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Review

How to properly evaluate cardiac vagal tone in oncology studies: a state-of-the-art review

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ABSTRACT

Heart rate variability (HRV) analysis provides an assessment of cardiac vagal tone and consequently global cardiac health as well as systemic condition. In systemic diseases such as cancer and during treatments that affect the whole body, like chemotherapy, the vagus nerve activity is low and deregulated. Some studies focus on using HRV to predict mortality in oncology. However, in cancer patients, systemic alterations substantially increase artifacts during HRV measurement, especially atrial ectopic beats. Moreover, HRV may be altered by various factors (duration and time of measurement, breathing, drugs, and other confounding factors) that alter each metric in different ways. The Standard Deviation of all Normal to Normal intervals (SDNN) is the most commonly used metric to evaluate HRV in oncology, but it does not appear to be specific to the cardiac vagal tone. Thus, cardiac vagal activity diagnosis and vital prognosis of cancer patients can be biased. Our review presents the main HRV metrics that can be currently used in oncology studies and their links with vagus nerve and cancer. We present the influence of external factors and the required duration and time of measurement. Considering all these parameters, this review proposes seven key points for an assessment of HRV and cardiac vagal tone in patients with cancer.

1. Introduction

Homeostasis maintains the body in a healthy condition by regulating its constants and various functions. Among its main factors, the vagus nerve acts as a guardian[1] and works closely with the endocrine and immune systems.[2,3] Vagal tone is also related to the Autonomic Nervous System (ANS). The latter can be divided into the parasympathetic nervous system (PSNS) and the (ortho)sympathetic nervous system (SNS). The ortho-parasympathetic balance is controlled by the vagus nerve. SNS activity increases as vagal tone decreases, and conversely. Several publications described the physiology of ANS, SNS/PSNS regulation, and HRV clinical use.[4–6]

The vagus nerve regulates metabolic homeostasis by controlling the heart rate (HR),[7] but also the interval between two heartbeats. The variability of this interval over the time is called Heart Rate Variability (HRV).[6] HRV provides an indirect measure of vagal tone, because it is primarily under the influence of cardiac vagal control.[8,9] Laborde et al.[10] and Shaffer et al.[11] reviewed HRV and its control by cardiac vagal tone.

HRV analysis provides an assessment of ANS condition and consequently global cardiac health.[12] In diseases, especially systemic ones such as cancer, and during treatments that affect the whole body, like chemotherapy, the vagus nerve activity is deregulated.[13] This has an impact on both the ANS and the HRV. This deteriorates homeostasis and further increases systemic problems.

The clinical interest of HRV was only recognized in 1963 by Hon and Lee[14] who noted that acute alterations in HRV were a marker of fetal distress and predicted fetal hypoxia. It is thus possible to diagnose a physiological imbalance by evaluating the action of the cardiac vagal nerve/tone via HRV. Since then, many studies have focused on using HRV to predict cardiac health and mortality,[15] especially in oncology, because cancer patients have low cardiac vagal activity.[16,17] Lin et al[18] observed that HRV in patients with metastatic cancer was lower than in patients without metastasis, and an increased HRV correlates with a better vital prognosis of cancer patients,[13,17,19–25] while a high resting heart rate has been shown to be predictive of cancer mortality.[21,26] In addition, several studies show that vagotomy accelerates tumor growth.[27,28] Globally, vagus nerve-cancer interactions have been

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highlighted[29] and proper vagus tone reduces the influence of other personal factors on prognosis, such as age or sex.[30,31]

Thus, stimulation of the vagus nerve has therapeutic potential in oncology,[32] like anti-metastatic effects.[33] As the vagus nerve regulates HRV, its stimulation would increase HRV and indirectly vital prognosis.[17] Indeed, the vagus nerve can inhibit oxidative stress, inflammation and excessive orthosympathetic activity.[13,17] Nevertheless, stimulation of the vagus must be adapted to the type of patient and the use of HRV must consider practical expectations of professionals: sensitivity to change, rapid feedback, easy to administer, low cost, noninvasive, reliable, etc.

Considering the interest of HRV measurement in oncology, some authors published reviews describing the benefits and the limitations of such metrics.[16,17,23,24] Nevertheless, the HRV assessment protocol has to be as suitable as possible for clinical practice and as unbiased as possible in its endpoint to properly diagnose the cardiac vagal tone in cancer patients. Many HRV metrics exist, including rMSSD (square root of the mean of the sum of the squares of differences between adjacent Normal to Normal NN intervals) and SDNN (standard deviation of all NN intervals), which are the mostly used in oncology. Estimating and understanding these metrics is one of the main issues as well as the most complex.

References have been established in healthy patients and those with cardiovascular disorders,[6] but they are used for patients in oncology as well.[34,35] However, in some diseases, HRV may be altered by various factors (duration and time of measurement, respiration, drugs, etc.), particularly in oncology where systemic alterations substantially increase artifacts, especially atrial ectopic beats.[36] Currently, an SDNN below the 50 ms threshold in a healthy patient is considered pathological.[37]

Our review aims to improve the cardiac vagal tone assessment in cancer patients. It presents the main HRV metrics currently used in oncology studies, their links with vagus nerve and cancer, their circadian fluctuations, as well as the influence of confounding factors and the choice of measurement duration. Finally, we talk about artifacts and software for HRV analysis to finally propose a specific protocol for an HRV measurement in patients with cancer.

