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Published in:
SN Comprehensive Clinical Medicine

DOI:
10.1007/s42399-024-01656-8

Publication date:
2024

SN Comprehensive Clinical Medicine (2024) 6:30
https://doi.org/10.1007/s42399-024-01656-8

ORIGINAL PAPER

The Effect of Cardiovascular Medication on Heart Rate Variability in Patients Presenting with Early Sepsis at the Emergency Department: A Prospective Cohort Study

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Accepted: 24 February 2024

Abstract

Our SepsiVit study showed that long-term, automatically analyzed ECG recordings can be used to determine heart rate variability (HRV) features associated with the clinical deterioration of early septic patients at the ED. This study focus on the influence of cardiovascular medication on HRV in patients with early sepsis at the ED. This study is an exploratory post-hoc analysis of our SepsiVit study. Eligible patients were connected to a mobile bedside monitor for continuously ECG measurements. The first 3 hours were analyzed for this study. Between January 2017 and December 2018, 171 patients were included with early sepsis, defined as infection and two or more systemic inflammatory response syndrome criteria. We excluded sixteen patients because of insufficient measurements. Therefore, we included 155 patients in the final analysis: 72.9% with sepsis, 2.6% with septic shock, and 24.5% classified as infection. In 9.0% of the patients, medication directly impacting cardiac contractility was administered, while 22.6% received medication with an indirect effect. A combination of both types of medication was prescribed to 17.4% of the patients. The majority of patients (51.0%) did not utilize any cardiovascular medication. Patients using both medication with direct and indirect effect were on average 10 years older than patients using no cardiovascular medication (p 0.037). No differences in vital signs or HRV parameters were found in patients using cardiovascular medication. Our results showed that HRV is not influenced by cardiovascular medication. Consequently, the correction of HRV features for the use of cardiovascular medication is unnecessary when analyzing, modelling, and interpreting these signals.

Keywords Sepsis · Infection · Emergency department · Heart rate variability · HRV · Cardiovascular medication · Beta-blockers · RAS-inhibitors · Dihydropyridine · Diuretics

Introduction

Early recognition of sepsis is crucial for timely treatment and resuscitation to prevent organ dysfunction and mortality in patients with sepsis [1]. Current diagnostic criteria employed to recognize early sepsis in the emergency department (ED) use a combination of vital parameters combined with the suspicion of infection. Yet, these criteria are insufficient to precisely estimate the severity of illness or monitor the response to treatment. A promising approach to improve

This article is part of the Topical Collection on *Medicine*

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Published online: 12 March 2024

early recognition of hemodynamic instability in sepsis and monitor the response to treatment seems analyses of changes in vital signs over time, called variability analysis. In the general population, high degrees of variability mark health, while disease is associated with reduced variability [2].

Heart rate variability (HRV) is one of the parameters studied in variability analysis. HRV refers to the variations in heartbeat intervals or correspondingly in the instantaneous heart rate, which gives a reliable reflection of the physiological factors influencing the normal rhythm of the heart [3]. Furthermore, it provides robust information about the interaction between the sympathetic and parasympathetic nervous systems [3]. HRV in septic patients has been primarily studied in small pilot studies and studies in Intensive Care Unit (ICU) patients [4–7]. However, HRV has not yet been studied in septic patients at the ED. The fact that septic patients at the ED are less severely ill than ICU patients, but are at major risk for deterioration, makes further analysis of HRV at the ED even more relevant [4].

HRV is influenced by numerous factors like age, sex, race, physiological determinants influencing the cardiac system, sepsis itself, and by medication. Based on a pilot study at our ED, we know that 34% of patients presenting with sepsis use beta-blockers, 15% use dihydropyridines, 24% diuretics, and 25% renin-angiotensin system (RAS)-inhibitors [1]. The influence of medication on HRV was investigated in different patient populations, including Multi Organ Dysfunction Syndrome (MODS) patients at ICU [8–14]. In these previous studies, beta-blockers, dihydropyridines, and RAS-inhibitors had ambiguous effects on HRV. These ambiguous effects on HRV were also found in patients with end stage renal disease or congestive heart failure using spironolactone [15–18]. This ambiguous effect may depend on underlying pathology or comorbidities [12].

