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**Declan Walsh**
**Kristine A. Nelson**

# Autonomic nervous system dysfunction in advanced cancer

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D. Walsh · K.A. Nelson (✉)
The Harry R Horvitz Center For Palliative Medicine, The Taussig Cancer Center, The Cleveland Clinic Foundation, 9500 Euclid Ave., M76, Cleveland, Ohio 44195, USA
web site: www.clevelandclinic.org/palliative
e-mail: kristine.nelson@ctca-corp.com
Tel.: +1-847-3427451

**Abstract** The autonomic nervous system (ANS) innervates every organ in the body and is largely involuntary. There have been reports of autonomic dysfunction in cancer patients, but most are case reports. There are suggestions that this abnormality may be common in advanced cancer. Inpatients and outpatients with advanced cancer were enrolled. Patients were excluded if they had a previous diagnosis of a disease associated with autonomic nervous system (ANS) abnormalities, or had taken or were taking drugs affecting the ANS. Autonomic function was evaluated using five bedside cardiovascular tests: (1) heart rate response to deep breathing, (2) heart rate response to standing, (3) heart rate response to the Valsalva maneuver, (4) blood pressure response to standing and (5) blood pressure response to static exercise. Each test result was scored according to a validated scale of 0,.5, or 1. The individual scores were added together and each patient received a dysfunction score: none (=0–1), mild (=1.5–2), moderate (=2.5–3) or severe (=3.5–5). Twenty-eight men and 22 women participated, median age was 64 years. The median ECOG performance status was 2. Lung and prostate cancer were the most common (*N*=9, 5). 245 tests were performed; 86 (35%) individual tests were normal or borderline. Composite dysfunction scores were calculated; all the participants had a score consistent with abnormality. The median number of symptoms was 6 (range 1–15). Twenty-eight rated at least one symptom as severe (median 2, range 0–5), but symptoms did not correlate with test abnormalities. The results reveal significant ANS dysfunction in advanced cancer. There are more invasive tests that may give more accurate descriptions of ANS abnormalities in this population. These tests may help define the lesion better than these simple bedside tests. Further research with sophisticated ANS testing is needed to clearly define this paraneoplastic syndrome.

**Keywords** Cancer · Autonomic nervous system · Symptoms

## Introduction

The autonomic nervous system (ANS) innervates every organ in the body and is largely involuntary. Multiple conditions may impair its function (Table 1); most are found in primary neurologic disorders, diabetes mellitus, or chronic renal disease. There have been reports of autonomic dysfunction in cancer patients patients [1, 2, 4, 5, 6, 7, 8, 11, 12, 13, 15, 16, 17, 19, 20, 22, 23, 24, 25, 26, 27, 28] (Table 2), but most are case reports. Our clinical experience suggests that this abnormality may be common in advanced cancer, where a fixed pulse rate, low blood pressure and symptoms of gastroparesis are common. A previous study has documented the presence of delayed gastric

**Table 1** Diseases associated with autonomic dysfunction

| | |
|---|---|
| 1. Primary | Chronic<br>Acute and subacute |
| 2. Secondary causes (associated with peripheral neuropathy) | Autonomic dysfunction clinically important<br>Autonomic dysfunction usually clinically unimportant<br>Chronic inflammatory demyelinating polyradiculoneuropathy<br>Metabolic disorders<br>Alcoholism and nutritional disorders<br>Malignancy<br>Toxic causes<br>Connective tissue disease<br>Infection |
| 3. Aging | |
| 4. Genetically determined metabolic disease | |
| 5. Spinal cord lesions | |
| 6. Drugs | Centrally acting<br>Ganglion-blocking drugs<br>Peripherally acting drugs |

