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Short communication

The relationship between heart rate variability and time-course of carcinoembryonic antigen in colorectal cancer

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ABSTRACT

Background: Identifying new prognostic factors is important for guiding treatments and preventing metastasis in cancer. Vagal nerve activity may predict prognosis in cancer due to its roles in modulating inflammation, sympathetic activity and oxidative stress. This study tested the relationship between heart rate variability (HRV), a vagal nerve index, and the colon cancer (CC) marker carcinoembryonic antigen (CEA), in an 'historical prospective' design.

Methods: We examined data of 72 CC patients, without inflammatory or cardiac diseases, of whom 38 had baseline electrocardiograms (ECG) and 12 month CEA levels. We measured HRV (SDNN, RMSSD) from brief archived ECG. Multiple confounders were considered.

Results: Controlling for effects of tumor stage and treatment-orientation, baseline HRV predicted CEA levels at 12 months ($r = -.43$, $p = .006$). Patients with SDNN < 20 ms had significantly higher CEA at 12 months than those with SDNN > 20 ms.

Conclusion: These preliminary results showed that higher HRV predicts lower levels of a tumor marker, one year later, independent of confounders. This supports the hypothesized role of vagal activity in tumor modulation. Replication in larger samples is needed.

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1. Introduction

Colon cancer (CC) is prevalent and one of the most fatal cancers (Labianca et al., 2010). Prognostic factors include stage at diagnosis (Van Cutsem et al., 1999), tumor location, number of lymph node metastases, tumor morphology and carcinoembryonic antigen (CEA) levels (Park et al., 1999; Forslund et al., 2002). CEA kinetics predicts response to therapies as well (Iwanicki-Caron et al., 2008). Research in recent years has revealed important effects of neural and inflammatory signals on tumor progression. Sympathetic neurotransmitters influence the destiny of and promote metastasis (Entschladen et al., 2004). Inflammatory markers play pivotal roles in early tumorigenesis (Pikarsky et al., 2004) and in late stages of tumor progression (Voronov et al., 2003; Mantovani et al., 2008). Based on converging evidence, investigators have hypothesized that the vagus nerve may modulate and slow down tumor progression, (Gidron et al., 2005; Mravec et al., 2006), since vagal activity informs the brain about,

and modulates, peripheral inflammation (Tracey, 2002), since vagotomy predicts cancer death in humans (Ekbom et al., 1998) and promotes peripheral tumors in animals (Erin et al., 2008). In addition, vagal activity modulates sympathetic tone (Vlcek et al., 2008) and oxidative stress, (Pavithran et al., 2008; Tsutsumi et al., 2008), the latter a key trigger of cancer onset and prognosis (Faux et al., 2009). A more recent review attempted to integrate the complexity of evidence on the role of the nervous system in cancer by providing evidence for the bi-directional relations between the tumor microenvironment and the nervous system (Ondicova and Mravec, 2010), including the vagus nerve. A few studies have shown in cancer patients that high vagal activity, indexed by heart rate variability (HRV), predicts better prognosis (Hoffmann et al., 2001; Chiang et al., 2010; Fadul et al., 2010). However, these studies did not consider important confounders. Kim do et al. (2010) found that HRV predicted survival time in terminal patients, independent of confounders, but did not consider initial tumor stage and included several cancer types. The relationship between HRV and tumor markers over time is still unknown. The present study aimed to preliminarily test whether initial HRV predicts 12-month levels of CEA in colon cancer patients. We hypothesized that levels of HRV would be inversely related to CEA, due to a hypothesized tumor modulatory role of the vagus nerve.

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2. Method

2.1. Patients and design

This study employed a historical prospective design. After approval of the Medical Ethics Committee, medical records of 246 colon cancer (CC) patients with electrocardiograms (ECG) treated at the Jules Bordet Hospital, Brussels, between March 2001 and December 2006, were reviewed. Exclusion criteria included conditions known to alter HRV or influence inflammation such as heart diseases, treatments with anti-arrhythmic drugs or beta-blockers, pacemaker, chronic inflammatory disease, anemia and thyroid disease. We initially included 72 CC patients. However, only for 38 CC patients, did we have data on baseline HRV and CEA at 12 months after diagnosis.

2.2. Confounders

Background information included patients' sex, age, previous patient history and family history of cancer, diabetes, hypertension, hypercholesterolemia, stage of cancer, time from diagnosis till ECG, smoking, treatments (surgery, chemotherapy, other) and treatment orientation (curative/palliative).

2.3. Vagal nerve activity

This was measured by deriving time domain heart-rate variability (HRV) obtained from routinely registered 10 s ECG recordings in computerized archives. The indices included the standard deviation of all normal RR intervals (SDNN) and the square root of the mean of the squared differences between adjacent normal RR intervals (RMSSD). Validity of the 10 s ECG method for determining HRV was established in relation to predicting 5-minute HRV and all-cause mortality (Dekker et al., 1997; Hamilton et al., 2004).