This study aimed to expand insight into the influence of cardiovascular medication on HRV in early sepsis. We hypothesized that the use of cardiovascular medication increases HRV in septic patients, which may thereby lead to an underestimation of the severity of illness in these patients.

Methods

Study Design and Setting

This study is an exploratory post-hoc analysis of the SepsiVit study in adult non-trauma patients presenting with fever, (suspected) infection, or (early) sepsis at the ED of the University Medical Centre Groningen (UMCG), a tertiary care teaching hospital with over 34.000 ED visits annually [4]. We aimed to determine whether HRV measurements can provide an early warning for deterioration in patients with early sepsis presenting at the ED. Therefore, ECG, heart rate, blood pressure, respiratory rate, and oxygen saturation were continuously recorded during the first 48 h of hospital admission [4].

Study Population and Protocol

The protocol of the SepsiVit study was published before [4]. In short, eligible patients visiting the ED of the UMCG between 8 a.m. and 11 p.m. were recruited for the study. Adult patients suspected for early sepsis were included. Early sepsis was defined as the presence of an infection and at least two Systemic Inflammatory Response Syndrome (SIRS) criteria: body temperature < 36 °C or > 38 °C, heart rate > 90/min, respiratory rate > 20/min or $PaCO_2$ < 4.3 kPa, or leukocytes < 4,000/mm^3 or > 12,000/mm^3 [19]. Exclusion criteria were known pregnancy, cardiac transplantation or no admission at our hospital after triage at the ED.

Eligible patients were equipped with a mobile patient monitor (Philips IntelliVue MP70 System with Multi-Measurement Module; Philips, Eindhoven, The Netherlands) which continuously recorded vital signs (ECG, heart rate, respiratory rate, oxygen saturation, and blood pressure every 4 hours) during the first 48 hours of admission. Only the first 3 hours at the ED were used for this analysis, with the assumption that the influence of medication is more significant during this time, while later on, advanced treatment may confound HRV measurements. Furthermore, more complete inclusions were realized during the first 3 hours.

In addition, we collected data on patient characteristics, prescription drug usage, treatment parameters, and vital signs measurements (blood pressure, heart rate, temperature, respiratory rate) every 30 min during the stay at the ED and follow-up during hospital admission [4].

Data Integration

Raw 500 Hz ECG data captured by the monitor were pre-processed prior to analysis. Pre-processing the raw ECG data is extensively discussed in the SepsiVit protocol by Quinten et al. [4, 20]. In short, noise was filtered out of the raw signal, non-sinus rhythm ectopic beats were corrected and the R-peaks were detected in the resulting signal. The pre-processing and analysis of HRV were performed by an automated algorithm implemented in MATLAB R2018a (The MathWorks Inc., Natick, MA, USA). The ECG data in the first 3 hours were used to calculate HRV parameters in time and frequency domains (Table 1). Patients with insufficient measurement time, < 3 hours, were excluded.

Table 1 Definitions of HRV parameters

Domain	Description
HRV feature	
Time	
AVNN	Average of all NN intervals
SDNN	Standard deviation of the NN intervals
CV	Coefficient of variation of the NN intervals
Frequency	
HF norm	Normalized high frequency power: HFnorm = HF/(HF + LF)
LF norm	Normalized low frequency power: LFnorm = LF/(LF + HF)
LF/HF ratio	Ratio between low and high frequency power
VLF	Power in the very low frequency range (0.0033 to 0.04 Hz)
Non-linear	
SD2	Standard deviation of the continuous long-term NN-interval variability in the Poincaré plot

NN interval is the cardiac beat interval between two normal sinus heart beats

HF High Frequency, *LF* Low Frequency

Statistical Analysis

HRV was compared between four subgroups: patients using [1] medication with direct effect on cardiac contractility, [2] medication with indirect effect on cardiac contractility, [3] medication from both groups, with direct and indirect effect on cardiac contractility, and [4] no cardiovascular medication.

Medication with direct effect on cardiac contractility was defined as usage of ß-blockers and/or digoxin. Medication with indirect effect on cardiac contractility was defined as usage of RAS-inhibitors, dihydropyridines, and/or diuretics. Patients using medication from both of these categories were classified into group 3. If none of this medication was used, patients were classified into the group using no cardiovascular medication.

