ORIGINAL ARTICLE
Oncology & Hematology

JKMS

DOI: 10.3346/jkms.2010.25.8.1140 • J Korean Med Sci 2010; 25: 1140-1145

Heart Rate Variability and Length of Survival in Hospice Cancer Patients

Do Hoon Kim[1], Jeong A Kim[1], Youn Seon Choi[1], Su Hyun Kim[1], June Young Lee[2], and Young Eun Kim[2]

Departments of Family Medicine[1] and Biostatistics[2], Korea University College of Medicine, Seoul, Korea

Received: 2 November 2009
Accepted: 19 January 2010

Address for Correspondence:
Youn Seon Choi, M.D.
Department of Family Medicine, Korea University Guro Hospital, 97 Guro-dong gil, Guro-gu, Seoul 152-703, Korea
Tel: +82.2-2626-3275, Fax: +82.2-837-0613
E-mail: younseon@korea.ac.kr

This work was supported by a Korea University Grant (#K0618221).

We examined the association between heart rate variability (HRV) and survival duration to evaluate the usefulness of HRV as a prognostic factor for hospice cancer patients. In terminally ill cancer patients who visited the Hospice clinic, we checked demographic data, Karnofsky performance scale (KPS), HRV, dyspnea, anorexia, as well as fasting blood glucose and total cholesterol. After following up their duration of survival, we examined meaningful prognostic factors for predicting life expectancy through the survival analysis. A total of 68 patients were included in final analysis. As KPS was lower, or when combined with dyspnea or anorexia, the survival duration was much shorter. HRV parameters except heart rate were all impaired in most patients. In particular, the group with mean heart rate of 100 or more beats per minute and the group with standard deviations of normal-to-normal R-R intervals (SDNN) of 21.3 ms (75 percentile) or less showed significantly shorter survival duration. The final multivariate analysis adjusting for age, gender, fasting blood glucose, and total cholesterol showed that KPS, dyspnea, anorexia, and SDNN were significant prognostic factors in survival duration. For the first time, we report that SDNN is a prognostic factor in terminal cancer patients.

Key Words: Terminal Care; Life Expectancy; Prognosis; Heart Rate Variability

INTRODUCTION

Cancer incidence rates and the number of cancer-related deaths continue to increase despite medical developments. In Korea, the number of deaths due to cancer went up from 51,449 in 1998 to 68,912 in 2008, and cancer has now become the leading cause of death in Korea (1). In particular, a high level of in-hospital mortality among terminal cancer patients is raising ethical issues as many patients die alone in hospitals, surrounded by medical equipment instead of family and friends, and the financial burden associated with increasing medical costs (2). Thus, more countries are adopting hospice and palliative care programs, and hospice services are being globally recognized as a means of improving quality of life and of reducing medical costs in terminal cancer patients (3-5). However, despite the advantages of hospice care, decision-making concerning eligibility for hospice care is problematic. In general, patients with less than six months to live with an underlying incurable disease are considered eligible for hospice care. However, in reality, as previous studies have reported, many predictions made by medical practitioners concerning time to death tend to be optimistic in terminal cancer patients (6, 7). As a result, many patients are not offered hospice care in a timely manner (8). Accordingly, the issue of accurately determining life span in terminal cancer patients is of great concern to patients, their caregivers, doctors, and policymakers.

Heart rate variability (HRV) is used in clinical research because fetal distress is preceded by alterations in the R-R interval. HRV reflects autonomic neuropathy in diabetic patients and predicts mortality in myocardial infarction patients (9-11). HRV also predicts mortality in cases of heart failure, cardiomyopathy, and renal failure; and HRV also predicts sudden death and cardiac death in apparently healthy individuals (12-16). Autonomic dysfunction is commonly associated with terminally ill cancer patients (17). Accordingly, we studied the relationship between HRV and survival duration to evaluate the usefulness of HRV as a prognostic factor for terminally ill cancer patients.

MATERIALS AND METHODS

Patients

Recruitment of potential subject was conducted from March 1, 2004, to August 31, 2006, among patients with terminal cancer. They were referred to the Department of Family Medicine at Korea University Guro-Hospital for hospice care after anticancer-therapy had proven ineffective. We consecutively enrolled patients who were eligible for HRV testing and agreed to participate in this study. Patients with arrhythmia or a cardiac disorder capable of affecting HRV parameters, such as paroxysmal

pISSN 1011-8934
eISSN 1598-6357

supraventricular tachycardia, atrial fibrillation, recent myocardial infarction, or myocardial ischemia, were excluded. Patients who were unable to maintain a stable supine posture for 5 min were also excluded. Finally, a total of 70 patients were enrolled and we observed their survival duration until death. However, two patients were lost to follow up. Thus, 68 patients were included in the final analysis.

