Chapter 13
HRV in Oncology and Palliative Medicine

Cancer Pathophysiology

Autonomic nervous system dysfunction is a problem that can be detected in about 50–100 % of patients with advanced cancer (Bruera et al. 1986; Walsh and Nelson 2002; Strasser et al. 2006). It has been described in various primary malignancies (Table 13.1).

It is, however, not easy and often not possible to distinguish between autonomous neuropathy as consequence of the tumor itself, as consequence of (often chemotherapeutic) treatment, or as consequence of both.

Fadul and colleagues used short-term HRV as well as the Ewing test battery consisting of three tests for the parasympathetic function (heart rate changes after different perturbations) and two tests for the sympathetic system (blood pressure changes after perturbations). Most patients had an Ewing score greater than 2, which is reported as cutoff point to diagnose moderate to severe autonomic dysfunction. Only six (12 %) patients had diabetes before onset of cancer (Fadul et al. 2010).

A decreased HRV parameter can also be based on increased CRP. Many patients with advanced cancer have increased CRP, which has been related to an activated immune system. Already moderate increased CRP again has correlations to lower HRV values, as observed in several studies (Kon et al. 2006; Araujo et al. 2006; Carney et al. 2007; Ziegler et al. 2008).

Explanations for a possible pathophysiological relation between lower heart rate variability and cancer death are interesting issue for debate. In contrast to cardiologic diseases, advanced cancer patients show a plethora of symptoms that can be associated with HRV changes (like depression, cachexia, sleep disturbances, autonomic dysfunction, pain, heart failure). An important point in the discussion is the ultimate reason for a cancer patient's death. This is not as simple. Cancer patients die from a variety of causes. Inagaki et al. (1974) reported on 816 cancer patients and summarized as most important causes of death: infection (47 %), organ failure (25 %), infarction (11 %), carcinomatosis (10 %), and hemorrhage (7 %).

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Table 13.1 Autonomic disturbance in various cancer types

Cancer	Method	ANS abnormalities	Reference
Various	Ewing test	81 %	Strasser et al. (2006)
Various	Test battery	100 %	Walsh and Nelson (2002)
Various	Test battery including HRV	52 %	Bruera et al. (1986)
All survivors	HRV	LF/HF increased, depressed diurnal rhythm	Kamath et al. (1998)

It is important to recall that cancer-related effects like paraneoplastic conditions leading to increased blood glucose may also cause diminished HRV (Haegele-Link et al. 2008).

Prognosis for Cancer Patients in a Palliative Phase

Prognosis is still a challenge in palliative patients. Prognostication in incurable diseases assists clinicians in their decision making and helps them provide patients and their family with information about the (likely) future (Glare and Christakis 2005). Nevertheless, clinical estimation is uncertain (Oxenham and Cornbleet 1998). Score systems have been proposed (Pirovano et al. 1999) and validated (Maltoni et al. 1999); and the European Association for Palliative Care recommends their use. But prognostication is rough, giving information about 30-day survival probability (>70, 30–70, or <30 %). Any further simple approach would be highly beneficial (Glare and Christakis 2005). In a small study of our own, we explored heart rate variability changes in a group of patients with advanced cancer in relation to survival.

In a study with a 10-year follow-up, 347 subjects under 65 were examined with a baseline that included HRV (Holter monitoring, frequency domain, SDNN, and Power slope). Different indices for mortality were found (among them: smoking, prior heart disease, increased glucose, decreased cholesterol (sic)). SDNN, VLF, and LF had an association with mortality, but not HF. The slope was the best univariate predictor with a cutoff value of 1.5. In a multivariate regression model, a steep slope of the power law regression line and congestive heart failure were the only independent predictors, with a relative risk of 2.01 and 1.85, respectively. None of the measures of HRV had a univariate association with cancer death or other nonvascular reasons for death (Huikuri et al. 1998).

