

Original Article

The Association Between Autonomic Dysfunction and Survival in Male Patients with Advanced Cancer: A Preliminary Report

Nada Fadul, MD, Florian Strasser, MD, J. Lynn Palmer, PhD,
Syed Wamique Yusuf, MD, Ying Guo, MD, Zhijun Li, MS, Julio Allo, MPH,
and Eduardo Bruera, MD

Department of Palliative Care and Rehabilitation Medicine (N.F., J.L.P., Y.G., Z.L., J.A., E.B.), and Department of Cardiology (S.W.Y.), The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA; and Section of Oncology (F.S.), Department of Internal Medicine & Palliative Care Centre, Cantonal Hospital, St. Gallen, Switzerland

Abstract

Context. Autonomic nervous system dysfunction (AD) is a common syndrome in patients with advanced cancer. It is associated with decreased survival in several patient populations, including diabetes mellitus, heart failure, and neurological diseases. Based on this evidence, we hypothesized that autonomic dysfunction is associated with decreased survival in patients with advanced cancer.

Objectives. The objective of this preliminary study was to test the association between AD, as measured by the standardized Ewing test and heart rate variability (HRV) measures, and survival in this patient population.

Methods. We examined the relationship between survival and parameters of AD in subjects who participated in a prospective study of autonomic dysfunction and hypogonadism in male patients with advanced cancer. Eligibility criteria were defined based on the prospective study protocol. We collected demographic information, date of death (obtained from the online Social Security Death Index database), date of study entry, and Ewing and HRV scores. We defined survival as the interval between study entry and date of death. A survival analysis was used to test the association between survival (in days) and Ewing test (0–5) and measures of HRV, including time domain (standard deviation of normal to normal beat interval [SDNN]) and frequency domain (ultra low, very low, low, and high). Four patients were still alive at the time of this study and included in the survival analysis as being censored.

Results. Forty-seven male patients were included in this study. Median age was 59 years (range: 20–79), and 30 out of 47 (63%) were Caucasians. AD, defined as Ewing score greater than 2, was present in 38 out of 47 (80%) of the patients. Median Ewing score was 3 (1–5), indicating moderate to severe AD. Spearman correlation for Ewing score and SDNN was 0.44 ($P = 0.002$). There was

Address correspondence to: Nada Fadul, MD, Department of Palliative Care and Rehabilitation Medicine, Unit 008, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe

Boulevard, Houston, TX 77030, USA. E-mail: nfadul@mdanderson.org

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a significant association between abnormal Ewing score and survival ($P < 0.0001$) and abnormal SDNN HRV and survival ($P = 0.056$).

Conclusion. AD is associated with shorter survival in male patients with advanced cancer. Further longitudinal research in a large cohort is justified based on. *J Pain Symptom Manage* 2010;39:283–290. © 2010 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Autonomic dysfunction, survival, male, advanced cancer

Introduction

Prognostication is very important for patients with advanced cancer, especially when the likelihood of cure is limited. Several studies have shown that physicians and other health care professionals are not very accurate when they rely solely on clinical judgment to make their estimate of survival.^{1–3} There is a pressing need for objective prognostic indicators in patients with advanced cancer.⁴

Autonomic nervous system dysfunction (AD) is a major problem that affects about 80% of patients with advanced cancer.^{5–7} AD was first described in patients with bronchogenic carcinoma, but it also can occur in multiple other primary malignancies, including lymphoma, leukemia, and pancreatic, prostatic, breast, ovarian, and testicular carcinomas.^{5–14} AD is characterized by decreased cholinergic and/or noradrenergic output to the periphery. AD is a complex syndrome that can manifest as dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal, genitourinary, sudomotor, or ocular); can have peripheral or central origins; and can involve either one branch or both the sympathetic and parasympathetic branches of the autonomic nervous system. Cardiovascular autonomic dysfunction is recognized as a risk for increased mortality in the general population and several patient populations.^{15–17} Decreased heart rate variability (HRV), a marker of cardiovascular autonomic dysfunction,¹⁸ specifically has been shown to predict mortality in several populations. For example, in patients with diabetes and coronary artery disease, cardiovascular AD, as characterized by reduced HRV, has been associated with ventricular arrhythmias, silent myocardial infarction, and sudden and unexpected death.¹⁹

