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Prognostic Value of Heart Rate Variability in Patients with Cancer

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Abstract

Introduction—Previous studies have shown that autonomic dysfunction is associated with shorter survival in patients with advanced cancer. We examined the association between heart rate variability (HRV), a measure of autonomic function, and survival in a large cohort of cancer patients.

Methods—We retrospectively examined the records of 651 cancer patients who had undergone ambulatory electrocardiogram (ECG) monitoring for 20–24 hours. Time domain HRV (standard deviation of normal-to-normal beat interval [SDNN]) was calculated using power spectral analysis. Survival data was compared between patients with SDNN ≥70 ms (Group 1, n = 520) and SDNN <70 ms (Group 2, n = 131).

Results—Two groups were similar in most variables, except group 2 patients had a significantly higher percentage of male patients (P=0.03), hematological malignancies (P=0.04), and use of non–selective serotonin reuptake inhibitor antidepressants (P=0.04). Patients in group 2 had a significantly shorter survival rate (25% patients in group 2 died by 18.7 weeks vs. 78.9 weeks in group 1; P <.0001). Multivariate analysis showed that SDNN<70 ms remained significant for survival (Hazard Ratio1.9, 95% Confidence Interval 1.4–2.5) independent of age, cancer stage and performance status.

Conclusion—The presence of cancer in combination with decreased heart rate variability (SDNN<70ms) is associated with shorter survival time.

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Keywords

Heart rate variability; cancer; autonomic dysfunction; survival; prognosis

Appropriate survival estimation is important in patients with cancer, especially when the likelihood of cure is limited. However, health care providers, when relying solely on clinical judgment, are frequently inaccurate at this estimation (Chen YT et al. 2014, Glare PA and Sinclair CT 2008, Chow E et al. 2001, Hui D et al. 2010). Hence better clinical tools are needed to provide more accurate survival estimates, facilitate clinical decision making, or arrange for end-of-life care.

Autonomic dysfunction (AD) affects about 80% of patients with advanced cancer (Hui D et al, 2011, Strasser F et al 2006,Walsh D and Nelson KA 2002) can be a result of cancer or its treatment (Bruera E et al 1986, Goldsmith DJ and Farmer CK 2000, Nelson K et al. 2002). In cancer patients, AD negatively impacts disease progression (Nuver et al. 2005, Mouton C et al. 2012) and survival (Fadul N et al. 2010). In recent years, heart rate variability (HRV) has been used to assess the autonomic nervous system (Chiang JK et al. 2010, Eckberg DL 1997). Reduced HRV predicts mortality in patients with myocardial infarction, DM, heart failure, renal failure, and even sudden death in apparently healthy individuals (Task force of European Society of Cardiology and North American Society of Pacing and Electrophysiology 1996, Frenneaux MP 2004, Laederach-Hofmann K et al. 2004, Molgaard H et al. 1991, Bilchick KC et al. 2002, Fukuta H et al. 2003).

Our hypothesis is that AD measured with HRV is associated with poor survival prognosis in patients with cancer. To investigate this hypothesis, we utilized ambulatory electrocardiogram (ECG) monitoring data to explore the pattern of autonomic dysfunction and its association with survival.

METHODS

Patients and Study Design

This retrospective study was approved by the Institutional Review Board. The study population was derived from a cohort of 740 consecutive patients who had undergone ambulatory ECG monitoring for 20–24 hours with a Holter monitor (Quinton Cardiology, Bothell, WA) between January 10th, 2008 and July 28th, 2011. We excluded patients who did not have a cancer diagnosis (n = 22), were younger than 18 years old (n = 6), had arrhythmia (which precluded HRV analysis; n = 18), or had a recording shorter than 20 hours (n =12). Among the patients who had multiple recordings, only the first recording was used for this study; 31 Holter monitor recordings were excluded due to multiple recordings. Thus, a total 651 Holter recordings were used for final analysis.