Continuous data are presented as mean ± standard deviation or median [interquartile range] in case of skewed distribution. Categorical data are presented as total numbers (percentages). Differences among the four groups were analyzed using one-way ANOVA for normally distributed continuous data and Kruskal–Wallis for skewed data. Categorical data were analyzed with a Chi-square test. A two-sided p-value of ≤ 0.05 was considered statistically significant. In the case of significance, groupwise comparison was conducted. The Mann–Whitney U test was used for skewed continuous data for each group combination, and the Chi-square test was employed for categorical data. Bonferroni correction was used to correct the p-values for multiple testing. All statistical analyzes were performed using SPSS Statistics (version 28, SPSS Inc., Chicago, IL, USA).

Results

Study Population

Between January 2017 and December 2018, 171 patients were included in the SepsiVit study. Sixteen patients were excluded because of insufficient measurement time (less than 3 hours). The data from the remaining 155 patients were used in the final analysis (Fig. 1).

Of these 155 patients, 72.9% presented with sepsis and 2.6% with septic shock. Sepsis severity was classified as infection in 24.5% of the patients, involving patients who demonstrated clinical signs of infection without a clearly identified focus. The overall population's median age was 65 years [52–75 years], and 54.8% were male (Table 2). Most common comorbidities were diabetes mellitus (26.5%), history of organ transplantation (25.2%), and malignancy (32.9%) (Table 2). In 9.0% of the patients, medication directly impacting cardiac contractility was administered, while 22.6% received medication with an indirect effect. A combination of both types of medication was prescribed to 17.4% of the patients. The majority of patients (51.0%) did not use any cardiovascular medication. Patients using both medication with direct and indirect effect were on average10 years older than patients using no cardiovascular medication (p 0.037). After pairwise comparison of the comorbidities diabetes mellitus, chronic renal insufficiency, and organ transplantation, no significant results were found.

Effects of Cardiovascular Medication on Vital Signs

Table 3 presents data about vital signs, stratification scores, organ failure development, hospital/ICU admission, and mortality. Nonetheless, no significant differences were observed among these variables across the four groups.

Table 4 shows the correlation between drug dose and vital signs. Dosage of beta-blockers and heart rate are negatively correlated. SBP, diastolic blood pressure (DBP), and MAP are positively correlated with the dosage of dihydropyridines (Table 4).

Effects of Cardiovascular Medication on HRV

HRV parameters were compared between patients with and without prescription of t medication with direct or indirect effect on cardiac contractility (Table 5). After pairwise comparison of VLF, no significant differences were found between the four groups. Dosage of beta-blockers and AVNN was