Data acquisition

Demographic variables were gender, age, primary cancer site, and previous treatment method. The Karnofsky performance status scale (KPS) and the presence of anorexia and dyspnea, which are parametric constituents of the palliative prognostic score (PaP), were also determined. In previous studies, fasting blood glucose (FBG) and total cholesterol were found to affect HRV (18-21). Therefore, we checked FBG and total cholesterol level, which were measured within one week before and after HRV test. After agreeing to participate in this study, the short term HRV was measured over five minutes using an HRV analyzer, BFM-5000 Plus (Medi-Core Co. Ltd., Seoul, Korea). By using time-domain analysis, mean heart rates, standard deviations of normal-to-normal R-R intervals (SDNN), and root mean square standard deviations of R-R intervals (RMSSD) were calculated. Frequency-domain analysis was applied to measure 5-min total power (TP), low frequency power (LFP), and high frequency power (HFP). HRV parameters were measured by the recommendations published by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology in 1996 (22). The HRV test was explained to patients in a quiet, pleasant medical office and conducted over 5 min after applying four limb leads. Patients were advised not to smoke or consume caffeine for 2 hr prior to HRV testing, and tests were conducted more than 2 hr after a meal. Survival duration was defined from HRV testing until the date of death. This study was approved by the Institutional Review Board (IRB) of Korea University Guro Hospital (IRB No. GR0514-002).

Statistical analysis

Univariate analysis of log-rank test for categorical variables or Wald test for continuous variables were performed to identify variables that significantly related to survival duration. The relationship between HRV measures and the variables related to HRV, fasting blood glucose and total cholesterol, was examined using correlation analysis. Finally, Cox's proportional hazard regression model was used to determine the effects of dyspnea, anorexia, KPS, mean heart rates, and SDNN, which were significant in univariate analysis, on survival duration after adjusting for gender, age, fasting blood glucose, and total cholesterol. All tests were two-tailed with 5% level of significance. SAS version 9.1 (SAS Institute Cary, NC, USA) was used for statistical analysis.

RESULTS

Basic statistics and HRV

We analyzed 68 patients (34 men and 34 women) aged between 26 and 84 yr old. The most common primary cancer sites were: lung (20.6%), stomach & esophagus (14.7%), hepatobiliary (14.7 %), gynecologic (13.2%), and colorectal (10.3%). Previous treatment types were (in descending order) surgery+chemotherapy (29.4%), no treatment (19.1%), chemotherapy (14.7%), surgery+chemotherapy+radiotherapy (11.8%), and chemotherapy+radiotherapy (11.8%) (Table 1). The distribution of HRV parameters are described in Table 2. HRV levels were considerably lower than the general Korean population except mean heart rate (23).

Clinical parameters and survival duration

Gender, age, fasting blood glucose, and total cholesterol were independent of survival duration (P=0.584, 0.064, 0.421, 0.467, respectively). However, patients with higher KPS survived longer than those with lower scores (P<0.001). Patients with symptoms of dyspnea or anorexia had shorter survival durations than those without symptoms (P=0.037, 0.015, respectively). Fig. 1A-C showed Kaplan-Meier Survival curves of groups subdivided by these clinical parameters.

Table 1. Demographic characteristics of study population (N=68)

Characteristics	No. (%)
Sex	
Male	34 (50)
Female	34 (50)
Age (yr)	
<40	3 (4.4)
40-59	32 (47.1)
60-79	30 (44.1)
≥80	3 (4.4)
Primary cancer site	
Stomach & Esophagus	10 (14.7)
Colorectal	7 (10.3)
Pancreas	3 (4.4)
Hepatobiliary	10 (14.7)
Prostate & Bladder	3 (4.4)
Lung	14 (20.6)
Breast	2 (2.9)
Gynecologic (Uterus, Cervix, Ovary)	9 (13.2)
Head & Neck	2 (2.9)
Others	7 (10.3)
Unknown	1 (1.5)
Previous treatment	
Surgery only	1 (1.5)
CTx	10 (14.7)
RTx	4 (5.9)
Surgery+RTx	4 (5.9)
Surgery+CTx	20 (29.4)
CTx+RTx	8 (11.8)
Surgery+CTx+RTx	8 (11.8)
None	13 (19.1)

CTx, chemotherapy; RTx, radiotherapy.