Patient medical records were reviewed for age, gender, ethnicity, weight, height, left ventricle ejection fraction (LVEF) from an echocardiogram within a year, smoking history, tumor type, metastasis, medical history, and medications recorded within 1 month of the monitoring. Body mass index (BMI) [weight (kg)/height (m^2)] was calculated. Information on survival time (the interval between the Holter monitor recording date and date of death)

was also collected; data from patients still alive at the time of our analysis were included in the survival analysis as censored data.

Autonomic Nervous System Activity Analysis

For each patient, 20–24 hours of digitized unfiltered ECG recordings was analyzed using power spectral analysis with customized Vision Premier 5 software (Cardiac Science Corporation 3003 Monte Villa Parkway, Bothell WA 98021). The ECG signals were first edited to exclude ectopic and artifactual signals (Bauer A et al. 2006). Recordings were eligible for time-domain analyses if at least 50% or more of data presented N-N interbeat intervals. Spectral analysis of HRV was performed according to standard methods with Vision Premier 5 software (Cardiac Science Corporation 3003 Monte Villa Parkway, Bothell WA 98021). The following time domain indexes were calculated: standard deviation of all normal-to-normal (NN) intervals (SDNN), standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), and number of successive NN intervals differing more than 50 ms divided by the total number of all NN intervals (pNN50). RMSSD and pNN50 reflect parasympathetic function of HRV alterations in autonomic tone (Task force of European Society of Cardiology and North American Society of Pacing and Electrophysiology 1996). According to the previously established normal value for HRV, a SDNN value of <70 ms falls outside 84% of the normal distribution for an individual older than 60, and outside of 97.5% for those younger than 60 (Umetani K et al. 1998). We therefore chose to divide patients into group 1 (SDNN ≥70 ms; n = 520) and group 2 (SDNN <70 ms; n = 131).

Statistical Analysis

Values are reported as means ± standard deviations or as numbers and percentages. Wilcoxon two-sample test was used for comparing age and Wilcoxon rank sum test for comparing BMI, EF and all parameters of HRV. Fisher's exact test was used for comparing brain metastasis, past medical history of angina, and using alpha agonist. The logrank test was used to compare the survival distributions. The rest of the variables were compared using Chi-Square test. We conducted a time-to-event analysis of overall survival from the day of ECG recording using the Kaplan Meier method and log rank test. We entered age, sex, ethnicity, cancer type, cancer stage (no evidence of disease, localized, advanced), performance status (0–2 vs. 3–4) and SDNN (<70 ms vs. ≥70 ms) in a multivariate Cox-regression analysis with backward selection. All tests were two tailed at a 5% level of significance. A P value <0.05 was considered statistically significant. SAS version 9.1 software (SAS Institute Cary, NC, USA) was used for statistical analysis.

RESULTS

The median age of the cohort was 60 years (range: 20–79 years), of which 72 % (475/651) were white. Most variables are not significantly different between the two groups, except group 2 (SDNN <70 ms) had significantly higher percentage of male patients (P=0.03), higher rate of patients with a diagnosis of hematological malignancy (P=0.04), and higher

rate of patients using non–selective serotonin reuptake inhibitor antidepressants (P=0.04) (Table 1).

We compared the two groups on other HRV indexes. Patients in group 2 exhibited significantly lower parasympathic function, which were represented by the mean rMSSD and pNN50 values (P<0.0001 for both, Table 2).

Patients in group 2 had a significantly lower survival rate than did patients in group 1 (25% group 2 patients died by 18.7 weeks vs. 78.8 weeks for group 1, P<.0001) (Fig. 1). The median survival time was 88 weeks for group 2 and group 1 had not reached 50% death, therefore median survival time could not be calculated for this group of patients. In the univariate analysis, we found SDNN<70ms, age, advanced cancer, and poor performance status significantly predict poor survival. The multivariate analysis revealed that SDNN<70ms, age, advanced cancer, and poor performance status were independent negative prognosticators for survival (Table 3).

