The Value of Cardiovascular Autonomic Function Tests: 10 Years Experience in Diabetes

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Five simple, noninvasive cardiovascular reflex tests have been used to assess autonomic function in one center over the past 10 yr. Seven hundred seventy-four diabetic subjects were tested for diagnostic and research purposes. In 543 subjects completing all five tests, abnormalities of heart rate tests occurred in 40%, while abnormal blood pressure tests occurred in <20%. Their results were grouped as normal (39%), early (15%), definite (18%), and severe (22%) involvement. Six percent had an atypical pattern of results. Two hundred thirty-seven diabetic subjects had the tests repeated ≥3 mo apart: 26% worsened, 71% were unchanged, and only 3% improved. The worsening followed a sequential pattern with first heart rate and later additional blood pressure abnormalities. Comparison between a single test (heart rate response to deep breathing) and the full battery in 360 subjects showed that one test alone does not distinguish the degree or severity of autonomic damage. These tests provide a useful framework to assess autonomic neuropathy simply, quickly, and noninvasively. DIABETES CARE 1985; 8:491–98.

Over the past decade there has been an increasing awareness of the role that the autonomic nervous system plays in a diversity of diseases.[1] A number of simple, objective tests based on cardiovascular reflexes have been developed and used particularly in individuals with diabetes mellitus.[2–4] There remains, however, considerable misunderstanding among many clinicians as to which tests are most appropriate for diagnostic and follow-up purposes, whether one or multiple tests are necessary, how each is performed, what abnormal results really indicate, and whether the test results relate to clinical realities. Elsewhere we have described in detail our methodology and protocols for the clinical evaluation of autonomic nerve function, which has evolved from our experience in Edinburgh over the past 10 yr.[2,5,6] This article summarizes the results of our cardiovascular reflex testing in normal and diabetic subjects during this period, and their relevance to current clinical practice.

METHODS

The five tests used in our standard cardiovascular autonomic assessment are: the heart rate responses to the Valsalva maneuver, standing up (30:15 ratio), and deep breathing (maximum-minimum heart rate); and the blood pressure responses to standing up (postural BP change), and sustained handgrip. Although we and others have previously argued that the heart rate responses are indicative of cardiac parasympathetic integrity, while the blood pressure changes are only abnormal with more extensive and widespread (extracardiac) sympathetic damage,[4,7] the autonomic pathways involved in these reflexes are complex. Both parasympathetic and sympathetic innervation plays some part in all five tests, and while a division into parasympathetic and sympathetic tests is clinically convenient, this does not strictly reflect all the complex underlying physiologic mechanisms. In this article, therefore, we have referred only to heart rate and blood pressure tests, rather than being dogmatic about the precise autonomic innervation of each reflex test.

Cardiovascular Tests Used

Valsalva maneuver. The subject sits quietly and then blows into a mouthpiece at a pressure of 40 mmHg for 15 s. The heart rate normally increases during the maneuver, followed by a rebound bradycardia after release. The ratio of the longest R-R interval shortly after the maneuver to the shortest R-R interval during the maneuver is then measured. We routinely express the result, the Valsalva ratio, as the mean ratio from three successive Valsalva maneuvers.

Heart rate response to standing up. The subject lies quietly on a couch and then stands up unaided. Normally an immediate increase in heart rate occurs that is maximal at about the 15th beat after starting to stand, followed by a relative

TABLE 1
Results of cardiovascular autonomic function tests in normal subjects

Test	Measurement	No. of subjects: All	Male	Female	Age range (yr)	Mean ± SD	Range	Relation to age	Previously defined values: Normal	Borderline	Abnormal
Valsalva maneuver	Valsalva ratio	135	92	43	16–69	1.75 ± 0.39	1.22–2.87	r = 0.2 (NS)	⩾1.21	1.11–1.20	⩽1.10
Lying to standing heart rate response	30:15 ratio	111	73	38	16–69	1.29 ± 0.17	1.00–1.79	r = −0.49 (P < 0.001)	⩾1.04	1.01–1.03	⩽1.00
Heart rate response to deep breathing	Maximum-minimum heart rate (beats/min)	71	39	32	16–65	31 ± 9	12–53	r = −0.57 (P < 0.001)	⩾15	11–14	⩽10
Postural blood pressure change	Fall in systolic BP (mmHg)	73	40	33	16–65	−1 ± 8	+30–15	r = 0.16 (NS)	⩽10	11–29	⩾30
Sustained handgrip test	Rise in diastolic BP (mmHg)	139	79	60	16–69	Men 34 ± 10 Women 25 ± 8	17–64 12–52	r = 0.02 (NS) r = −0.35 (P < 0.05)	⩾16	11–15	⩽10

