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Heart Rate Variability and renal organ damage in hypertensive patients

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Abstract— **Heart rate variability (HRV), a noninvasive measure of autonomic dysfunction and a risk factor for cardiovascular disease (CVD), has not been systematically studied in hypertensive patients in relation with renal involvement. A retrospective analysis on a cohort of hypertensive patients was performed to show differences in groups of patients categorized according to renal involvement, assessed by glomerular filtration rate (GFR). Patient with 24-h ECG Holter monitoring and other clinical information registered in the database of the Hypertension Clinic of the University of Naples Federico II were selected. Linear standard HRV measures were computed according to international guidelines on 24-h nominal ECG. A total of 200 patients were included in the present study. Decreased ratio of low to high frequency power (LF/HF) was associated with patient with moderate GFR, the highest grade of renal involvement considered in this study. These results were consistent with the findings of previous studies which concluded that depressed HRV was associated with higher risk of progression to end-stage renal disease and suggested that autonomic dysfunction may lead to kidney damage. Further research is needed to define the role of autonomic dysfunction in the development of renal disease and of HRV as a diagnostic or prognostic maker in hypertensive patients.**

I. Introduction

Cardiovascular (CV) diseases are one of the most relevant causes of morbidity and mortality in developed countries[1]. At this regard, it is important to remember that there is a preclinical and asymptomatic phase in which CV diseases can be detected by evaluating target organ damage at cardiac, vascular and renal level. If CV involvement is early detected by physicians, it is possible to influence the progression or regression of the disease by the therapy[2].

Indeed, despite there is still a little information on the specific aethiology of these pathologies, it is well known that some physiological or pathological conditions (sympathetic drive) are more frequently related to CV involvement and to CV events[3]. Analysis of heart rate variability (HRV) on the basis of routine 24-hour Holter recordings has been shown to provide a sensitive, noninvasive measurement of cardiac autonomic control[4, 5]. HRV is a non-invasive measure reflecting the variation over time of the period between consecutive heartbeats (RR intervals)[4]. Clinical studies have shown reduced HRV in patients with chronic heart failure[6-10], diabetes[11, 12], and ventricular arrhythmias[13]. Regarding hypertensive patients a sympatho-vagal imbalance as evaluated by HRV with increased sympathetic activity and reduced vagal tone has been reported[14] but few data are in literature on the relation of HRV and different cardiovascular involvement (i.e. cardiac, vascular and renal).

The aim of this study was to evaluate the correlation of HRV with asymptomatic development of CV disease at renal level in hypertensive treated patients registered in the Campania Salute network. The Campania Salute network is an open registry collecting information from a network of general practitioners and community hospitals networked with the Hypertension Clinic of the University of Naples Federico II. The centralized database collects all demographics and clinical information.

II. Methods and Materials

A. Population study

For the present study, among the initial cohort of 12,000 patients registered in the database of the Campania Salute Network, we selected all the hypertensive subjects referred to the Hypertension Clinic of the University of Naples Federico II from 2000 to 2010 which were evaluated by cardiac and carotid ultrasonography and by an 24h Holter ECG. Details on this cohort have been previously reported[15, 16]. Exclusion criteria for the present analysis were: diagnosis of secondary resistant and/or uncontrolled hypertension, previous CV disease, clinical history of cancer, liver cirrhosis and/or failure, narcotics abuse, lifestyle changes in the last 12 months. Previous CV diseases were excluded by an ad-hoc committee in the Hypertension Center, based on patient's history, clinical evaluation, contact with the referring general practitioner and CV diagnostic evaluations.

B. Ethical issues

The database generation of the Campania Salute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for used data for scientific purposes was obtained from all the participants.

C. Protocol

At the first visit all patients were given a detailed questionnaire inquiring about specifics lifestyle behaviors and smoking habit, in the current study they were categorized as non-smokers, ex-smorkers or smokers. Blood

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pressure (BP) values, clinical, biochemical and ultrasounds parameters were analyzed and recorded at the first visit and during the screening period. All patients underwent multiple clinical visits and performed baseline and follow-up Echocardiogram and Carotid Ultrasound procedure.