DISCUSSION

The result of the present study shows a direct association between a time-domain measure of HRV (specifically, SDNN) and survival rate in a large patient population across all cancer types, supporting the hypothesis that survival in patients with cancer is closely associated with HRV. In recent years, HRV has been used to assess the autonomic nervous system (Chiang JK et al. 2010 and Eckberg DL 1997), and was considered highly specific (England JD et al. 2009). HRV correlates well with established cardiovascular reflex tests, like Ewing's test batteries (Guo Y et al. 2013). Ewing's test batteries are established method with good sensitivity, specificity, reproducibility and are noninvasive, safe, and well-standardized (American Academy of Neurology. 1996). However, it is time-consuming and difficult to administer (Stone CA et al. 2012); hence not frequently used. Several small studies have shown that low HRV is significantly associated with decreased survival among patients with various types and stages of cancer (Wang YM et al 2013,Giese-Davis J 2015, Kim do H et al. 2010, Hoffman J et al. 2001), one study (Fadul N et al. 2010) showed a trend of association (p=0.056). However, the sample size in those studies was relatively small, and the recording time for HRV used in most of these studies was less than 10 minutes. These short HRV recordings (<15 minutes) can be easily influenced by time of day, activity level, posture, respiratory rate and other factors, and such short recordings require strict control of recording conditions. The present study used longer term recording (20–24 hours) which provides more realistic results, because it included HRV with various activities, such as physiologically enhanced parasympathetic flow during sleep and enhanced sympathetic flow during daily activities (Kleiger RE et al. 2005 and Malik M 1999). The 24-hour recording has been shown to reflect a patient's overall degree of physical condition rather than the type of activity one performed (Lazoglu AH et al. 1996). HRV is well reproducible within subjects, and has been considered useful in assessing autonomic function (Malik M 1999 and Huikuri HV et al. 1990). The using 24 hour HRV measurement to predict prognosis can be time consuming. Future study is needed to assess the reliability and validity of short time recording, and its correlation with the long time recording, and hopefully can be used in clinical setting.

Antidepressants can decrease vagal tone (Licht CM et al. 2010), their use has been associated with an increased risk of sudden cardiac death (Krantz DS 2009). Using anti-depressants did not demonstrate as an independent risk factor in this study using regression analysis. Generally, females have higher HRV than males do, but the difference in mean SDNN between gender has been reported to be <10 ms for persons over 30 years old (Umetani K et al. 1998).

In the present study, we found that patients in group 2 (SDNN <70 ms) had significantly lower mean pNN50 and RMSSD values than did those in group 1 (SDNN ≥ 70 ms) (Table 2). SDNN index reflects both sympathetic and parasympathetic activity, while the rMSSD and pNN50 indexes represent parasympathetic function mediated by the vagus nerve (Eckberg DL et al. 1997 and Zulfiqar U et al. 2010). In a previous study with the healthy individual, longevity is associated with preserved parasympathetic function (Zulfiqar U et al. 2010).

Although low HRV has been shown to be associated with shorter survival in present study, it can potentially be reversed. HRV has been shown to increase with acupuncture, meditation, diet and exercise in non-cancer populations (Section of Geriatric Medicine 2011, Lee JH et al. 2011, Nolan RP et al. 2008) and cancer population (Munk PS et al. 2010 and Niederer D 2013). Future studies are needed to study whether interventions that enhance HRV can improve cancer patient survival.

Study Limitations and Strengths

This study is limited by its retrospective nature. However, the cohort size was large, each subject had robust 20–24 hours of recorded monitoring data, and analysis included potential confounders. We expanded on previous studies of HRV as a predictor for survival highlighted the importance of assessing autonomic function using HRV in cancer patients.

Future studies need to address whether cancer disease progression, cancer treatment, patient mood (depression and anxiety) is associated with HRV, and assess whether interventions that improve autonomic function, especially parasympathetic activity would affect cancer survival and AD symptoms in cancer patients.

The presence of cancer in combination with decreased heart rate variability is associated with shorter survival rate. The finding of our study is clinically relevant, as HRV is a simple tool for measuring AD and is important for prognosis.

