Reliability of ultrashort electrocardiographic indices in hypertension: the quest for a clinically applicable prognostic marker

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Heart rate variability (HRV) is an accepted clinical

function and a marker of adverse cardiac outcome.

Although 5 min long HRV recordings are considered

methodologically acceptable, it remains impractical

in most clinical settings. Also, while some ultrashort

HRV (usHRV) parameters were found useful in

healthy individuals, their applicability to patients

Therefore, our goal was to evaluate the reliability

of ultrashort ECG (usECG) indices for HRV among

patients with hypertension. One-hundred and two

patients with essential hypertension were included.

HRV was recorded for 5 min in strictly monitored

settings. HRV parameters from randomly chosen

correlations were found between 1 min SD of RR

interval (SDNN) (intraclass correlation coefficient

results. An excellent correlation was also found

between 1 min root mean square of successive

(ICC) 0.973), 10s SDNN (ICC 0.92) and 5 min SDNN

differences in RR intervals (RMSSD) (ICC 0.992), 10 s

RMSSD (ICC 0.982) and 5 min RMSSD. Logarithmic

transformation of ultrashort 1 min HRV-triangular

index using the natural logarithm (Ln) also had

excellent correlation with 5 min measurements

(ICC 0.9). Also, excellent correlations were found

and 5 min measurements. Other HRV parameters

correlations. In conclusion, evaluation of SDNN,

RMSSD or Ln(RMSSD) from 10s ECG recordings

can be used to estimate autonomic nervous system function in patients with hypertension. These

appealing markers can be readily calculated from any

patients with cardiovascular risk factors needs to be

standard ECG tracing. The prognostic significance of ultrashort SDNN and ultrashort RMSSD in

determined in future prospective cohort studies.

between 10s and 1 min Ln(RMSSD), 10 s Ln(RMSSD)

measured from 1 min and 10 s periods showed lower

1 min and 10 s series were analyzed. Excellent

with cardiovascular risk factors is largely unknown.

tool for evaluating autonomic nervous system

ABSTRACT

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Heart rate variability (HRV) is a clinical tool for measuring cyclic changes in heart rate. HRV is influenced by autonomic nervous system (ANS) function and is commonly used to estimate this.^{1 2} Also, HRV has been successfully utilized for cardiac risk stratification in certain patients.^{3 4} Five-minute long recordings are

Significance of this study

What is already known about this subject?

- Autonomic nervous system function can be evaluated according to heart rate variability (HRV), yet current measurement techniques for HRV makes it clinically impractical.
- HRV may be used as a marker of adverse cardiac outcomes, especially for patients with cardiovascular diseases or risk factors.
- Some 10s ultrashort HRV (usHRV) parameters were found to be useful in healthy individuals but their applicability for patients with hypertension is unknown.

What are the new findings?

- Ultrashort SD of RR interval (usSDNN), ultrashort root mean square of successive differences in RR intervals (usRMSSD) and 1 min ultrashort natural logarithm (usLn(HRV-triangular index (TI))) were found to be equivalent to 5 min SDNN, RMSSD and Ln(HRV-TI), respectively, in the study population.
- Evaluation of SDNN and RMSSD and the natural logarithm value of RMSSD from ultrashort 10 s ECG recordings can be used to estimate autonomic nervous system (ANS) function in patients with hypertension.
- Other usHRV variables were found to be unreliable for evaluating ANS in patients with hypertension.

How might these results change the focus of research or clinical practice?

- Study of 10 s usSDNN, usRMSSD, and Ln(RMSSD) can be easily implemented in any emergency department or clinic.
- These ultrashort indices have promising prognostic implications in patients with hypertension, which require further confirmation in future studies.
- Ultrashort Ln(HRV-TI) and Ln(SDNN) may be of clinical value, but the need for 1 min measurements limit its use.

considered methodically acceptable for HRV evaluation.⁵ In recent years, low-cost commercial devices for evaluating HRV have become

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Their medical records were screened and complete physical examinations were conducted to determine health status. Hypertension was defined as blood pressure threshold of 140/90 mm Hg according to the 2018 European Society of Cardiology/European Society of Hypertension guide-line.¹³ Patients were diagnosed with essential hypertension following a medical workup and exclusion of secondary causes. They had been under continuous treatment for their hypertension for at least 3 months prior to enrollment. None of the patients had an acute condition known to have an effect on heart rate or other electrocardiographic parameters.

