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Heart rate variability as a measure of autonomic dysfunction in men with advanced cancer

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Abstract

Autonomic dysfunction is common in patients with cancer and may have considerable negative effects on quality of life and mortality. This study retrospectively compared heart rate variability measured by the standard deviation of normal-to-normal intervals (SDNN) to Ewing test score, a composite score from a battery of five defined autonomic tests, in detection of autonomic dysfunction in 47 men with advanced cancer. The Ewing test score has been validated for diagnosis of autonomic dysfunction but is time-consuming and requires considerable patient cooperation; we hypothesized that SDNN, a much simpler test, is a useful alternative. The patients were categorised into three groups according to Ewing score: 2 (mild or no autonomic dysfunction), 2.5–3 (moderate) and 3.5 (severe). The SDNN (mean $\pm$ SD) for the three groups were 57.1 $\pm$ 26.9 ms 62.3 $\pm$ 22.4 ms and 37.7 $\pm$ 20.3 ms, respectively. A significant negative correlation was found between Ewing score and SDNN ($r = -0.40$, $p = 0.005$). A SDNN of 40 ms had 63% sensitivity and 75% specificity in the diagnosis of severe autonomic dysfunction (i.e., Ewing score 3.5). The positive predictive value of SDNN 40 ms in predicting moderate/severe autonomic dysfunction was 89%.

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Keywords

autonomic dysfunction; palliative care; Ewing test; heart rate variability

INTRODUCTION

The autonomic nervous system innervates every organ in the body and is largely involuntary. Autonomic dysfunction occurs in primary neurologic disorders, diabetes mellitus, and chronic renal disease, as well as in cancer (England et al, 2009; Walsh and Nelson, 2002). Autonomic neuropathy has been shown to be a risk factor for falls in older adults with dementia (Allan et al, 2009). In diabetic patients, cardiac autonomic neuropathy is manifested as exercise intolerance, intraoperative cardiovascular liability, orthostatic hypotension, painless myocardial ischemia, and increased risk of mortality, thereby having a great impact on morbidity, mortality and quality of life. Although many cancer patients present with symptoms suggesting autonomic dysfunction, such as orthostasis, low blood pressure, gastroparesis, and constipation, autonomic dysfunction is underdiagnosed in this population because of a lack of adequate diagnostic tools. Autonomic dysfunction is often treatable, thus many cancer patients could benefit from accurate diagnosis and treatment.

The Ewing test score (range, 0–5) is considered a standard for diagnosis of autonomic dysfunction. The Ewing score is a composite of scores from a battery of five autonomic tests, each scored as normal (0 points), borderline (0.5 points), or positive (1 point). A patient's scores on the five tests are summed to arrive at the composite Ewing score. A Ewing score of 2.5 has been reported as the cut-off for diagnosis of moderate-to-severe autonomic dysfunction (Ewing and Clarke, 1986; Osterhues et al, 1998; Walsh and Nelson, 2002). The Ewing test battery is not performed routinely, however, because administering all five of the required tests is very time-consuming and requires considerable patient cooperation. Recently, heart rate variability (HRV) has been investigated as a surrogate for autonomic function and thus as a diagnostic tool for autonomic dysfunction.

For this study, we hypothesized that HRV is a useful test for autonomic dysfunction in patients with cancer. To test this, we retrospectively correlated HRV with the Ewing test scores of a group of patients with advanced cancer and determined the sensitivity and specificity of HRV for diagnosis of autonomic dysfunction in this patient population.

MATERIALS AND METHODS

Patients and Methods

The data used for this study, including Ewing test scores and HRV measurements, were obtained from participants who enrolled in our previous study of autonomic dysfunction and hypogonadism in men with advanced cancer (Strasser et al, 2006). All participants were recruited prospectively for that study from various outpatient services at The University of Texas MD Anderson Cancer Center. The study was approved by the Institutional Review Board (Protocol ID 01-643), and all patients signed a written consent form. The participants had not received chemotherapy or radiation therapy or undergone major surgery in the 2 weeks preceding the testing.

Ewing Test Score

The Ewing test score is a validated test for autonomic dysfunction. It comprises five autonomic tests (listed below), each test scored as normal (0 points), borderline (0.5 points) or abnormal (1 point). The scores on the individual tests were added together, and each

patient received a dysfunction score: none ($=0-1$), mild ($=1.5-2$), moderate ($=2.5-3$) or severe ($=3.5-5$) (Ewing and Clarke, 1986; Walsh and Nelson, 2002).

Ewing Tests

1. Heart rate response to deep breathing (also known as beat-to-beat variation in heart rate; normal value: >15 beats/min).
2. Heart rate response to standing (also known as the 30:15 ratio; normal value: 1.04).
3. Heart rate response to the Valsalva manoeuvre (normal value: 1.21).
4. Blood pressure response to standing (normal value: drop of 10 mmHg in pressure).
5. Blood pressure response to static exercise (sustained handgrip; normal value: increase by 16 mmHg).