2. Study selection

2.1. Data source

Electronic searches were conducted between January 2021 and July 2023 using MeSH and non-MeSH terms. We firstly investigated two databases, PubMed and ScienceDirect. These databases were supplemented by searching in publications' references (snowball procedure), and through google scholar and specific peer-reviewed journals, since few studies were not available on databases. No language or date restrictions were applied.

The included articles were clinical trials, randomized or not, observational studies, preliminary or pilot studies, narrative and systematic reviews, meta-analysis, and case reports. The following keywords were used: heart rate variability, HRV, cardiac vagal tone, vagal tone, vagus nerve, autonomic nerve system, sympathic nervous system, healthy patients, cancer, prognosis, and all metrics' names.

Studies were to focus on healthy and/or cancer patients and were to include HRV measures. No selection was done concerning treatments, types of cancer or cancer stages since information on terminal cancer patients is important for the prognosis role of HRV. However, studies on children or on cancer patients suffering from a concomitant disease (cardiac disease for example) were excluded. Lists of studies were imported to Microsoft Excel and duplicates were removed.

2.2. Data collection and analysis

Two investigators independently identified studies meeting inclusion criteria on the basis of titles then abstracts. One investigator extracted all data concerning HRV metrics, duration and time of measurement, software, tools (Electrocardiogram, Chest belt, etc.), breathing procedures, artifacts (Yes/No), chemotherapy or radiotherapy (Yes/No), types of cancer, and all confounding factors in HRV measurements. A second author verified extracted data. If data appeared in more than one study, we used the primary publication. A consensus between all authors was settled when differences of opinion arouse during data extraction. Assessment of studies' quality was not performed.

We pooled the data of a given metric if data were given for cancer patients and not only for healthy patients. For example, no data exists for Respiratory Sinus Arythmia (RSA), HRV triangular Index (HRVI) or Total power in cancer patients, so theses metrics were excluded from analysis.

2.3. Choice of HRV metrics

Considering that HRV has only been used in oncology for a few years, HRV metrics were selected mainly on the basis of available data and their relevance to assess cardiac vagal tone. Consequently, data for some HRV metrics were excluded from our review, even if they had been used for patients with other diseases.

3. Main HRV measurements

A number of methods can be used to calculate variations in heart rate,[38] basically classified in non-linear and linear methods. We focus on the latter one, which includes time-based and frequency-based methods, because they provide metrics used in oncology to analyze the HR variation in the short term (around 5 min monitoring period) and/or long term (24 h).[39] Some authors suggested ultra-short term measurement periods of 60 s [40] to 240 s,[41] but these periods do not appear to be appropriated in oncology as discussed later.

3.1. Time-domain variables

The time-domain analysis consists of monitoring heart rate data over a given period of time. In a continuous electrocardiogram (ECG) record, metrics are calculated from the interval between two R peaks (RR interval) of the QRS complex (Fig. 1). However, this interval may include ectopic beats, mainly considered as artifacts, which should be excluded from the analysis. The "cleaned" RR interval, without artifacts that bias results, is called Normal to Normal interval (NN interval), on which HRV parameters must be estimated. This time-method is better for short-term recordings analysis.[42] The metrics are expressed in original units (ms). This domain includes several metrics such as SDNN or rMSSD.

SDNN. Standard deviation of NN intervals throughout the recording period. While considered as the gold standard of HRV, SDNN is not specific to the vagus nerve and does not reflect the cardiac vagal tone only. It reflects both cardiac vagal and sympathetic functions.[10,43]

rMSSD. Square root of the mean of the sum of the squares of differences between adjacent NN intervals. It is known as a good estimate of PSNS activity and reflects the short-term variation of HR.[10,44,45] rMSSD doesn't seem to be significantly affected by breathing rate in several studies,[46–48] even if Laborde et al. describe less clear results.[49] However, rMSSD seems to be mainly affected by a respiratory arrest.[50] To the contrary, SDNN appears to be more impacted by breathing stimulations.[51] Consequently, it seems to be suitable for cardiac vagal tone measurement, especially in oncology.

NN50 count/pNN50. NN50 corresponds to the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. It requires a 2 min (min) period.[11] The pNN50 is the percentage of successive RR intervals that differ by more than 50 ms. The pNN50 reflects short term variations of the HRV and the cardiac vagal tone,[10,45] especially the PSNS function.[22,44] NN50 is strongly correlated with rMSSD.[52]

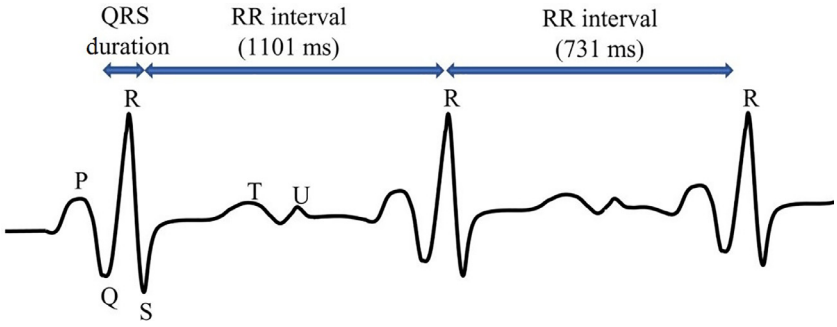

Fig. 1. QRS complex and RR interval. ms, milliseconds; RR interval, interval between two R peaks.