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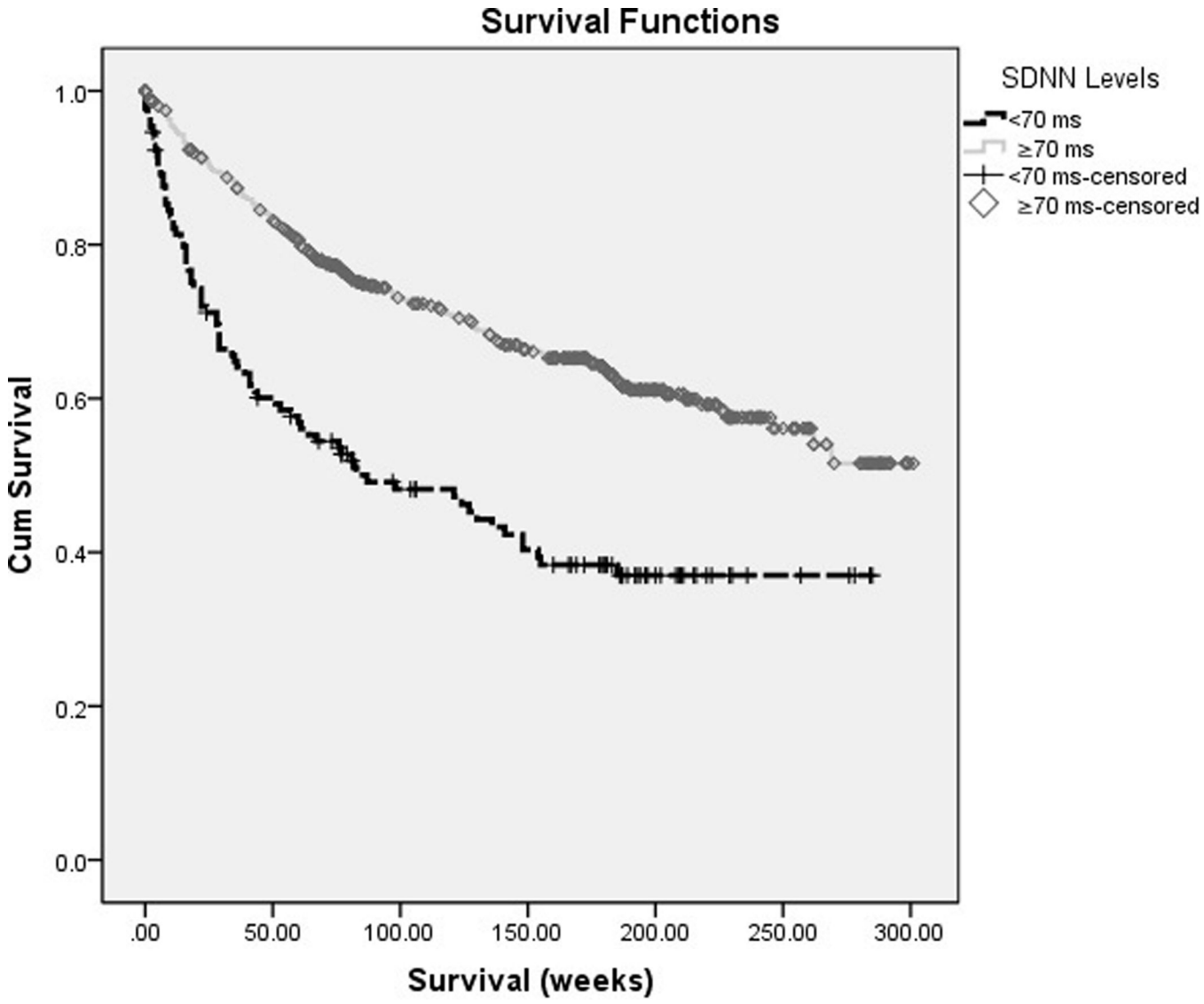

Figure 1.
Kaplan-Meier Survival Curves for Patients with SDNN<70ms and those with SDNN ≥70ms