Procedure

For at least 3 hours prior to the test participants were asked not to drink caffeinated beverages, smoke or take other stimulants. The test was conducted during the morning hours in order to avoid circadian influences on ANS function. Studies were carried out in a quiet room where temperature was maintained at approximately 22°C. Participants were asked to remain in a supine position for 10 min prior to commencement of the study. Blood pressure was measured twice and the results were averaged. Measurements were carried out with a digital ECG device with a sampling rate of 2000 Hz (Norav Medical, Yokne'am, Israel). Recordings were made from the limb leads for 5 min. Poor quality recordings were repeated. The data were saved and processed using designated commercial computer software (PC-ECG, HRV V.5.514, Norav Medical).⁵

Time-domain measures were based on the normal-tonormal (NN) intervals. The mean heart rate and the square root of the mean of the squares of the successive differences between adjacent NN intervals (RMSSD) were calculated. Additional time domains were computed by the software, including SDNN (the SD of RR intervals); the absolute NN intervals that were >50 ms from the preceding ones (NN50) and the ratio of NN50 to the total number of RR intervals recorded (pNN50).

Table 1 Baseline characteristics of study subjects							
Characteristics	Study sample (n=102)						
Male/female	81 (79.4%)/21 (20.6%)						
Age, years	59.7±11.1						
Height, m	1.72±0.08						
Body mass index, kg/m ²	28.5±4.3						
Systolic blood pressure, mm Hg	137.9±17.3						
Diastolic blood pressure, mm Hg	82.2±10.8						
Dyslipidemia, n (%)	70 (68.6)						
Diabetes mellitus, n (%)	24 (23.5)						
Smoking, n (%)	13 (12.7)						
Family history, n (%)	56 (54.9)						
ACE inhibitors/ARBs, n (%)	62 (60.8)						
Diuretics, n (%)	32 (31.4)						
β-Blockers, n (%)	49 (48.0)						
Calcium channel blockers, n (%)	38 (37.2)						
Antiplatelet drugs, n (%)	52 (51.0)						
Anti-arrhythmic drugs (type 1, 3), n (%)	5 (4.9)						
Lipid-lowering statin drugs, n (%)	51 (50.0)						
ARBs, angiotensin receptor blockers.							

increasingly accessible, and even heart rate monitor watches have proven useful for HRV study.⁶ The average patient appointment time for most general practitioners and family doctors rarely exceeds 10-15 min.⁷⁻⁹ Therefore, unlike resting ECG and blood pressure, which take a few seconds to measure, evaluating HRV remains impractical for most practitioners. For this reason, more practical tools for ultrashort (us) evaluation of HRV and ANS function is warranted for inpatient clinical risk stratification. Several studies have shown that specific usHRV parameters are clinically useful. Karp et al demonstrated that SD of RR intervals (SDNN) calculated from a 10s ECG have prognostic implications for patients with a recent myocardial infarction.¹⁰ Our research group reported that some us parameters of HRV are more reliable than others for HRV measurements in healthy individuals (ie, average RR interval and root mean square of successive differences in RR intervals (RMSSD)).¹¹ Schroeder et al also reported high correlation coefficients of mean RR and RMSSD between 10s and 2 min measurements, and 6 min HRV measurements in healthy controls.¹² Nevertheless, the results of the latter studies differ regarding SDNN reliability; presumably due to factors associated with patient selection.^{11 12} Similar results were reported by Munoz et al, namely that RMSSD computed from 10 s long measurements is sufficiently reliable.¹³ Yet, they did not evaluate ECG-based HRV, but rather studied pulse variability based on non-invasive continuous blood pressure monitoring. Also, Munoz et al included individuals followed for deteriorating renal function (Prevention of Renal and Vascular Endstage Disease (PREVEND) study) and did not focus on other specific patient populations.

Some ultrashort frequency domain HRV measures were found to be reliable markers for longer measurements in healthy adults.¹¹ Yet, it should be emphasized that experience gained from healthy volunteers does not necessarily reflect the expected results in other patient groups, including those with cardiovascular risk factors, such as hypertension.

Hypertension is a common medical condition associated with increased risk for end-organ damage and arrhythmias, and may be associated with abnormal ANS function. Hypertension was also reported to be associated with abnormal HRV parameters measured from 5 min intervals,¹⁴ and from 24 hours measurements.¹⁵ Due to a paucity of knowledge regarding the reliability of ultrashort indices of HRV in patients with hypertension, we sought to study the association between usHRV indices and a standardized HRV test, and estimate which parameters were more reliable for usHRV evaluation. The present study focuses both on time and frequency domains of HRV parameters.

MATERIALS AND METHODS Study design

A case series study design was used. The participants were included after they provided written informed consent.

