of urine, the urinary bladder comprises three layers of interdigitating smooth muscle (i.e., detrusor muscle). This muscle forms an internal sphincter at the junction of the bladder neck and urethra, and although it is not anatomically discrete, there is localized autonomic innervation so that it functions as a physiological sphincter. Afferent nerve impulses of bladder sensation and reflex bladder contraction are carried by sympathetic, parasympathetic, and somatic nerves to the spinal cord (128). The earliest bladder autonomic dysfunctions are sensory abnormalities that result in impaired bladder sensation, an elevated threshold for initiating the micturition reflex and an asymptomatic increase in bladder capacity and retention.

The parasympathetic nerves that originate in the intermediolateral column of sacral segments S2–S4 provide the major excitatory input to the urinary bladder. Activation of the muscarinic, cholinergic, and postganglionic pelvic nerve fibers result in contraction of the urinary bladder. When there is damage to the efferent parasympathetic fibers to the urinary bladder, symptoms such as hesitancy in micturition, weak stream, and dribbling ensue, with a reduction in detrusor activity (i.e., detrusor areflexia). This leads to incomplete bladder emptying, an increased postvoid residual, decreased peak urinary flow rate, bladder overdistention, and urine retention. Finally, overflow incontinence occurs because of denervation of the external and internal sphincter (129,130). The somatic pudendal nerve innervates the external sphincter, whereas the sympathetic hypogastric nerves innervate the internal sphincter. Individuals with bladder dysfunction are predisposed to the development of urinary tract infections, including pyelonephritis, which may accelerate or exacerbate renal failure (131,132).

Urinary frequency is another commonly associated symptom of autonomic dysfunction of the genitourinary system. Unfortunately, 37–50% of individuals with diabetes have symptoms of bladder dysfunction, and 43–87% of individuals with type 1 diabetes have physiological evidence of bladder dysfunction (129, 133,134).

Erectile dysfunction

Erectile dysfunction (ED) is the most common form of organic sexual dysfunction in males with diabetes, with an incidence estimated to be between 35 and 75% (135). ED is defined as the consistent inability to attain and maintain an erection adequate for sexual intercourse, usually qualified by being present for several months and occurring at least half the time. An estimated 20–30 million men in the U.S. have ED (136). In a large cohort study of men 53–90 years old, a significant association between diabetes (and duration of diabetes) and ED was found when comparing diabetic men with nondiabetic men of similar age (137). ED is a marker for the development of generalized vascular disease and for premature demise from a myocardial infarct, and penile failure may be a portent of upcoming, and possible preventable, cardiovascular events (138). ED etiology in diabetes is multifactorial, including neuropathy, vascular disease, metabolic control, nutrition, endocrine disorders, psychogenic factors, and anti-diabetes drugs. Retrograde ejaculation into the bladder also occurs in diabetic males. ED should alert physicians to perform cardiovascular evaluations for these patients.

Sexual dysfunction in women

Females with diabetes may have decreased sexual desire and increased pain during intercourse and are at risk of decreased sexual arousal and inadequate lubrication (139).

Anemia of autonomic dysfunction

It has been shown that type 1 diabetic individuals with early nephropathy and symptomatic autonomic neuropathy have inappropriately low levels of erythropoietin for the severity of their anemia (140). These individuals can, however, mount an appropriate erythropoietin response to moderate hypoxia. The mechanism that underlies the erythropoietin-deficient anemia is unclear. Reduced sympathetic stimulation of erythropoietin production has been previously hypothesized as the cause of ineffective erythropoiesis resulting in anemia (141).

RELATIONSHIP OF AUTONOMIC NEUROPATHY TO HYPOGLYCEMIA RESPONSIVENESS

Hypoglycemic unawareness and DAN

DAN plausibly could cause or contribute to hypoglycemia unawareness, but this relationship is complex. Two groups concluded that unawareness of hypoglycemia and inadequate counterregulation occur independently of autonomic neuropathy. Ryder et al. (142) noted "little evidence" of autonomic neuropathy in 12 diabetic patients with a history of unawareness of hypoglycemia and 7 patients with inadequate hypoglycemic counterregulation. They also observed no history of unawareness of hypoglycemia in seven patients with clear evidence of autonomic neuropathy, and in six of the seven, there

was adequate hypoglycemic counterregulation. Based on these findings, they suggested that there was no causal relation between DAN and unawareness of hypoglycemia or inadequate hypoglycemic counterregulation (142). Hepburn et al. (143) reported that 7 of 17 patients with absent awareness of hypoglycemia had no evidence of autonomic dysfunction. Based on these data, they suggested that loss of hypoglycemia awareness is not invariably associated with abnormal cardiovascular autonomic function tests.

Careful examination of these studies suggests, however, that the relationship between autonomic neuropathy and hypoglycemic unawareness may be more complex than these reports suggest. Ryder et al. observed that patients with autonomic neuropathy had a negligible plasma pancreatic polypeptide response (3.7 pmol/l), and this response was also blunted in the patients with inadequate hypoglycemic counterregulation (72.4 pmol/l) compared with that of the control subjects (414 pmol/l; $P < 0.05$) (142). Furthermore, 10 of 17 individuals with hypoglycemia unawareness reported by Hepburn et al. had evidence of autonomic dysfunction (145). Taken together, even these data suggest that there is some overlap between the features of autonomic neuropathy and hypoglycemic unawareness. More recent data suggest that the presence of autonomic neuropathy further attenuates the epinephrine response to hypoglycemia in diabetic individuals after recent hypoglycemic exposure (144–146).

Hypoglycemic autonomic failure

The spectrum of reduced counterregulatory hormone responses (in particular epinephrine) and decreased symptom perception of hypoglycemia due to decreased ANS activation after recent antecedent hypoglycemia has been termed "hypoglycemia-induced autonomic failure" (147–149). Hypoglycemia-induced autonomic failure leads to a vicious cycle of hypoglycemia unawareness that induces a further decrease in counterregulatory hormone responses to hypoglycemia. This vicious cycle occurs commonly in individuals with diabetes who are in strict glycemic control. The reduced epinephrine response to antecedent hypoglycemia occurs in the absence of DAN as measured by standard tests of autonomic function (143,148, 150). The presence of autonomic neuropathy, however, further attenuates the epinephrine response to hypoglycemia in diabetic subjects after recent hypoglycemic exposure (144–146) in most, but not all, studies (148). Furthermore, individuals with abnormal autonomic function have a greater risk for severe hypoglycemia (151).

RELATIONSHIP OF AUTONOMIC NEUROPATHY TO TISSUE PERFUSION

Microvascular skin flow is under the control of the ANS and is regulated by both the central and peripheral components. In diabetes, the rhythmic contraction of arterioles and small arteries is disordered. Microvascular insufficiency may be a cause of diabetic neuropathy (152). Microvascular blood flow can be accurately measured noninvasively using laser Doppler flowmetry. Defective blood flow in the small capillary circulation is found with decreased responsiveness to mental arithmetic, cold pressor, handgrip, and heating. The defect is associated with a reduction in the amplitude of vasomotion and resembles premature aging (153). There are differences in the glabrous and hairy skin circulations. In hairy skin, a functional defect is found before the development of neuropathy (154). The clinical counterpart is dry skin, loss of sweating, and the development of fissures and cracks that are portals of entry for microorganisms leading to infectious ulcers and ultimately gangrene. A prospective study by Boyko et al. (155) demonstrated the effect of autonomic neuropathy on the risk of developing a foot ulcer independent of other measures of sensory neuropathy. Autonomic neuropathy may also lead to increased osteoclastic activity resulting in reduced bone density. Thus, Young et al. (156) suggested that the significant relationship between reduced bone mineral density and severity of diabetic neuropathy in the lower extremities of individuals with Charcot neuroarthropathy may reflect the severity of autonomic neuropathy.