A case cohort study was conducted within a longitudinal study of 15,792 middle-aged men and women. A sample of 900 subjects without prevalent coronary heart disease in baseline was drawn and compared with all subjects with CHD and all subjects who died before follow-up. HRV was determined by a 2-min rhythm strip where RR distances were later measured half-automatized. In addition plasma levels for cholesterol, HDL, LDL, triglycerides, serum

Table 13.2 HRV in cancer patients short before death (Ernst and Rostrup 2013a, b)

	Study	Fadul	Sztajzel (2004)	Schumacher (2004)
SDNN	25.32 ± 20.75	51.4 ± 24.33	141 ± 39	
RMSSD	24.9 ± 28.41		27 ± 12	
TP	409.32 ± 898		21,222 ± 11,663	
LF	86.33 ± 159	356.4 ± 228.39	791 ± 563	1,170 ± 416
HF	32.92 ± 52.1	477 ± 321.99	229 ± 282	975 ± 203
LF/HF	2.33 ± 1.85		4.61 ± 2.33	1.5 – 2.0
Sampen	2.0526 ± 0.416		–	

In comparison results from advanced cancer patients (Fadul et al. 2010) and from healthy persons (Sztajzel 2004; Schumacher 2004)

insulin, and glucose were determined and diabetes was diagnosed according to the fasting blood glucose levels. Blood pressure, waist and hip circumferences, and carotid intima-media thickness were assessed. Four measures of HRV were determined: SDNN, rMSSD, SDSD, and pNN50, but no frequency-domain measures. Generally, low HRV was associated with an adverse cardiovascular risk profile and elevated risk of death from all causes, including cancer, and of incident CHD. The elevated risk could not be attributed to other risk factors. Relative risk of low SDNN was lower than from the other parameters. The authors conclude that low HRV possibly precedes different manifest diseases (Dekker et al. 2000).

Thirty-five patients with metastatic carcinoid tumors were studied with the help of 24 h Holter ECG calculating SDNN, rMSSD, and pNN50. During the follow-up of 18 ± 7 months, 15 of 35 (43 %) patients died. Patients with the combination of SDNN <100 ms and presence of carcinoid heart disease had a worse prognosis compared to the other patients (Hoffmann et al. 2001).

Fadul examined 47 patients with advanced metastatic solid cancers with a median survival of 139 days after inclusion (but a wide range between 4 and 2,266 days) using short-term HRV (20 min). Frequency-domain measures were not associated with survival. They report a trend toward a significant association between survival and SDNN ($p = 0.056$) (Fadul et al. 2010).

We conducted a study that included 24 patients with advanced cancer due to solid tumors. Short-term HRV (10 min) was taken at course of the disease, if available, several times. The last available HRV taken in mean 33 days before death was significantly lower than healthy controls from other studies (Table 13.2).

Most HRV parameters, with exception of SampEn did not change the last 3 months before death (Table 13.3).

It is not clear whether or not HRV can have a role in survival estimation for cancer patients. Only a few studies with a low number of patients included have been published. Only our small study examined cancer patients more than one time in the course of the disease. On the other hand we have some bigger longitudinal studies that show a statistical relation between lower HRV parameters and cancer mortality. More studies have to be conducted before conclusions can be drawn.

Table 13.3 HRV changes in cancer patients during disease progression (Ernst and Rostrup 2013a, b)

Survival	>60 days	30–59 days	7–29 days	<7 days
SDNN	24.71	25.87	21.56	21.38
RMSSD	17.6	17.12	33.55	14.2
TP	243	525	88.9	438
VLF	115	29.8	39	118
LF	68.7	46.8	19.8	90.1
HF	30.9	28.5	42.7	20.96
LF/HF	2.3	1.46	1.64	2.4
Entropy	**2.2013**	**2.0350**	**1.9391**	**1.8555**

Cancer Treatment and HRV: The Case of Anthracyclines

Particular challenges in cancer treatment are chemotherapeutic agents that induce cardiac dysfunction. In some treatment programs, evaluation of heart function at baseline and during the process is an integral part of the treatment, for instance, with anthracyclines. Since their introduction in the late 1960s, doxorubicin and epirubicin have been used successfully in the treatment of a wide variety of hematopoietic and solid tumors. However, their use is limited by the occurrence of cardiotoxicity, which may result in congestive heart failure (Meinardi et al. 1999). This has resulted in maximum dosage recommendations to avoid major heart disease. To detect cardiac dysfunction in patients who are treated with anthracyclines, regular monitoring of the heart function during treatment is important. After completion of chemotherapy, detection of cardiac dysfunction is also of relevance, since this might lead to timely medical intervention aiming at improving the cardiac prognosis. Multigated radionuclide angiography (MUGA) is a noninvasive technique that makes use of intravenously injected radionuclides (^{99}Technetium) that bind to erythrocytes and enable the cardiac pool to be visualized with a γ-camera. MUGA is widely considered a gold standard.

The value of HRV analysis for the detection of anthracycline-induced cardiotoxicity has been evaluated in some studies.