Fasting blood glucose, total cholesterol, and HRV

Correlation analysis between HRV parameters and fasting blood glucose or total cholesterol showed that all of the HRV parameters except mean heart rate were significantly correlated with total cholesterol (for SDNN, correlation coefficients 0.43, P< 0.001).

HRV and survival duration

As in previous studies on the association between HRV and prognosis, patients were dichotomized by the highest quartile (75%) of each HRV parameter (11, 14-16). However, 100 beats per min (bpm) was adopted as the reference level for grouping by mean heart rate because it is generally accepted as the definition of

Table 3. Univariate analysis of survival duration for dichotomized HRV parameters (N=68)

Variables	Subdivision of groups		*P* value†
Mean heart rate	<100/min	≥100/min	0.003
SDNN	<21.3 msec	≥21.3 msec	0.012
RMSSD	<16.975 msec	≥16.975 msec	0.726
TP	<358.425 msec^2	≥358.425 msec^2	0.076
LFP	<100.3 msec^2	≥100.3 msec^2	0.243
HFP	<62.4 msec^2	≥62.4 msec^2	0.778
LFP/HFP	<3.345	≥3.345	0.658

*HRV parameters were dichotomized about the highest quartile; †Log-rank test.
HRV, heart rate variability; SDNN, standard deviations of normal-to-normal R-R intervals; RMSSD, root mean square standard deviations of R-R intervals; TP, total power; LFP, low frequency power; HFP, high frequency power.

Table 2. Distribution of HRV parameters (N=68)

Parameters	Mean heart rate (bpm)	SDNN (ms)	RMSSD (ms)	TP (ms^2)	LFP (ms^2)	HFP (ms^2)
Mean±SD	94.5±18.2	17.9±13.5	13.8±11.8	365.5±669.9	103.2±257.6	49.4±108.2
Median	93.000	14.400	11.35	136.750	20.750	17.100
Minimum	52	3.5	2	1.2	0.1	0.1
Maximum	142	57.7	71.8	3,396.5	1,758.0	839.7
Quartile						
25	84.500	8.625	5.325	39.25	6.975	4.3
50	93.000	14.4	11.35	136.75	20.75	17.1
75	104.375	21.3	16.975	358.425	100.3	62.4

HRV, heart rate variability; SDNN, standard deviations of normal-to-normal R-R intervals; RMSSD, root mean square standard deviations of R-R intervals; TP, total power; LFP, low frequency power; HFP, high frequency power; bpm, beat per minute; ms, millisecond.