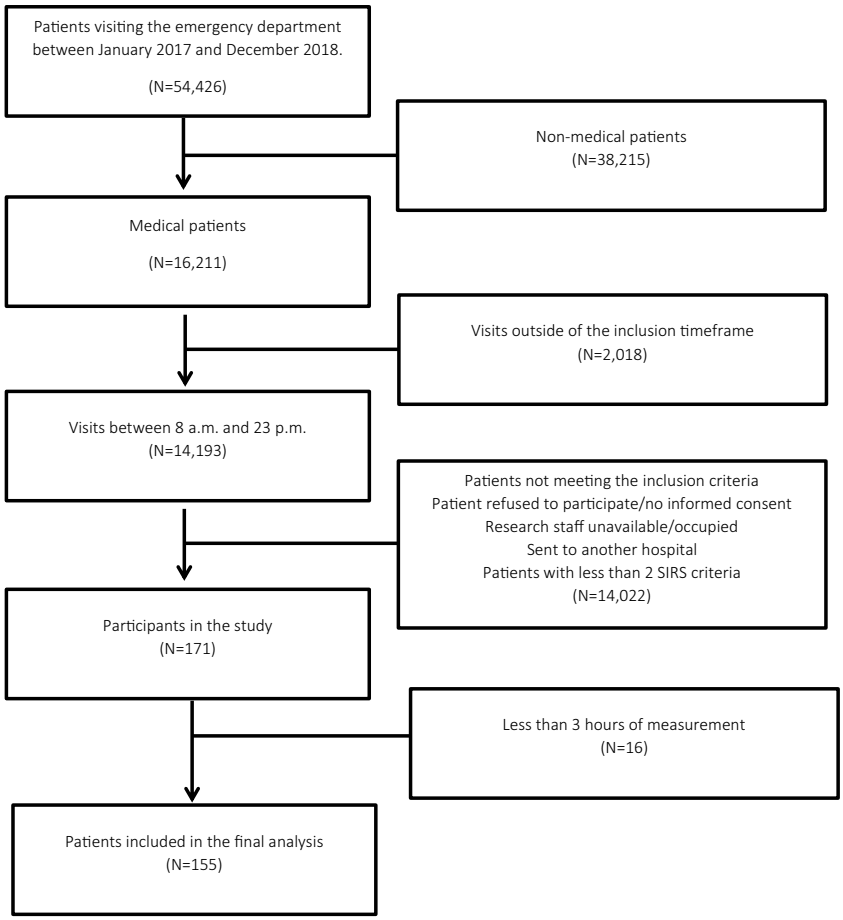

Fig. 1 Flow chart of patient selection

positively correlated, while dosage of beta-blockers and LF/HF ratio was negatively correlated (Table 4).

Discussion

The current study is a subanalysis of the SepsiVit study, which showed that continuous HRV measurement can provide an early warning for deterioration in patients with an infection and sepsis presenting at the ED. Here, we aimed to gain more insight into the influence of cardiovascular medication on HRV. We found that medication with direct or indirect effect on cardiac contractility had no significant impact on vital signs or HRV parameters.

Effects of cardiovascular medication on vital signs and HRV parameters

Our study revealed that cardiovascular medication had no impact on vital signs or HRV parameters. No effect on heart rate is remarkable based on the pharmacodynamics of beta-blockers, especially blockage of the ß1-receptors lowers the heart rate and is expected to increase the AVNN [23, 24]. We found a positive correlation between the dosage of dihydropyridines and SBP, DBP, and MAP. Based on the pharmacodynamics a lower blood pressure would be expected [25].

Previous studies showed a higher VLF in MODS patients using beta-blockers or RAS-inhibitors [8, 13]. Our study could not confirm these results, probably because the study population is different. Patients presenting at the ED with infection or (early) sepsis appear to be less severely ill than ICU patients, in general. Furthermore, 72.9% of our patients were in an early septic stage rather than having sepsis or MODS. Besides that, VLF is best monitored over 24 hours. However, only the first 3 hours of measurement were used in this analysis, which implies that our time window may have been too short to identify the effect on VLF [26].

The effect of dihydropyridines and diuretics on HRV was, to the best of our knowledge, not previously investigated in septic patients. Also, Sahin et al. did not find any significant changes in HRV parameters in patients using amlodipine prescribed because of previously untreated essential hypertension [10]. Zaliunas et al. found a lower VLF, LF (norm), HF norm, and LF/HF ratio in patients with stable angina pectoris, atrial hypertension, and isolated left ventricular diastolic dysfunction using amlodipine [14]. Furthermore, in the same study, a lower VLF, LF, and HF in patients using

Table 2 Patient characteristics, comorbidities, and cardiovascular medication at presentation at the ED