DC/AC capacities. Deceleration Capacity (DC) and Acceleration Capacity (AC) of HR are recent measurements that seem to be relevant in oncology. DC is a measure of cardiac parasympathetic modulation capturing the lengthening of the RR interval over 2 to 4 successive beats; the opposite for AC. DC is more robust to artifacts and noise,[53] while AC describes SNS activity and is not a measure of cardiac vagal tone.

3.2. Frequency-domain variables

The frequency domain provides information on the spectral density as a function of frequency of Inter-Beat Interval. Thanks to a Fast Fourier transform (FFT), one gets a relative distribution of different frequencies of the HRV components (HRV Power Spectrum). This technique identifies three main peaks: the High and Low frequencies (HF and LF, respectively; Power in High Frequency range and Power in Low Frequency range) and the Very Low frequencies (VLF). These frequency metrics are given in Hertz (Hz). Note that some software display autoregressive (AR) spectrum in addition to FFT spectrum, like Kubios software, and can compute metrics from both estimation methods, leading to different metric's values.

LF. The Low Frequency band (0.04–0.15 Hz) mainly represents PSNS and SNS activity but not whole cardiac vagal tone,[10] as well as baroreceptor activity in resting conditions.[54] Thus, the LF power can be produced by PSNS, SNS, blood pressure regulation by baroceptors or by the baroreflex activity.[11,55]

HF. The High Frequency band (0.15–0.4 Hz) indicates PSNS activity.[54] It is mainly due to HR variations during breathing (RSA). Consequently, Grossman et al.[56] consider that it does not completely represent the cardiac vagal tone. Some other authors says that HF reflects short-term variation of HRV (as rMSSD does) and is a response to cardiac vagal tone changes.

LF/HF ratio. While LF illustrates PSNS and SNS activity and HF only PSNS activity, the LF/HF ratio provides information about the relation between both systems. A low ratio could mean a PSNS dominance. Yet, some authors warn that only a part of LF is due to PSNS and as a consequence, the ratio would not describe the vagal balance.[57–59]

VLF. This band represents long-term regulation mechanisms, thermoregulation and hormonal mechanisms.[6,10] The Very Low Frequency (0.0033 to 0.04 Hz) is strongly related to mortality[15] and health.[58]

RSA. It corresponds to HR variability due to breathing (increased during inhalation and decreased during exhalation). This low physiological variation of HR can be observed in a 0.15–0.4 Hz band. RSA is highly correlated to HF when breathing rate is comprised between 9 and 24 cycles per minute.[54,60] Several authors consider that RSA is not a direct measurement of vagus nerve activity,[11,56,61,62] but rather a partial measurement.[56] Even if RSA is correlated to vagal tone, Farmer et al.[63] show that a significant proportion of cardiac vagal tone arises independently of RSA. The RSA may reflect the respiratory component of cardiac vagal tone, which is generated by the respiratory centers acting on the cardioregulatory centers.[64] Consequently, it should not be used to assess the cardiac vagal tone. Moreover, no long term changes in cardiac vagal tone have been studied with current methods of respiratory stimulation (controlled breathing, biofeedback, etc.) and no data for cancer patients are available.

3.3. Metrics specific to cardiac vagal tone and HRV

Some metrics are specific to cardiac vagal tone, while others provide broader information. Thus, each of them describes different characteristics of the HRV and cardiac vagal tone, like the rMSSD which focuses on short-term variation and corresponds to the activity of the PSNS.

Table 1 presents the main HRV metrics that can currently be useful in oncology. Especially because no data are available for cancer patients or because they do not describe vagal tone, other metrics in the Time domain, such as, NN50 count, HRVI (HRV triangular index), AC and in Frequency domain, such as Total power, LnHF (natural logarithm of HF), Very Low Frequency VLF, Ultra Low Frequency ULF, and RSA show currently a limited interest.

In the Frequency-domain, most publications display data in Absolute (ms^2) or Normalized power (n.u.). Some software, such as Kubios, display frequencies in Peak (Hz), Relative (%), and Logarithmic transform (log) as well. To improve analysis, Laborde et al.[10] advise to analyze several parameters together (such as rMMSD for PSNS and SDNN for the SNS and PSNS), in addition to unrelated to cardiac vagal tone ones.

4. Reference data in healthy and cancer patients

To properly assess treatment effects on HRV metrics, norms on healthy and unhealthy patients have to be defined. Various diseases affect cardiac vagal tone. For example, in cancer patients, a significant imbalance of the ANS is observed, resulting in an SDNN generally under 20 ms and an rMSSD under 30 ms. Even if SDNN jointly decreases with rMSSD in most of studies, SDNN seems to remain a better predictor of survival.

It has to be noticed that HRV metrics fluctuate along the daytime and display maximal and minimal values at specific times of the day. For example, SDNN reaches maximal values around 6 AM instead of midday for rMSSD. While circadian rhythm could affect HRV parameters, the time of measurement is of great importance. All measurements among a study have to be carried out within a 4 h range of time, preferentially early in the morning while maximum values are reached for most of the parameters. Moreover, special attention must be paid to cancer patients because of a particularly altered circadian rhythm.[65]

Table 2 shows values for short and long term measurements in healthy people as well as observed data on patients with cancers. No prognostic or survival data are available for RSA and LF.