CLINICAL TESTING OF AUTONOMIC FUNCTION

Assessing cardiovascular autonomic function

Quantitative tests of autonomic function have historically lagged behind measures of motor nerve function and sensory nerve function deficits. The lack of interest in the development of such measures was partly due to the erroneous but commonly held view that autonomic neuropathy was only a small and relatively obscure contributor to the peripheral neuropathies affecting individuals with diabetes (116,118,120).

In the early 1970s, Ewing et al. (95) proposed five simple noninvasive cardiovascular reflex tests (i.e., Valsalva maneuver, heart rate response to deep breathing, heart rate response to standing up, blood pressure response to standing up, and blood pressure response to sustained handgrip) that have been applied successfully by many. The clinical literature has consistently identified these five tests as they have been widely used in a variety of studies. The tests are valid as specific markers of autonomic neuropathy if end-organ failure has been carefully ruled out and other potential factors such as concomitant illness, drug use (including antidepressants, over-the-counter antihistamines and cough/cold preparations, diuretics, and aspirin), lifestyle issues (such as exercise, smoking, and caffeine intake), and age are taken into account. A large body of evidence indicates that these factors can, to various degrees, affect the cardiovascular ANS and potentially other autonomic organ systems (157).

Heart rate response to deep breathing is for the most part a function of parasympathetic activity, although the sympathetic nervous system may affect this measure (158). Similarly, it is parasympathetic activity that plays the greatest role in the heart rate regulation for short-term standing, where the act of standing involves low-level exercise and parasympathetic tone is withdrawn to produce a sudden tachycardic response (159). In response to subsequent underlying blood pressure changes while standing, a baroreceptor-mediated reflex involves the sympathetic nerves for further heart rate control (160). Heart rate response to the Valsalva maneuver is influenced by both parasympathetic and sympathetic activity. Measurements of blood pressure response to standing and blood pressure response to sustained handgrip are used to assess sympathetic activity.

Heart rate response to deep breathing (i.e., beat-to-beat heart rate variation, R-R variation). Beat-to-beat variation in heart rate with respiration depends on

parasympathetic innervation. Pharmacological blockade of the vagus nerve with atropine all but abolishes respiratory sinus arrhythmia, whereas sympathetic blockade with the use or pretreatment of propranolol has only a slight effect on it (158). Several different techniques have been described in clinical literature, but measurement during paced deep breathing is considered the most reliable. The patient lies quietly and breathes deeply at a rate of six breaths per minute (a rate that produces maximum variation in heart rate) while a heart monitor records the difference between the maximum and minimum heart rates. Over a number of years, there have been several different measures of R-R variation. The following six measures have most consistently been reported (standard deviation, coefficient of variation, mean circular resultant, maximum minus minimum, expiration-to-inspiration [E:I] ratio, and spectral analysis) (43). There are advantages, disadvantages, and considerations that need to be recognized for all of the measures of R-R variation.

Heart rate response to standing. This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. The typical heart rate response to standing is largely attenuated by a parasympathetic blockade achieved with atropine (159). In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30th beat after standing. In patients with diabetes and autonomic neuropathy, there is only a gradual increase in heart rate. The patient is connected to an electrocardiogram (ECG) monitor while lying down and then stands to a full upright position. ECG tracings are used to determine the 30:15 ratio, calculated as the ratio of the longest R-R interval (found at about beat 30) to the shortest R-R interval (found at about beat 15). Because the maximum and minimum R-R intervals may not always occur at exactly the 15th or 30th beats after standing, Ziegler et al. (161) redefined the maximum/minimum 30:15 ratio as the longest R-R interval during beats 20–40 divided by the shortest R-R interval during beats 5–25.

Valsalva maneuver. In healthy subjects, the reflex response to the Valsalva maneuver includes tachycardia and peripheral vasoconstriction during strain, followed by an overshoot in blood pressure and bradycardia after release of strain. The response is mediated through alternating activation of parasympathetic and sympathetic nerve fibers. Pharmacological blockade studies using atropine, phentolamine (an α-adrenergic antagonist), and propranolol (a nonspecific β-adrenergic blocker) confirm dual involvement of autonomic nerve branches for the response to this maneuver by demonstrating the drugs' varied effects of attenuation or augmentation of the hemodynamic response to the maneuver at specific times during the response (162). In patients with autonomic damage from diabetes, the reflex pathways are damaged. This is seen as a blunted heart rate response and sometimes as a lower-than-normal decline in blood pressure during strain, followed by a slow recovery after release.

In the standard Valsalva maneuver, the supine patient, connected to an ECG monitor, forcibly exhales for 15 s against a fixed resistance (40 mmHg) with an open glottis. A sudden transient increase in intrathoracic and intra-abdominal pressures, with a consequent hemodynamic response, results. With performance of the Valsalva maneuver, there is a transient increase in intraocular and intracranial pressure, creating a small theoretical risk of intraocular hemorrhage and lens dislocation (163). In practical terms, however, the risk is minimal because comparable pressures occur in the performance of daily activities.

The response to performance of the Valsalva maneuver has four phases and in healthy individuals can be observed as follows:

- **Phase I:** Transient rise in blood pressure and a fall in heart rate due to compression of the aorta and propulsion of blood into the peripheral circulation. Hemodynamic changes are mostly secondary to mechanical factors.
- **Phase II:** Early fall in blood pressure with a subsequent recovery of blood pressure later in the phase. The blood pressure changes are accompanied by an increase in heart rate. There is a fall in cardiac output due to impaired venous return causing compensatory cardiac acceleration, increased muscle sympathetic activity, and peripheral resistance.
- **Phase III:** Blood pressure falls and heart rate increases with cessation of expiration.
- **Phase IV:** Blood pressure increases above the baseline value (overshoot) because of residual vasoconstriction and restored normal venous return and cardiac output.

The Valsalva ratio is determined from the ECG tracings by calculating the ratio of the longest R-R interval after the maneuver (reflecting the bradycardic response to blood pressure overshoot) to the shortest R-R interval during or shortly after the maneuver (reflecting tachycardia as a result of strain).

With regard to the progression of autonomic dysfunction in diabetes, the Valsalva maneuver may be the best method to monitor this longitudinally (121). Quantitative analysis of nerve function (e.g., autonomic function testing) parallels that of clinical neuropathy in that the rate of progression is slow, gradual, and an insidious process (164). In a study by Levitt et al. (121), the rate of deterioration of the Valsalva ratio was 0.015 per year for individuals with type 1 diabetes, which was more than twice that expected from cross-sectional studies of the aging effect in normal individuals of a similar age range.