	All patients, $N=155$	Patients using medication with direct effect on cardiac contractility[1], $N=14$	Patients using medication with indirect effect on cardiac contractility[2], $N=35$	Patients using medication from both groups, with direct and indirect effect on cardiac contractility, $N=27$	Patients without the use of cardiovascular medication, $N=79$	*P* value
Demographics						
Age▼	65 [52–75]	67 [61–76]	69 [57–78]	72 [57–79]	62 [46-1]	0.016*
Gender●						0.876
Male	85 (54.8)	8 (57.1)	21 (60.0)	15 (55.6)	41 (51.9)	
Female	70 (45.2)	6 (42.9)	14 (40.0)	12 (44.4)	38 (48.1)	
Comorbidity●						
Cardiac disease◦	27 (17.4)	2 (14.3)	7 (20.0)	13 (48.1)	5 (6.3)	<0.001***
COPD	14 (9.0)	0 (0.0)	5 (14.3)	2 (7.4)	7 (8.9)	0.448
Diabetes mellitus	41 (26.5)	3 (21.4)	14 (40.0)	10 (37.0)	14 (17.7)	0.043*
Chronic liver disease	9 (5.8)	1 (7.1)	3 (8.6)	1 (3.7)	4 (5.1)	0.842
Chronic renal insufficiency	25 (16.1)	5 (35.7)	7 (20.0)	6 (22.2)	7 (8.9)	0.042*
Organ transplantation	39 (25.2)	8 (57.1)	8 (22.9)	7 (25.9)	16 (20.3)	0.033*
Malignancy	51 (32.9)	4 (28.6)	11 (31.4)	5 (18.5)	31 (39.2)	0.249
Cardiovascular medication prior to ED presentation●						
ß-Blockers	41 (26.5)	14 (100.0)	NA	27 (100.0)	NA	<0.001***
RAS-inhibitors	36 (23.2)	NA	19 (54.3	17 (63.0)	NA	<0.001***
Dihydropyridines	17 (11.0)	NA	9 (25.7)	8 (29.6)	NA	<0.001***
Diuretics	40 (25.8)	NA	23 (65.7)	17 (63.0)	NA	<0.001***
Digoxin	1 (0.6)	0 (0.0)	NA	1 (3.7)	NA	0.189
> 1 cardiovascular treatment	42 (25.6)	0 (0.0)	15 (42.9)	27 (100.0)	NA	<0.001***

COPD Chronic Obstructive Pulmonary Disease, *ED* Emergency Department, *RAS* Renin Angiotensin System, *NA* Not Applicable

▼Median [interquartile range]

●Absolute number (percentage)

◦Ischemic cardiac disease or congestive heart failure

*Significant result: * < 0.05, ** < 0.01, *** < 0.001 (differences between the groups were tested)

[1]Medication with direct effect on cardiac contractility = ß-blockers and/or digoxin

[2]Medication with indirect effect on cardiac contractility = RAS-inhibitors, dihydropyridines, and/or diuretics

lacidipine were found [14]. Patients with end stage renal disease using spironolactone showed a significantly higher SDNN [15]. A significantly lower HF was found in patients with congestive heart failure using spironolactone [18]. We could not confirm this result in our study.

Non-pharmacological factors influencing HRV parameters

HRV is influenced by many factors, which have to be considered when analyzing and modelling the effect of cardiovascular medication on HRV. One of the factors influencing HRV is age; a higher age leads to a lower HRV [27]. Patients using both medication with direct and indirect effect on cardiac contractility were on average 10 years older in contrast to patients using no cardiovascular medication. So, one might expect a lower HRV in this group [27]. However, our results showed no differences in HRV parameters.

Another factor influencing HRV is cardiac disease [28]. Patients surviving an acute myocardial infarction showed an increased LF norm and a diminished HF norm [28]. In contrast, our findings indicated no significant alterations in LF norm or HF norm, even when comparing groups with and without cardiovascular medication. Buttà et al. demonstrated the influence of several comorbidities on HRV, including among others obesity, pneumonia, dysthyroidism, ischemic stroke, and arterial hypertension [12]. Patients with several comorbidities were included in our study, which is representative for patients presenting at the ED with fever or suspected infection and/or sepsis.

Table 3 Disease indices and outcomes for all patients and patients on cardiovascular drugs

