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LETTER TO THE EDITOR

Relationships between heart rate variability and aortic hemodynamic variables in healthy subjects

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pulse wave analysis;
non-linear dynamics;
approximate entropy;
wave reflections

Analysis of Heart Rate Variability (HRV) is performed with linear and non-linear methods.[1] Both types of analyses have provided useful biomarkers for autonomic activity, which has been demonstrated to be an independent predictor of risk in cardiovascular (CV) disease.[2] Several aortic hemodynamic parameters were found to be premature indicators of pressure-induced CV complications. The intensity and timing of pressure wave reflections at the level of the central aorta as well as the aortic systolic blood pressure (BP), which is modulated by reflected waves, play a critical role in atrioventricular coupling and CV prognosis.[3] The aim of this study was to examine whether HRV in healthy subjects, as assessed by linear and non-linear dynamic indices, is associated with aortic hemodynamics, such as wave reflections and aortic BP.

A total of 73 healthy subjects were included in the study (age 39.6 $\pm$ 13.8 yrs, 45 males, 28 females, Body Mass Index 25.8 $\pm$ 4.2 kg/m^2, Height 173 $\pm$ 9.3 cm). All subjects provided informed consent before entering the study, and the study protocol was approved by the Institutional Research Committee.

Pressure recordings were conducted with patients in the supine position at least 12 hours from their last meal, coffee or cigarette. The SphygmoCor system was used for non-invasive assessment of aortic hemodynamics. Peripheral pressure waves were recorded at the radial artery with applanation tonometry, transformed by transfer functions[4] and the respective average aortic pressure waveform was computed. Aortic pulse wave analysis (PWA) was performed, and the parameters listed in Table 1 were determined.

A continuous electrocardiogram (ECG) was recorded for 24-hours at ambulatory conditions with a Holter device. After the ECG data were transferred to the computer, the time intervals between successive R peaks were calculated to obtain a normal RR time series. All of the RR time series went through manual editing to eliminate noise, ectopic beats and artifacts.

Linear HRV assessed by time domain and frequency domain measures, such as SDNN, RMSSD, pNN50, LF, HF, LF/HF[1] that were automatically calculated by the Holter interfaced software (Synescope, version 3.1, ELA Medical, France). Non-linear HRV was described by four measures containing complexity (Approximate Entropy – ApEn,[5] Fractal Dimension – FD[6]) and time-scale correlation features (α_1, α_2 from Detrended Fluctuation Analysis[7]), which were computed with a validated, *non-linear dynamics* tool.[8] All HRV indices are shown in Table 1.

All parameters were checked for normal distribution using the Kolmogorov–Smirnov test. The relationships between PWA and physiological variables with HRV were initially assessed by Pearson's or Spearman's correlation analysis (data not shown). P-values less than 0.05 (2-tailed) were considered to be statistical significance. All demographic and hemodynamic data presenting significant correlations with HRV parameters were entered as predictors of HRV in a backward method of multiple regression analysis. All significant predictors were reemployed as predictors for forced entry multiple regression models. Statistical analyses were performed using IBM SPSS Statistics (v.21).

Univariate analysis: All time domains and the majority of frequency domain measures were negatively correlated with age [$r = -0.33$ to -0.67, $p < 0.01$] or average Heart Rate (HR), [$r = -0.44$ to -0.77, $p < 0.01$], which indicated there were improved HRV profiles when the aforementioned parameters decreased. Regarding non-linear indices, the complexity features (ApEn, FD) appear to be degraded

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Table 1 Pulse wave analysis and heart rate variability measures.