There also is vast evidence to support its significant negative impact on the morbidity and mortality of diabetics and other patient populations.^{16,20–24} For instance, AD has been shown to lead to multiple symptoms, such as fatigue, nausea, erectile dysfunction, and constipation;^{5–7,25} increased proinflammatory cytokines;²⁶ and increased risk of sudden death.²⁷

The clinical utility of the routine testing for AD in patients with advanced cancer is not yet clear. However, based on the evidence from other patient populations, it is hypothesized that AD can aid in the prognostication, decision making, communication, and symptom management of these patients. For instance, patients with advanced cancer who have AD can potentially benefit from discontinuation of certain drugs that can worsen AD, such as anticholinergics. These patients also can benefit from initiation of discussion regarding advance care planning and early involvement of palliative care services.

Kim et al.²⁸ conducted a recent study in 71 hospice patients in Korea. Sixty-two (87%) were dead at the time of study. On univariate and multivariate analyses, they found that decreased HRV, defined as standard deviation of normal to normal beat interval (SDNN) of 21.3 milliseconds or less or mean heart rate greater than 100, was associated with a statistically significant shorter length of survival. Unfortunately, this study was available only in an abstract format, therefore limiting the interpretation of the findings.

Based on the available evidence in cancer and noncancer patients, we hypothesized that AD is associated with reduced survival in patients with advanced cancer. The purpose of this study was to examine the associations

between AD and survival in male patients with advanced cancer who were enrolled in a previous prospective study.⁵

Patients and Methods

The data used for this study were obtained from participants who enrolled in a previous AD and hypogonadism study in male patients with advanced cancer.⁵ Participants who were eligible for this study were male patients with locally recurrent or metastatic cancer; 18 years of age or older; able to understand and complete questionnaires; and able to bear weight on both legs. Eligible patients could not have received chemotherapy, radiation therapy, or underwent major surgery in the preceding two weeks.

All patients underwent autonomic testing as per the standardized Ewing reflex autonomic battery and a 20-minute HRV recording. The Ewing test is a validated test for autonomic dysfunction. This test is generally regarded as the gold standard and is a widely used test for cardiovascular autonomic function. It has been used by our group and others to study AD in patients with advanced cancer.^{5,6} The Ewing test score (range 0–5) is composed of five autonomic tests, and each is scored as normal (0 points), borderline (0.5 points), or abnormal (1 point); greater than 2 is reported as the cutoff score to diagnose moderate to severe autonomic dysfunction.^{24,29} The Ewing test battery comprises the following five tests:

Parasympathetic function

1. Heart rate response to deep breathing (also known as beat-to-beat variation in heart rate; normal value > 15 beats/minute).
2. Heart rate response to standing (also known as the 30:15 ratio; normal value: 1.04 or more).
3. Heart rate response to the Valsalva maneuver (normal value: 1.21 or more).

Sympathetic function

4. Blood pressure response to standing (normal value: drop of up to 10 mm Hg in pressure).
5. Blood pressure response to static exercise (sustained handgrip, normal value: increase by 16 mm Hg or more).

All patients underwent a three-channel, 20-minute Holter ambulatory electrocardiogram (ECG) monitoring by using the Burdick Vision Holter Recorder (Cardiac Science, Bothell, WA). The digitized unfiltered ECG was analyzed using customized Vision Premier software to obtain spectral components of HRV.³⁰ Before analysis, the ECG signal was examined for artifact correction and rejection following established procedures.³¹ All data acquisition and postacquisition analyses were carried out in accordance with established standards, including those put forth by the task force on HRV interpretation.³⁰ Episodes containing ectopic runs were also excluded. The SDNN in milliseconds was measured in the time domain analysis of HRV. The power in very-low-frequency (<0.04 Hz), low-frequency (0.04–0.15 Hz), and high-frequency (>0.15–0.40 Hz) ranges was measured in the frequency domain analysis of HRV. Spectral components for HRV analysis were expressed as absolute units of squared milliseconds (millisecond²).³²

We collected demographics, including age, race, ethnicity, cancer type, and the date of study entry. Date of death was obtained from the online, freely accessible Social Security Death Index database. For the purpose of this study, we defined survival as the interval (in days) between date of study entry and date of death.