bradycardia, maximal around the 30th beat. This can be quantified as the 30:15 ratio, which is the ratio of the longest R-R interval around the 30th beat to the shortest R-R interval around the 15th beat.

Heart rate response to deep breathing. The subject sits quietly and then breathes deeply and evenly at 6 breaths/min. The maximum and minimum heart rates during each breathing cycle are measured, and the mean of the differences during three successive breathing cycles are taken to give the maximum-minimum heart rate.

Blood pressure response to standing up. The blood pressure is measured using a standard sphygmomanometer while the subject is lying down, and again after standing up. The difference in systolic blood pressure is taken as the measure of postural blood pressure change.

Blood pressure reponse to sustained handgrip. Handgrip is maintained at 30% of the maximum voluntary contraction using a handgrip dynamometer up to a maximum of 5 min, and the blood pressure measured each minute. The difference between the diastolic blood pressure just before release of handgrip, and before starting, is taken as the measure of response.

We have recently developed an on-line microprocessor-based computer program, which we now use routinely for the measurement and analysis of these five tests.

Analysis of Results

Based on our experience of both the pattern and the sequence of test abnormalities in diabetic subjects with first heart rate and later blood pressure tests becoming abnormal, we now group the results from this standard battery of tests into one of five categories, depending on the individual test results: normal (N), all tests normal or one borderline; early involvement (E), one of the three heart rate tests abnormal or two borderline; definite involvement (D), two or more of the heart rate tests abnormal; severe involvement (S), two or more of the heart rate tests abnormal plus one or both of the blood pressure tests abnormal, or both borderline; atypical pattern (A), any other combination of abnormal tests.

Elsewhere[6] we have referred to categories E, D, and S as "early parasympathetic" (EPS), "definite parasympathetic" (PS), and "parasympathetic plus additional sympathetic" (PS + S). As other workers have suggested scoring systems to grade the severity of autonomic damage,[8] we have also compared our categorization with two different ways of scoring the tests: (1) giving 0 for a normal result, $\frac{1}{2}$ for a borderline result, and 1 for an abnormal result, thus giving a score of 0–5 for each subject who underwent the standard battery of all five tests; and (2) according to the number of tests definitely abnormal, again giving a score of 0–5 for each subject.

SUBJECTS

Normal subjects. Normal ranges for each of the tests have been established with healthy subjects aged between 16 and 69 yr. These normal subjects were selected from healthy laboratory personnel and medical staff, normal volunteers, and some patients preparing to undergo minor elective surgical procedures, but who were otherwise well.

Diabetic subjects. Seven hundred seventy-four subjects have been tested, of whom 543 (329 men and 214 women) had the complete battery of all five tests. The remaining 231 had fewer tests for three main reasons: (1) in our earlier assessment, we had included only the Valsalva maneuver, postural blood pressure measurements, and sustained handgrip; (2) some of the subjects had to omit one or more of the tests for