Study subjects

One-hundred and two volunteers with hypertension were included in the study. Participants were recruited after a routine health check-up in the outpatient clinic. All participants were interviewed regarding their health history.

Table 2 Correlation of electrocardiographic measurements of HRV from 1 min to 5 min recordings

	1 min		5 min			
	Mean	SD	Mean	SD	ICC	95% CI
Maximal RR (ms)	1050.9	176.55	1095.2	176.55	0.986*	0.979 to 0.990
Minimal RR (ms)	897.9	139.76	838.9	139.76	0.951*	0.928 to 0.967
Average RR (ms)	972.4	154.96	970.2	154.96	0.998*	0.997 to 0.999
Average HR (bpm)	63.1	10.91	63.0	10.91	0.995*	0.993 to 0.997
SDNN (ms)	34.0	24.18	41.1	24.18	0.973*	0.960 to 0.982
RMSSD (ms)	32.5	29.98	34.3	29.98	0.992*	0.988 to 0.995
HRV-TI	7.9	2.53	12.2	2.53	0.786	0.683 to 0.855
NN50	28	4.12	14.9	4.12	0.542	0.323 to 0.691
pNN50	2.0	3.05	5.2	3.05	0.785	0.682 to 0.855
VLF (ms ²)	167.8	109.11	220.2	109.11	0.656	0.490 to 0.767
LF (ms ²)	160.2	89.65	136.7	89.65	0.726	0.594 to 0.815
HF (ms ²)	161.9	92.42	112.7	92.42	0.832	0.751 to 0.886
Total power (ms ²)	495.6	101.01	520.4	101.01	0.863	0.798 to 0.908
LF/HF	1.7	2.07	1.8	2.07	0.85	0.777 to 0.898
Ln(SDNN)	3.351	0.560	3.584	0.489	0.947*	0.922 to 0.964
Ln(RMSSD)	3.230	0.664	3.310	0.614	0.981*	0.972 to 0.987
Ln(HRV-TI)	2.019	0.322	2.421	0.397	0.9*	0.853 to 0.933
Ln(VLF)	4.853	0.836	5.311	0.455	0.634	0.459 to 0.753
Ln(LF)	4.923	0.571	4.820	0.465	0.88	0.823 to 0.919
Ln(HF)	4.883	0.697	4.552	0.617	0.874	0.813 to 0.915
Ln(total power)	6.172	0.316	6.241	0.169	0.648	0.478 to 0.762
Ln(LF/HF)	0.041	0.981	0.268	0.823	0.88	0.823 to 0.919

Correlation of 1 min and 5 min electrocardiographic HRV measurements.

*Excellent correlation

HF, high frequency components; HRV, heart rate variability; HRV-TI, HRV-triangular index; ICC, intraclass correlation; LF, low frequency components; NN50, number of intervals differing by >50 ms from preceding interval; pNN50, NN50 divided by total number of intervals; RMSSD, root mean square of successive differences in RR intervals; SDNN, SD of RR interval; VLF, very low-frequency components.

HRV-triangular index (HRV-TI) was calculated from an integral of the density distribution (count of all NN QRS intervals) divided by the maximum of the density distribution. Power spectral analysis was further performed using a fast Fourier transform-based non-parametric algorithm. The power spectrum was then converted into frequency-domain indices, which consisted of the low-frequency power (0.04–0.15 Hz), the high-frequency (HF) power (0.15–0.4 Hz) and the total power. The latter was computed as the sum of all spectra (ie, variance of all NN intervals <0.4 Hz). HRV indices were log-transformed using the natural logarithm (Ln).

HRV parameters were reanalyzed from a randomly chosen 1 min long series and another randomly chosen 10 s series. None of the recordings included premature beats.

Statistical analysis

Results were expressed as mean and SD. Intraclass correlation coefficient (ICC) was used in order to quantify the agreement between measurements obtained from the entire 5 min recording with the 1 min and 10s interval recordings. An ICC significantly (p<0.05) above 0.9 was considered to have excellent correlation, and an satisfactory measure of reliability.¹⁶ Analyses were performed using JMP V.7.0 (SAS Institute, Cary, North Carolina, USA) and SPSS V.25 for Windows software (SPSS, Chicago, Illinois, USA).

RESULTS

The demographic and clinical characteristics of the study group are described in table 1. There were 81 men; mean age was 59.7 ± 11.1 years. Some patients had additional cardiovascular risk factors, such as dyslipidemia (68.6%), diabetes mellitus (23.5%), smoking (12.7%) and family history of heart disease (54.9%). Mean systolic blood pressure was 137.9 ± 17.3 mm Hg; mean diastolic blood pressure was 82.2 ± 10.8 mm Hg. All patients were treated with antihypertensive drugs, such as ACE inhibitors or angiotensin receptor blockers (60.8%), diuretics (31.4%), β -blockers (48.0%) or calcium channel blockers (37.2%). Antiplatelet drugs were administrated to 51.0%, and antiarrhythmic drugs (type 1, 3) were used by 4.9%. Half of the patient group used lipid-lowering therapy.