All of the tests described above for the assessment of cardiovascular autonomic function can be performed by a general practitioner. Those patients with cardiovascular autonomic dysfunction who have system-specific symptoms will need to be referred to a specialist for refined testing.

Power spectral analysis. Analysis of HRV can also be assessed by spectral analysis of a series of successive R-R intervals (frequency domain analyses). This can be performed on short R-R sequences (e.g., 7 min) or on 24-h ECG recordings. The main advantage of power spectral analysis (PSA) is that HRV can be measured across a range of frequencies and that less patient participation is necessary (165). The heart rate power spectrum is typically divided into two frequency bands: low (0.04–0.15 Hz) and high (0.15–0.4 Hz). The high-frequency region is generally considered a marker of vagal activity, whereas the low-frequency component is influenced by both sympathetic and vagal activity (165).

A study providing a direct compar-

ison of PSA and some time-domain techniques for quantifying HRV was completed by Freeman et al. (166). In this study, conventional methods to calculate "max-min," standard deviation, E:I ratio, Valsalva ratio, and 30:15 ratio were used, as were those for the low-frequency (0.02–0.15 Hz) and high-frequency (0.15–1.0 Hz) power for the heart rate power spectra of 15 type 1 diabetic patients. Intrasubject comparisons were achieved through multiple linear regression analysis for which the "predicted" spectral power was plotted against the actual time-domain values. The time-domain values were found to correlate very strongly with high-frequency spectral indexes, especially the Valsalva and 30:15 ratios (linear regression gave R^2 values of 0.85 and 0.90, respectively). Another study by Howorka et al. (167) compared the spectral and time-domain test results for a population of 119 diabetic patients. A band from 0.15 to 5.0 Hz was assigned as the high-frequency band, whereas low frequency was 0.005 to 0.15 Hz. Spectral indexes were power and density and were compared with standard Ewing tests of HRV (I:E difference, Valsalva ratio, and 30:15 ratio). The multiple correlation between variables of PSA and the Ewing battery "was high, and over 83% of cases were classified in an identical way by both diagnostic tests." These researchers went on to conclude that their investigation "showed that short-term PSA of HRV is of similar diagnostic value as the Ewing battery concerning the presence of cardiovascular autonomic neuropathy" (167). Ziegler et al. (161) made their own test comparison using 120 healthy subjects and 21 diabetic patients. PSA testing with subjects at rest was performed with low frequency being defined as 0.01–0.05 Hz, mid-frequency as 0.05–0.15 Hz, and high frequency as 0.15–0.5 Hz. This study also used a standard Ewing battery of tests, which included coefficient of variation, E:I ratio, Valsalva ratio, max-min, 30:15 ratio, and other time-domain measures. Findings for HRV tests were that, with the exception of the Valsalva ratio, "results of most tests were significantly associated with each other. . ." and that correlations between time-domain measures were highest for the high-frequency band ($r = 0.36–0.81$; $P < 0.001$) (161).

Assessing cardiovascular adrenergic (sympathetic) function

Systolic blood pressure response to standing. Blood pressure normally changes only slightly on standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex-mediated peripheral vasoconstriction and tachycardia. In normal individuals, the systolic blood pressure falls by <10 mmHg in 30 s. In diabetic patients with autonomic neuropathy, baroreflex compensation is impaired. A response is considered abnormal when the diastolic blood pressure decreases more than 10 mmHg or the systolic blood pressure falls by 30 mmHg within 2 min after standing (32,168,169). A task force of the American Academy of Neurology (AAN) and the American Autonomic Society defined orthostatic hypotension as a fall in systolic blood pressure of ≥20 mmHg or diastolic blood pressure of ≥10 mmHg accompanied by symptoms (51).

Diastolic blood pressure response to sustained handgrip. In this test, sustained muscle contraction as measured by a handgrip dynamometer causes a rise in systolic and diastolic blood pressure and heart rate. This rise is caused by a reflex arc from the exercising muscle to central command and back along efferent fibers. The efferent fibers innervate the heart and muscle, resulting in increased cardiac output, blood pressure, and heart rate. The dynamometer is first squeezed to isometric maximum, then held at 30% maximum for 5 min. The normal response is a rise of diastolic blood pressure >16 mmHg, whereas a response of <10 mmHg is considered abnormal (168). Patients with DAN are more likely to exhibit only a small diastolic blood pressure rise.

Response to tilting. The hemodynamic response to standing is a commonly performed measure of autonomic function. Passive head-up tilting provides a more precise level of standardization to the orthostatic stimulus and reduces the muscular contraction of the legs, which can reduce lower-leg pooling of blood. A tilt angle of 60° is commonly used for this test. The tilt may be maintained for 10–60 min or until the patient's orthostatic symptoms can be reproduced. The orthostatic stress of tilting evokes a sequence of compensatory cardiovascular responses to maintain homeostasis. As for the stand response, the normal tilted reflex consists of an elevation in heart rate and vasoconstriction. If reflex pathways are defective, blood pressure falls markedly with hemodynamic pooling. An abnormal response is defined similarly to that associated with standing.

Assessing GI autonomic function.

Even with mild symptoms, gastroparesis interferes with nutrient delivery to the small bowel and therefore disrupts the relationship between glucose absorption and exogenous insulin administration. This can result in wide swings of glucose levels and unexpected episodes of postprandial hypoglycemia and apparent "brittle diabetes." Therefore, gastroparesis should be suspected in patients with erratic glucose control.

The finding of retained food in the stomach after an 8- to 12-h fast in the absence of obstruction is diagnostic of gastroparesis. Basic diagnostic tests include upper-GI endoscopy or barium series to rule out structural or mucosal abnormalities of the GI tract. Evaluation of the patient with suspected diabetic gastroparesis might include the following:

- Assessment of glycemic control
- Medication history, including the use of anticholinergic agents, ganglion blockers, and psychotropic drugs
- Gastroduodenoscopy to exclude pyloric or other mechanical obstruction
- Manometry to detect antral hypomotility and/or pylorospasm
- Double-isotope scintigraphy to measure solid-phase gastric emptying; this requires ingestion of a solid labeled with radionuclides. Liquid emptying gives false-negative results. The blood glucose should be normal at the time of testing because hyperglycemia decreases gastric motility.
- Electrogastrography detects abnormalities in GI pacemaking, but its role has not been established in diagnosis or treatment decision making.

Most of the specialized evaluations for assessment of gastroparesis will typically be performed by a gastroenterologist.

Constipation. Constipation is the most common GI complication, affecting nearly 60% of diabetic patients (1). It is believed to be due to DAN rather than

myopathic changes. The gastrocolic reflex is impaired, but stimulation of colonic smooth muscle with neostigmine is normal (170).

Tests for the diagnosis and assessment of constipation might include the following:

- Anorectal manometry for evaluating sphincter tone and the rectal anal inhibitory reflex to distinguish colonic hypomotility from rectosigmoid dysfunction causing outlet obstructive symptoms
- Assessment of colonic segmental transit time. This may be accomplished by means of segmental transit of radiopaque markers that are ingested orally.
- Pelvic examination, with careful bimanual examination for women
- Three stools tested for occult blood (which, if present, requires that a complete blood count, iron count, TIBG, proctosigmoidoscopy and barium enema, or full colonoscopy be performed)

Most of these procedures will typically be performed by a specialist.