**Table 2** Cancer related autonomic dysfunction

| Year | Reference | Cancer site | *N* |
|---|---|---|---|
| 1961 | [13] | Lung | 1 |
| 1963 | [24] | Lung | 1 |
| 1970 | [26] | Prostate | 1 |
| 1971 | [20] | Lung | 1 |
| 1972 | [19] | Lung | 1 |
| 1975 | [1] | Lung | 1 |
| 1977 | [2] | Diverse | 5 |
| 1978 | [7] | Lung | 1 |
| 1979 | [6] | Lung | 1 |
| 1979 | [12] | Lung | 1 |
| 1981 | [27] | Lung | 1 |
| 1983 | [23] | Lung | 1 |
| 1985 | [17] | Breast | 1 |
| 1985 | [22] | Lung/leiomyosarcoma | 1 |
| 1986 | [11] | Lung | 69 |
| 1986 | [5] | Breast | 43 |
| 1988 | [8] | Lung | 7 |
| 1989 | [4] | Esophageal | 1 |
| 1989 | [25] | Lung/unknown primary | 2 |
| 1990 | [28] | Lung | 1 |
| 1991 | [15] | Lung | 5 |
| 1992 | [16] | Diverse | 48 |

emptying in advanced cancer without gastrointestinal involvement by the tumor [18]. Two studies have evaluated patients with advanced cancer using the five cardiovascular tests used in our study. In one the subjects had breast cancer [16], and in the other a mixed group of patients with cancer and lymphoma was investigated [5]. However, the results were only reported as normal or abnormal; they were not scored or given a composite (dysfunction) score. We have conducted a study of autonomic function in a heterogeneous group of patients with advanced cancer in our palliative medicine program. Five noninvasive, bedside cardiovascular tests were used [10]. These have been previously validated and used extensively in several populations and disease states. Each test result was scored, and each patient was then given a composite dysfunction score.

## Methods

Fifty consecutive patients with advanced cancer were enrolled. Patients were excluded if they had a previous diagnosis of diabetes mellitus, renal failure, cardiovascular or mediastinal disease, hypertension, porphyria, Shy-Drager disease, Addison's disease, Parkinson's disease, primary neurologic disorder, or tabes dorsalis. Also excluded were those taking the following medications: antitumor chemotherapy, diuretics, beta blockers, antihypertensives, or antiarrhythmics. All participants had a normal resting electrocardiogram (ECG) and adequate hydration as measured by clinical criteria (skin turgor, mucous membranes). The population included both inpatients and outpatients.

After informed consent was obtained, data were collected on diagnosis, current and past treatment, and patient-rated symptom assessment. The symptoms included those known to be associated with autonomic neuropathy and those common in advanced cancer possibly due to ANS dysfunction. The symptom assessment was an empirically derived checklist. Each symptom present was rated as mild, moderate, or severe in intensity. The Eastern Cooperative Oncology Group Performance (ECOG) rating was used to assess performance status (a score of 0–4, with 0 indicating usually active and 4 indicating bed bound and needing hospitalization). A physical examination was performed to document hydration status, exclude peripheral neuropathy, and establish that peripheral reflexes were intact and there were no other focal neurologic deficits. Autonomic function was evaluated with the following tests [10].

### Parasympathetic function

1 Heart rate response: deep breathing (also known as: beat-to-beat variation in heart rate; normal value: >15 beats or more/min).
The patient sits quietly and then breathes deeply and evenly at 6 breaths/min. The maximum and minimum heart rates during each breathing cycle are measured on an ECG, and the mean of the difference during three successive breathing cycles is taken to give the maximum–minimum heart rate.
2. Heart rate response: standing (also known as the 30:15 ratio; normal value: 1.04 or over).
The patient lies quietly for 5 min and the resting heart rate is recorded using an ECG; the subject then stands up unaided. Normally an immediate increase in heart rate occurs, which is maximal at about the 15th beat after starting to stand, followed by a relative bradycardia, which is maximal around the 30th

**Table 3** Sequence for tests of autonomic function. Order in table is the order tests are performed. # corresponds to the test number in the text

| # | Test | Position | Time (min) | Apparatus |
|---|---|---|---|---|
| 3 | Heart rate Response: Valsalva Maneuver | Sitting | 5 | Aneroid manometer ECG machine |
| 1 | Heart rate Response: Deep Breathing | Sitting | 2 | ECG machine |
| 5 | Blood Pressure Response: Sustained Handgrip | Sitting | 5 | Handgrip dynamometer sphygmomanometer |
| 2 | Heart rate Response: Standing | Lying Standing | 3 | ECG machine |
| 4 | Blood pressure Response: Standing | Standing | 2 | Sphygmomanometer |

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.

