Received: 10 January 2019 | Revised: 7 February 2019 | Accepted: 13 February 2019

DOI: 10.1111/anec.12643

ORIGINAL ARTICLE

WILEY

Effect of short-term fasting on electrocardiographic parameters

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Abstract

Introduction: During early drug development trials, electrocardiograms (ECGs) in healthy volunteers who are in a fasting state are evaluated to screen for possible adverse cardiac effects. However, the effect of the duration of fasting on electrocardiographic parameters is largely unknown. We compared the effects of fasting on standard 12-lead electrocardiographic recordings.

Methods: Electrocardiograms were available for 432 healthy subjects (mean age 28.5 ± 12.5; 88.9% male) who participated in early drug development studies after 4- and 10-hr fasting. All ECGs were automatically analyzed for conduction intervals and wave amplitudes with the Marquette 12SL algorithm and compared among fasting duration. Mixed model analyses were used to identify confounding variables.

Results: After 10 hr of fasting, compared to after 4 hr of fasting, mean P-wave duration and amplitude were reduced by 1.95 ± 1.48 ms and 2.18 ± 2.75 μV, mean R wave and S wave amplitude were decreased by 25.83 ± 31.16 μV and 55.39 ± 78.72 μV, mean QRS duration was decreased by 1.84 ± 6.61 ms, and mean T-wave duration and amplitude were decreased by 2.06 ± 0.72 ms and 9.36 ± 17.21 μV (lead II). The mean PR interval was prolonged by 4.26 ± 17.67 ms, the ventricular rate was reduced by 3.64 ± 8.61 min, and QTcF was reduced by 3.87 ± 14.50 ms. These observations persisted after correction for demographics, electrolytes, blood pressure, heart rate variability, and diurnal variation.

Conclusion: The present analysis showed that 10-hr fasting compared to 4-hr fasting resulted in changes to the surface ECG, consisting of a reduced wave amplitude and duration and increased isoelectric interval duration.

KEYWORDS

basic, pharmacology - pharmacokinetics/dynamics, cellular electrophysiology/electropharmacology, clinical, non-invasive techniques - electrocardiography, clinical, non-invasive techniques - heart rate variability

1 | INTRODUCTION

In most early drug development trials, participants are required to be in a fasting state before administration of the investigational compound, since food intake is known to introduce physiological changes that show substantial intersubject variability and, among other effects, may influence the pharmacokinetics of the investigational drug (Abuhelwa, Williams, Upton, & Foster, 2017). During these trials, electrocardiograms (ECGs) are performed frequently to screen for adverse cardiac effects, and it is known that food intake can influence ECG parameters, such as changes in duration of the QTc interval (Taubel, Wong, Naseem, Ferber, & Camm, 2012) and/or QRS and T-wave morphology. Based upon ECG findings in early drug development studies, additional electrophysiological studies or even discontinuation of compound development are not uncommon (Food and Drug Administration, HHS, 2005; Gralinski, 2000; Theorell, Kjellberg, & Palmblad, 1978). However, there is a paucity of data on the effect of commonly applied short-term fasting on ECG parameters. This knowledge gap may hamper drug development trials, where ECG parameters are used to assess cardiac effects of the drug. The aim of the present study was to determine the change in ECG parameters after short-term fasting.

2 | METHODS

2.1 | Data collection

All subjects who were included in these studies were screened for eligibility prior to inclusion, during which their medical history was documented, an ECG was recorded, a physical examination was performed, and urine and blood were analyzed. Subjects were required to be in a fasting state for 4 hr prior to this screening visit. They were included in the study in case they were considered to be healthy by a physician. All subjects consented to their data being registered, and the study was performed in accordance with Dutch law on medical scientific research. Data were retrieved from seventeen (17) studies conducted between 2010 and 2016 at the Centre for Human Drug Research (Leiden, the Netherlands) from a CFR part 11 compliant database system (Promasys®, Omnicomm, Leiden, the Netherlands) where ECGs were recorded after 10 hr of fasting. For this study, we used the ECGs of the screening visit recorded after 4 hr of fasting, and the ECGs recorded during the drug trial after 10 hr of fasting; hence, all patients served as their own controls.