Statistical Considerations

Descriptive statistics were used to summarize demographic and clinical variables. We determined the association between AD (categorized as present or absent as measured by the Ewing test and HRV) and survival (in days) using survival analyses. We did not expect to find censored values for survival; hence, initially, we were only planning to measure these associations using Spearman correlation coefficients. We found that four patients were still alive at the time of analysis; their last known values for length of survival were used in the correlation analyses. In the survival analysis, information about patients who died and those who were still alive is included in the analysis. Patients still alive contributed the amount of time they have been alive without dying and were analyzed as being “censored” (i.e., have not yet died).³³ We performed a Spearman correlation analysis to test whether there was

an association between the degree of severity of AD, as measured by the Ewing score, and the SDNN HRV value and survival. Associations between other endpoints were also analyzed using Spearman correlation coefficients.

We powered the study expecting information from approximately 50 patients. We expected to be able to declare as statistically significant any correlation coefficients that were at least 0.39 or greater (or -0.39 or less), assuming a two-sided significance level of 0.05 and 80% power.

Results

Forty-seven male patients with advanced cancer were included in this study. The two most common cancer types were lung cancer (27 of 47 [57%]) and gastrointestinal cancer (8 of 47 [17%]). Median (range) age was 59 years (20–79), and there were 30 of 47 (63%) Caucasians. Six patients (12%) had diabetes mellitus and two (4%) had chronic heart failure.

Median (range) survival was 139 (4–2,266) days. Median (range) Ewing score was 3 (1–5), indicating moderate to severe AD. Table 1 shows the mean (standard deviation [SD]) and median (range) of Ewing test and HRV indices.

Figure 1 illustrates the association between survival and measures of AD, as tested by using survival analysis. There was a statistically significant association between survival duration in days and presence of AD, as measured by the Ewing test score ($P < 0.0001$). Figure 2 shows a Kaplan-Meier survival curve in patients with and without AD, as measured by the Ewing test (AD present if Ewing score is ≥ 2). There was also a trend toward a significant association between survival in days and the time domain measure of HRV SDNN ($P = 0.056$).

Table 1
Ewing and Heart Rate Variability Test Results
($n = 47$)

Variable	Mean (SD)	Median (Range)
Ewing score (0–5)	3.1 (0.97)	3 (1–5)
SDNN (ms)	51.4 (24.83)	46 (7–125)
High-frequency power (millisecond ²)	477.8 (321.99)	401 (64–1363)
Very-low-frequency power (millisecond ²)	304 (166.96)	271 (45–787)
Low-frequency power (millisecond ²)	356.4 (228.39)	288 (47–997)

There was no significant association between survival and frequency domain measures, including high-frequency power, which is associated with parasympathetic function ($P = 0.12$) and low ($P = 0.73$) and very-low-frequency ($P = 0.23$) powers, which are associated with sympathetic function.

In addition, we used correlation coefficients to test the association between the degree of severity of AD (Ewing and SDNN HRV numerical scores) and survival. Spearman correlation coefficients between Ewing scores and survival and between SDNN HRV and survival were $r = -0.27$ ($P = 0.06$) and $r = 0.24$ ($P = 0.1$), respectively.

We found a statistically significant association between the Ewing test and the time domain measure SDNN, where $r = -0.44$ ($P = 0.002$), and between the Ewing test and the frequency domain measures ultra low and very-low-frequency power, with $r = -0.37$ ($P = 0.009$) and $r = -0.32$ ($P = 0.03$), respectively.