	Number	All patients, $N=155$	Number	Patients using medication with direct effect on cardiac contractility[1], $N=14$	Number	Patients using medication with indirect effect on cardiac contractility[2], $N=35$	Number	Patients using medication from both groups, with direct and indirect effect on cardiac contractility, $N=27$	Number	Patients without the use of cardiovascular medication, $N=79$	*P* value
Vital signs											
Heart rate (bpm)▼	149	106 [95–117]	14	107 [87–121]	33	107 [95–115]	24	98 [86–118]	78	108 [97–117]	0.494
Systolic blood pressure (mmHg)■	150	126 ± 21	14	129 ± 17	33	129 ± 20	25	128 ± 24	78	124 ± 21	0.634
Diastolic blood pressure (mmHg)■	150	74 ± 15	14	79 ± 13	33	75 ± 15	25	75 ± 21	78	73 ± 12	0.591
MAP (mmHg)■	150	92 ± 15	14	96 ± 13	33	93 ± 15	25	92 ± 21	78	90 ± 14	0.580
Respiratory rate (rpm)▼	84	22 [18–27]	9	22 [19–24]	19	23 [17–27]	16	25 [21–34]	40	20 [18–27]	0.104
Oxygen saturation (%)▼	139	96 [94–98]	13	96 [94–98]	30	96 [94–97]	24	95 [91–98]	72	97 [95–98]	0.489
Supplemental oxygen (L)▼	21	3 [2–4]	1	5	12	3 [2–4]	2	3 [2–3]	6	3 [2–7]	0.632
Temperature (°C)▼	146	38.3 [37.5–39.1]	13	38.2 [37.8–39.1]	33	38.5 [37.5–39.2]	23	38.3 [36.9–39.5]	77	38.3 [37.4–38.9]	0.885
Capillary refill (sec)▼	36	3 [2–3]	1	2	12	3 [2–3]	6	3 [2–3]	17	3 [2–4]	0.415
Stratification scores▼											
qSOFA score	151	0 [0–1]	14	1 [0–1]	33	0 [0–1]	27	0 [0–1]	77	0 [0–1]	0.951
SIRS score	143	2 [2–3]	13	2 [2–3]	32	2 [1–3]	26	3 [2–3]	72	2 [2–3]	0.195
Organ failure during hospital admission●											
Liver failure▫	154	10 (6.5)	14	1 (7.1)	34	2 (5.9)	27	2 (7.4)	79	5 (6.3)	0.995
Kidney failure◦	154	36 (23.4)	14	2 (14.3)	34	8 (23.5)	27	10 (27.0)	79	16 (20.3)	0.274
Respiratory failure◊	154	37 (24.0)	14	2 (14.3)	34	11 (32.4)	27	9 (33.3)	79	15 (19.0)	0.221
Hospital admission											
Length of stay (days)▼	154	5 [3–10]	14	6 [3–12]	34	4 [3–9]	27	5 [3–6]	79	5 [3–10]	0.865
ICU admission●	154	6 (3.9)	14	0 (0.0)	34	2 (5.9)	27	1 (3.7)	79	3 (3.8)	0.818
Length of stay in ICU (hours)▼	6	68 [40–213]	-	NA	2	131 [47–131]	1	19	3	88 [47–88]	0.322
Mortality											
Died in hospital●	154	8 (5.2)	14	0 (0.0)	34	3 (8.8)	27	0 (0.0)	79	5 (6.3)	0.339
Days till dead in hospital▼	8	9 [4–18]	-	NA	3	11 [3–11]	-	NA	5	7 [4–20]	0.881

MAP Mean Arterial Pressure, *qSOFA* quick Sequential Organ Failure Assessment, *SIRS* Systemic Inflammatory Response Syndrome, *ICU*, Intensive Care Unit, *NA* Not Applicable

▼Median [interquartile range]

■Mean ± standard deviation

●Absolute number and (percentage)

▫Bilirubine > 35.2 µmol/L and alkaline phosphatase, ALAT, or ASAT more than two times normal [21]

◦Based on the KDIGO criteria [21]

◊Based on the need for mechanical ventilation or any of the following: PaO2 < 8.0 kPa, PaCO2 > 6.5 kPa, SpO2 < 90% (ambient air) or SpO2 < 95% (at least 2 L/min oxygen supply) [22]

*Significant result: * < 0.05, ** < 0.01, *** < 0.001 (differences between the groups were tested)

[1]Medication with direct effect on cardiac contractility = ß-blockers and/or digoxin

[2]Medication with indirect effect on cardiac contractility = RAS-inhibitors, dihydropyridines, and/or diuretics

Table 4 Correlation between drugs dose and vital signs and heart rate variability (HRV) parameters