2.4. Tumor burden

This included serum levels of CEA at 12 months from diagnosis, obtained from computerized archives. We also examined the pattern of evolution of CEA at diagnosis, 6 and 12 months later.

2.5. Statistical analysis

We first tested univariate associations between all background data and the HRV indices, with 12-month follow-up CEA, using Pearson correlations for continuous variables and t-tests for categorical data. A partial correlation tested whether a significant univariate HRV index, predicted follow-up CEA levels at 12 months, after controlling for all significant background or prognostic factors. Using an analysis of covariance, we tested whether the cut-off of 20 ms for SDNN (Thong, 2008) predicted 12-month CEA, independent of confounders.

3. Results

Due to lack of normal distributions, the scores of CEA, SDNN and RMSSD were log transformed. Due to large heterogeneity in the time from diagnosis till ECGs, we categorized patients into those with an absolute gap smaller than and larger than 6 months between diagnosis and ECGs. Descriptive statistics of the study variables are shown in Table 1.

In univariate analyses, log transformed SDNN significantly inversely predicted CEA levels at 12 months ($r = -.34$, $p = .025$). However, RMSSD was not predictive of CEA levels ($r = -.260$, $p > .10$) and heart-rate (HR) only tented to predict CEA levels ($r = .270$, $p = .09$). Age was unrelated to CEA ($r = -.18$, $p = .26$). Woman tended to have significantly lower logCEA levels (0.62) than men (1.15), t

Table 1

Descriptive statistics for continuous and categorical variables in colon cancer patients.

| Continuous variables | | | | |
|------------------------------------|-----------------|-----------|------------------|-----------|
| Variable | | Mean | | SD |
| Age (years) | | 63.7 | | 10.8 |
| HR (bpm) | | 74.0 | | 11.5 |
| SDNN (ms) | | 23.4 | | 21.0 |
| RMSSD (ms) | | 24.7 | | 21.3 |
| CEA at diagnosis | | 68.1 | | 151.7 |
| CEA at 6 months | | 54.8 | | 199.8 |
| CEA at 12 months | | 87.9 | | 291.6 |
| Categorical variables | | | | |
| Variable | | | | % |
| Gender (% women) | | | | 62.5% |
| Smoking at diagnosis | | | | 35.0% |
| Past smoking | | | | 77.5% |
| Hypertension | | | | 12.5% |
| Diabetes mellitus | | | | 2.5% |
| Hypercholesterolemia | | | | 15.0% |
| Family cancer history | | | | 37.5% |
| Past cancer | | | | 10.0% |
| Cancer stage | I: 20.0% | II: 12.5% | III: 27.5% | IV: 40.0% |
| Chemotherapy | 32.5% | | | |
| Surgery | 97.5% | | | |
| Treatment orientation | Curative: 55.0% | | Paliative: 45.0% | |
| Time since diagnosis (%> 6 months) | 50% | | | |

Note: HR = heart rate; SDNN = standard deviation of all normal RR intervals; RMSSD = squared root of the mean of the squared differences between adjacent normal RR intervals. bpm = beats per minute; ms = milliseconds.

(18.5) = 1.77, $p = 0.09$. Patients with palliative treatment had significantly higher logCEA (1.37) than patients with curative treatment (0.39), $t(21) = 4.2$, $p < 0.001$. Patients treated with chemotherapy had significantly higher logCEA (1.07) than patients not treated with chemotherapy (0.29), $t(32.2) = 4.36$, $p < 0.001$. Cancer stage significantly predicted levels of CEA at 12 months ($F(3,38) = 6.71$, $p = .001$). All other confounders (smoking, diabetes mellitus, hypertension, hypercholesterolemia, past cancer and family history of cancer, other treatments, surgery, time from diagnosis till ECG), did not significantly predict CEA at 12 months (all $p > 0.05$).

In a multivariate partial correlation, baseline SDNN still remained a significant predictor of CEA at 12 months from diagnosis, controlling for initial tumor stage, treatment orientation and chemotherapy: $r = -0.435$, $p = 0.006$. This result remained intact when adding time since diagnosis till ECG ($r = -.436$, $p = .006$), gender ($r = -.416$, $p = .009$) or HR ($r = -.417$, $p = .007$) into the partial correlations. The HRV–CEA relation occurred in patients receiving palliative treatment ($r = -.58$, $p = .018$), not curative treatment ($r = .01$, NS). Using a cut-off of 20 ms for HRV, patients with low HRV (SDNN < 20 ms) had significantly higher CEA levels at 12 months than patients with higher HRV (> 20 ms; ($F(1,37) = 8.37$, $p = .006$), independent of tumor stage, treatment orientation and chemotherapy. The evolution of CEA levels over 12 months, as a function of this HRV cut-off is depicted in Fig. 1.