Diarrhea. Assessment of diarrhea in patients with diabetes might include the following:

- History to rule out diarrhea secondary to ingestion of lactose, nonabsorbable hexitols, or medication (especially biguanides, α-glucosidase inhibitors, and tetrahydrolipostatin)
- History to rule out other causes, especially iatrogenic ones
- Travel and sexual histories and questioning regarding similar illnesses among both household members and coworkers
- History of prior ethanol consumption
- History of pancreatitis and biliary stone diseases
- Examination for enteric pathogens and ova and parasites
- Patients with large-volume diarrhea or fecal fat should be further studied with a 72-h fecal fat collection: the d-xylose test is an appropriate screen for small bowel malabsorptive disorders.
- If significant steatorrhea is detected, assess pancreatic calcification with plain film of abdomen and perform formal pancreatic function tests.
- If celiac disease is suspected, measure serum levels of celiac disease antibody profile, including gliadin, endomysial, gluten, and reticulin antibodies.
- A trial on a gluten-free diet is warranted, and confirmation of the diagnosis with upper-GI endoscopy and/or small bowel biopsy may be required.
- If Crohn's disease is suspected, upper-GI barium examination with dedicated small bowel follow-through
- Measurement of vitamin B-12 and folate
- If history and examination suggest small bowel disease, hydrogen breath test and Schilling's test are required. Positive breath means lactose intolerance and/or bacterial overgrowth. Positive Schilling's test may be diagnostic of bacterial overgrowth.
- Stools tested for occult blood (which, if present, requires follow-up upper- and lower-GI endoscopy)

Specialized tests for the assessment of diabetic diarrhea will typically be performed by a gastroenterologist.

The severe and intermittent nature of diabetic diarrhea makes treatment and assessment difficult. Because afferent denervation may contribute to the problem, a bowel program that includes restriction of soluble fiber and regular effort to move the bowels is indicated. In addition, trials of gluten-free diet, restriction of lactose, cholestyramine, clonidine, somatostatin analog, pancreatic enzyme supplements, and antibiotics such as metronidazole may be indicated.

Assessing genitourinary autonomic function

ED. ED is assessed by both taking a medical history and specific tests, which might include the following:

- Sexual function history (libido, erectile function, ejaculatory function, fertility)
- Medication history
- Assessment of glycemic control
- Measurement of nocturnal penile tumescence
- Measurement of penile and brachial blood pressure with Doppler probes and calculation of the penile-brachial pressure index (<0.7 suggests penile vascular disease)
- Sacral outflow (S2, S3, and S4) assessment, which represents the sacral parasympathetic divisions: anal sphincter tone, perianal sensation, anal wink, and bulbocavernous reflex are clinical features of denervation of the important nerve supply that enable erections to occur.
- Autonomic neuropathy testing (e.g., HRV)
- Intracavernosal injection of vasoactive compound (e.g., papaverine and prostaglandin E_1 [PGE_1]) with a response of ~65–70% of the time reflecting a predominantly neurogenic cause of ED and compatible with a significant arterial component. Failure of the response suggests venous incompetence.
- Hormonal evaluation (luteinizing hormone, testosterone, free testosterone, prolactin)
- Psychological evaluation (Minnesota Multiphasic Personality Inventory [MMPI])

A proposed scheme for evaluation of ED is shown in Fig. 3 (1).

Once diagnosed, treatment may include withdrawal from offending medications coupled with psychological counseling, medical treatment, or surgery. Medical treatment may include sildenafil taken at a dose of 50 mg. A lower dosage is needed for individuals with renal failure or liver dysfunction. Sildenafil should not be taken by individuals with unstable ischemic heart disease or those using nitroglycerin or other nitrate-containing medications. Specialized assessment of ED will typically be performed by a urologist.

Female sexual dysfunction. Female sexual dysfunction assessment using vaginal plethysmography to measure lubrication and vaginal flushing has not been well established or standardized.

Bladder dysfunction. Evaluation of diabetic bladder dysfunction should be done for any diabetic patient with recurrent urinary tract infection, pyelonephritis, incontinence, or a palpable bladder. The evaluation might include the following:

- Assessment of renal function
- Urinary culture
- Postvoid ultrasound to assess residual volume and upper–urinary tract dilation
- Cystometry and voiding cystometrogram to measure bladder sensation and volume pressure changes associated with bladder filling with known volumes of water and voiding

Specialized assessment of bladder dysfunction will typically be performed by a urologist.