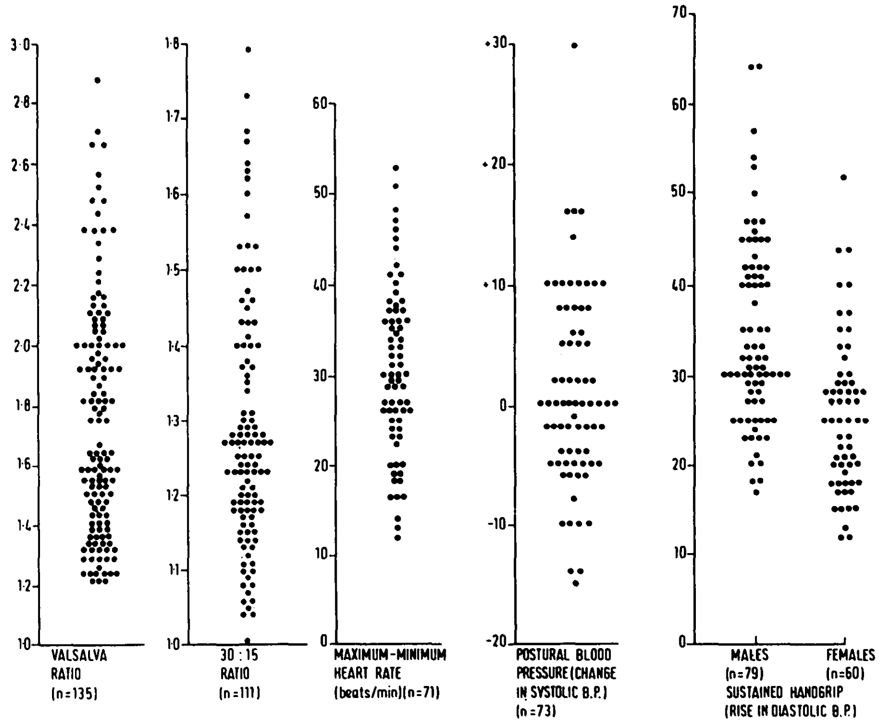

FIG. 1. Individual responses to five cardiovascular autonomic function tests in normal subjects aged 16–69 yr.

such reasons as proliferative retinopathy (Valsalva), painful or stiff hands (handgrip), amputations or being bedridden (lying to standing tests), and failure to comprehend the procedures (various tests); and (3) the heart rate tests were rendered uninterpretable in subjects with cardiac arrhythmias, such as atrial fibrillation or frequent ventricular ectopic beats.

Of the 543 diabetic subjects who completed all the tests, 366 were assessed only once, while the other 177 repeated them at least twice at different times, separated by ≥3 mo. This made a total of 839 complete batteries of tests. It is not possible to extract from the results given below the prevalence of abnormal autonomic function tests in a diabetic population because our subjects were selected for a number of different purposes and are therefore not representative.

RESULTS

Normal Subjects

Individual results. Table 1 details the number of subjects who were tested, the range of results, and the relation to age. Figure 1 shows the individual responses to the tests. Apart from sustained handgrip, where there was a smaller reponse in women, there were no sex differences found in the results. Age correlated strongly with the heart rate responses during lying to standing and deep breathing, but not with the responses during the Valsalva maneuver; and weakly with the handgrip response in women. This correlation was, however, not present in men, or when both male and female handgrip responses were combined. Neither the Valsalva ratio ($r = 0.11$ NS), the maximum-minimum heart rate differences ($r = 0.07$ NS), nor the 30:15 ratio ($r = -0.06$ NS) were related significantly to the resting heart rate, and therefore the prevailing heart rate does not influence the result of these heart rate–based tests.

The normal, borderline, and abnormal ranges that we have assigned to each test are given in Table 1. Those for the Valsalva maneuver, the lying to standing heart rate response (30:15 ratio), and the sustained handgrip response are based on our own earlier work with smaller numbers of normal subjects.[5,9,10] While the values for the 30:15 ratio are lower in older, normal subjects, this does not affect the interpretation because the abnormal responses are of a different pattern.[9] Nor does the smaller female handgrip response affect interpretation of the results.[10] Although we have defined a borderline range for the Valsalva ratio, none of our normal subjects had values <1.21. We therefore now regard our previous borderline results as frankly abnormal. This is not the case for the other borderline values, which indicate a degree of uncertainty at the lower end of the normal range.