Most of HRV analyses in cancer patients are short-term HRV measurements and focus on solid cancers. SDNN appears to be a relevant marker of survival, although not a pure vagal metric. SDNN in healthy individuals is found around 50 ms, whereas it varies between 7.6 ms and 70 ms (mean = 21.65 16.78 ms) in cancer patients, depending on study. rMSSD seems to be a relevant cardiac vagal marker, but a poor prognostic one. Data show higher rMSSD values in healthy individuals (mean = 42±15 ms) than in cancer patients (mean = 23.79±20.48 ms,

Table 1
Main HRV metrics and analysis domains useful in oncology.

Domain/etric	Vagal tone	Unit	SNS/PSNS	Cause and reflected activity
Time-domain				
SDNN	Both[10,43]	ms	Both	Global HRV, reflecting cardiac vagal and SNS functions. Short and long term variations.
rMSSD	Yes[6,10,22]	ms	Both but mainly PSNS	Short term variation.
pNN50	Yes[10,22]	%	Both but mainly PSNS	Short term variation.
DC	Yes[130]	ms	Both but mainly PSNS	Short term variation.
Frequency-domain				
HF	Yes,[6,10] No[11]	*	Both but mainly PSNS	Heart variability induced by breathing.
LF	Both[10]	*	Both[10] or SNS[131]	Baroreceptors activity.
LF/HF ratio	Both[10]	None	Both[10]	SNS-PSNS balance.[11]

* HF and LF peak = Hz, HF and LF absolute power = ms^2, HF and LF relative power = normalized unit (n.u.)
Abbreviations: DC, deceleration capacity of heart rate; HF, high frequency; HRV, heart rate variability; Hz, Hertz; LF, low frequency; ms, milliseconds; NN interval, Normal to Normal interval; PSNS, parasympathetic nervous system; pNN50, NN intervals more than 50 ms; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN, standard deviation of all NN intervals; SNS, sympathetic nervous system.

Table 2
Observed data in healthy and cancer patients.

Metric	Daytime peak	Healthy + n^{ref}		Cancer patients + n^{ref}	
		Long-term	Short-term	Prognosis	Observed data
SDNN	6–8 AM[132,133]	141±39 ms (n^{6}= 228, n^{134} = 274) 146±37 ms (n^{68} = 543)	50±16 ms (n^{86} = 21.438)	Poor prognosis for SDNN≤7.6 ms, n^{53} = 39; ≤10 ms, n^{78} = 97; ≤20 ms, $n^{99,100}$ = 103;272; ≤40 ms, n^{43} = 47; ≤70 ms, n^{22}= 131. Reference data used in HRV studies: 20 ms, $n^{99–102}$= 113;103;272;38.	All cancers 21.65±16.78 ms, n^{103} = 657; lung 17±14.6 ms, n^{102} = 133; prostate 31.24±30.27 ms, n^{102} = 246; ovarian cancer 11.1 ms (min = 1.93; max = 74.5), n^{135} = 202.
rMSSD	12 PM[136]	27±12 ms (n^{6} = 228); 41±21 ms (n^{68} = 543)	42±15 ms (n^{86} = 21.438)	Not a survival prognostic factor.[20,53,101,102] Significant correlation with PSA levels at 6 months.[102]	All cancers 23.79±20.48 ms n^{103} = 657; lung NSCLC 19.1±21.1 ms and prostate 32.34±40.25 ms, n^{102} = 246; breast 19.8±8.5 ms (<18 months after surgery) and 15.0±6.0 ms (>18 months after surgery), n^{95} = 30; leukemia 26±11 ms, n^{137} = 36; ovarian cancer 11.5 ms (min = 1.70; max = 84.8), n^{135} = 202. Always significantly lower values than in heathy people $n^{137,138}$= 184.
pNN50	3 AM[139]	12±10 ms (n^{68} = 543)	No data.	No data.	Leukemia 16±5 ms, n^{137} = 36.
HF	5 AM[132]	13 n.u. (men) (n^{140} = 979); 16 n.u. (women) (n^{140} = 1,117)	975 ±203 ms^2 and 29±3 n.u. (n^{6} = 228); 657±777 ms^2 and 40±10 n.u. (n^{86} = 21.438)	Breast cancer: higher baseline resting HF significantly predicted longer survival, HR = 0.75, 95% CI=[0.60–0.92].[97] HF power significantly associated with longer time to death in hepatocellular carcinoma.[19] lnHF power significantly associated with longer 7-day survival in non-lung cancer.[98] No significant association between frequency domain parameters and survival in advanced cancer.[21]	No statistical difference in HF: metastatic cancer 135.4±186.4 ms^2, n^{18} = 61; control (non metastatic) 185.3±219.4 ms^2, n^{18} = 63. Lower lnHF 3.55±2.61 ms^2, n^{100} = 103 in low grade cancers and lnHF 2.61±1.18 ms^2 in high grade cancers, n^{100} = 50. Lung cancers (7 days survival): lnHF = 0.92±2.26 ≤ 7 days, n^{98} = 29; lnHF = 2.25±3.07 > 7 days, n^{98} = 109.
LF/HF Ratio	No data.	No data.	2.8±2.6 (n^{86}= 21.438)	Metastasis do not affect LF/HF ratio.[18] Brain tumor: no difference in LF/HF.[141]	No statistical difference in LF/HF ratio: metastatic cancer 1.60±1.83, n^{18} = 61; control (non metastatic) 1.87±1.36, n^{18} = 63.
DC	No data.	6.5±2.0 ms (n^{130} = 65); 7.2 ms (n^{142} = 212)	12.40±5.46 ms (n^{143} = 191)	Poor prognosis for DC≤2.3 ms, n^{53} = 39. Poor prognosis for DC≤4.5 ms, n^{144} = 140.	Patients who died within the hospital, survivors DC ≤4.0±2.6 ms and non-survivors DC ≤2.6±1.8 ms, n^{144} = 140. Patients who died within 180 days, survivors DC ≤4.3±2.9 ms and non-survivors DC ≤3.3±2.0 ms, n^{144} = 140