2.2 | Electrocardiogram recording and analysis

All ECGs were performed following the standard operating procedure at our center. In short, subjects were in a resting, supine position for at least 5 min before the ECG was recorded, and electrodes were placed in the standard anatomical positions. During the measurements, subjects were instructed to remain still and relaxed. The ECGs were analyzed automatically with the commercially available MUSE Cardiology Information System, version 7.1.1 (General Electric Company, Fairfield, CT, USA). The Muse Cardiology Management System automatically assesses interval and amplitude data from the digital ECGs. The details of the Marquette 12SL algorithm are described elsewhere. (Healthcare G, 2007).

We chose to report the results of nine parameters per lead: the amplitude and duration of the P, R, S, and T wave, and mid-ST amplitude level, along with seven parameters concerning an average value of the ECG: such as PR-, QRS-, and QT-interval duration, QTc Fridericia (QTcF), R axis, and ventricular rate. These parameters, a total of 115, were chosen because of their frequent use in common clinical practice.

2.3 | Heart rate variability (HRV)

The RR intervals were exported to Kubios HRV analysis software v2.2 (Biosignal analysis and medical imaging group, University of Eastern Finland, Finland). (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014) Variation after fasting in time-domain parameters (SDNN, RMSSD, NN50, and pNN50) and frequency-domain parameters (VLF, LF, HF, LF/HF ratio) was evaluated.

TABLE 1 Subject characteristics, n = 432

Age in years ± *SD*	28.5 ± 12.5
Gender	
Male	88.9%
Female	11.1%
Ethnicity	
White	83.5%
Black/African	3.5%
Asian	2.3%
Hispanic	0.7%
Mixed	2.1%
Other	7.9%
Height in cm ± *SD*	180.8 ± 8.8
Weight in kg ± *SD*	75.7 ± 11.6
BMI in kg/m^2 ± *SD*	23.1 ± 2.8
Systolic blood pressure in mmHg ± *SD*	121 ± 10
Diastolic blood pressure in mmHg ± *SD*	72 ± 8
Alcohol use in units/day ± *SD*	1.0 ± 0.9
Smokers	
Yes	6.6%
No	93.4%
Xanthine use in units/day ± *SD*	1.8 ± 1.5
Use of any systemic concomitant medication	
No concomitant medication	92.6%
Use of oral contraceptives	7.4%

TABLE 2 Value after 4 hr of fasting and mean change after 10 hr of fasting, per ECG lead