Diabetic cystopathy manifests as an increase in threshold of occurrence of a

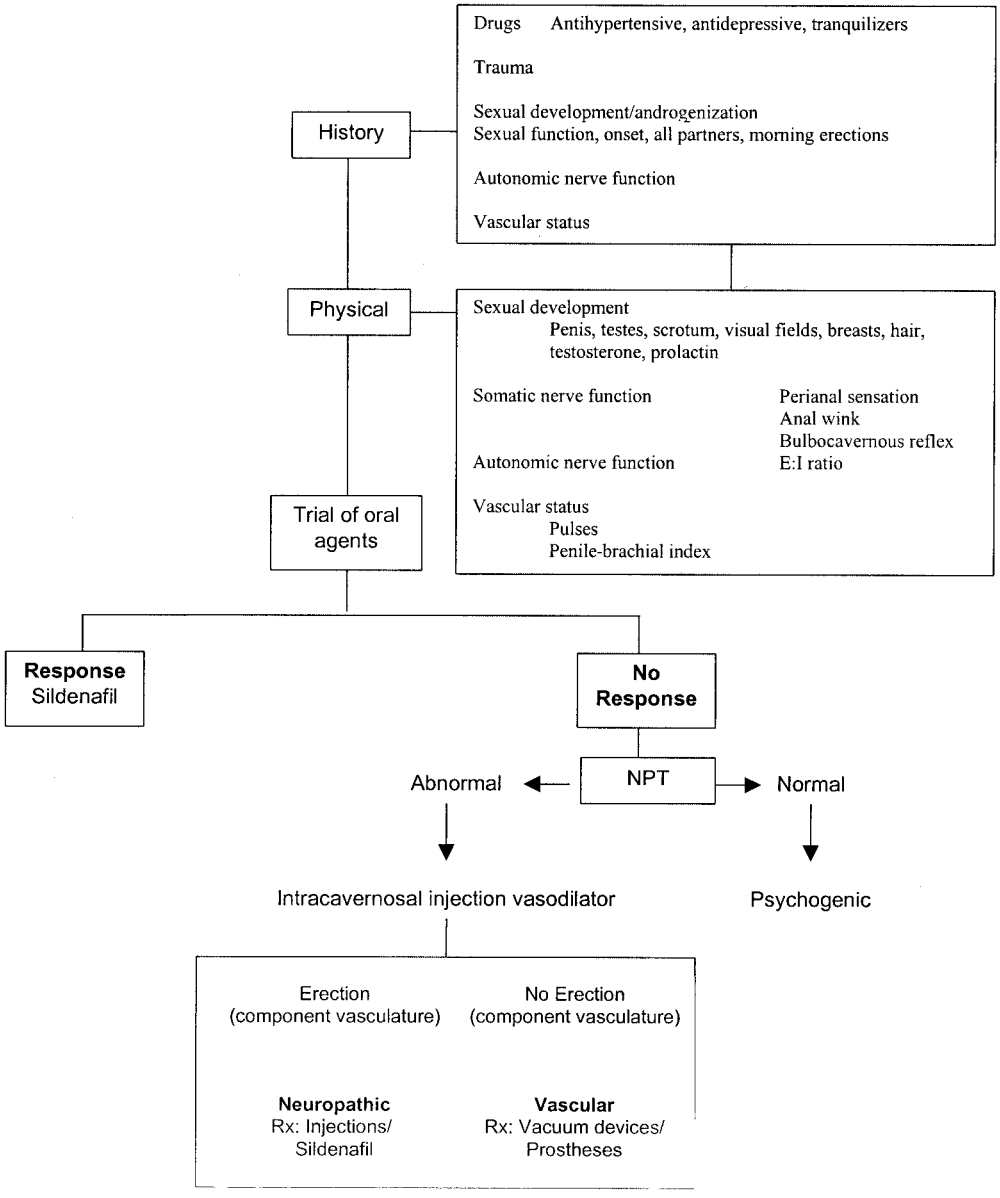

Figure 3—*Evaluation of diabetic patients with ED (138). NPT, nocturnal peniletumescence.*

detrusor reflex contraction. A grossly overdistended bladder should be drained by catheter to improve contractility, and the patient should be instructed to void by the clock rather than waiting for the sensation of bladder distention. Cholinergic agents or clean intermittent self-catheterization may also be used to facility emptying.

Assessing sudomotor function

Testing of the eccrine sweat glands provides a measure of sympathetic cholinergic function. Thermoregulatory sweat testing assesses both central and peripheral aspects of the efferent sympathetic nervous system, from the hypothalamus to the sweat glands, but is not able to differentiate between pre- and postganglionic causes of anhidrosis. Postganglionic sudomotor function can be determined by measuring sweat output after iontophoresis or intradermal injection of cholinergic agonists.

Tests of sudomotor function evaluate the extent, distribution, and location of deficits in sympathetic cholinergic function. These tests include the quantitative sudomotor axon reflex test (QSART), the sweat imprint, the thermoregulatory sweat test (TST), and the sympathetic skin response.

The QSART involves iontophoresis of a cholinergic agonist to measure axon reflex–medicated sudomotor responses quantitatively to evaluate postganglionic sudomotor function. Four sites are used and studied simultaneously with the patient supine. The test, typically done by recording from the forearm and three lower-extremity skin sites, has high sensitivity, specificity, and reproducibility, with a coefficient of variation of 20% if performed by trained personnel. The test is not generally available and requires the purchase of expensive specialized equipment.

A sweat imprint may be formed by the

secretion of active sweat glands into a plastic or silicone mold in response to iontophoresis of a cholinergic agonist. This test can be used to determine sweat gland density, sweat droplet size, and sweat volume per area.

The TST assesses both central and peripheral aspects of the efferent sympathetic nervous system, from the hypothalamus to the sweat glands. It is a well-standardized test and evaluates the distribution of sweat by a change in color of an indicator powder on the skin after exposure to infrared light. The TST is semiquantitative (percentage of anterior body anhidrosis) and has a high sensitivity. The specificity is low, however, because it is not able to differentiate between pre- and postganglionic causes of anhidrosis. In combination with QSART, the specificity of the TST for delineating the lesion site is significantly increased.

The sympathetic skin response (or peripheral autonomic surface potential) is generated by the sweat glands and overlying epidermis. This response may occur spontaneously or can be evoked by stimuli such as respiration and startle. The sympathetic skin response can be measured with surface electrodes connected to a standard electromyogram instrument. The response habituates with repeated stimuli and is subject to variability. Delivering stimuli at irregular intervals may minimize habituation. Concordance between the sympathetic skin response and sudomotor function has been shown in some but not all studies.

Peripheral neurovascular responses. Smooth muscle microvasculature in the periphery reacts sympathetically to a number of stressor tasks. These may be divided into those dependent on the integrity of the central nervous system (orienting response and mental arithmetic) and those dependent on the distal sympathetic axon (handgrip and cold pressor tests):

- **Orienting response.** Orienting response is the vasoconstriction and resulting drop in peripheral (index finger, pulp surface) skin blood flow when a subject engages in speech after several minutes of relaxation with music.
- **Mental arithmetic.** Mental arithmetic as a serial subtraction task typically results in a 30% reduction in peripheral (index finger, pulp surface) skin blood flow. There is no response in the presence of either a proximal or distal ANS lesion.
- **Hand grip.** Peripheral contralateral (index finger, pulp surface) response to sustained 40% maximum grip on a dynamometer is biphasic over 60 s. The initial normal response is 40–50% reduction of flow from basal during the initial 20–30 s, followed by a dilation resulting in a return to typically superbasal levels; there is no response if the peripheral ANS is damaged.
- **Cold pressor.** Immersion of the contralateral hand in cold (ice) water typically results in a 50–60% reduction in peripheral skin blood flow at the contralateral pulp index surface. In some individuals, this response becomes biphasic after prolonged exposure (30 s) to such intense cold because it is extremely uncomfortable. There is a predominately peripheral component, but pain generates a centrally mediated response.
- **Heating and gravity.** Heating the limb to 44°C and dropping it below the level of the heart results in a marked increase in blood flow in normal subjects. The response is a measure of autonomic microvascular integrity and is markedly depressed in patients with AN.

Assessing pupillary function

Patients with DAN show delayed or absent reflex response to light and diminished hippus due to decreased sympathetic activity and reduced resting pupillary diameter (7). Pupillary measurements are usually only performed in a research setting.

CURRENT GUIDELINES FOR THE DIAGNOSIS OF AUTONOMIC NEUROPATHY

Several worldwide consensus meetings have been convened since the 1980s to evaluate the growing evidence concerning tests for the assessment of diabetic neuropathy. Two of the meetings (the San Antonio Conference on Diabetic Neuropathy held in 1988 and a second conference in 1992) were jointly sponsored by the American Diabetes Association and AAN. The consensus statement published by the expert panel at the 1988 San Antonio Conference was a synthesis of reviewed research efforts to date in the clinical assessment of neuropathies and offered recommendations for the testing of diabetic neuropathy (including autonomic neuropathy) in clinical studies. The selection of standardized measurement techniques based on reliability and precision studies was encouraged. The expressed purpose was to recommend common inter-study methodologies that would facilitate the comparison of results from one clinical investigation to another. Specifically concerning the assessment of CAN, the panel recognized strong evidence for three tests of heart rate control (mainly tests of parasympathetic control). The three tests recommended were heart rate response to *1*) deep breathing, *2*) standing, and *3*) the Valsalva maneuver. Two tests of blood pressure control were also recommended: blood pressure response to *1*) standing or passive tilting and *2*) sustained handgrip. These tests were judged suitable for both routine screening and monitoring the progress of autonomic neuropathy (3). No tests of sweating, sympathetic skin responses, pupillary reflexes, or genitourinary or GI function were considered to be sufficiently well standardized for routine clinical use.