Abbreviations: AM, ante meridiem; CI, confidence interval; DC, deceleration capacity of heart rate; HF, high frequency; HR, hazard ratio; HRV, heart rate variability; LF, low frequency; lnHF, natural logarithm of high frequency; min, minimum; max, maximum; ms, millisecond; NSCLC, non-small-cell lung cancer; n.u., normalized unit; PM, post meridiem; pNN50, NN intervals more than 50 ms; PSA, prostate specific antigen; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN, standard deviation of all NN intervals.

Table 3
Physical activity's effect on HRV metrics in healthy and cancer patients.

Population	Ref.	Metric	Number	Effects
Healthy				
Midage patients (mean=67.8 yo)	[145]	SDNN, rMSSD, HF	289	↑ except for resistance training
High level athletes, young adults	[146]	rMSSD, HF	87	↑ with HIT
		LF/HF ratio	87	↓ with HIT
Student athletes, students	[147]	Time-domain (men), time and frequency domain (women)	200	↑ except SDANN in men and SDNN + LF/HF ratio in women
Professional freedivers	[148]	All HRV metrics	13	↑
Elite freedivers + less-trained patients	[50]	rMSSD	5 + 5	↑ during SA
Cancer				
Colorectal, lung, breast, genital, gastrointestinal, and hematological	[149]	SDNN, rMSSD, HF, LF	146	↑
		LF/HF ratio	146	↓

Abbreviations: HF, high frequency; HIT, high intensity training; HRV, heart rate variability; LF, low frequency; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SA, static apnea; SDANN, standard deviation of the 5 min average NN intervals; SDNN, standard deviation of all NN intervals.

[range 11.5–32.34 ms]). pNN50 is also an relevant cardiac vagal marker, but data are scarce.

In the Frequency domain, HF represent a partial measure of vagal tone, and its role in cancer prognosis is uncertain. While reference measurements in healthy patients range from 657±777 ms^2 to 975±203 ms^2, these values are lower in cancer patients (185.3±219.4 ms^2 in non-metastatic cancers and 135.4±186.4 ms^2 in metastatic cancers). Same is observed for LF/HF ratio, with 2.8±2.6 in healthy patients while 1.87±1.36 for non-metastatic cancer and 1.60±1.83 for metastatic cancer patients. Finally, DC appears to be an interesting prognostic and cardiac vagal marker, although further studies are mandatory to confirm these results. In healthy patients, DC has been evaluated at 12.40±5.46 ms. In cancer patients, it may be a prognostic indicator when values fall below ≤4.5 ms.

On metastatic cancers, effects of treatments such as chemotherapy and radiotherapy could be reduced[66] and vagal activity could play a greater role.[17] This may explain the recent interest in the role of the vagus nerve in the prognosis of metastatic cancer.[17,23,24] In the future, this could represent a complementary therapeutic strategy for these cancers.

5. External factors' influence

Several external factors could affect the HRV metrics and induce confounding effects. For example, age and sex affect HRV parameters. Globally, higher values in males than females are observed for all ages.[67] rMSSD and pNN50 show a U-shape distribution along the ages (lowest value around 53 yo and an increase over 60 yo). To the contrary, estimators describing whole ANS, as SDNN, linearly decrease with age.[68] However, Acharya et al.[69] found that all metrics display a linear decrease until 55 yo, then linearly increase from 60 yo.

Other factors can affect HRV: health status, food,[70] water consumption and bladder filling,[71] as well as genetics, body mass index, coffee consumption, smoking, drugs, chronic diseases, etc.,[72] or fatigue.[73] To limit these factors' influence, some authors recommend to take measurements in supine position early in the morning.[74]

Physical activity (Table 3) globally stimulates cardiac vagal activity in healthy and cancer patients as well, even though not all activities have the same effect and HRV metrics. Endurance sports and breathing-related sports like apnea improve HRV more than resistance training sports. Consequently, training programs should pay particular attention to endurance sports.

Drugs are the factor leading to the highest variability in HRV in the midage patients.[72] Alpha-1 blockers, Benzodiazepines, Beta blocker, Bupropion, Clozapine, Cocaine, Fanatrex, Flecainide, Scopolamine, Thioridazine, Tricyclics, etc., globally affects HRV.[75] A vagal neuropathy has been observed in male chronic alcoholics.[76] Overall, drugs acting on the heart tend to stimulate vagus nerve activity, whereas psychotropic drugs, sedatives, and antidepressants decrease cardiac vagal tone. Few data are available for radiotherapy, but it tends to decrease DC, rMSSD, SDNN, LF, and HF while it increases AC and FC.[77]

Chemotherapeutic agents also appear to reduce cardiac vagal tone. However, current studies do not indicate whether these effects remain long-term and further studies should be done. Table 4 focuses on chemotherapy's effects on HRV metrics. Despite these effects, HRV metrics are not systematically measured before therapies. While some studies have estimated metrics before therapies,[78] others measured it during[79,80] or after[81] chemotherapy. To minimize the drug's influence, it seems advisable to take measurement before starting treatment and, during follow-up, before each new chemotherapy session.