The two other tests used routinely have had normal ranges established by other investigators,[11–13] although our own results can be seen to fall within their previously defined ranges. The heart rate during deep breathing usually varies >10 beats/min[11,12] and, although a clear correlation with age is well recognized,[11,14] a response of ≤10 beats/min is abnormal, even in older subjects. Thus for routine diagnostic purposes we have not taken age into account in the interpretation of the results of these tests. For research purposes in young subjects, however, we have used slightly different ranges based on results from young, age-matched normal controls.[15]

Repeatability. We have previously published figures for repeatability in normal subjects during the Valsalva maneuver,[16]

TABLE 2
Repeatability of cardiovascular autonomic function test results in normal subjects

Test	Measurement	No. of subjects	No. of times	Group mean	Between-subject standard deviation	Mean within-subject standard deviation (range)
Valsalva maneuver	Valsalva ratio	19	5–10	1.71	0.35	0.15 (0.06–0.24)
Lying to standing heart rate response	30:15 ratio	18	5–10	1.27	0.08	0.11 (0.06–0.20)
Heart rate response to deep breathing	Maximum-minimum heart rate (beats/min)	13	10	31	6	4 (3–5)
Postural blood pressure change	Fall in systolic BP (mmHg)	13	10	1	3	5 (3–8)
Sustained handgrip test	Rise in diastolic BP (mmHg)	5	5	35	9	8 (4–10)

the lying to standing heart rate response,[9] and sustained handgrip.[10] These are included in Table 2, along with new and additional information on the heart rate responses to deep breathing and standing, and the blood pressure response to standing in 13 young, normal subjects (6 men and 7 women) and all medical and laboratory staff, whose tests were repeated 10 times over a 2-mo period. Two components of variation are shown in Table 2. The between-subject standard deviation has been calculated for each of the five tests from the mean values obtained for each subject. The degree of within-subject variation differed between subjects, thereby invalidating the analysis of variance technique usually applied in this situation. Thus for the within-subject variation we have calculated the individual within-subject standard deviations, and in Table 2 we present the mean and range of these figures.

Diabetic Subjects

Individual results. Figure 2 details the results from the 543 diabetic subjects who completed all five tests at the same session. Only the first set of results are included for those individuals who repeated tests. The percentage of each heart rate test found abnormal was ≈40% if, as discussed above, the borderline Valsalva responses are in fact considered abnormal; whereas this was well under 20% for the blood pressure tests. Of the remaining 231 diabetic subjects who did not complete all five tests, between one-quarter and one-half of the individual tests were abnormal.

For diagnostic purposes it is helpful to categorize the tests in more detail. This has been done for all 839 batteries of complete tests in three different ways in Table 3: by pattern of abnormality, by scoring, and by the number of tests actually abnormal. As can be seen, the different methods of categorizing gave roughly equivalent results, from minimal involvement to abnormalities in all five tests.

Fifty-three (6%) subjects had atypical patterns of abnormality. Further analysis of results showed that 31 (3.7%) had evidence of both heart rate and blood pressure abnormalities, but with results that did not strictly comply with the defined criteria given in METHODS; all scored 2–3 points. The remaining 22 (2.6%) had either postural blood pressure or handgrip abnormalities, or both, in the presence of relatively normal heart rate tests, and scores of 1 or 1½ points. Ten (8 women and 2 men) had isolated handgrip abnormalities, while four had only an abnormal blood pressure response to standing.

Repeated tests. We have previously published our experience with diabetic subjects whose tests had been repeated over a period of ≥2 yr.[17] This current analysis represents our further and more extensive experience with follow-up of cardiovascular autonomic function tests. The repeat test results have been analyzed in two ways: by the changes in overall categorization and by a comparison between the first and last

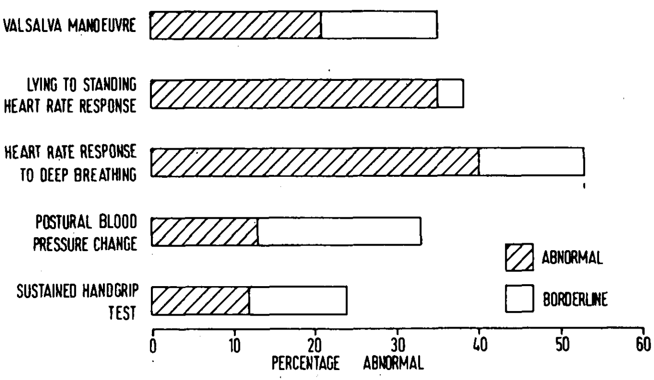

FIG. 2. Percentage of abnormal and borderline test responses in one set of complete batteries of five cardiovascular autonomic function tests undertaken by 543 diabetic subjects.