3. Heart rate response: the Valsalva maneuver (normal value: 1.21 or more).
   The patient 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. The mean of three successive ratios is taken.

Sympathetic function

4. Blood pressure response: standing (normal value: drop of up to 10 mmHg in pressure).
   The blood pressure is measured according to the method recommended by the American Heart Association [23] after the patient has been lying at rest for 5 min and again 1 min after standing up. While the patient is standing the arm is extended horizontally, as the hydrostatic effect of the column of blood in the dependent arm may give a falsely elevated reading. The difference in systolic and diastolic blood pressures is taken as the measure of postural blood pressure change.
5. Blood pressure response: static exercise (sustained handgrip, normal value: increase by 16 mmHg or more).
   Handgrip is maintained at 30% of the maximum voluntary contraction using an adjustable handgrip dynamometer (Asimow Engineering Company, Los Angeles, Calif.) up to a maximum of 5 min, and the blood pressure measure each minute. The difference between the diastolic blood pressure just before release of handgrip, and just before starting, is taken as the measure of response of adrenergic activity.

The tests were performed in a previously suggested order (Table 3). Each test result was scored according to a validated scale [10] of 0, 0.5, or 1 (Table 4). The individual scores were added together and each patient received a dysfunction score based on previously established criteria: none (=0–1), mild (=1.5–2), moderate (=2.5–3) or severe (=3.5–5). A database was created using Paradox Relational Database 3.5 (Borland International, Scotts Valley, Calif.). Statistical analysis was performed using Solo Statistical System 2.0 (BMDP Statistical Software, Los Angeles, Calif.).

## Results

Fifty patients were entered: 28 men and 22 women. The median age was 64 years (range 48–72). The median ECOG performance status was 2 (range 0–3). There was a heterogeneous group of malignancies; lung and prostate cancer were the most common (*N*=9, 5). In all, 245 tests were performed; 86 (35%) individual tests gave normal or borderline results. Composite dysfunction scores were calculated, and based on this all the participants had a score consistent with abnormality (Tables 5, 6).

1. Heart rate response: deep breathing (normal 15 beats/min or more)
   All 50 were able to perform this test. Five were normal (15 beats/min or more) and 45 abnormal. The median result for the group was 9/min (range 7–20/min).
2. Heart rate response: standing (normal 1.04 or over)
   Forty-nine were able to perform this test. Nine had normal results (1.04 or over) and 40 abnormal. The median result for the group was 0.9 (range 0.8–1.05).
3. Heart rate response: the Valsalva maneuver (normal 1.21 or over)
   Forty-eightpatients were able to perform this test. Nine gave normal results (1.21 or higher), 9 borderline, and 30 abnormal. The median result for the group was 1.05 (range=1.0–1.21).

**Table 4** Scoring for tests of autonomic function

| Test | Normal = 0 | Borderline = 0.5 | Abnormal = 1 |
|---|---|---|---|
| Heart rate response | | | |
| Valsalva maneuver | 1.21 or more | – | 1.20 or less |
| Deep breathing | 15 Beats/min or more | 11–14 Beats/min | 10 Beats/min or less |
| Standing (30:15 ratio) | 1.04 or more | 1.01–1.03 | 1.00 or less |
| Blood pressure response | | | |
| Standing | 10 mmHg or more | 11–29 mmHg | 30 mmHg or less |
| Sustained handgrip | 16 mmHg or more | 11–15 mmHg | 10 mmHg or less |