Postma studied 31 young patients for late cardiotoxicity (9 years follow-up) with several techniques (MUGA, echocardiography) and also HRV. No correlation between the anthracycline dose and echocardiographic and MUGA parameters was found, but HRV analysis revealed a significantly impaired HRV in the patients who received more than 400 mg/m^2 doxorubicin compared to those who received less than 400 mg/m^2. This suggests that HRV could be a sensitive indicator for cardiotoxicity (Postma et al. 1996). Tjeerdsma et al. (1999) found significantly impaired HRV in breast cancer patients who had been treated with anthracyclines and high-dose chemotherapy compared to healthy age-matched females. They included 20 patients with LVEF >50 %. They used Holter monitoring technique and time and frequency domain. SDNN and SDANN were not different to healthy controls. In contrast, PNN50 and rMSSD were significantly lower in patients than in healthy controls. All frequency-domain indices were reduced.

Ekholm looked at nine women treated for metastatic breast cancer with docetaxel. They were studied prior to the docetaxel treatment and after the third or fourth course and exhibited no differences in HRV (Ekholm et al. 2000).

Nousiainen was not interested in cancer, but in left ventricular dysfunction. Knowing that doxorubicin causes decreased LVEF, he investigated patients receiving this agent as a clinical model and focused on neuroendocrinological changes. After cumulative doxorubicin doses of 400 and 500 mg/m^2, there was a decrease of HFnu and increase in LFnu leading also to an increase of LF/HF. However, after the cumulative doxorubicin dose of 500 mg/m^2, the changes in HRV components returned toward baseline. This might suggest that doxorubicin-induced left ventricular dysfunction is associated with an early change in sympathovagal balance toward sympathetic predominance. Further progression of left ventricular dysfunction is then associated with an attenuation of sympathetic tone (Nousiainen et al. 2001).

Meinardi followed breast cancer patients treated with five cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Mean LVEF declined from 0.61 at T0 to 0.54 during the treatment course, but no HRV changes were observed (Meinardi et al. 2001).

Twenty-four breast cancer patients were treated with docetaxel alone and 34 with a combination of docetaxel and epirubicin. Already after a therapeutic course of 3 weeks, HRV alterations could be observed (Syvanen et al. 2003).

Salminen followed breast cancer patients treated with eight cycles of an epirubicin–docetaxel combination. The patients had no clinical symptoms of cardiotoxicity. Neither echocardiography nor HRV (Holter monitoring) changed compared to baseline (Salminen et al. 2003).

Brouwer followed doxorubicin-treated survivors of a malignant bone tumor (osteogenic sarcoma and malignant fibrous histiocytoma) with echocardiography and HRV (Holter monitoring) 22 years after treatment. Compared with age-matched controls, patients showed lower values of HRV parameters except for LF/HF and LFNU. Almost all HRV parameters decreased compared with the measurements in 1997 while LF/HF and LFnu increased (Brouwer et al. 2006).

So *in conclusion* I have found conflicting results. Brouwer's long-time follow-up study convincingly showed deterioration of former doxorubicin-treated patients while earlier studies had shown promising results. Later studies, however, were not able to show HRV decline during or after the treatment course, even in patients where mild echocardiographic was described. As usual in the HRV field, the studies are (too) small. In addition, no nonlinear indices were used.

Cancer Symptoms and HRV

Only few studies have been conducted on the association between different cancer symptoms and changes in HRV. *Cardiac cachexia* is associated with a lower LF, BRS, and higher catecholamine concentrations than matched controls of

noncachectic cardiac patients or healthy controls (Ponikowski et al. 1999a, b). In an experimental study, 17 female (healthy) subjects were exposed to *nauseogenic* visual stimuli and HRV changes were analyzed. LF/HF increased associated with the extense of nausea, 1.54 ± 2.11 in relation to moderate, 2.57 ± 3.49 to strong nausea, suggesting increased sympathetic involvement. They also observed short increases of HF preceding increased nausea (LaCount et al. 2011).

Fatigue is the most common problem among long-term cancer survivors, particularly observed in breast cancer survivors. Fagundes included women who had completed treatment for stage 0–IIIA breast cancer within the past 2 years (except for tamoxifen/aromatase inhibitors) and were at least 2 months post-surgery, radiation, or chemotherapy. HRV was continuously measured with the Polar s810 wristwatch and wearlink 31 belt band. HRV (only RMSSD documented in the publication) was lower among more fatigued women compared to those who were less fatigued (22.145 ± 13.327 vs. 28.875 ± 16.905) (Fagundes et al. 2011).

Cheyne–Stokes respiration patterns reduce LF and HF power, but increase VLF (Mortara et al. 1997).

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