TABLE 3
Results of 839 completed batteries of tests in 543 diabetic subjects analyzed in three different ways

By category		By scoring system*			By number of abnormal tests†	
Normal (N)	323 (39%)	0	219	(37%)	0	324 (39%)
		½	90			
		1	95	(18%)	1	153 (18%)
Early involvement (E)	127 (15%)	1½	55			
		2	65	(14%)	2	120 (14%)
		2½	54			
Definite involvement (D)	149 (18%)	3	64	(15%)	3	126 (15%)
		3½	64			
		4	72	(12%)	4	82 (10%)
Severe involvement (S)	187 (22%)	4½	27			
		5	34	(4%)	5	34 (4%)
Atypical pattern (A)	53 (6%)					

*Normal test = 0, borderline = ½, abnormal = 1.
†A borderline Valsalva response has been included as abnormal and given a score of 1 (see text).

individual test result in each subject. Two hundred thirty-seven subjects had two or more tests performed ≥3 mo apart. The overall progression of their tests is shown in Table 4. About one-quarter deteriorated, with only 8 (3%) showing any improvement in the categorization of test results. Of the 41 diabetic subjects who were tested ≥5 yr apart, 19 (46%) showed deterioration and 22 (54%) were unchanged. The worsening of the cardiovascular autonomic function tests followed a fairly uniform pattern, with first heart rate and later blood pressure tests becoming abnormal, confirming the trend we have previously described.[17,18]

There were some small but significant changes in the means of the individual numerical test results when the first and last tests were compared in each diabetic subject, irrespective of the time between testing. The mean Valsalva ratio decreased from 1.50 ± 0.46 (SD) to 1.43 ± 0.44 ($P < 0.001$, N = 266). The mean postural blood pressure drop increased from 11 ± 18 mmHg to 17 ± 22 ($P < 0.001$, N = 265) and the mean blood pressure response to sustained handgrip decreased from 26 ± 13 mmHg to 21 ± 11 ($P < 0.001$, N = 266). The mean heart rate responses to deep breathing and standing remained unchanged.

Further analysis of the sequence of deterioration of the tests revealed 39 diabetic subjects in whom first one test became abnormal and later other tests, as well. Twenty six subjects (67%) developed an abnormal 30:15 ratio first, 5(13%) an abnormal Valsalva ratio, and 5 (13%) an abnormal maximum-minimum heart rate first, while in 3 (7%) handgrip was the first abnormal test.

Comparison between a single test and a battery of tests. A view has been put forward that autonomic neuropathy can be diagnosed by a single cardiovascular test. In most cases this has been the heart rate response to deep breathing (maximum-minimum heart rate).[19,20] We found 360 abnormal maximum-minimum heart rate tests among the 839 complete batteries of tests. In 45 (12%) this was the only abnormal test (E), in 139 (39%) the other tests suggested definite damage (D), and in 167 (46%) there were test abnormalities suggesting severe damage (S). Nine (3%) had an atypical pattern of tests (A). Additionally, in 20 tests categorized as (S) and 10 tests categorized as (D) the maximum-minimum heart rate was either borderline or normal.