Diagnosis and stratification of essential hypertension was performed according to the criteria established by the Guidelines for the Management of Arterial Hypertension. Systolic and diastolic blood pressure were measured by standard aneroid sphygmomanometer after 5 min rest in the supine position, according to the current guidelines[17].

Serum creatinine, fasting plasma glucose, total-cholesterol, and triglycerides were measured with the standard methods. Glomerular filtration rate (GFR) was calculated by the Modification of Diet in Renal Disease (MDRD) formula[18]. Diabetes was defined as a fasting blood glucose ≥126 mg/dL or active glucose-lowering therapy[19]. Dyslipidaemia was defined by the presence of elevated cholesterol (>200 mg/dL) and/or triglycerides (>150 mg/dL) or active lipid-lowering therapy[20].

D. Echocardiography and Carotid Ultrasound

Two-dimensional-guided M-mode echocardiograms were performed using a dedicated ultrasound machine (SONOS 5500, Philips) with an ultrasound transducer of 2.5 MHz. The examinations were recorded on a digital recorder and analyzed by three independent, trained and experienced physicians. Left ventricle mass was determined by using the formula developed by Devereux and Reichek[21] and divided by the body surface area to calculate LV mass index (LVMi, g/m^2).

B-mode ultrasonography of carotid arteries was performed with patients in the supine position with the neck extended in mild rotation. The scanning protocol was performed with an ultrasound device (SONOS 5500, Philips) equipped with a 7.5-MHz high-resolution transducer with an axial resolution of 0.1 nm. All measurement were analyzed by three different trained experienced physicians. An average of two readings were considered for subsequent calculations. The accuracy of determinations was evaluated as previously described by Lembo et al.[22]. The maximum arterial intima media thickness (IMT max) in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation, and proximal internal carotid artery were estimated offline with an image processing workstation.

E. Assessment of kidney organ damage

Kidney organ damage was assessed as e-cleareance by determination of Glomerular filtration rate (GFR) using the simplified MDRD formula[23] and involvement was quantified as grade 1 to 3. The patients were stratified by the glomerular filtration rate (GFR) in three groups: Group 1: increased or normal GFR (GFR≥90 mL/min/1.73 m2); Group 2: mild GFR (60<GFR<90 mL/min/1.73 m2); Group 3: moderate GFR (GFR≤60 mL/min/1.73 m2)[24].

F. Processing 24-Hour Holter Recordings

On 2 consecutive days, patients underwent 24-hour ambulatory BP monitoring, 24-hour ECG Holter recording. The recorders were applied between 9 and 11 AM on a working day, and patients were asked to follow as closely as possible their usual daily activities during each monitoring session. They were asked to stay in bed from 11 PM to 7 AM, and all reported to have slept normally during the nights they were monitored.

The series of normal to normal (NN) beat intervals were obtained from ECG recordings using OSAS, an open-source software for QRS detection and beat classification. Standard long-term HRV analysis on nominal 24-h recordings according to International Guidelines was performed [4]. The HRV analysis was performed using PhysioNet's HRV Toolkit[25]. We chose this toolkit as it is an open source and a rigorously validated package. The NN/RR ratio was computed as the fraction of total RR intervals classified as normal-to-normal (NN) intervals. This ratio has been used as a measure of data reliability, excluding records with a ratio less than a threshold. The authors chose a threshold of 80%, as it was a satisfactory trade-off between numbers of included subjects and quality of NN signals.

All the computed basic time- and frequency-domain HRV measures were widely used in the literature[4]. A number of standard statistical time-domain HRV measures are calculated: Average of all NN intervals (AVNN), standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments of a 24-h recording (SDANN), mean of the standard deviations of NN intervals in all 5-min segments of a 24-h recording (SDNN IDX), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), percentage of differences between adjacent NN intervals that are longer than 50 ms (pNN50). The frequency-domain HRV measures rely on the estimation of power spectral density (PSD) computed by Lomb-Scamble periodogram [26]. After PSD estimation, six standard frequency-domain HRV measures were calculated: total spectral power of all NN intervals up to 0.4 Hz (TOTPWR), between 0 and 0.003 Hz (ULF), between 0.003 and 0.04 Hz (VLF), between 0.04 and 0.15 Hz (LF), and between 0.15 and 0.4 Hz (HF), ratio of low to high frequency power (LF/HF).