4. Discussion

This study preliminarily tested the relationship between baseline HRV, a vagal nerve index, and CEA levels 12 months after CC diagnosis, using a 'historical prospective' design. Baseline HRV (SDNN) was inversely significantly related to CEA levels at 12 months after diagnosis, independent of prognostic factors (e.g. tumor stage, treatments). This finding was specifically found in patients receiving palliative treatment, not curative treatment. Furthermore, CC patients with low HRV (SDNN < 20 ms) had significantly higher CEA at 12 months and even at study entry (Fig. 1), than patients with higher HRV. RMSSD did not

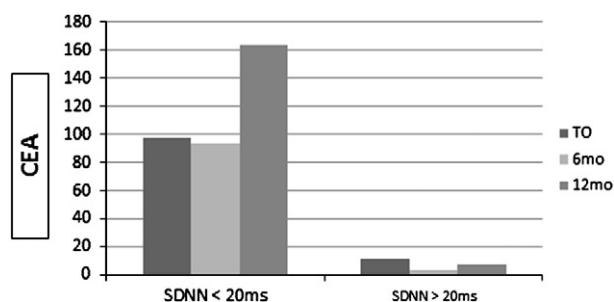


Fig. 1. The relationship between low and high baseline SDNN and CEA changes in colon cancer patients during one year follow-up from diagnosis. Note: SDNN = standard deviation of all normal RR intervals; ms = milliseconds.

predict CEA levels in univariate analyses. However, in multivariate analyses, controlling for confounders, RMSSD predicted CEA (data not shown), confirming the reliability of our finding with SDNN. These results support the hypothesized prognostic role of HRV in cancer, and support to the hypothesized neuromodulatory role of the vagus nerve in cancer prognosis (Gidron et al., 2005). These results replicate past studies (Chiang et al., 2010; Hoffmann et al., 2001; Fadul et al., 2010; Kim do et al., 2010) in relation to survival. However, except one past study (Kim do et al., 2010), all other studies did not consider confounders. In contrast, the present study considered numerous confounders and extends those studies to the prediction of a tumor marker in CC. Given that CEA may reflect actual tumor burden, and given its prognostic significance in CC (Park et al., 1999; Forslund et al., 2002), our findings suggest that vagal activity may influence actual tumor burden. However, this statement requires replication in larger samples and verification by an experimental (RCT) design in future studies.

How may vagal nerve activity influence tumorigenesis? Converging evidence supports vagal neuromodulation of tumors. Vagotomy was found in some studies to increase human cancer incidence (Ekblom et al., 1998) and enhances metastasis of existing peripheral tumors in animals (Erin et al., 2008). The efferent vagus nerve has anti-inflammatory effects via acetylcholine (Tracey, 2002), can modulate sympathetic responses (Vlcek et al., 2008) and reduces oxidative stress (Pavithran et al., 2008; Tsutsumi et al., 2008), three factors with crucial roles in cancer-onset and prognosis (see above). Based on these, it is hypothesized that enhanced vagal activity may slow down tumor progression (Gidron et al., 2005). However, it is important to note that only some parts of the vagus nerve innervate the colon, whereas other parts are innervated by the sacral vagus portion, whose local anti-inflammatory effects are not clear. Yet, Tracey (2002) suggested an alternative systemic anti-inflammatory route – vagal mediation of information concerning peripheral inflammation triggers the anti-inflammatory hypothalamic–pituitary–adrenal (HPA) axis activity. Future research needs to examine whether the local or systemic routes have anti-inflammatory effects on colon cancer tumors, thereby possibly explaining the pattern of our observed results.

This study had several limitations. HRV was derived from brief 10 s ECGs, the study included a small sample, it was not a formal prospective study, possible changes in cancer stage and treatment during follow-up were not considered, and we did not measure inflammatory cytokines or oxidative stress to test hypothesized mechanisms linking HRV to cancer prognosis. Future studies need to measure HRV over longer periods and repeated measures, also to control for effects of stress or other factors on this measure. Nevertheless, in past studies, such brief measure of HRV predicted prognosis in other conditions and correlated with a longer measure of HRV (Dekker et al., 1997; Hamilton et al., 2004). Future studies also must test in larger samples if the HRV–CEA relation occurs only in advanced disease (receiving palliative care) or in all patients. Nevertheless, our findings replicate and extend previous ones, while considering numerous

confounders, and provide support to the neuromodulatory theory of the vagus in cancer prognosis (Gidron et al., 2005; Ondicova and Mravec, 2010). Finally, HRV may not fully reflect all vagal activity to organs other than the heart, such as the colon. However, Kuo et al. (2005) found that vagal nerve activity correlated highly ($r = .88$) with high-frequency HRV (a typical vagal nerve segment of HRV) in rats, supporting the validity of the claim that HRV strongly represents (non-cardiac) vagal nerve activity.

Future studies need to address these limitations and test whether stimulating the vagus nerve can improve prognosis in cancer. Vagal activity may be increased by HRV biofeedback (Lehrer et al., 2004; Karavidas et al., 2007), vagal stimulating drugs (D'Souza et al., 1999; Atkins et al., 2001; Bernik et al., 2002) and vagal nerve stimulators (Murphy and Patil, 2003), and these could eventually be tested in cancer patients.

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