Pulse wave analysis measures	Abbreviation
Peripheral Systolic Pressure (mmHg)	PSP
Peripheral Diastolic Pressure (mmHg)	PDP
Pulse Pressure (mmHg)	PP
Mean Pressure (mmHg)	P_{MEAN}
Central Systolic Pressure (mmHg)	C-SP
Central Diastolic Pressure (mmHg)	CDP
Augmented Pressure (mmHg)	AP
Augmentation Index (%)	AI
Augmentation Index adjusted for 75bpm (%)	AI@75
Arrival time of reflected waves at central aorta (msec)	t_r
Subendocardial Viability Index	SVI
Central Pulse Pressure (mmHg)	c-PP
Heart rate variability measures	
Time domain	
Standard deviation of all RR intervals	SDNN
Square root of the mean sum of squared differences between adjacent RR intervals	RMSSD
Mean of the SD of RR intervals for all 5 min segments in the entire recording	ASDNN
SD of the averages of RR intervals for all 5 min segments of the entire recording	SDANN
The percentage of adjacent RR pairs with differences larger than 50 ms	pNN50
Frequency domain	
Total Power (Variance of all RR intervals) $\leq$ 0.4 Hz	TP
Natural logarithm of TP	log (TP)
Power in the very low frequency range 0.003—0.04 Hz	VLF
Natural logarithm of VLF	log (VLF)
Power in the low frequency range 0.04—0.15 Hz	LF
Natural logarithm of LF	log (LF)
LF as a percentage of TP	LF%
LF as a percentage of TP-VLF	LFn.u.
Power in the high frequency range 0.15—0.4 Hz	HF
Natural logarithm of HF	log (HF)
HF as a percentage of TP	HF%
HF as a percentage of TP-VLF	HFn.u.
LF to HF ratio	LF/HF
Non-linear	
Approximate Entropy	ApEn
Short-term scaling exponent derived from Detrended Fluctuation Analysis	$\alpha 1$
Long term scaling exponent derived from Detrended Fluctuation Analysis	$\alpha 2$
Fractal Dimension	FD

[$r_{ApEn} = -0.4$, $r_{fd} = -0.6$, $p < 0.01$] while time scale correlation features (α_1, α_2) appear elevated [$r_{\alpha 1} = 0.24$, $r_{\alpha 2} = 0.40$, $p < 0.05$] as age increases. ApEn and the long-term exponent α_2 declined [$r_{ApEn} = -0.24$, $r_{\alpha 2} = -0.25$, $p < 0.05$], while the short-term exponent α_1 increased [$r_{\alpha 1} = 0.27$, $p < 0.05$] with HR.

According to univariate analysis, subjects characterized by better hemodynamic profiles, i.e., by lower central pressures (systolic/diastolic) and lower pressure wave reflections, demonstrated increased HRV measures. Correlations between HRV and wave reflection indices (e.g., Augmented pressure) [$r = -0.30$ to -0.57, $p < 0.01$] were stronger rather than correlations between HRV and central pressure rates [$r = -0.24$ to -0.29, $p < 0.05$]. The relationship between HRV and peripheral pressure (PDP, PSP) was non-significant. Increased reflections (AI@75) were related to reduced HRV, which was reflected by the majority of time and frequency measures [$r = -0.3$ to -0.7, $p < 0.01$], complexity loss [$r_{ApEn} = -0.29$, $p < 0.05$] and a decreased scale invariance regarding long-term correlations [$r_{\alpha 2} = -0.32$, $p < 0.01$].

Multivariate analysis: All linear HRV factors (except from LF/HF) were predominantly predicted by age and HR. The subordinate physiological predictors were Body Mass Index and height. Complementary and independent PWA predictors were the augmentation index corrected for heart rate (AI@75), reflection timing (t_r) and central systolic pressure C-SP. Non-linear variables were exclusively predicted by demographic variables, such as age, height, HR and gender. The variance of non-linear variables explained by the models is rather poor though (R^2 value: 0.14 to 0.34). The independent determinants of linear and non-linear HRV parameters are presented in Table 2.

To the best of our knowledge, there are no published studies exploring the relationships between short-term aortic hemodynamic indices and long-term HRV in healthy subjects. Correlations among non-linear dynamic parameters of HRV and hemodynamic indices have never been mentioned in a case study. In our final regression models, wave reflections (AI@75, t_r) seemed to have an independent impact on some traditional HRV features (ASDNN, RMSSD, TP, LF, LF/HF), which indicated that intense wave reflections resulted in lower HRV. The controversial positive relationship between C-SP and VLF is rather weak.

Non-linear variables were exclusively predicted by demographic variables, such as age, height, HR and gender. Age was negatively associated with complexity measures, which implied that more aged systems were less complex. Previous studies demonstrated that subjects with lower ApEn and FD values, which implies they have an autonomic system with lower complexity, are more susceptible to risk.[9] Scaling exponents, α_1 and α_2 were positively correlated with age, which indicated there were altered fractal scaling components with aging. Concerning ApEn and α_1, gender was a stronger predictor than height, but it was still weak. Increased HR predicted lower values of α_2 pointing to more abrupt changes among RR patterns. Based on our analysis, traditional CV disease factors (age, heart rate) are evidently outclassing PWA (AI@75, t_r) variables in predicting HRV measures.