**Table 5** Test results and dysfunction scores[a]

| Test | N | No. normal (=0) | No. borderline (=0.5) | No. abnormal (=1) |
|---|---|---|---|---|
| 1. Heart rate response: deep breathing | 50 | 5 | – | 45 |
| 2. Heart rate response: standing | 49 | 9 | 0 | 40 |
| 3. Heart rate response: the Valsalva maneuver | 48 | 9 | 9 | 30 |
| 4. Blood pressure response: standing | 50 | 46 | 2 | 2 |
| 5. Blood pressure response: static exercise | 48 | 2 | 2 | 44 |

[a] Each autonomic function test result was scored on a scale of 0, 0.5, or 1 as noted in Table 4. The individual scores of the five tests were added together, and each patient received a dusfunction score based on the folowing: none = 0–1, mild = 1.5–2, moderate = 2.5–3, severe = 3.5–5

**Table 6** Population dysfunction scores[a]

| Score | N |
|---|---|
| None | 0 |
| Mild | 9 |
| Moderate | 18 |
| Severe | 23 |

[a] *n* = number of patients in the total population with each dysfunction score

**Table 7** Number of patients reporting severe symptoms

| *n* | Symptom |
|---|---|
| 23 | Weight loss |
| 10 | Anorexia |
| 10 | Early satiety |
| 10 | Weakness |
| 8 | Nocturia |
| 5 | Taste change |
| 3 | Dysphagia |
| 3 | Constipation |
| 2 | Dry mouth |
| 1 | Shortness of breath |
| 0 | Blackouts, light-headedness, nausea, nasal stuffiness, incontinence of stool, incontinence of urine, decreased sweating |

4. Blood pressure response: standing (normal drop by10 mmHg or more)
   All 50 were able to perform this test. Forty-six were normal (blood pressure drop of 10 mmHg or less), 2 borderline and 2 abnormal. The median result for the group was 5 mmHg (range 0–32 mmHg).
5. Blood pressure response: static exercise (normal increase by 16 mmHg or more)
   Forty-six patients were able to perform this test. In 2 results were normal (blood pressure increase of 16 mmHg or more), in 2, borderline and in 42, abnormal. The median result for the group was 8 mmHg (range 0–18 mmHg).

### Symptoms

All symptoms from the checklist are listed in in Table 7 with their prevalence. The median number of symptoms was 6 (range 1–15). Twenty-eight rated at least one symptom as severe (median 2, range 0–5). The most common severe symptom was weight loss (Table 7). Symptoms did not correlate with test results.

## Discussion

The ANS is primarily an effector system controlling smooth muscle, heart muscle and exocrine glands. It has three major divisions: sympathetic, parasympathetic, and enteric. Anatomically, these differ in the position of the preganglionic neurons and the organization of the postganglionic neurons. Abnormality of the ANS was first postulated by Hill and Bernard in 1895. The first description of postural hypotension and accompanying symptoms was published by Bradbury and Eggleston in 1925 [3]. Since that time, many disorders associated with autonomic insufficiency have been defined.

The ANS of patients with advanced malignancy appears to be impaired. Thomas and Shields, in 1970, first reported evidence of autonomic dysfunction in carcinoma of the pancreas [24]. The literature now contains several reports of cancer-related autonomic insufficiency. Three studies have systematically evaluated autonomic function in cancer patients. Gould et al. did not report specific scores, but only compared means obtained in patients and in controls, so that no dysfunction scores are available from their study [11]. Bruera [5] and Martin [16] obtained slightly lower overall abnormality rates than we found in our study (52%, 50% versus 63%). Neither study calculated a dysfunction score, but both used the same tests as ours. Gould did not use the blood pressure response to static exercise used by others. This is important, as it is one of the tests that is not influenced by age [14].