	ß-Blocker, Pearson's *r*	Dihydropyridine, Pearson's *r*	ACE inhibitors, Pearson's *r*	ARB, Pearson's *r*
DDD, mg/day▼	0.50 [0.27–0.67]	0.20 [0.05–0.20]	1.0 [0.50–2.0]	1.50 [0.50–2.00]
Vital signs				
Heart rate	−0.268***	0.011	−0.420	0.418
Systolic blood pressure	0.122	0.176*	−0.095	0.343
Diastolic blood pressure	0.048	0.171*	−0.233	0.555
MAP	0.087	0.191*	−0.199	0.511
Temperature	0.067	0.125	0.120	0.277
HRV—time domain parameters				
AVNN	0.269***	0.053	0.335	0.011
SDNN	−0.036	0.015	−0.308	0.264
CV	−0.041	0.023	−0.325	0.264
HRV—frequency domain parameters				
HF norm	0.134	−0.094	0.112	−0.71
LF norm	−0.134	0.094	−0.112	0.071
LF/HF ratio	−0.163*	0.110	−0.194	−0.178
VLF	−0.038	−0.021	−0.305	0.264
HRV—non-linear parameters				
SD2	−0.030	0.020	−0.301	0.248

Correlations were calculated between the DDD per group and the vital signs and HRV parameters by Pearson's *r*

Digoxin and diuretics are missing in this table. Only one patient used digoxin. Analyzing diuretics requires them to be subdivided into different medications; however, these subgroups contain < 10 patients, making them unsuitable for correlation analysis

DDD defined daily dose (mg/day), *AVNN* average of all NN intervals, *SDNN* standard deviation of the NN intervals, *CV* coefficient of variation of the NN-intervals, *HF norm* normalized high frequency power, *LF norm* normalized low frequency power, *LF/HF ratio* ratio between low and high frequency power, *VLF* power in the very low frequency range, *SD2* standard deviation of the continuous long-term NN-interval variability in the Poincaré plot, *ACE inhibitors* angiotensin-converting enzyme inhibors, *ARB* angiotensin receptor blockers

▼Median [interquartile range]

*Significant result: * < 0.05, ** < 0.01, *** < 0.001 (as compared to patients not using the specific drug)

Technical and clinical implications

Before this study, HRV in septic patients has been primarily studied in ICU patients [4]. Our SepsiVit study showed that long-term, automatically analyzed ECG recordings can be used to determine HRV features that are associated with clinical deterioration of early septic patients at the ED [20]. The results of this current subanalysis indicate that the use of cardiovascular medication is not associated with changes in HRV in the early sepsis ED population. Correcting HRV measurements for cardiovascular medication seems to be unnecessary, however may still be relevant in a different setting and population. Recommendations for further research are to analyze the influence of more different types of medication and polypharmacy on HRV in septic patients at the ED. Thereby, it would be interesting to assess the diagnostic accuracy of potential screening tools utilizing HRV features, for detecting patient deterioration in septic patients at the ED and to examine the influence of cardiovascular medication on this interpretation.

Strengths and Limitations

Our study is the first observational study analyzing the influence of cardiovascular medicine on HRV in patients with early sepsis at the ED [4]. The inclusion criteria of the current study were based on sepsis-2 definitions [19], instead of the sepsis-3 definitions that were introduced in 2016 [29]. This allowed to include a heterogeneous population with a severe infection at risk for deterioration, which represents a real-world population at the ED. We used the first three hours of data at the ED, since later on advanced treatment (e.g., vasopressors, inotropics) may confound HRV measurements. Our study had