Previous studies conducted on healthy subjects presented significant correlations between frequency parameters of HRV and pulse wave velocity (PWV). Although their prediction models were designed for the opposite direction (HRV variables predict stiffness variables), traditional CV risk variables appeared again as more powerful predictors of PWV than HRV variables.[10,11] When traditional factors entered the model, HRV predictors were totally outplaced or appeared to have a decrease in their prediction power.

Table 2 Multivariate analysis — Prediction of time domain, frequency domain and non-linear HRV variables by physiological and hemodynamic measures.

Time domain	Beta (p value)			Adjusted R^2
SDNN	**Age**	**Heart Rate**	**Body Mass Index**	**0.701**
	−1.46 (<0.001)	−3.24 (<0.001)	1.60 (0.025)	
ASDNN	**Age**	**Heart Rate**	**t_r**	**0.850**
	−0.87 (<0.001)	−1.71 (<0.001)	0.19 (0.008)*	
SDANN	**Age**	**Heart Rate**		**0.489**
	−1.01 (<0.001)	−2.59 (<0.001)		
RMSSD	**Age**	**Heart Rate**	**t_r**	**0.640**
	−0.66 (<0.001)	−1.14 (<0.001)	0.22 (0.028)*	
pNN50	**Age**	**Heart Rate**		**0.660**
	−0.40 (<0.001)	−0.68 (<0.001)		
Frequency domain				
TP	**Age**	**Heart Rate**	**t_r**	**0.814**
	−112 (<0.001)	−234 (<0.001)	27.2 (0.012)*	
VLF	**Age**	**Heart Rate**	**C-SP**	**0.842**
	−71.9 (<0.001)	−160 (<0.001)	12.7 (0.036)*	
LF	**Age**	**Heart Rate**	**AI@75**	**0.623**
	−26.5 (<0.001)	−44.9 (<0.001)	−16.2 (0.017)*	
HF	**Age**	**Heart Rate**		**0.382**
	−15.5 (<0.001)	−18.0 (<0.001)		
LF/HF	**Height**	**AI@75**		**0.148**
	0.11 (<0.001)	0.06 (0.007)**		
Non-linear				
ApEn	**Age**	**Height**	**Gender**	**0.220**
	−0.006 (<0.001)	−0.008 (0.005)	−0.11 (0.026)	
α1	**Age**	**Height**	**Gender**	**0.141**
	0.004 (0.002)	0.009 (0.002)	0.12 (0.014)	
α_2	**Age**	**Height**	**Gender**	**0.260**
	0.003 (<0.001)	−0.003 (0.002)	0.05 (0.017)	
FD	**Age**	**Height**	**Gender**	**0.344**
	−0.001 (<0.001)			

Abbreviations are explained in Table 1.
* Hemodynamic factor that significantly improves the model ($1\% \leq \Delta R^2 \leq 5\%$).
** Hemodynamic factor that significantly improves the model ($\Delta R^2 > 5\%$).

Relationships between arterial stiffness and HRV in diabetics are probably more sustainable when adjusted for physiological covariates. The SEARCH CVD study explored relationships between HRV and arterial stiffness in youth with and without type I diabetes. Diabetics presented important correlations among all HRV and arterial stiffness measures. All hemodynamic predictors, except AI@75, remained significant in the fully adjusted model for all physiological variables, but when resting HR was incorporated, the model relationships ceased to exist.[12] Swedish scientists used 24-hr ECGs and showed negative correlations among all spectral parameters and arterial stiffness ($r = -0.37$ to $r = -0.40$) in a group of patients with type I diabetes mellitus. In a multiple regression analysis with frequency measures against stiffness and age, only stiffness was an independent predictor.[13]

Our data suggest there were significant correlations between HRV and hemodynamic variables in healthy subjects. Wave reflection measures (AI@75, t_r) appeared to have a small but independent effect on HRV, which suggests the central aorta's afterload has the potential to influence the control center for heart rate, the ANS. Given that both HRV and central hemodynamics play a critical role in CV risk prognosis, searching for ways to concurrently minimize their adverse impact on cardiovascular system are needed urgently. However, traditional CV disease factors (age, HR) rather than hemodynamic measures predominantly influenced long-term time- and frequency-domain HRV indices in healthy subjects. Non-linear variables were independently predicted only by physiological variables. Features, such as complexity and time scale correlations, appear to be degraded as age increases. Concerning HF, LF/HF and all non-linear measures, the largest amount of variance cannot be explained (R^2 value: 0.14 to 0.38) by the traditional CV and hemodynamic factors used in this study. Finding the major determinants of all of the HRV features (linear and non-linear) could provide clinicians with an opportunity to intervene and improve HRV in their patients.

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