Repeated test results, duration of diabetes, and glycemic control. There were 93 diabetic subjects with tests repeated ≥2 yr apart whose first tests were categorized as normal, in whom information was available on duration of diabetes and gly-

TABLE 4
Changes in cardiovascular autonomic function test results in 237 diabetic subjects with two or more tests performed ≥3 mo apart

(Length of time between tests)	3 mo–2 yr	2–3 yr	≥3 yr	Total
No. of subjects	68	85	84	237
Improved				
E → N	2	3	0	5
D → N	1	1	0	2
D → S	1	0	0	1
Total	4 (6%)	4 (5%)	0 (0%)	8 (3%)
Unchanged				
N	12	42	22	76
E/D	13	15	15	45
S	21	10	17	48
Total	46 (68%)	67 (79%)	54 (64%)	167 (71%)
Worsened				
N/E → D/S	11	14	13	13
N → S	1	0	13	14
E/D → S	6	0	4	10
Total	18 (26%)	14 (16%)	30 (36%)	62 (26%)

cemic control (mean of three immediately previous clinic blood sugar results) at the time of first testing. Fifty-five diabetic subjects had repeat tests that remained normal, while in 38 diabetic subjects the test results deteriorated (18 to E, 8 to D, and 12 to S). Those with tests remaining normal had a significantly shorter mean duration of diabetes than those whose tests deteriorated (8.7 yr versus 14.0 yr, $P < 0.01$). Those with greatest deterioration had the longest duration of diabetes: E 11.7, D 15.7, and S 17.1 yr. Mean blood sugar was, however, higher in those whose tests remained normal (13.3 mmol/L versus 10.9 mmol/L, $P < 0.01$), and there were no significant differences between the three groups whose tests deteriorated.

DISCUSSION

The aim of using cardiovascular autonomic function tests is to provide an objective diagnosis of autonomic nervous system involvement and to relate any abnormalities to clinical features. While the role of these tests is now widely accepted as providing simple bedside assessment of autonomic function, there have been different views as to which ones should be used. This is particularly so if autonomic neuropathy is regarded as an all-or-none phenomenon and only one diagnostic test is used. Damage to the autonomic nerves can occur minimally or severely, and individuals may be asymptomatic or severely disabled. The tests we have selected as being most useful for our standardized cardiovascular autonomic assessment are based on our experience in Edinburgh over the past 10 yr. The results given in this survey show the normal values that we have obtained, and from which we can confidently diagnose abnormality. While it is true that some of these tests are age dependent, it is often forgotten that there is an area of uncertainty at the lower end of the normal range, and that measurement of the test responses have limitations in accuracy. Accordingly, we feel that the ranges we give for normal, borderline, and abnormal represent standards that can simply be applied in any center performing the tests in the manner we describe.

Each of the five cardiovascular tests has a well-established rationale, both in terms of normal results, and of its physiologic and pharmacologic basis, the details of which have been given elsewhere.[2,4] The autonomic pathways involved in all these reflexes are however extremely complex and include both parasympathetic and sympathetic fibers to a greater or lesser extent. While the heart rate responses are primarily mediated via cardiac parasympathetic pathways, additional sympathetic influences, particularly in the Valsalva maneuver, can also alter these responses. Similarly, blood pressure is controlled by many different factors and, although in diabetic subjects peripheral sympathetic vasoconstriction is probably the most important mechanism in postural hypotension, other components such as subclinical volume depletion[21] may also contribute. We and others have previously classified these tests into parasympathetic and sympathetic, depending on whether heart rate alone or both heart rate and blood pressure control was affected.[4,7] This approach has proved extremely useful clinically because it reflects the sequence of damage seen in diabetic subjects and has been widely used. However, we would stress that, although clinically useful, such a classification should not be considered physiologically precise because of the complexity of the autonomic pathways.

We have previously described in detail the relevance of abnormal autonomic function tests in the clinical situation in diabetic subjects and their relation to symptoms, abnormalities in systems other than the cardiovascular system, and mortality.[3,5] We have shown, for example, in a prospective 5-yr study that diabetic subjects with symptoms suggestive of autonomic damage and abnormal tests have a very high mortality.[17] These tests therefore have been and continue to be extremely valuable for diagnostic and prognostic reasons in diabetic subjects. However, while the natural history of late autonomic neuropathy in diabetic subjects is known, there is no evidence currently available about the natural history of early autonomic involvement. Individuals with abnormal tests but no symptoms may in some cases go on to develop symptoms and further autonomic abnormalities, but it is clear that in some the tests may stay unchanged. A further important new area for the clinical relevance of these tests is the reversal of abnormal function. There is some early evidence that autonomic tests can be reversed in subjects on insulin infusion systems.[22] Another approach has been the use of aldose reductase inhibitor drugs,[23] but it is too early to know whether any reversal of autonomic abnormalities can be obtained with them.