	P duration (ms)	P peak ampl (mV)	R duration (ms)	R peak ampl (mV)	S duration (ms)	S peak ampl (mV)	T duration (ms)	T peak ampl (mV)	Mid-ST amplitude (mV)
I									
4 hr	100.64	77.13	53.41	661.47	26.16	160.85	182.36	345.31	59.22
10 hr (90% CI)	−2.83** (−4.47; −1.19)	−4.38** (−6.25; −2.52)	+0.02 (−0.91; +0.94)	−40.71** (−49.49; −31.94)	−1.66** (−2.31; −1.00)	−14.94** (−21.45; −8.43)	−2.15** (−3.34; −0.95)	−24.65** (−30.52; −18.77)	+1.50 (−0.26; +3.26)
II									
4 hr	101.19	115.41	57.90	1160.20	22.02	150.52	182.29	424.56	73.00
10 hr (90% CI)	−2.72** (−4.21; −1.23)	−4.95** (−8.03; −1.86)	+0.94 (−0.06; +1.94)	−37.19** (−46.76; −27.62)	−2.63** (−3.18; −2.07)	−21.38** (−25.61; −17.15)	−1.66* (−3.00; −0.31)	−22.19** (−28.36; −16.02)	+1.75 (−0.06; +3.57)
III									
4 hr	83.68	57.83	50.13	651.38	22.00	157.86	156.73	80.94	13.68
10 hr (90% CI)	−0.72 (−3.03; +1.59)	−2.33 (−6.08; +1.42)	+0.78 (−0.57; +2.12)	+5.74 (−9.31; +20.79)	−1.94** (−2.97; −0.92)	−13.65* (−22.48; 4.81)	−3.27 (−7.13; +0.59)	+1.02 (−5.39; +7.42)	−0.08 (−1.77; +1.61)
AVR									
4 hr	102.05	−93.61	22.05	99.50	30.35	540.41	182.74	−381.07	−67.41
10 hr (90% CI)	−2.91** (−4.17; −1.66)	+3.65** (+1.50; +5.80)	−1.14** (−1.73; −0.55)	−12.15** (−20.94; −3.35)	+1.08 (.0.40; +2.56)	−18.22 (−39.93; +3.49)	−1.77* (−2.93; −0.61)	+20.34** (+13.78; +26.89)	−2.47* (−4.06; −0.88)
AVL									
4 hr	79.96	10.46	40.72	298.45	34.38	263.14	161.21	143.96	23.67
10 hr (90% CI)	−2.79 (−5.49; −0.10)	−2.15 (−5.68; +1.34)	−0.89 (−2.00; +0.22)	−24.80** (−35.86; −13.74)	−1.13 (−2.19; −0.07)	−0.24 (−7.52; +7.05)	−3.34 (−7.06; +0.39)	−13.66** (−19.21; −8.12)	+0.60 (−0.85; +2.05)
AVF									
4 hr	96.85	86.90	59.21	884.39	20.63	118.00	179.82	263.68	44.78
10 hr (90% CI)	−2.16 (−4.03; −0.30)	−3.23 (−6.37; −0.09)	−0.85 (−1.97; +0.28)	−23.89** (−36.35; −11.42)	−2.55** (−3.31; −7.78)	−13.95** (−18.51; −9.40)	−2.18 (−4.06; −0.31)	−12.73** (−18.94; −6.53)	+0.75 (−0.92; +2.42)
V_1									
4 hr	61.18	55.55	29.95	301.34	59.39	973.29	148.85	47.43	51.68
10 hr (90% CI)	+0.356 (−2.34; +3.05)	−7.01** (−9.83; −4.18)	−0.43 (−0.81; −0.05)	−43.46** (−52.57; −34.35)	−1.05 (−2.14; +0.05)	−133.88** (−156.23; −111.53)	−2.72 (−7.54; +2.09)	−9.60 (−20.93; +1.73)	−2.33 (−5.05; +0.39)
V_2									
4 hr	91.97	72.13	34.04	702.48	54.72	1698.53	181.12	709.65	200.49
10 hr (90% CI)	+1.44 (−0.71; +3.60)	−2.59 (−4.91; −0.26)	+1.61** (+0.99; +2.24)	+4.02 (−14.79; +22.82)	−3.98** (−4.82; −3.14)	−260.16** (−302.48; −217.93)	−1.70 (−3.21; −0.18)	+20.27 (+0.93; +39.61)	+20.01** (+14.02; +26.01)
V_3									
4 hr	101.46	75.81	48.10	1191.86	38.74	966.05	182.54	792.08	194.22

(Continues)

TABLE 2 (Continued)

	P duration (ms)	P peak ampl (mV)	R duration (ms)	R peak ampl (mV)	S duration (ms)	S peak ampl (mV)	T duration (ms)	T peak ampl (mV)	Mid-ST amplitude (mV)
10 hr (90% CI)	−2.94** (−4.36; −1.51)	−1.79 (−3.66; +0.08)	+1.53** (+0.69; +2.37)	−45.96 (−93.34; +1.41)	−3.90** (−4.78; −3.02)	−127.95** (−158.53; −97.38)	−1.78* (−3.03; −0.53)	−34.30** (−48.57; −20.04)	+4.68 (−0.01; +9.36)
V_4									
4 hr	101.59	72.08	50.66	1898.37	29.12	459.66	182.27	696.31	125.58
10 hr (90% CI)	−2.69** (−4.08; −1.31)	−1.59 (−3.11; −0.07)	+1.36** (+0.48; +2.30)	−93.45** (−125.00; −61.90)	−2.58** (−3.04; −2.12)	−28.60** (−45.64; −11.55)	−0.97 (−2.23; +0.29)	−21.15* (−36.17; −6.12)	+10.81** (+7.25; +14.36)
V_5									
4 hr	101.83	65.41	50.32	1666.74	25.05	202.63	182.50	542.01	81.44
10 hr (90% CI)	−2.99** (−4.39; −1.59)	−0.50 (−2.16; +1.17)	+1.39* (+0.48; +2.30)	−27.74 (−50.88; −2.60)	−3.07** (−3.70; −2.45)	−27.80** (37.31; −18.30)	−1.41 (−2.69; −0.17)	−17.77* (−30.06; −5.48)	+5.83** (+3.35; +8.30)
V_6									
4 hr	100.97	59.04	56.38	1246.13	18.78	82.84	182.36	391.21	53.62
10 hr (90% CI)	−2.46** (−4.01; −0.91)	+0.75 (−0.66; +2.15)	−0.22 (−1.22; +0.79)	+28.60** (+8.11; +49.08)	−1.36** (−2.10; −0.62)	−3.86 (−9.07; +1.35)	−1.72 (−3.23; −0.22)	+2.12 (−6.50; +10.74)	+5.59** (+3.82; +7.35)