Table 2 and figure 1 include the correlations between 1 min and 5 min HRV parameters. Excellent correlations were found between 1 min and 5 min average RR results (ICC 0.998, 95% CI 0.997 to 0.999). An excellent correlation was also found between 1 min RMSSD and 5 min RMSSD (ICC 0.992, 95% CI 0.988 to 0.995) as well as between 1 min SDNN and 5 min SDNN (ICC 0.973, 95% CI 0.960 to 0.982). Ln of 1 min SDNN and 1 min RMSSD also had excellent agreement with the 5 min measurements (table 2). In addition, 1 min Ln(HRV-TI) had excellent correlation with 5 min Ln(HRV-TI) (ICC 0.9, 95% CI 0.853 to 0.933). The other HRV parameters had lower correlations.

Original research



Figure 1 Correlation between 1 min heart rate variability (HRV) parameters and 5 min HRV parameters. (A) Average RR; (B) Ln(average RR); (C) SD of RR interval (SDNN); (D) Ln(SDNN); (E) RMSSD; (F) HRV-triangular index; (G) Ln(HRV-triangular index).

Table 3 and figure 2 include the correlations between 10s and 5 min HRV parameters. Excellent correlations were found between 10s and 5 min average RR results (ICC 0.99, 95% CI 0.985 to 0.993). Excellent correlations were also

found between 10s RMSSD and 5 min RMSSD (ICC 0.982, 95% CI 0.973 to 0.988; figure 2), as well as between 10s and 5 min SDNN (ICC 0.92, 95% CI 0.882 to 0.946). Ln of 1 min RMSSD (but not SDNN or HRV-TI) had excellent

Table 3 Correlation of 10s and 5 min electrocardiographic HRV measurements

	10 s		5 min	5 min		
	Mean	SD	Mean	SD	ICC	95% CI
Maximal RR (ms)	1023.3	169.3	1095.2	180.6	0.975*	0.963 to 0.983
Minimal RR (ms)	936.6	148.0	838.9	128.4	0.931*	0.897 to 0.953
Average RR (ms)	976.8	154.5	970.2	152.1	0.99*	0.985 to 0.993
Average HR (bpm)	62.6	10.9	63.0	10.8	0.993*	0.989 to 0.995
SDNN (ms)	28.6	24.1	41.1	25.0	0.92*	0.882 to 0.946
RMSSD (ms)	31.9	28.7	34.3	30.7	0.982*	0.973 to 0.988
HRV-triangular index	4.8	1.8	12.2	5.2	0.371	0.068 to 0.575
NN50	0.42	0.78	14.9	20.3	0.108	-0.321 to 0.397
pNN50	0.45	0.83	5.2	7.7	0.271	-0.079 to 0.507
LF (ms ²)	168.3	106.1	136.7	58.2	0.564	0.354 to 0.705
HF (ms ²)	239.3	105.5	112.7	63.4	0.463	0.205 to 0.637
Total power (ms ²)	446.9	88.6	520.4	89.0	0.849	0.776 to 0.898
LF/HF	1.33	1.99	1.81	1.70	0.625	0.445 to 0.747
Ln(SDNN)	3.351	0.560	3.584	0.489	0.862	0.796 to 0.907
Ln(RMSSD)	3.230	0.664	3.310	0.614	0.953*	0.931 to 0.968
Ln(HRV-triangular index)	2.019	0.322	2.421	0.397	0.634	0.459 to 0.753
Ln LF (ms ²)	4.923	0.571	4.820	0.465	0.561	0.350 to 0.703
Ln HF (ms ²)	4.883	0.697	4.552	0.617	0.573	0.368 to 0.712
Ln(total power)	6.172	0.316	6.241	0.169	0.727	0.596 to 0.816
Ln(LF/HF)	0.041	0.981	1.820	1.700	0.646	0.477 to 0.761

*Excellent correlation.

HF, high frequency components; HRV, heart rate variability; HRV-TI, HRV-triangular index; ICC, intraclass correlation; LF, low frequency components; NN50, number of intervals differing by >50 ms from preceding interval; pNN50, NN50 divided by total number of intervals; RMSSD, root mean square of successive differences in RR intervals; SDNN, SD of RR interval.

agreement with the $5 \min$ measurements. The other 10s HRV parameters had lower correlations with $5 \min$ HRV parameters.