The current analysis of our results in diabetic subjects both confirms our previous observations and adds to them in a number of ways. Far more diabetic subjects had abnormal heart rate tests alone than additional abnormal blood pressure tests. This has been observed by ourselves and others previously.[3,7,24] It is not clear, however, whether this is because parasympathetic involvement occurs earlier in the natural history of diabetic autonomic neuropathy or whether it is simply that the cardiovascular reflex heart rate tests are rather more sensitive than the blood pressure tests. Whichever is the case, it does not alter the way in which it is possible to categorize diabetic autonomic damage. We did not see blood pressure abnormalities without heart rate changes. Other workers have suggested a scoring system for autonomic neuropathy.[8] As can be seen from our own results, this would give a roughly equivalent categorization of the subjects in most cases, and seems to carry no real advantages.

The present analysis of repeated autonomic function tests is much more extensive than our previously reported experience but confirms the trend we described;[17,18] that is, that subjects either remain static or deteriorate. Very few improve at all and worsening follows a characteristic pattern, with first the heart rate and then the blood pressure tests becoming abnormal. Detailed analysis showed that about one-quarter deteriorated and that this number increased with increasing duration of testing. Why the tests become abnormal or deteriorate further in some diabetic individuals and not in others is at present unknown. The lack of deterioration in the numerical results of the lying to standing heart rate response and the deep breathing tests might at first appear surprising. However, as these are tests that become abnormal early, it may be a reflection of our subject selection, many of whom already had abnormal responses at their first testing. Of those in whom it was possible to trace the sequence of development of abnormality starting with a single test abnormality, it was the lying to standing heart rate response that was abnormal earliest in about two-thirds of subjects. Our results emphasize the fallacy of relying on a single test, particularly heart rate variation during deep breathing, to make a diagnosis of autonomic neuropathy; an abnormal deep breathing test did not distinguish between those with very minimal involvement and those with severe damage. There were, however, only 13 (4%) of all the subjects with marked autonomic damage in whom the heart rate variation was actually normal. It could therefore be argued that heart rate variation might provide a simple screening test for the presence or absence of neuropathy but since the other tests are so easy to perform, it would seem unwise not to do as many tests as possible to get rather more information than can be obtained from a single test.

Prevailing glycemic control appeared to have little influence on the deterioration of test results, except that surprisingly those whose tests remained normal had higher mean clinic blood sugars. Longer duration of diabetes was associated with greater deterioration in test results. These observations must, however, be interpreted with caution because they were retrospective analyses in groups of diabetic subjects selected for other reasons.

In this analysis we have not taken the possible confounding effects of additional renal failure and alcoholism into account in the interpretation of the cardiovascular reflex tests. Both must be severe before autonomic damage occurs. In such circumstances the exact causal factor of autonomic damage is, in our experience, irrelevant to the clinical management of the diabetic subject. Drugs such as tricyclic antidepressants and hypotensive agents also influence autonomic reflexes. In practice, in the very few diabetic subjects in whom there is diagnostic difficulty about the cause of postural hypotension, we have stopped the offending drug and repeated the tests after a few days. We have recently described a new method of measuring cardiac parasympathetic activity using 24-h EKG tape recording, which is probably more sensitive than the tests described here.[25] This requires a tape recording and replay system to analyze the results. This may be important for research purposes, but for routine clinical practice, the 15–20 min spent in one visit outweighs the possible benefits of two visits with 24-h tape recording in between. It is too early, also, to say whether other cardiovascular reflex measures such as the standing to lying test[26,27] or the use of the 15:30 ratio or equivalent[11] will add anything to the diagnostic discrimination of the current tests.

In this article we have analyzed the results of our cardiovascular autonomic function testing over the past 10 yr. Our experience shows that these five cardiovascular autonomic function tests give accurate and reliable information, that can be obtained simply and noninvasively, about the state of the autonomic nervous system in diabetes.

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