Table 5 Heart rate variability

	All patients, $N=155$	Patients using medication with direct effect on cardiac contractility[1], $N=14$	Patients using medication with indirect effect on cardiac contractility[2], $N=35$	Patients using medication from both groups, with direct and indirect effect on cardiac contractility, $N=27$	Patients without the use of cardiovascular medication, $N=79$	*P* value
HRV—time domain parameters						
AVNN ($\bullet 10^{-3}$) s^2	630.5 [571.8–727.7]	643.1 [605.6–742.1]	633.9 [560.6–737.8]	655.1 [597.9–755.3]	628.7 [562.6–700.6]	0.508
SDNN ($\bullet 10^{-3}$) s^2	50.2 [31.2–87.0]	87.2 [27.7–117.7]	63.1 [35.4–129.1]*	52.3 [29.7–94.3]	47.1 [31.1–67.7]*	0.103
CV ($\bullet 10^{-3}$) s^2	78.7 [51.1–130.0]	131.6 [41.2–189.8]	89.9 [61.2–224.0]*	71.3 [50.2–124.7]	65.5 [51.1 – 105.9]*	0.130
HRV—frequency domain parameters						
HF norm %	34.5 [22.2–50.3]	41.8 [28.5–53.8]	37.2 [18.5–50.3]	39.9 [29.6–52.9]	31.2 [19.4–43.8]	0.104
LF norm %	65.5 [49.7–77.8]	58.2 [46.2–71.5]	62.8 [49.7–81.5]	60.1 [47.1–70.4]	68.8 [56.2–80.6]	0.104
LF/HF ratio	1.9 [1.0–3.5]	1.4 [0.9–2.5]	1.7 [1.0–4.4]	1.5 [0.9–2.4]	2.2 [1.3–4.1]	0.104
VLF ($\bullet 10^{-3}$) s^2	1.8 [1.3–2.8]	2.6 [1.8–3.2]	2.1 [1.4–7.2]	1.9 [1.1–2.8]	1.6 [1.2–2.3]*	0.035*
HRV—non-linear parameters						
SD2 ($\bullet 10^{-3}$) s^2	64.8 [42.1–102.1]	94.5 [33.4–150.3]	82.7 [46.3–165.7]	66.7 [36.4–112.6]	59.8 [41.0–84.5]	0.184

Data is presented as median [interquartile range]

AVNN average of all NN intervals, *SDNN* standard deviation of the NN intervals, *CV* coefficient of variation of the NN-intervals, *HF norm* normalized high frequency power, *LF* norm normalized low frequency power, *LF/HF* ratio ratio between low and high frequency power, *VLF* power in the very low frequency range, *SD2* standard deviation of the continuous long-term NN-interval variability in the Poincaré plot

*Significant result: * < 0.05, ** < 0.01, *** < 0.001 (differences between the groups were tested)

[1]Medication with direct effect on cardiac contractility = ß-blockers and/or digoxin

[2]Medication with indirect effect on cardiac contractility = RAS-inhibitors, dihydropyridines, and/or diuretics

several limitations: First, the study focuses on the use of cardiovascular medication, while HRV is influenced by many factors, including demographic factors (e.g., age, sex) and comorbidities. Second, the current study was a single-center study in a tertiary care teaching hospital with the referral of patients for academic specialist care, which may limit its generalizability.

Conclusion

Our results showed that HRV is not influenced by cardiovascular medication in patients presenting with early sepsis at the ED. Consequently, the correction of HRV features for the use of cardiovascular medication is unnecessary when analyzing, modelling, and interpreting these signals.

Abbreviations *AVNN*: Average of all NN intervals; *CV*: Coefficient of variation of the NN-intervals; *DBP*: Diastolic blood pressure; *ED* : Emergency department; *HF norm*: Normalized high frequency power; *HRV*: Heart rate variability; *ICU*: Intensive Care Unit; *LF norm*: Normalized low frequency power; *LF/HF ratio*: Ratio between low and high frequency power; *MAP*: Mean arterial pressure; *MODS*: Multi Organ Dysfunction Syndrome; *RAS*: Renin-angiotensin system; *SBP*: Systolic blood pressure; *SDNN*: Standard deviation of the NN intervals; *SIRS*: Systemic Inflammatory Response Syndrome; *UMCG*: University Medical Center Groningen; *VLF*: Very low frequency

Acknowledgements The authors thank the nurses, students, and physicians in the ED for their assistance during the acquisition of the data.

Author Contribution LvdL participated in data acquisition, analyzed data, and drafted the manuscript. RJvW participated in data acquisition, analyzed data, and revised the manuscript. VMQ designed the study and assisted with data acquisition and data analysis. HRB assisted with data interpretation and revised the manuscript. JCtM supervised the study, participated in the study design, assisted with data interpretation, revised the manuscript, and has given final approval of the version to be published.

Funding This study is funded by the emergency department of the University Medical Center Groningen.

Data Availability Data is available upon reasonable request.

Code Availability Upon reasonable request.

Declarations

Ethics Approval The study was performed in the University Medical Centre Groningen (UMCG, Groningen, the Netherlands), a tertiary care teaching hospital and approved by the institutional review board of the UMCG (METC 2015/164). The protocol of the study was published by us previously [4].

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication Patients signed informed consent regarding publishing their anoymized data.

Competing Interests The authors declare no competing interests.

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