All other external factors' effects on healthy patients are resumed in Table 5, but no data on patients with cancer are available for caffeine, alcohol, and tobacco. However, considering the significant impact they have on HRV metrics in healthy patients, they have to be taken into account as possible confounding factors in cancer patients. Indeed, in healthy patients, lifestyle seems to influence HRV metrics. Alcohol and tobacco affect all HRV markers, even in regular users. Although less expected, the observed influence of diet, nutrients and fasting implies that these factors should be considered therapeutic factors. Fasting combined with chemotherapy has already shown encouraging results.[82] To the contrary, caffeine's effects are less clear, and call into question about the sympathetic influence usually attributed to it.

Influence of breathing simulation is highly debated and no consensus exists. Breathing seems to globally increase HRV in healthy patients, while it could be more variable depending on disease. On healthy patients, slow breathing,[83] short apnea,[84] and controlled breathing[85] would increase LF, LF/HF as well as slow and controlled breathing would increase SDNN and rMSSD, respectively. To the contrary, slow and controlled breathing would decrease HF, while short apnea will decrease rMSSD.

6. Collecting data

The main objective is to collect data that reflects cardiac vagal tone properly. To achieve this goal, several points must be addressed: recording duration, measurement tool, analysis software, and artifact corrections.

6.1. Recording duration

Several durations are found in literature: long-term (24 h, sometimes 1 to 24 h), short-term (5–10 min, sometimes 2–30 min), ultra-short term (10 s to 2 min). The same duration of 2 min could be called short-term and ultra-short term depending on studies.

Table 4
Chemotherapy's effect on HRV metrics in cancer patients.

Cancer type	Ref.	Metric	Number	Effects
Lung	79	LF/HF ratio	12	Higher fatigue correlate with higher LF/HF ratio during sleeping time
Breast	80	SDNN	44	↓
Breast	150	All HRV metrics	40	↓ non-significant with high-dose of chemotherapy
Breast	81	rMSSD, pNN50, HF, LF	20	↓

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; pNN50, NN intervals more than 50 ms; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN, standard deviation of all NN intervals.

Table 5
External factors' effect on HRV metrics in healthy patients.

Factor/population	Ref.	Metric	Number	Effects
Caffeine				
All patients (regular or non regular consumers)	151	rMSSD, HF	77	↑ with caffeinated espresso in habitual consumers
		LF/HF ratio	77	↓ with caffeinated espresso in habitual consumers
All patients	152	SDNN, rMSSD	62	↑ (one study) or ↓ (one study)
		pNN50	10	↓ (one study)
		HF	89	↑ (only one study found ↓)
		LF	18	↑ (2 studies)
		LF/HF ratio	95	↑ or ↓ depending on study
Regular young consumers	153	All HRV metrics	30	No effect
Alcohol				
All patients	128	rMSSD, SDNN, HF	12	↓
All patients (acute effect)	129	HF	133	↓ (8 studies) 1 study no change
		LF	98	↓ (2 studies) ↑ (2 studies) and 2 studies no change
Non alcohol dependent consumers (healthy)	154	SDNN	28	↓
		rMSSD	196	↓
Tobacco				
All patients (acute effect)	127	SDNN, rMSSD, HF	15	↓ during the next 5 to 10 min
		LF, LF/HF ratio	15	↑ during the next 5 to 10 min
Mediterranean Diet				
All patients	155	All HRV metrics	276	↑
Fish consumption				
All patients	156	SDNN (short-term), rMSSD (short + long-term), HF, VLF	4263 (ECG), 1152 (24 h Holter-ECG)	↑
		LF, LF/HF ratio	4263 (ECG), 1152 (24 h Holter)	↓
All patients	157	rMSSD, HF, SDNN	157	↑ with increased DHA and increased DHA+EPA.
Vitamine D				
All patients	158	SDNN, rMSDD, pNN50, HF	24	↓ in deficient group
		LF, LF/HF ratio	24	↑ in deficient group
All patients	159	HF	13	↑
Fasting				
All patients	160	SDNN, rMSSD, pNN50	80	↑

Abbreviations: DHA, docosahexaenoic acid; ECG, electrocardiogram; EPA, eicosapentaenoic acid; h, hour; HF, high frequency; HRV, heart rate variability; LF, low frequency; pNN50, NN intervals more than 50 ms; rMSSD, square root of the mean of the sum of the squares of differences between adjacent NN intervals; SDNN, standard deviation of all NN intervals; VLF, very low frequency.

Some authors, such as Heathers,[71] consider that the measurement must last for at least 1 h. Frequency analysis from short-term recordings to characterize ANS state or sympathicovagal balance would be problematic. Indeed, a large variation in HRV during measurement can be observed.[86] Others consider short-term recording data to be sufficient.[87] The rMSSD appears to be a reliable metric for assessing HRV from even ultra-short ECG recordings (1 min or 10 s), but the SDNN does not.[88,89] Moreover, the reliability of ultra-short term measurements may contain a small percentage of error due to extraneous physiological influences, particularly respiratory.[90] Currently, to obtain a measurement as reliable as a 24-hour measurement, the reference guidelines recommend 5 to 10 min of measurement.[4,6]

In unhealthy patients (especially heart disease or mental illness), no consensus exists as well. Munoz et al.[91] mention that long-term recording is not necessary to obtain accurate measurements of rMSSD and SDNN. Others indicate that short-term HRV recording is related to long-term (24-hour) measurements in patients at risk for sudden cardiac death.[92]

Patients with cancer. Short-term is the most frequently used time duration in oncology.[17,23,24,93] De Couck et al.[17] advise a minimum duration of 5 min to reduce methodological bias.