90% CI: 90% confidence interval.
*$p < 0.05$; **$p < 0.01$

2.4 | Electrolytes and blood pressure

Measurements of serum electrolytes and automated blood pressure measurements for both fasting durations were available for all subjects.

2.5 | Statistics

Data are presented as frequencies or percentages for categorical variables and as means ± standard deviation for normally distributed continuous variables. Continuous variables with dependent measures and normal distribution were analyzed using the paired samples *t* test. A mixed models analysis was performed, with fasting as a fixed factor and covariates as random factors. The tested covariates were as follows: BMI, smoking, recording time, age, gender, serum sodium level, serum potassium level, and HRV parameters (VLF, LF, and HF) as a measure for parasympathetic activity. All statistical analyses were executed using the SPSS software version 20 (IBM Inc. Chicago, IL, USA).

3 | RESULTS

Out of 515 subjects with an available ECG after both 4 and 10 hr of fasting, 83 subjects were excluded because of concomitant use of any systemic medication, with the exception of oral contraceptives ($n = 7$), chest, heart, or lung abnormalities during physical examination ($n = 67$) and ECGs with a lead reversal ($n = 9$). Thus, a total of 432 subjects were included. Subject characteristics are presented in Table 1.

3.1 | Electrocardiographic parameters after fasting

The differences in electrocardiographic parameters per lead are provided in Tables 2 and 3. In summary, for lead II, 10 hr of fasting resulted in a reduction in P wave duration and peak amplitude (−2.72 ± 18.82 ms, $p = 0.003$ and −4.95 ± 38.92 mV, $p = 0.009$), a reduction in QRS wave duration (−1.84 ± 6.61 ms, $p < 0.001$), and a reduction in T-wave duration and peak amplitude (−1.66 ± 16.98 ms, $p = 0.043$ and −22.19 ± 77.82 mV, $p < 0.001$). In addition, the PR interval was increased after 10 hr of fasting (+4.26 ± 17.67 ms, $p < 0.001$), the ventricular rate was reduced by −3.64 ± 8.61 beats per minute ($p < 0.001$), as well as the QTcF (−3.87 ± 14.50 ms, $p < 0.001$). Finally, the R axis rotated more rightward by 1.38 ± 10.06° ($p = 0.005$). All significant changes for lead II are displayed in Figure 1. We chose to highlight the changes in lead II because this lead usually gives a good view of both the P wave and the QRS wave. Table 4 shows the difference in HRV parameters, time of day at ECG recording, electrolytes, and blood pressure after 4 and 10 hr of fasting. However, all electrocardiographic changes that were found persisted after controlling for confounding variables.

TABLE 3 Value after 4 hr of fasting and mean change after 10 hr of fasting, average of all leads

ECG parameter	4 hr	10 hr (90% CI)
PR interval (ms)	153.75	+4.26** (+2.85; +5.66)
QRS duration (ms)	98.49	−1.84** (−2.37; −1.32)
QT interval (ms)	404.35	+4.27** (+2.64; +5.91)
QTc Fridericia (ms)	406.00	−3.87** (−5.02; −2.72)
R axis (°)	54.18	+1.38** (+0.58; +2.18)
Ventricular rate (bpm)	61.89	−3.64** (−4.33; −2.96)

90% CI: 90% confidence interval.
*$p < 0.05$; **$p < 0.01$

4 | DISCUSSION

The present analysis showed that a 10-hr fasting period, as compared to a 4-hr fasting period, has a substantial impact on electrocardiographic parameters, summarized by a reduced wave amplitude and duration and an increased isoelectric interval duration. These changes persisted after correction for confounding variables concerning overall health (age, BMI, smoking, blood pressure), electrolytes (serum sodium level, serum potassium level), and parasympathetic activity (HRV parameters).