Heart Rate Variability Measurement

All patients underwent electrocardiography (ECG) monitoring for 20 minutes by a three-channel ambulatory Holter monitor (Burdick Vision Holter Recorder, Cardiac Science, Bothell, Washington, USA). The digitised unfiltered ECG data were analysed using customised Vision Premier Software to obtain spectral components of HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Before analysis, the ECG signal was examined for artifact correction and rejection by following established procedures (Zhong et al, 2005). All data acquisition and post-acquisition analysis were carried out in accordance with established standards, including those put forth by the Task Force on HRV interpretation. Episodes containing ectopic runs were excluded. The standard deviation of all normal-to-normal intervals (SDNN) was measured in the time domain analysis of HRV. Spectral components for HRV analysis were expressed as absolute units (ms) (Malliani et al, 1991).

The Fisher exact test was used to assess the association between the categorised SDNN and Ewing scores; these categorisations were also used to calculate sensitivity, specificity and predictive values. Simple correlations were made for the continuous values of the SDNN and Ewing score using the Pearson correlation coefficient (or the Spearman correlation coefficient if the data were not approximately normally distributed). Analysis of variance or its nonparametric equivalent was used when there were more than two independent categories.

RESULTS

Forty-seven men with advanced cancer were included in this retrospective analysis. Their median age at time of testing was 59 years (range, 20–79). The participants' ethnicity distribution was 29 white (62%), 8 black (17%), 8 Hispanic (17%), and 2 other (4%). The two most common cancer sites were lung (27, 57%) and gastrointestinal (8, 17%), followed by sarcoma (4, 9%) and genitourinary (5, 11%). Six patients (13%) had diabetes mellitus and 2 (4%) had chronic heart failure. Twenty-eight patients (60%) had previously received at least one of the following chemotherapy agents: paclitaxel, docetaxel, cisplatin, oxaliplatin, vincristine, vinblastine, or vinorelbine.

Out of the 47 patients, 9/47 (19%) had Ewing test score <2 , indicating no AD or mild AD; 19/47 (40%) had Ewing test score 2.5–3.0 and 19/47 (40%) had >3.5 , indicating moderate AD and severe AD respectively. Table 1 shows the association between the SDNN and

Ewing test scores. An analysis of variance found that the SDNN of the group with severe autonomic dysfunction differed significantly from those of the groups with mild or moderate autonomic dysfunction ($p=0.005$). A significant negative correlation was found between Ewing test score and SDNN ($r=-0.40$, $p=0.005$). Table 2 indicates the number of patients in each category.

Using Ewing test score as a standard, the sensitivity of SDNN was calculated as $(\text{True Positive}) \div (\text{True Positive} + \text{False Negative})$; the specificity was calculated as $(\text{True Negative}) \div (\text{True Negative} + \text{False Positive})$; the positive predictive value was calculated as $(\text{True Positive}) \div (\text{True Positive} + \text{False Positive})$; the negative predictive value was calculated as $(\text{True Negative}) \div (\text{True Negative} + \text{False Negative})$. SDNN less than the cut-off of 40 ms had a sensitivity of 63% and a specificity of 75% in detecting severe autonomic dysfunction (Ewing score of ≥ 3.5) and a sensitivity of 45% and a specificity of 78% in detecting moderately severe autonomic dysfunction (Ewing score 2.5–3). The positive predictive value of SDNN ≥ 40 ms in predicting moderate/severe autonomic dysfunction was 89% (17/19). The negative predictive value of SDNN >40 ms in predicting mild autonomic dysfunction/normal was 25% (7/28).

DISCUSSION

There is an urgent need for an easy-to-use tool to diagnose autonomic dysfunction in cancer patient. This study demonstrated that heart rate variability can be a useful tool in identify autonomic dysfunction when compared to the Ewing tests.

Autonomic dysfunction affects about 80% of patients with advanced cancer (Bruera et al, 1986; Gould et al, 1986; Strasser et al, 2006; Walsh and Nelson, 2002). Autonomic dysfunction has been reported in patients with lymphoma, leukaemia and carcinomas of the lung, pancreas, prostate, breast, ovary, and testicle (Goldsmith and Farmer, 2000; Kamath et al, 1998; Mousa and Al-Din, 1985; Nelson et al, 2002; Nuver et al, 2005; Thomas and Shields, 1970).

The Ewing test has been used frequently as a standard for the diagnosis of autonomic dysfunction. Unfortunately, the Ewing test battery is time-consuming and requires significant patient cooperation. In a prospective study by Stone *et al.* (2012), 83 (45%) participants were unable to complete the Valsalva manoeuvre, demonstrating the poor feasibility of conducting autonomic function testing with the Ewing test battery in patients with advanced cancer.