Results from earlier research suggested that using a battery of cardiovascular tests (some indicating parasympathetic involvement and others indicating possible sympathetic involvement) would make it possible to follow the progression of autonomic function over time (30). The San Antonio consensus panel further extended the utility of tests of cardiovascular autonomic function by suggesting that a battery of tests could be used to stage patients with autonomic neuropathy. A three-stage model was proposed as follows:

- Early stage: abnormality of heart rate response during deep breathing alone
- Intermediate stage: an abnormality of Valsalva response
- Severe stage: the presence of postural hypotension

The San Antonio Consensus Panel also made several general recommendations regarding the need to fully classify DAN:

- Symptoms possibly reflecting autonomic neuropathy should not, by themselves, be considered markers for its presence.
- Noninvasive validated measures of autonomic neural reflexes should be used

as specific markers of autonomic neuropathy if end-organ failure is carefully ruled out and other important factors such as concomitant illness, drug use, and age are taken into account.
- An abnormality on more than one test on more than one occasion is desirable to establish the presence of autonomic dysfunction.
- Independent tests of both parasympathetic and sympathetic function should be performed.
- A battery of quantitative measures of autonomic reflexes should be used to monitor improvement or deterioration of autonomic nerve function.

In 1992, a second jointly sponsored conference was convened to review the state-of-the-art of diabetic neuropathy measures used in epidemiological and clinical studies including cross-sectional, longitudinal, and therapeutic trials. While recognizing the importance of clinical measures such as medical and neurological history and physical examination, conference participants also recognized the subjective nature of such measures and emphasized the importance of objective measures, including autonomic function tests in the case of autonomic neuropathy. The panel in 1992 also revised its recommendation to include three tests for the longitudinal testing of the cardiovascular ANS: *1*) heart rate response during deep breathing, *2*) Valsalva maneuver, and *3*) postural blood pressure testing (157).

It is important to note that tests that specifically evaluate cardiovascular autonomic function are part of the consensus guidelines. Although there is an association between the presence of peripheral somatic neuropathy and DAN, researchers have reported that the appearance of parasympathetic dysfunction may be independent of peripheral neuropathy (171). Weinberg and Pfeifer (172) have also shown that reduced HRV may be predictive of the development of symptomatic somatic neuropathy, although these results require follow-up in a larger study cohort. Therefore, assessment modalities that are used to measure other forms of diabetic peripheral neuropathy, such as tests of sensory or motor nerve fiber function (e.g., monofilament probe, quantitative sensory tests, or nerve conduction studies) and tests of muscle strength, may not be effective in detecting the cardiovascular involvement that autonomic function tests detect at early stages of emergence. Thus, tests for other forms of diabetic peripheral neuropathy should not be substituted for tests of cardiovascular autonomic dysfunction.

SAFETY OF TESTING PROCEDURES

An expert panel from the AAN reviewed a number of standardized measures and found that noninvasive autonomic tests were found to have a high value-to-risk ratio (163). Some tests do, however, carry a small risk for an adverse event. The Valsalva maneuver transiently increases intrathoracic, intraocular, and intracranial pressure, creating, for example, a small theoretical risk of intraocular hemorrhage and lens dislocation (163). In practical terms, the risk is minimal because comparable intrathoracic pressures occur in the performance of daily activities. In the published literature of over 100 studies, there have been no reports of deaths during testing and no reports of adverse events after completion of the tests attributable to the procedures. The Diabetes Control and Complications Trial (DCCT), one of the largest trials to use cardiovascular autonomic function tests, evaluated 1,441 patients with type 1 diabetes in 29 centers over a mean duration of 6.5 years without procedural complications (37). When used by properly trained individuals, autonomic function tests are a safe and effective diagnostic tool.

Patient cooperation is required for performing autonomic function tests. Thus, children may pose some challenges related to performance (such as the attainment of the expiration pressure target required for the Valsalva maneuver and the performance of metronomic breathing) and the cooperation and attention requirements of the test situation. These same challenges may also apply to elderly patients, where deterioration of physiological response is of concern, and to developmentally and cognitively disabled individuals.

WHO IS A CANDIDATE FOR TESTING?

Autonomic function tests based on changes in heart rate variation and blood pressure regulation can detect cardiovascular complications at early stages of involvement in asymptomatic patients. Because late stages of CAN are indicators of poor prognosis in diabetic patients, early prognostic capabilities offer a significant contribution to diagnosis and subsequent therapy.

Evidence from clinical literature can be found that support recommendations for various subpopulations. They include the following.

Diabetic patients with a history of poor glycemic control

Long-term poor glycemic control can only increase the risk of developing advanced diabetic neuropathy, although long-term follow-up studies are lacking (117). Mustonen et al. (173) showed in a 4-year follow-up study of 32 individuals with type 2 diabetes that poor glycemic control was an important determinant of the progression of autonomic nerve dysfunction.

The DCCT provided extensive clinical evidence that good metabolic control reduces diabetic complications. Specifically with regard to cardiovascular autonomic function, the DCCT showed that intensive glycemic control prevented the development of abnormal heart rate variation and slowed the deterioration of autonomic dysfunction over time for individuals with type 1 diabetes (37). Unfortunately, however, one cannot predict what the metabolic control will be (or has been) over a long period of time by looking at current HbA_{1c} results.

Poor glycemic control may also be a consequence of DAN (e.g., gastroparesis that goes unidentified). Treatment of GI dysfunction often improves glycemic control.

Diagnosed diabetic patients

Primary prevention of diabetes is the absolute goal. Unfortunately, that goal has not yet been obtained. However, it has been shown that lifestyle intervention can reduce the incidence of type 2 diabetes (174). Individuals that do develop diabetes, however, are likely to suffer from its complications. In fact, researchers have confirmed the presence of autonomic neuropathy at presentation (24). Some manifestations of autonomic neuropathy may even precede the diagnosis of diabetes by several years (175).

In its entirety, the evidence supports the contention that all patients with diabetes, regardless of metabolic control, are

at risk for autonomic complications. Given that CAN may be life-threatening and the assessment for its presence can be easily performed, testing for cardiovascular autonomic dysfunction is suggested for individuals with diabetes. This includes testing to identify children and adolescents with autonomic neuropathy. As some researchers have reported, the incidence of reduced HRV (measured using PSA) has been shown to be 15% in children (176). Massin et al. (177) demonstrated that early puberty is a critical period for the development of CAN and suggested that all type 1 diabetic patients should be screened for CAN beginning at the first stage of puberty. With regard to whether either sex is more likely to develop autonomic dysfunction, the literature has revealed conflicting reports. For example, in the DCCT, the presence of autonomic neuropathy correlated with male sex along with age and duration (178). Jaffe et al. (179) show male sex to be predictive of depressed HRV in addition to age, duration, and retinopathy. However, in another study of type 1 diabetic individuals, females along with other parameters (e.g., lipids and hypertension) were found to be independent determinants of autonomic dysfunction (97). May et al. (180) showed a significantly reduced E:I ratio for females in a random sample of 120 type 1 diabetic individuals, along with older age, longer duration, and elevated glucose, triglycerides, blood pressure, and urinary albumin excretion.