The present analysis, with 115 parameters that were analyzed per ECG in 432 healthy subjects, showed that many electrocardiographic parameters change after 10-hr fasting compared to 4-hr fasting, as shown in Table 2. The duration of the P wave (−2.72 ms), QRS wave (−1.84 ms), and T wave (−1.66 ms), as well as the QTcF interval (−3.87 ms) is reduced after fasting, but the PR interval (+4.26 ms) is prolonged. The reduced wave durations suggest an accelerated depolarization of the myocardium of the atrium and ventricle, but the prolonged PR interval hints to a delayed conduction through the atrioventricular node. More translational research is needed to elucidate the underlying process.

HRV parameters were also evaluated, since the autonomous nervous system influences the myocardial conduction velocity. Parasympathetic activity has a negative chronotropic and dromotropic effect on the heart. Our observations that the PR interval is prolonged and the heart rate is reduced are in line with the observations of an increased parasympathetic activity during fasting, although this is not confirmed by our HRV analysis. However, HRV analysis is usually performed on recordings that are substantially longer than an ECG. Nussinovitch (Nussinovitch, Cohen, Kaminer, Ilani, & Nussinovitch, 2011) demonstrated that the reliability of HRV analysis is highly dependent on the duration of the recordings. Besides, nearly all heart rate variability parameters of 10-second recordings are less reliable than those calculated from 5-min recordings. This implies that changes in the autonomic nervous system may still be an explanation for the results in our study, even though we found no proof of an increased parasympathetic activity. We recommend to do an HRV analysis on Holter recordings to evaluate the change in autonomic nervous activity after fasting and the association with myocardial conduction.

Second, we considered the circadian rhythm as a possible explanation for our results, as sympathetic activity peaks in the first hour after awakening (Tofler et al., 1987). The diurnal variability in QTc is previously reported by Molnar (Molnar, Zhang, Weiss, Ehlert, & Rosenthal, 1996), who found a large variation in QTc between sleep and wakefulness and a distinct increase in the QTc interval during

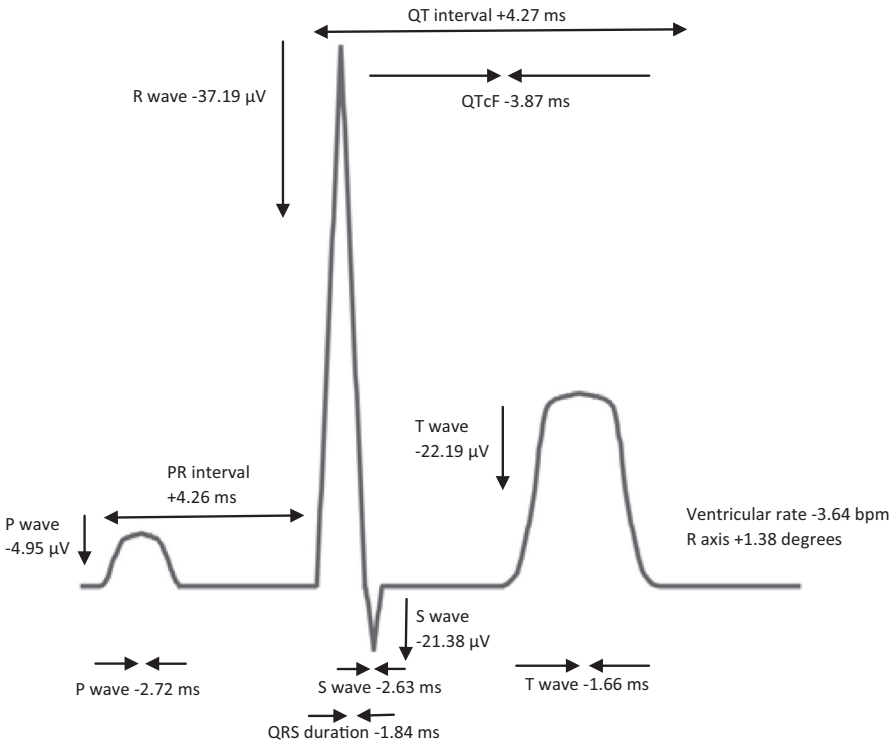

FIGURE 1 Overview of significant changes in lead II. This figure displays all significant changes in ECG parameters in lead II after 10-hr fasting compared to 4-hr fasting