HRV, however, can be recorded via a Holter monitor, which is easy to apply and requires less effort from the patient than the Ewing test battery (Kim et al, 2007). The HRV test is simple to perform, and SDNN indicates both the cardiovagal and sympathetic functions. Our results confirm that the SDNN measure in HRV has a good sensitivity (63%) and specificity (75%) in the detection of severe autonomic dysfunction. The positive predictive value of SDNN ≥ 40 ms in predicting moderate/severe autonomic dysfunction was very high, 89%. This indicates that 89% of patients with a positive test (i.e., SDNN ≥ 40 ms) were correctly diagnosed with moderate to severe autonomic dysfunction. Positive predictive value is the most important measure of a diagnostic method, as it estimates the probability that a positive test reflects the underlying condition being tested for. Our results indicate that the HRV method showed diagnostic value for autonomic dysfunction similar to that of the classic Ewing score, while its application proved to be shorter, less stressful for patients and less dependent on patient cooperation. Therefore, we are confident in stating that when a patient's SDNN value is ≥ 40 ms, he/she should be evaluated for autonomic dysfunction-associated symptoms. It should be pointed out that SDNN >40 ms was not a good indicator

for normal autonomic function. Further study is needed to compare patients with autonomic dysfunction to the normal control group to determine a HRV value that will be more sensitive in detecting early, mild autonomic dysfunction.

Many cancer patients suffer from autonomic dysfunction. They may present with symptoms such as postural hypotension; nausea, vomiting and early satiety related to gastroparesis; nocturnal diarrhoea; fatigue; bladder-emptying problems and male erectile dysfunction (Bruera et al, 1987; Chinn and Schuffler, 1988; Fagundes et al, 2011; Stone et al, 2012). The combination of fatigue, postural hypotension and poor appetite can severely affect cancer patients' physical functioning and psychological well-being. Early detection and treatment of autonomic dysfunction-related hypotension, for example, may result in improvement in fatigue caused by impaired organ perfusion. In a cross-sectional study of patients with vasovagal syncope diagnosed and treated on a single Falls and Syncope Service (n = 91), patients whose syncopal symptoms had responded to conventional treatment (pharmaceutical interventions such as fludrocortisone, midodrine or a selective serotonin reuptake inhibitor) reported less severe fatigue and daytime sleepiness than those with persistent syncopal symptoms (Legge et al, 2008). In a pilot study of 10 patients with chronic fatigue syndrome who had abnormal cardiovascular responses to a head-up tilt test, six had normalisation of cardiovascular responses and fatigue after treatment with midodrine (Naschitz et al, 2003).

Autonomic dysfunction is associated with increased mortality. In a meta-analysis of data from 2900 subjects, the relative risk of mortality for diabetic patients with cardiac autonomic neuropathy was 2.14 higher than for those without cardiac autonomic neuropathy (Howorka et al, 1998). Autonomic dysfunction is also associated with sudden death (Maser et al, 2003). A previous study showed that SDNN of 21.3 ms or less was associated with statistically significantly shorter survival duration in cancer patients (Vinik and Ziegler, 2007). The prognostic value of HRV warrants further study.

Since autonomic dysfunction is highly prevalent in patients with advanced cancer and is associated with multiple symptoms and shorter survival, it is important that autonomic dysfunction be studied in the cancer population. Specifically, prospective studies are necessary focusing on the relationship between autonomic dysfunction and fatigue, the potential for reversibility of autonomic dysfunction with pharmaceutical interventions and the impact of various interventions on fatigue and survival in patients with advanced cancer. Therefore, identifying and testing an easy-to-use diagnostic tool for autonomic dysfunction is crucial to furthering our knowledge and enhancing the delivery of multidisciplinary patient-centred care in cancer.

In conclusion, our study showed the HRV has good specificity and positive predictive value for the diagnosis of moderate/severe autonomic dysfunction and can be used as a reliable diagnostic method for moderate/severe autonomic dysfunction in cancer patients.

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Table 1

Association of SDNN and Ewing test score in patients with advanced cancer

Number of patients (n=47)	Ewing Score	Autonomic Dysfunction	SDNN (ms)
9 (19%)	2	No AD or Mild	57.1±26.9
19 (40%)	2.5–3.0	Moderate	62.3±22.4
19 (40%)	3.5	Severe	37.7±20.3 *

* Difference between this group and other groups statistically significant (p=0.005).

Table 2

Number of patients in each testing category

	Ewing score 3.5	Ewing score 2.5–3.0	Ewing score 2.0
SDNN ≤ 40 (ms ²)	12	5	2
SDNN >40 (ms ²)	7	14	7