6.2. *Measurement tools*

The 24-hour ECG remains the reference material.[11] However, the Polar H10 chest belt has been validated against the ECG gold standard at rest and during exercise.[94]

Patients with cancer. Only Polar S810i has been used in a published oncology study.[95] However, some current studies used Polar H10 too, such as Martinez et al.[96] ECG is the most commonly used mate-

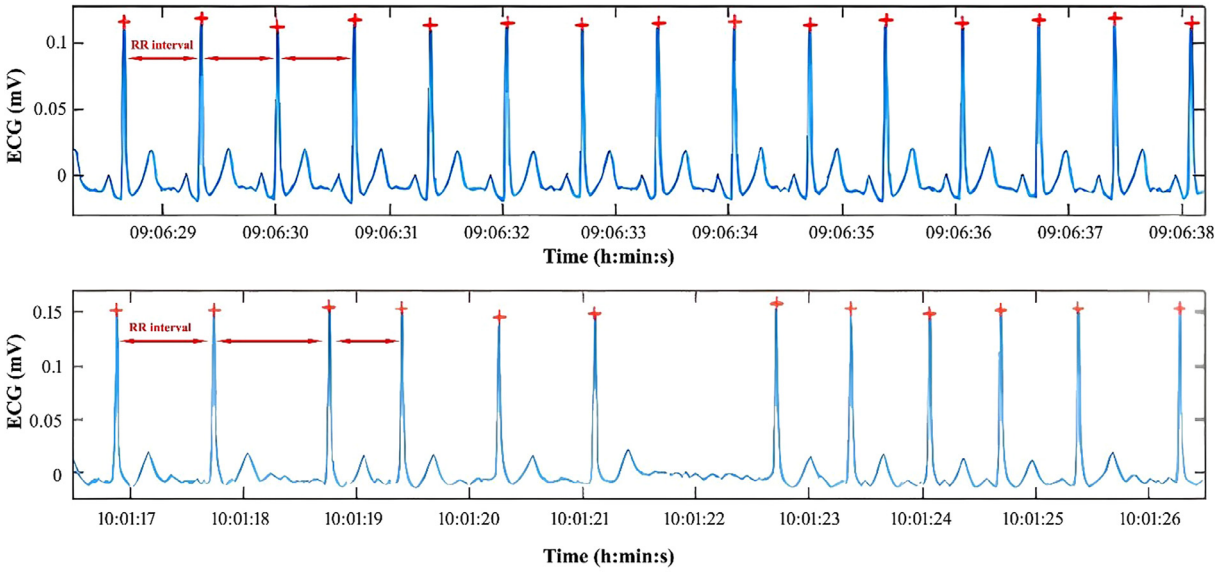

Fig. 2. Differences between normal ECG (top) and ECG with artifacts (bottom). ECG, electrocardiogram.

rial (sometimes with Lead II configuration[97]), with a short-term Holter-ECG[17–20,23,24,78,93,97–100] or ultra-short term ECG.[17,23,24,30,99,101–103]

6.3. Analysis software

Several software allow ECG analysis: HRVAnalysis, ECGLab, HRV Toolkit, RHRV, KARDIA, POLYAN, Artiifact, Codesna, and Kubios HRV. Few software comparisons have been conducted, especially to compare various software to Kubios,[104] which is considered as the reference for research purpose and should be preferably used. In addition, Kubios displays Frequency domain metrics obtained from FFT and AR methods. Some measurement tools include analysis software. For example, Synescope Spiderview is included with the spiderview Holter-ECG.[105]

6.4. Artifact's corrections

Artifacts may appear when the recording tool detects missing, extra, or misaligned beats as well as ectopic beats such as premature ventricular contractions (PVC) or other arrhythmias. Artifacts may be caused by electrical interference due to bad contact or external disturbances.[75] Fig. 2 highlights differences between a normal ECG and an ECG with artifacts.

Ectopic beats are the most frequent cause of artifacts.[106] Its can be generated by external factors (sighing or coughing for example) as well as by circadian rhythm, physical or emotional stress,[4,107] or cardiac diseases.[108] Treatments, in particular chemotherapy, can induce arrhythmias as well.[109–111] Patient movements can also introduce ectopic beats.[75]

Only a few ectopic beats are enough to bias the HRV analysis, and even only one in a short-term recording of 2 min[4] or 10 min.[112] 1% of ectopic beats can significantly affect most of HRV metrics and 0.1% is sufficient to modify rMSSD measurement.[113] They can also mask physiological beats.[114,115]

Therefore, non-physiological beats that are not generated by sinus node depolarization must be eliminated from the recording.[116] As opposed to non-physiological artifacts caused by cough and movement, the ectopic beats have to be included. The regularity of the beats, the interval between them and their amplitude has to be visually checked to determine which ones must be excluded from the analysis.[6,10,11,117,118] It is advised that analyses always be performed by a single trained investigator.[119] Catai et al.[120] published guidelines and procedures for HRV analysis.