Patients with advanced cancer have symptoms consistent with autonomic insufficiency. Much of the speculation regarding these symptoms originates in the observation of similar symptoms in diabetics with gastroparesis due to autonomic neuropathy. For further investigation of the ANS dysfunction, we have used five simple bedside examinations. There are at least 20 tests of ANS function, varying in their levels of simplicity and invasiveness. We chose these five tests because they have been validated and there is evidence that they represent widespread dysfunction when abnormal. Further, most patients are able to perform them correctly, and at least some (beat-to-beat variation in heart rate and blood pressure response to static exercise) are independent of age. However, when abnormal, they do not localize the lesion.

The results obtained in the present study reveal significant ANS dysfunction. Eighty-six of 245 tests were abnormal, and no one in our population had a dysfunction score compatible with normality. Test #2 (blood pressure response to sustained handgrip) was difficult for our participants: the weight of the dynamometer is significant and the lack of counterresistance confusing. Late in the study ($N$=41) we found a better test: a rolled, inflated blood pressure cuff works well and increases success in performance of the maneuver. However, for consistency, all results are based on the dynamometer. Test #3 was stressful for most, but they were able to manage. Tests #4 and 5 (heart rate and blood pressure response to rising) also presented some difficulty. After remaining in a supine position, the patients had problems in rising to a standing position without assistance. This stress may be reflected in test #5 results; it may be that so much work was required that the blood pressure rose significantly with the stress. We are suspicious of this result. It is interesting that even though most patients had results in this test that fell in the normal range, there were still no normal dysfunction scores.

We were surprised to find that neither symptoms nor performance status correlated with the test results. Perhaps a larger study would be needed to examine this issue, as most of our patients had abnormalities. It has been noted that there is no close correlation between symptoms and known ANS dysfunction in diabetics. Our choice of performance scale (ECOG) may not be sensitive enough to detect differences in advanced cancer. Also, our patients' age range is probably not wide enough to correlate with test scores. It is noteworthy that age is known to alter the function of the ANS; however, there is some inconsistency in the changes reported. Furthermore, age-related changes in autonomic function are similar to many other diseases in the elderly: there is no guarantee that aging alone will produce the abnormality. One study has shown that at least 2 of the tests are not influenced by aging [14]. Hence, it is suggested that abnormal tests of autonomic function be considered pathologic, rather than a function of age, until proven otherwise. It is difficult to implicate malignancy alone as the cause of autonomic dysfunction in our population, since the majority are also elderly. Our study, like others, showed no test differences between men and women. Because of the study design, we are unable to show current medications or previous treatments as contributing to the ANS abnormalities. It is noteworthy, however, that only 1 patient (dysfunction score, moderate) had a documented history of treatment with a vinca alkaloid (vincristine), a chemotherapeutic agent previously implicated in autonomic dysfunction [21].

Although these tests were difficult because of weakness, only 5 were not performed. We consider this battery of tests an excellent method for evaluation of the ANS in advanced cancer; they are well validated, noninvasive and inexpensive and can be completed quickly with little difficulty. There are other studies with healthy control groups matched for age, but none report being matched for performance status or symptomatology. Our assessment of ANS abnormality in advanced cancer is based on frequently seen symptoms [9] consistent with ANS dysfunction. For this reason, to match only for age may be misleading. There are more invasive tests that may give more accurate descriptions of ANS abnormalities in advanced cancer. These tests may help define the lesion better than these simple bedside tests. Other studies have evaluated gastric emptying in cancer patients as a proxy for autonomic dysfunction. Delay in gastric emptying (gastroparesis) is presumed to result from autonomic dysfunction. These studies suggest that gastroparesis is present and that correction of this with prokinetic agents may be therapeutically useful. None has demonstrated gastroparesis in the presence of proven autonomic dysfunction. The five tests we used provide a useful screening tool to preselect patients before a lengthy, expensive work-up. Further research with sophisticated ANS testing is needed for clear definition of this paraneoplastic syndrome.

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