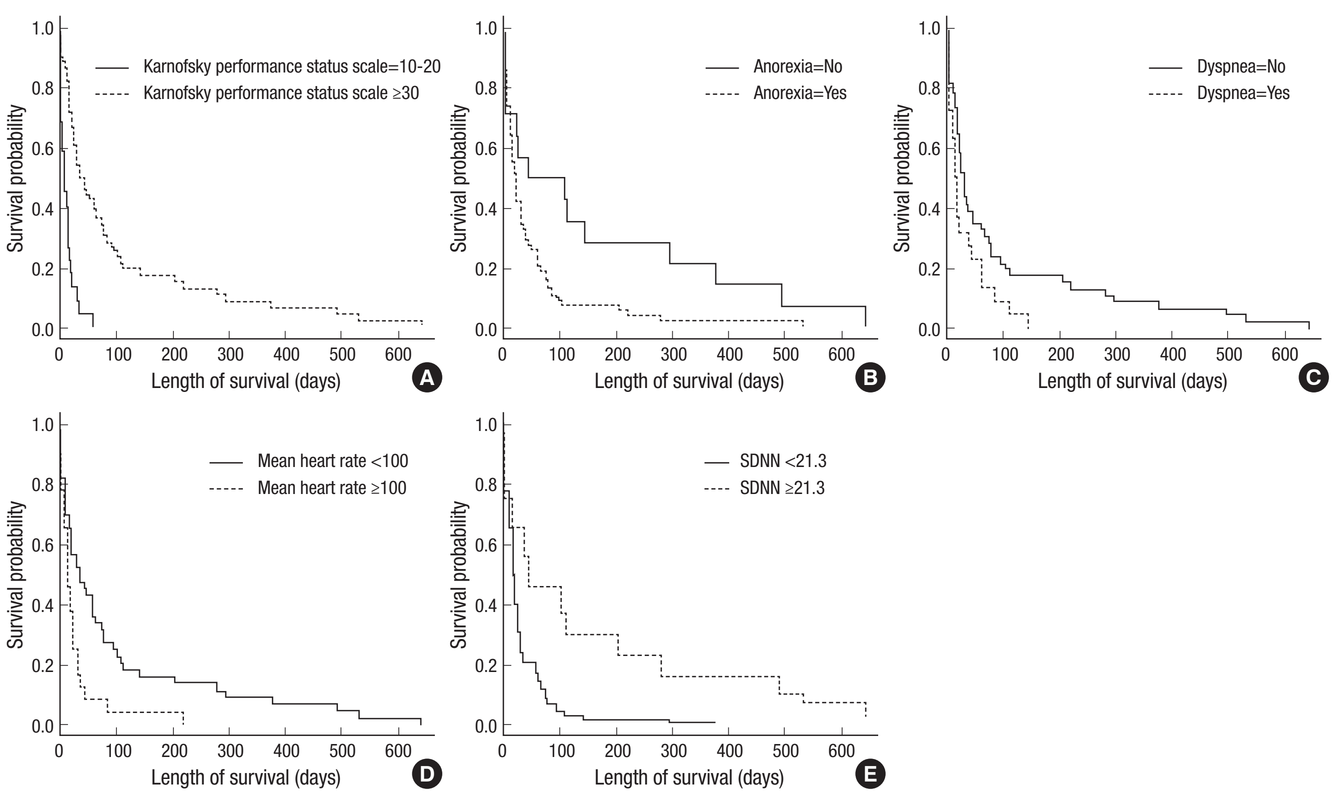

Fig. 1. Kaplan-Meier survival curves (n=68). (**A**) Karnofsky performance status scale* (P<0.001). (**B**) Anorexia (P=0.015). (**C**) Dyspnea (P=0.037). (**D**) Mean heart rate (dichotomized by 100 bpm). (**E**) SDNN (dichotomized by quartile 3, 21.3 msec).
*KPS variable was grouped according to the reference level of palliative prognostic score.

 DOI: 10.3346/jkms.2010.25.8.1140

Table 4. Multivariate analysis using Cox's proportional hazard model to identify factors associated with survival duration (N=54)

Variables	Parameter estimate	Standard error	Hazard ratio	95% Hazard ratio confidence limits		*P* value
Karnofsky scale	-0.99854	0.35907	0.368	0.182	0.745	0.005
Dyspnea	0.87627	0.34194	2.402	1.229	4.695	0.01
Anorexia	0.95624	0.40461	2.602	1.177	5.75	0.018
SDNN	-2.77822	1.21511	0.062	0.006	0.673	0.022
Inter	0.01042	0.00488	1.01	1.001	1.02	0.033

SDNN, standard deviations of normal-to-normal R-R intervals; Inter, SDNN×total cholesterol.

tachycardia. Subsequently, significant differences in survival duration were found between patients with an SDNN of <21.3 ms or ≥21.3 ms and between patients with mean heart rate of <100 bpm or ≥100 bpm (Table 3). Fig. 1D, E showed Kaplan-Meier survival curves of patients dichotomized on mean heart rate and SDNN, respectively. For HRV parameters other than SDNN and mean heart rate, survival durations after dichotomization were not significantly different.

Multivariate regression analysis using Cox's proportional hazard model

To identify factors associated with survival duration among all variables examined, we performed multivariate regression analysis using Cox's proportional hazard model. The final model included gender, age, fasting blood glucose, total cholesterol, KPS, dyspnea, anorexia, mean heart rate, and SDNN. In addition to these variables, we added an interaction variable (inter= Cholesterol×SDNN) to the final regression model because total cholesterol level was significantly correlated with SDNN, indicating a possible interaction. Finally, SDNN, KPS, the interaction variable, dyspnea, and anorexia were significant variables by Backward selection (Table 4).