MANAGEMENT IMPLICATIONS OF CARDIOVASCULAR AUTONOMIC NEUROPATHY

Identifying individuals at risk is only the first step in managing patients and ultimately affecting outcomes. After identification, effective management must be provided. Proactive measures are required, because if those patients at high risk or those shown to be in early stages are not treated until advanced symptomatology is present, little has been achieved.

Unfortunately, information presented at the fifth Regenstrief conference on the intensive management of type 2 diabetes indicated that physicians may feel that screening is not of value because treatment options for identified complications are limited (181). Such a view does not take into account the clinical research advances that have been made in the treatment of diabetes. Tests that provide evidence of further health consequences may bring patients to medical attention before other signs of diabetic end-organ injury emerge, making proactive treatment, particularly the establishment of intensive diabetes care, possible. The results of autonomic function testing can contribute to good patient management in the following ways.

To assist in the establishment (or reestablishment) of tight glycemic control

Early observations by researchers that near-normal glycemic control seems to be the most effective way to delay the onset of CAN in type 1 diabetes has been confirmed by evidence from the DCCT (37). Intensive insulin therapy has been shown to be effective at preventing multiple complications in patients with type 1 diabetes and is postulated to be effective for patients with type 2 diabetes, although clinical studies are underway in the latter.

In its earliest stages, there has been some clinical demonstration that autonomic dysfunction may be influenced within a few days to a few weeks with effective treatment (44,112). Delay in instituting appropriate interventions can only increase the likelihood of developing advanced neuropathies. Stabilization of the neuropathies (generally considered to be any delays in further progression) through tight glycemic control seems possible, whereas reversal of the condition may be less likely (44,182). Again, the results from the DCCT show that intensive glycemic treatment can prevent the development of abnormal heart rate variation and slow the deterioration of autonomic dysfunction over time for individuals with type 1 diabetes (37).

Although the relationship between features of autonomic neuropathy and hypoglycemic unawareness is complex and there is overlap, it is recognized that autonomic neuropathy may cause or contribute to the development of hypoglycemic unawareness. In most individuals with hypoglycemic unawareness, raising the target may be necessary to prevent repeat episodes. Thus, emphasizing tight control for individuals with autonomic dysfunction should also include increased vigilance in glycemic monitoring and reeducation of the patient with regard to hypoglycemia.

To facilitate the decision to initiate treatment for cardiovascular autonomic dysfunction

Several different factors have been implicated in the potential metabolic-vascular pathogenic process of diabetic neuropathy (e.g., activation of the polyol pathway, increased oxidative stress, reduction in neurotrophic growth factors, deficiency of essential fatty acids, and formation of advanced glycosylation end products) (10,21,183,184). Thus, timely identification of autonomic dysfunction in diabetic patients may expedite end-organ prophylaxis such as the use of ACE inhibitors and aspirin and the use of pharmacological and nonpharmacological interventions to improve blood pressure and lipid control. Improved nutrition and reduced alcohol and tobacco consumption are additional options available to patients with diabetes who are identified with autonomic nerve dysfunction. Interventions to modulate reduced heart rate variation currently being studied in clinical trials are based on theories of the pathogenesis of CAN.

Evidence from clinical trials evaluating the use of antioxidants is promising. Early identification of CAN permits timely initiation of therapy with the antioxidant α-lipoic acid (thioctic acid), which appears to slow or reverse progression of neuropathies in some studies (185), but further testing is necessary. Other antioxidants such as vitamin E have been shown to improve the ratio of cardiac sympathetic to parasympathetic tone in type 2 diabetic individuals with CAN (186) but may mitigate the effects of statins and niacin in treating or preventing macrovascular disease.

Studies using ACE inhibitors as a means to improve heart rate variation have resulted in conflicting results. Whereas quinapril significantly increased parasympathetic activity after 3 months of treatment (187), cardiovascular autonomic function did not change significantly after 12 months of treatment with trandolapril (188).

The use of cardioselective (e.g., atenolol) or lipophilic (e.g., propranolol) β-blockers may also modulate the effects of autonomic dysfunction (1). By opposing the sympathetic stimulus, they may restore the parasympathetic-sympathetic balance. Recently, the administration of

metoprolol to ramipril-treated type 1 diabetic patients with abnormal albuminuria has been shown to improve autonomic dysfunction (189).

Although the benefit of currently available agents in treating neuropathies is unproven, the investment in research (time, labor, and money) attests to the potential for treatment of detected neuropathies. Because the pathogenesis of CAN is most likely a multifactorial process, a combination of therapies directed simultaneously at different parts of the pathogenic pathway may be needed. In addition, the goal of these interventions should be directed at the prevention of further deterioration of cardiovascular autonomic dysfunction rather than expecting to realize improved function.

To emphasize the importance of adherence to diet and exercise interventions

It is again emphasized that lifestyle interventions (e.g., adherence to diet and exercise) can reduce the incidence of type 2 diabetes (174). Recently, a report indicated that impaired glucose tolerance may be associated with the development of diabetic neuropathy (i.e., sensory polyneuropathy) (190). Should this be confirmed in large prospective studies coupled with evidence that primary intervention would prevent the development of neuropathy, this would put even greater emphasis on the importance of lifestyle interventions and screening at or soon after diagnosis.

Motivation to adhere and remain compliant with nonpharmacological interventions is difficult. Current research suggests that preventive measures (glycemic control, diet, and exercise) introduced to the general diabetic population are difficult to sustain and consequently less than effective. This is due, in part, to the long-term commitment that must be made to the practice of preventive measures. Although individuals with diabetes are faced with the immediate pressures of disease management on a day-to-day basis, it is the long-term risks of micro- and macrovascular complications that pose the most serious risks (191). The ability to determine early stages of autonomic dysfunction could intensify the salience of measures such as diet and exercise that directly affect efforts to establish tight glycemic control and delay the development of autonomic dysfunction. Colloquial patient management strategies could be introduced to a now potentially motivated patient.

As mentioned previously, clinicians must be careful when giving recommendations with regard to exercise for individuals with CAN. This does not mean, however, that exercise is inappropriate for individuals with CAN. In fact, Howorka et al. (192) showed that physical training improved heart rate variation in insulin-requiring diabetic individuals with early CAN. Thus, careful testing to evaluate cardiovascular autonomic function and its degree of development is extremely important. Clinicians working together with the patient can develop an appropriate exercise program that will yield a plan for reaping maximum benefits.

SUMMARY — Autonomic dysfunction is a prevalent and serious complication for individuals with diabetes. The clinical manifestations of autonomic dysfunction can affect daily activities (e.g., exercise), produce troubling symptoms (e.g., syncope), and cause lethal outcomes. The patient's history and physical examination are ineffective for early indications of autonomic nerve dysfunction, and thus recommendations for the use of noninvasive tests that have demonstrated efficacy are warranted.