Table 1

Patients Characteristics

	Group 1 (n= 520) SDNN≥ 70ms	Group 2 (n= 131) SDNN<70ms	*P* value
Mean Age ± SD	61±16	59±15	NS*
Male (%)	236(45%)	73 (56%)	0.03
Ethnicity (%)			
Africa American	67(13%)	19(15%)	
Hispanic	49(9%)	8(6%)	
Asian	19(4%)	7(5%)	
White	380(73%)	94(72%)	
Other	5(1%)	2(1%)	NS
Smoking history (%)			
No	259(50%)	67(51%)	
Yes, quit >1 year ago	201(39%)	48(37%)	
Yes, current smoker or quit <1 year ago	59(11 %)	16(12%)	NS
Tumor (%)			
Solid Tumor	378(73%)	83(63%)	
Hematological	142(27%)	48(37%)	0.04
Advance disease(%)	275(53%)	79(60%)	NS
Bone metastasis	32(6%)	11(8%)	NS
Brain metastasis	15(3%)	4(3%)	NS§
Visceral metastasis	54(10%)	18(14%)	NS
Past Medical History (%)			
Hypertension	297(57%)	68 (52%)	NS
Diabetes	87(17%)	23(18%)	NS
Hyperlipidemia	175(34%)	38(29%)	NS
Coronary artery disease	61(12%)	20(15%)	NS
Myocardial Infarction	18(3%)	9(7%)	NS
Angina	7(1%)	1(1%)	NS §
Depression	70(14%)	19(15%)	NS
Medication (%)			
Antiarrhythmic agent	35(7%)	12(9%)	NS
Alpha Agonist	8(2%)	3(2%)	NS §
Diuretic	124(24%)	39(30%)	NS
Beta blocker	185(36%)	48(37%)	NS
CalciumChannel blocker	88(17%)	17(13%)	NS
Vasodilator	24(5%)	9(7%)	NS

	Group 1 (n= 520) SDNN≥ 70ms	**Group 2 (n= 131) SDNN<70ms**	***P* value**
Antilipemic agent	143(28%)	32(24%)	NS
ACE inhibitor	166(32%)	41(31%)	NS
SSRI	45(9%)	13(10%)	NS
Other Anti-depressant	21(4%)	11(8%)	0.04
BMI (Mean ± SD)	27±16	26±14	NS **
EF within 6 months (Mean ± SD)	60±20	55±20	NS **

SSRI: selective serotonin reuptake inhibitor; ACE: angiotensin-converting-enzyme; NS: not significant; BMI: body mass index; EF: Ejection Fraction; Advance disease: cancer that has advanced locally or has metastasis;

*Wilcoxon 2-sample test;

**Wilcoxon Rank Sum Tests;

§Fisher's Exact Test;

Table 2

Comparison of HRV in the Two Groups

	Group 1 (n=520) (SDNN>=70ms)	**Group 2 (n=131) (SDNN<70ms)**	***p* value**
SDNN	127±47	57±11	<0.0001**
SDANN	104±40	48±10	<0.0001**
rMSSD	56±47	26±13	<0.0001**
pNN-50	14±20	2±3	<0.0001**

SDNN = standard deviation of all NN intervals; SDANN = standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; rMSSD = square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50 = NN50 count divided by the total number of all NN intervals; HRV = heart rate variability;

** Wilcoxon Rank Sum Tests

Table 3

Multivariate Cox Regression Analysis

Variable	Hazard ratio	95% CI	*P*-value
SDNN <70	1.9	1.4–2.5	<0.001
Age (per year increase)	1.02	1.01–1.03	<0.001
Cancer stage			<0.001
No evidence of disease	0.1	0.1–0.2	<0.001
Localized cancer	0.5	0.3–0.6	<0.001
Advanced cancer	1.0	Ref	Ref
ECOG Performance status 0–2	0.4	0.3-0.5	<0.001

SDNN = standard deviation of all NN intervals; ECOG: Eastern Cooperative Oncology Group