DISCUSSION

The scientific community has begun to appreciate usHRV as a useful clinical tool, especially in the context of cardiovascular risk stratification. Nevertheless, its use extends beyond merely evaluating ANS function. For example, Adjei et al evaluated 10 s SDNN changes in subclinical electroencephalographic seizure patterns, although the study yielded limited results.¹⁷ Kon et al evaluated the coefficient of variation of the RR interval from a 2 min recording and suggested that lower values were associated with higher CRP levels.¹⁸ Bikkina et al evaluated HRV (calculated in this particular study by subtracting the minimal from the maximal RR interval, and corrected to a heart rate of 75 bpm) from 10 consecutive RR intervals prior to the electrophysiological study. They reported that inducible VT was associated with lower variability.¹⁹ de Bruyne et al reported that 10s SDNN, when either excessively low or high, reflected increased risk for mortality in the elderly.²

The current study is an extension of our previous research in which we found that us measurements of average RR and RMSSD are useful for evaluating 5 min values of these parameters in healthy individuals.¹¹ Nevertheless, our previous study did not include patients with cardiovascular risk factors such

as hypertension, and this population has not been adequately investigated.

The present study included a large cohort of patients with essential hypertension, some of whom had other cardiovascular risk factors. Notably, there is a paucity of knowledge as to the reliability of usECG indices for HRV, and no study has previously included large cohorts of patients with hypertension. We found that average RR, RMSSD, SDNN, Ln(RMSSD), L(SDNN) and Ln(HRV-TI) measured from 1 min recordings have an excellent correlation with 5 min measurements of these variables. Also, average RR, RMSSD, SDNN and Ln(RMSSD) calculated from 10 s long periods also have excellent correlations with 5 min recordings. These results extend our previous findings in healthy individuals,¹¹ in that more usHRV variables were found to be reliable for patients with hypertension. This difference may stem from the known tendency towards autonomic dysregulation among patients with hypertension.²¹ Other variables showed lower correlations, and therefore are less reliable markers for 5 min HRV. These results are important in light of the higher accessibility and practicality of usHRV compared with 5 min measurements. Our results are similar to those of Hamilton et al who reported that RMSSD reflected cardiac vagal tone in a heterogeneous group of 50 patients.²² Our results are also supported by those of McNames and Aboy who found that mean heart rate and RMSSD are less affected by the measured duration (although they also reported high reliability of HF, which was not found in our two studies).²³ Salahuddin et al demonstrated that mean RR interval and RMSSD measured from 10s intervals are comparable to longer measurements.²⁴



Figure 2 Correlation between 10 s heart rate variability (HRV) parameters and 5 min HRV parameters. (A) Average RR; (B) Ln(average RR); (C) SDNN; (D) Ln(SDNN); (E) root mean square of successive differences in RR interval (RMSSD); (F) HRV-triangular index; (G) Ln(HRV-triangular index).

Thong *et al*, by using ECGs from the Physionet database, reported that 10s RMSSD, but not SDNN, was a reliable index for 5 min results, and suggested that the reliability of HF merits further research.²⁵ Munoz *et al* reported that a single 10s recording yields a valid RMSSD measurement,

although they concluded that an average over multiple 10s ECGs is preferable.¹³ Nevertheless, all the above studies included heterogeneous groups of patients, and did not focus on patients with hypertension. Also, the reliability of all parameters was not evaluated in some studies, while others

did not use standard ECG-based methods for HRV quantification, which limit comparisons with the current research.

Limitations

HRV measurements were conducted under strict conditions (controlled environment, appropriate preceding rest, etc) that do not necessarily reflect the conditions found in the emergency department or outpatient clinics, where ECG are regularly recorded. Also, HRV measurements were conducted in the present study without paced breathing to simulate a typical ECG recording. This method is also in agreement with the accepted methodological approach towards routine HRV evaluation. We cannot predict whether a study conducted in an uncontrolled environment or using paced breathing would have yielded different results. It also remains to be explored whether specific usHRV parameters can reflect on circadian-associated or long-term ANS alterations, and if the current findings are applicable in persons with undiagnosed hypertension, patients with drug-resistant hypertension and those who are non-compliant with medical therapy.

CONCLUSIONS

Ultrashort 10 s long evaluation of RMSSD, SDNN, and Ln(RMSSD) should be used for evaluating 5 min HRV and therefore, as an estimate of ANS function in patients with hypertension. These parameters represent appealing markers that can be readily calculated in various clinical settings from any ECG tracing.

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