The economic impact of the recommendation to use autonomic function testing is minimal compared with the economic impact of the catastrophic events related to advanced cardiovascular, cerebrovascular, and renal complications. The relative cost of testing will always be less than the incremental costs of treating either a detected complication or the more catastrophic event that could eventually occur.

Despite research evidence that clinical observations (whether they be symptoms or routine vital signs) should not be the sole basis for the diagnosis of cardiovascular autonomic dysfunction, screening for abnormalities is infrequently done. This is also despite the fact that office-based commercially available instrumentation for detection is readily available.

Given the clinical and economic impact of this complication, testing of diabetic individuals for cardiovascular autonomic dysfunction should be part of their standard of care. Such a recommendation does not diminish the importance of clinical evaluation and patient observation; rather, it enhances the clinical assessment of the diabetic patient by providing an objective, quantifiable, and reproducible measure of autonomic function.

GLOSSARY

Autonomic nervous system (ANS) – The portion of the nervous system that regulates individual organ function and homeostasis not under voluntary control. An efferent and afferent system, the ANS transmits impulses from the central nervous system to peripheral organ systems. This results in control of heart rate and force of contraction, constriction and dilatation of blood vessels, contraction and relaxation of smooth muscle in various organs, visual accommodation, pupillary size, and secretions from exocrine and endocrine glands. The ANS is also responsible for conveying visceral sensation. The ANS is typically divided into two divisions: the parasympathetic and the sympathetic systems on the basis of anatomical and functional differences.

Cardiovascular autonomic function testing – A number of simple objective tests of cardiovascular autonomic function and reflexes to aid in the diagnosis of cardiovascular autonomic neuropathy.

Cardiovascular autonomic neuropathy (CAN) – This disorder results from damage to the fibers of the ANS with associated abnormalities of heart rate control and vascular dynamics.

Diabetic autonomic neuropathy (DAN) – A neuropathic disorder associated with diabetes that includes manifestations in the peripheral components of the ANS. DAN affects sensory, motor, and vasomotor fibers innervating a large number of organs. DAN may thus affect a number of different organ systems (e.g., cardiovascular, GI, and genitourinary).

Diabetic neuropathy – "A descriptive term meaning a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system" (3).

Heart rate variability (HRV) – The magnitude of heart rate fluctuations (R-R interval) around the mean heart rate that are modulated by the ANS. HRV is con-

sidered the earliest indicator and most frequent finding in symptomatic cardiovascular autonomic dysfunction.

Parasympathetic nervous system – The portion of the ANS concerned with conservation and restoration of energy. It causes a reduction in heart rate and blood pressure, facilitates the digestion and absorption of nutrients, and facilitates the excretion of waste products from the body.

Sympathetic nervous system – The portion of the ANS that enables the body to be prepared for fear, flight, or fight. Sympathetic responses include increases in heart rate, blood pressure, and cardiac output and diversion of blood flow from the skin and splanchnic vessels to those supplying skeletal muscle.

APPENDIX: STANDARDIZED TESTS OF AUTONOMIC FUNCTION

The important criteria for appraising clinical tests of autonomic function include reliability, reproducibility, general correlation with each other and with tests of peripheral somatic nerve function, well-established normal values, and demonstrated prognostic value. Three tests of cardiovascular autonomic nerve function that fulfill these criteria are *1*) the E:I ratio (obtained from R-R variations), *2*) the Valsalva ratio, and *3*) the standing 30:15 ratio. These tests use deep breathing, the Valsalva maneuver, and standing from a supine position, respectively, as provocative stimuli. For purposes of reimbursement, the three tests are grouped together under *Current Procedural Terminology* code 95921. At least two of these three tests should be performed to provide adequate diagnostic information and to support reimbursement claims.

An abnormal result for each test is defined as HRV below that of the 5th percentile of the normal age-matched population. Abnormal HRV in one test is indicative of early autonomic neuropathy.

Because of the technical requirements for these tests, they should be performed at the point-of-care office or in a clinical laboratory setting. The tests are not currently appropriate for nonclinical screening venues.

The sensitivity, specificity, and positive/negative predictive values listed in Table A1 summarize results obtained using standardized algorithms and an offsite processing center. These currently unpublished data (from A.I.V. and Risk) were based on standardized testing of 205 normal subjects and 3,516 patients with type 1 or type 2 diabetes from 42 centers.

Table A1—*Summary of HRV test performance*

	E:I ratio	Valsalva ratio	Standing (30:15) ratio
Sensitivity	0.93	0.98	0.93
Specificity	0.93	0.91	0.93
Positive predictive value	0.93	0.91	0.92
Negative predictive value	0.94	0.98	0.93

From A.I. Vinik and M. Risk, unpublished data.

E:I ratio

The beat-to-beat HRV assesses the heart rate response to an autonomic reflex arc using an electrocardiography and a means for standardizing the patient's breathing rate (e.g., visual cues to guide inspiration and expiration). The time intervals between R-waves of the QRS complexes are measured in milliseconds. This measurement should be obtained using the deep respiration test and the results evaluated by determining the E:I ratio.

To perform the test, the subject remains supine and breathes deeply at the rate of one breath per 10 s (i.e., six breaths per minute) for 1 min while being monitored by ECG. The E:I is the ratio of the mean of the longest R-R intervals during deep expirations to the mean of the shortest R-R intervals during deep inspirations. The E:I ratio is significantly affected by shifting of the heart rate and regularity of the respiratory cycling. HRV decreases with increasing respiration rate, with the greatest variation occurring at a respiratory rate of six breaths per minute. Respiration should therefore be standardized at six breaths per minute to optimize test results. E:I ratios are based on the fact that inspiration shortens R-R intervals while expiration lengthens them.

Valsalva maneuver

The complex effect of the Valsalva maneuver on cardiovascular function is the basis of its usefulness as a measure of autonomic function. In the standard Valsalva maneuver, the supine patient, connected to an ECG monitor, forcibly exhales for 15 s against a fixed resistance with an open glottis. The patient should maintain constant pressure at 40 ml over the 15-s interval. This causes a sudden transient increase in intrathoracic and intra-abdominal pressure and a consequent hemodynamic response. Healthy patients develop tachycardia and peripheral vasoconstriction during the strain and an overshoot in blood pressure and bradycardia on release. However, in patients with autonomic damage from diabetes, the reflex pathways are damaged, resulting in a slow and steady decline in blood pressure during strain, followed by gradual return to normal after release. Heart rate responses are often unchanged in this situation.

The Valsalva ratio is the longest R-R divided by the shortest R-R occurring within 45 s of peak heart rate and is indicative of overall condition of the parasympathetic and sympathetic fibers.

Heart rate response to standing

To test the heart rate response to standing, the patient is connected to the heart rate monitor while in the supine position. The patient then stands to a full upright position, and the ECG is monitored for an additional period while standing. Standing causes an immediate rapid increase in heart rate with the maximum rate generally found at or around the 15th beat after standing. The heart rate slows at or around the 30th beat. The heart rate tracing is used to calculate the ratio of the longest R-R interval (about beat 30) after the stand to the shortest R-R interval (about beat 15). This measure, called the 30:15 ratio, reflects the overall condition of the parasympathetic fibers. Normal ranges are age dependent.

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