Discussion

In this preliminary study, we found a significant association between AD, as measured by the Ewing test and HRV measures, and survival in male patients with advanced cancer. These results suggest an important role for AD in the mortality of these patients. Our findings agree with previous research in other patient populations that found AD to be a predictor of increased mortality and risk of sudden death. For instance, in patients with Type 2 diabetes mellitus and diabetic nephropathy, abnormal HRV was associated with fatal and nonfatal cardiovascular disease after adjustment for cardiovascular risk factors. The adjusted hazard ratio for death in a patient with abnormal HRV was 6.4 (1.5–26.3, $P = 0.010$) as compared with a normal HRV. In the general population, reduced HRV also was found to be a predictor for cardiovascular risk factors and increased mortality.^{17,34}

Despite the high incidence of AD in patients with advanced cancer, there is a relative paucity of evidence on its role in the morbidity and mortality of these patients. Our preliminary findings agree with the report by Kim et al.,²⁸ reporting a strong association between

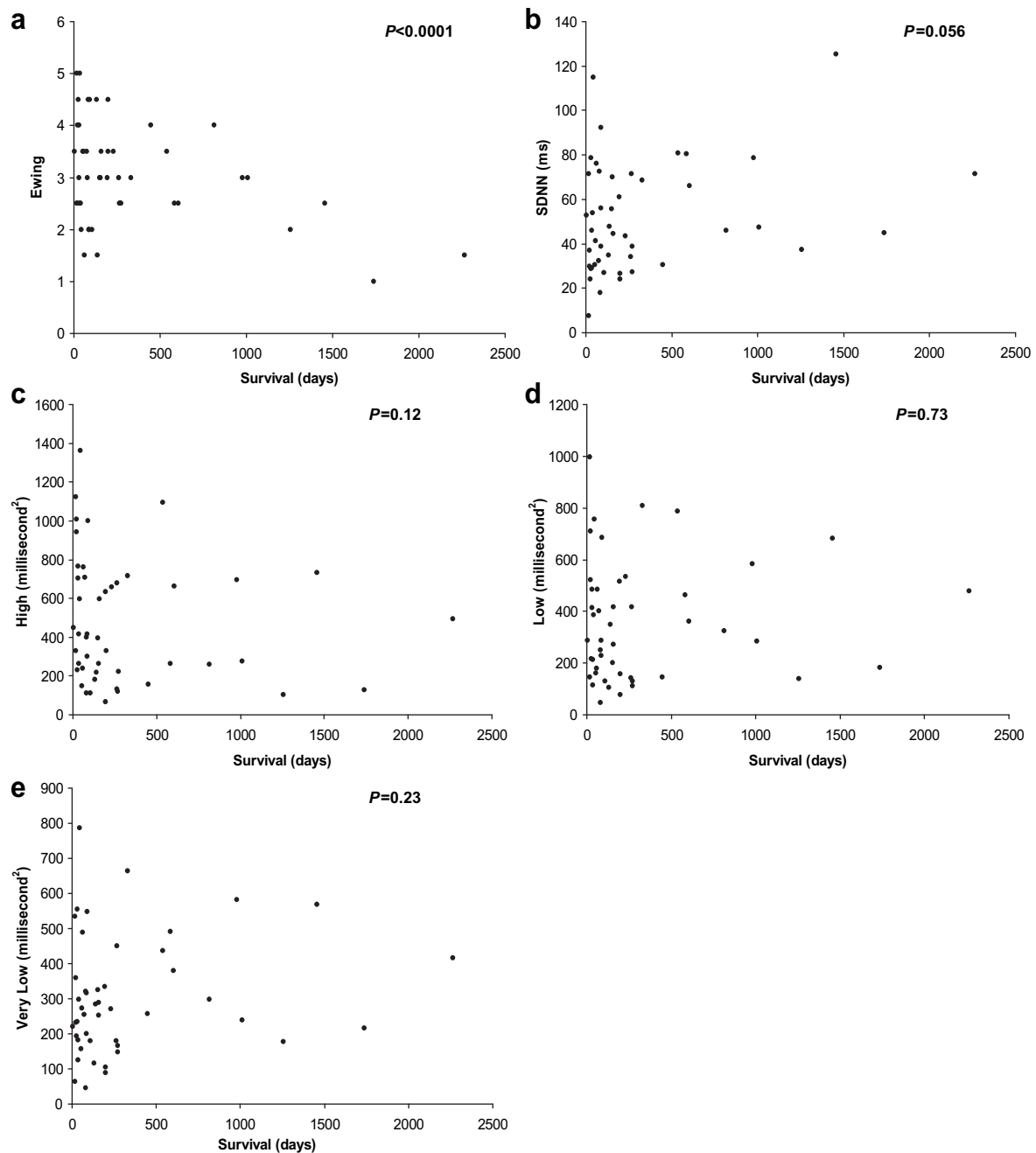


Fig. 1. Survival associations of Ewing and heart rate variability tests. a) Ewing = Ewing autonomic test (0–5); b) SDNN = standard deviation of normal to normal beat interval in milliseconds; c) high = high-frequency power in millisecond² (measure of parasympathetic function); d) low = low-frequency power in millisecond² (measure of sympathetic function); e) very low = very-low-frequency power in millisecond² (measure of sympathetic function).