For Sheridan et al.,[121] up to one third of the beats could be deleted in a short-term duration (1 min) to measure rMSSD and SDNN without impacting the whole HRV measure by more than 5%. Others suggest that SDNN and rMSSD are not affected at all with a loss of 2.5% of data.[122]

Consequently, several adjustments are possible[123]: Uncorrected (no correction applied to any intervals; data were left as recorded), Deletion (erroneous RR interval[s] were deleted from the recording), Interpolation (erroneous non-normal RR intervals are replaced by interpolated intervals), Degree Zero (substitution of artifact[s] with a mean value calculated from surrounding R-R intervals), Degree One (a straight line is drawn over the irregular intervals to obtain new values), Cubic (cubic interpolation uses four datum points to compute the polynomial; no constraints on the derivatives), and Spline (cubic spline interpolation that computes a third order polynomial from only two datum points with the additional constraint that first and second derivatives at the interpolation points are continuous).

HRV analysis software offer automatic adjustment. For example, Kubios provides options for the detection and correction of ectopic beats and artifacts, with several correction modes depending of the sensitivity threshold (in second): very low 0.45 s; low 0.35 s; medium 0.25 s; strong 0.15 s; very strong 0.05 s; and custom threshold.[124] While using medium and strong corrections, Kubios displays fewer errors than other software such as Polar Protrainer 5 or Macalester. However, Alcantara et al.[125] suggest the lowest Kubios filters (very low, low, or medium) in younger populations and a stronger one in older populations (strong). In any case, the very strong Kubios filter has to be used with caution.

Kubios offers an automatic beat correction algorithm which seems to be the most accurate.[126] However, Laborde et al.[10] warn that this correction may detect physiological beats as artifacts. This can bias the whole HRV analysis. Kubios indicates that only two artifacts in the 5-min analysis recording have a significant effect on HRV parameters, as previously noted. Nonetheless, Kubios specifies that less than 5% should be removed to avoid suppressing variability.[124]

7. Suggested protocol to evaluate cardiac vagal tone in oncology

Our review aims to offer clear and easy-to-use guidelines to properly evaluate cardiac vagal tone. We previously described all confounding factors that would bias HRV measurements and analysis, focusing on patients with cancer and undergoing chemotherapy treatment. The following seven key points below will help to considerably reduce errors in HRV analysis.

Key points:

- **Confounding factors**. No alcohol two hours before recording and no nicotine 10 min before recording.[127–129] To minimize the drug's influence, we recommend taking measurement before starting chemotherapy treatment, during follow-up, and before each new chemotherapy session.
- **Breathing**. Spontaneous breathing is the better breathing protocol. Measurements with respiratory stimulation (biofeedback for example) are not easy to perform due to the systemic state of patients with cancer and undergoing chemotherapy.[36,109–111] However, if the respiratory stimulation does not produce too many artifacts, it could be used.[17]
- **Circadian rhythm**. Recordings should be done in the morning, in a 4 h interval of time.[71]
- **Duration**. Allow the patient to rest for at least 5 min in the supine position before measurement. Avoid any recording shorter than 5 min in unhealthy patients, especially patients with cancer.[6,17]
- **Tool**. Holter-ECG is the reference tool in oncology for HRV measurement.[17,23,24,93] Polar H10 chest belt appears to be the most accurate portable device for HRV recording if a Holter-ECG is not available.
- **HRV metric**. Use rMSSD to estimate the cardiac vagal tone.[6] It has to be combined with other variables such as SDNN for vital prognosis assessment. DC offers interesting prospects for the future as it could lead to less artifacts and may represent a relevant cardio vagal prognostic marker.[53] Kubios can be used for HRV analysis.
- **Artifacts**. Select R-R interval sections without artifacts. If it is not possible, artifacts must be corrected or removed.[11,75,118] They have to be visually identified by a trained investigator.[6,10,11,117] Automatic beat correction algorithm is not recommended.

8. Conclusion

Literature provides complex and spread data about HRV and confounding factors. Our review proposes a checklist of key points to properly measure HRV in oncology, in an easy-to-use way. These simple recommendations can be followed in clinical practice as well as in clinical research to assess the cardiac vagal tone. An important key point is that, even if SDNN appears as a better predictor of survival for patients with cancer,[17,23,24] the rMSSD is the most specific estimator for the cardiac vagal tone (especially in short-term measurement).

By identifying and synthesizing the confounding factors that can affect HRV metrics, targeted therapies to improve HRV in cancer patients can be more easily implemented. For example, physical activity is used in some medical departments to improve patients' global health and quality of life, and in a same approach, it would be possible to organize HRV stimulation protocols in routine practice to improve vital prognosis. To evaluate the effectiveness of such protocols, clinical trials have to be carried out by controlling the confounding factors, with controlled food, physical activity with apnea, reduction of certain drugs (not essential to the treatment), tobacco, or alcohol. Our review would be helpful for future clinical trials.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

All authors have made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data, to draft the article or revising it critically for important intellectual content, and to the final approval of the version to be submitted. P.M, G.G, and M.G designed the study (conceptualization, formal analysis, investigation and methodology). P.M. and G.G. were involved in analysis and writing the original draft. P.M. analyzed the data. S.C. and J.T. helped in reviewing the manuscript and provided critical revisions. G.G. and M.G. were in charge of project administration and supervision.

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