DISCUSSION

When faced with the reality that anticancer treatment is no longer effective, the patient and his or her family as well as health professionals are faced with a number of difficult decisions; for example, breaking bad news about prognosis, complications of treatment associated with progressive cancer, ect. One of most difficult questions put to doctors by cancer patients and their families is likely to be patient's survival duration (24, 25). The question is very important to the patient or family members, because knowledge of time remaining might help a patient spend the time more effectively and meaningfully. Therefore, an accurate estimation of survival duration may help patients and their families resolve conflicts and better cope with emotional issues. Not surprisingly, such considerations have prompted many studies on predicting survival duration in terminal cancer patients.

The KPS is a common method to objectively quantify the ability to perform daily activities in cancer patients and is essential for predicting survival duration. We also found that KPS was a significant predictor of survival duration. Patients with difficulty to perform daily activities generally have only a short time to live. However, a good ability to perform daily activities does not necessarily mean longer survival (26). The palliative prognostic score (PaP) also proved a useful tool for survival prediction, and has been used to estimate 30 day survival probability based on doctors' clinical prediction, clinical manifestations (dyspnea, anorexia, KPS), and blood count (the number of white blood cells and lymphocyte fraction) (27, 28). In our study, dyspnea, anorexia, and KPS were all significant prognostic factors of survival duration. Fasting blood glucose and total cholesterol were checked due to their relationship with heart rate variability, but they didn't effect on survival duration in univariate analysis. On the other hand, relatively high correlations were found between total cholesterol and HRV parameters (except mean heart rate), implying interactions between these variables in multivariate analysis.

HRV tests are objective, non-invasive, and quantitative tools for assessing changes in cardiac autonomic nervous activity. HRV is calculated from variations in beat-to-beat (R-R) intervals, which are controlled by the parasympathetic and sympathetic nervous systems. These activities change according to internal and external stimuli if they are normal. However, HRV decreases if the autonomic nervous system is impaired (22). Along with traditional time-domain analysis, frequency-domain analysis based on power spectrum analysis, which began to attract attention in the early 1980s, has been used to measure HRV. In frequency-domain analysis, R-R heartbeat intervals are altered by breathing, baroreceptor reflex, renin-angiotensin-aldosterone system, vasomotor activity, and parasympathetic and sympathetic activities, the latter of which generates impulses of constant frequency. When determining R-R intervals associated with these specific impulses by power spectrum analysis, parasympathetic and sympathetic nervous activities can be classified and quantified (10, 22).

After HRV parameters were found to be a significant prognostic factor in patients with myocardial infarction, many studies were conducted to determine whether HRV parameters can predict mortality in other disorders (11, 13-16). We tested the usefulness of HRV parameters in terms of predicting survival duration in terminally ill cancer patients. Survival analyses were performed by dichotomizing patients using specific levels, namely the highest quartiles of HRV measures to conduct the Kaplan-Meier survival analysis. Mean heart rate and SDNN were significantly related to survival duration in univariate analysis (Table 3). Final multivariate regression analysis was performed using Cox's proportional hazard model by adjusting for gender, age, fasting blood glucose level and total cholesterol level, and considering KPS, dyspnea, anorexia, mean heart rate, and SDNN. There was high correlation between total cholesterol and SDNN, which could lead to an interaction. Therefore, we considered an interaction variable between total cholesterol and SDNN in the final regression model. Consequently, SDNN, KPS, dyspnea, anorexia, and the interaction variable were all significant variables (Table 4). These results suggest that HRV is impaired in most terminal cancer patients and SDNN could be useful to predict survival duration in terminal cancer patients. Heart rate is associated with survival duration in terminally ill cancer patients (29). We also verified a similar result in univariate analysis.

This study was conducted at a single medical institution in Korea and is therefore preliminary data for Korean hospice cancer patients. Furthermore, if all palliative prognostic score (PaP) variables including doctor's clinical prediction, white blood cell count, and lymphocyte fraction could be evaluated, we could discover more interesting facts as to whether HRV can improve the prediction power of PaP as prognostic factor.

To our knowledge, this is the first study to suggest that SDNN can play a role in survival prediction for terminal cancer patients. As the short-term HRV test is a simple, non-invasive, objective, and quantitative tool, it has advantages over other prognostic factors. Future work is needed to verify the usefulness and character of SDNN for predicting survival duration in terminally ill cancer patients.

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