TABLE 4 Difference in parameters after fasting of 10 hr, compared to 4 hr

Parameter	Value after 4-hr fasting	Value after 10-hr fasting	*p* value
VLF (ms^2)	197.37	248.24	0.147
LF (ms^2)	1139.61	1305.99	0.257
HF (ms^2)	2492.11	2171.42	0.425
LF/HF ratio	0.79	0.74	0.361
SDNN (ms)	57.11	60.16	0.230
RMSSD (ms)	62.02	65.66	0.288
NN50	2.45	2.56	0.296
pNN50 (%)	32.22	35.31	0.024
Median time of day at ECG recording	12:18:20 p.m.	8:44:40 a.m.	<0.001
Sodium (mmol/L)	141.4 (±1.75)	141.3 (±2.16)	0.683
Potassium (mmol/L)	4.38 (±0.26)	4.26 (±0.38)	0.001
Calcium (mmol/L)	2.44 (±0.09)	2.38 (±0.09)	<0.001
MAP (mmHg)	88.09 (±8.01)	81.86 (±8.37)	<0.001
Systolic BP (mmHg)	120.82 (±10.37)	115.54 (±11.27)	<0.001
Diastolic BP (mmHg)	71.72 (±8.43)	65.02 (±8.39)	<0.001

HF: high frequency; LF: low frequency; NN50: the number of pairs of successive NN intervals that differ by more than 50 ms; pNN50: proportion of NN50 divided by total number of NN intervals; RMSSD: root-mean-square of successive differences; SDNN: standard deviation of NN intervals (beat-to-beat); VLF: Very low frequency.

the first hour after awakening. In the present analysis, the average time of the day at which the ECGs were recorded differed significantly between the two ECG recordings. The ECG after 4 hr of fasting was usually recorded in the afternoon, with the ECG after 10 hr recorded in the early morning. However, covariate analysis showed that the recording time of the ECG was not associated with any of the ECG parameters, suggesting that our results are solely the effect of 10 hr of fasting.

There is currently no consensus concerning the choice of upper limit values for changes in QT or QTc interval in clinical drug trials; however, a prolongation of QTc > 500 ms is a signal of concern (Food and Drug Administration, HHS, 2005). At this moment, it is customary to evaluate the cardiac effects of investigational compounds by monitoring multiple ECGs during the study course while the subjects are in a fasting state. Because the effect of fasting on the change of the QTc interval is not considered during this evaluation, it is possible that compounds are unnecessarily re-investigated or even erroneously rejected. This emphasizes the need for close and detailed comparison of the ECGs of the study group with those of the placebo group, which is in the same fasting state. At this moment, this comparison is customary in most clinical trials. Another way to prevent erroneous rejection of compounds is to do a clinical trial in both a fasting and a fed state. Despite being a more time-consuming and expensive solution, this would provide very detailed information regarding the cardiac adverse effects of the investigational compound. We strongly recommend that research institutions implement one of these methods to avoid unnecessary re-investigations or rejections due to the effects of fasting on the ECG, such as the reduction of the QTcF by −3.87 ms demonstrated in this study.

4.1 | Limitations

In the interpretation of this manuscript, several limitations need to be considered. Foremost, HRV is known to be less reliable with electrocardiographic recordings of only 10 s. Furthermore, with a prospective study design, a better distinction can be made between the effect of the circadian rhythm, different circumstances between the two recordings, and the electrocardiographic differences after fasting. Finally, subjects were required to be in a fasting state for 4 hr prior to the screening visit, but this was only subjectively checked as the subjects were not supervised.

5 | CONCLUSION

Fasting has a profound impact on electrocardiographic parameters, summarized by a reduced wave amplitude and duration and increased isoelectric interval duration, which persisted after correction for various covariates.

CONFLICT OF INTEREST

None.

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How to cite this article: van der Stuijt W, Gal P, Kemme MJB, Burggraaf J. Effect of short-term fasting on electrocardiographic parameters. *Ann Noninvasive Electrocardiol*. 2019;24:e12643. https://doi.org/10.1111/anec.12643