reduced HRV and survival in hospice patients in Korea.

We observed a strong association between the time domain measure SDNN and survival, but no association between the frequency domain measures very-low-frequency, low-

frequency, and high-frequency power and survival. These findings could be attributed to the fact that, in short-term recordings, SDNN is mathematically equal to the total power of the spectral analysis. Therefore, SDNN reflects overall HRV, including its long- and short-

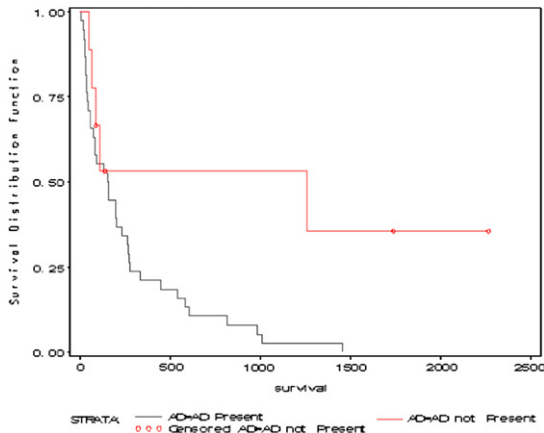


Fig. 2. Kaplan-Meier curve for survival in patients with and without autonomic dysfunction (AD). AD is present if Ewing score is >2 .

term components responsible for variability in the period of recording, and is unlike HF and LF power, which represent the limited variance in the high-frequency band and the low-frequency band, respectively.

We found a strong association between Ewing test and the time domain measure SDNN, and the frequency domain measures ultra low and very low power. These results support the use of HRV analysis to study the syndrome of AD in patients with advanced cancer. HRV is an easy, noninvasive, bedside technique that can potentially replace the more complex autonomic reflex techniques applied by the Ewing test.

Our study did not directly examine the exact mechanism of death in patients with AD. Previous research has shown that AD can lead to sudden cardiopulmonary arrest as a result of circulatory and baroreflex failure or ventricular arrhythmias.^{35–37} Recent evidence has linked cardiovascular AD with corrected QT interval (QTc) prolongation, suggesting that increased susceptibility to ventricular arrhythmias and torsade de pointes is a potential mechanism.³⁸ Another possible mechanism is through the increased risk of inflammation and subsequent cardiovascular risk, as evidenced by increased C-reactive protein, TNF- α , and IL-6 in subjects with AD.^{27,39–42} However, an alternative explanation is that the association between AD and survival does not infer a direct cause and effect relationship. Because depressed HRV is regarded as

a marker for severe illness in other chronic conditions, it is possible that patients with AD are generally sicker than those without AD and, therefore, have reduced survival. Whether AD is a direct cause of reduced survival or just merely a coexisting condition reflecting the severity of illness in advanced cancer patients needs to be further investigated. However, regardless of the mechanism of the association between AD and survival, our results suggest that AD, as measured by cardiovascular reflex test and HRV, can be an important prognostic indicator in patients with advanced cancer.

Our study has some limitations, including the small sample size and inclusion of only male patients with advanced cancer, which adds a further limitation to the interpretation and generalization of the findings. In addition, the unbalanced distribution of patients (38 with AD and only nine without AD) could have had an impact of the findings of the study, particularly because of the low frequency of patients without AD.

Our preliminary findings, however, provide the basis for larger, more inclusive future longitudinal studies to better define the possible interaction between AD and survival in patients with advanced cancer. Such studies are needed to formulate clinical guidelines in the application of autonomic testing and the impact of AD in the care of these patients.

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