G . Statistical Analysis

Data were analyzed by the use of PASW software (version 18; SPSS, Chicago, IL, USA). Univariate differences were analyzed using Kruskal-Wallis test for HRV measures, ANOVA for the other continuous variables (i.e. age, IMT, etc) and χ test for the categorical variables (i.e. sex, smoking). For each HRV measure, which differs significantly among the three groups, an adjusted model was proposed by performing a multinomial logistic regression.

III. RESULTS

200 hypertensive participants aged from 25 to 88 years were included. Demographic, clinical and laboratory

characteristics of all the study population are shown in Table I. Tables II shows the characteristic of the study sample of patients categorized by GFR in three groups. The Group 3 is significantly older than the others and has a significantly higher proportion of patients taking diuretic. Diastolic BP, Systolic BP and Pulse Pressure values were significantly higher in Group 2, where IMT value were significantly lower in Group 1. Table III shows the HRV measures in the groups. The three groups differed significantly in LF/HF. This difference persisted even in the adjusted model, as shown in Table IV. Among all the variables of Table I, which were considered in the adjusted model, the multinomial logistic regression selected age, family history of hypertension and systolic BP. Higher values of LF/HF are associated with an increased probability that a subject belongs to the Groups 1 or 2 rather than to the Group 3 (odd ratio OR 2.655 and 2.699 respectively). Older age is associated with a decreased probability of being in Group 1 or 2 (OR 0.901 and 0.950 respectively). The absence of family history of hypertension is associated with an increased probability of belonging to Group 1 (OR 3.168). Higher value of systolic blood seems to be associated with a slightly increased probability of belonging to Group 2 (OR 1.021).

IV. DISCUSSION

In this study we investigate standard linear HRV measures in hypertensive patients, categorized by GFR.

TABLE I. CHARACTERISTICS OF THE STUDY SAMPLE OF PATIENTS

Characteristic	Value
Age (years)	62.4±12
Sex (male/female, %)	63.5/46.5
Family history of hypertension (yes/no, %)	57/43
Family history of stroke (yes/no, %)	18/82
Smokers (yes/ex/no, %)	18/21/62
Systolic BP (mmHg)	133±22.6
Diastolic BP (mmHg)	75.6±11.9
Pulse pressure (mmHg)	57.5±17.8
Fasting blood glucose (mmHg)	102.9±24
Total Cholesterol (mg/dl)	186±40.5
Beta-blockers (yes/no, %)	33.5/66.5
Alphabeta-blockers (yes/no, %)	10/90
Alpha-blockers (yes/no, %)	8/92
Diuretics (yes/no, %)	43/57
ACE inhibitor (yes/no, %)	37/63
Dihydropyridine (yes/no, %)	26/74
MDRD	77.3±18.5
Kidney Involvment (Group 1/ 2 /3 %)	13,5/11/86,5
IMT max	2.24±1.56
LVMi	130.2±30.8

TABLE II. CHARACTERISTICS OF THE STUDY SAMPLE OF PATIENTS STRATIFIED BY GFR

Characteristic	Group 1	Group 2	Group 3
Age (years)	56±11.4	63±11.6	69.7±9.2 [a]
Sex (male/female)	64.6/35.4	64.2/35.8	59.4/40.6
Systolic BP	124.5±23.1	137.3±19.7 [a]	129.5±27
Fam history of hypertension(yes/no)	52.1/47.9	58.3/41.7	59.4/40.6
Family history of stroke (yes/no)	20.8/79.2	18.3/81.7	12.5/87.5
Smokers (yes/ex/no)	27.1/16.7/56.2	14.2/22.5/63.3	15.6/18.8/65.6
Diastolic BP	73.2±13.8	77.3±11.4 [a]	72.6±9.6
Pulse pressure	51.3±14	60±16.8 [a]	57±23.2
Fasting blood glucose	99.7±31.9	102.9±19.9	107.4±23.5
Total Cholesterol	178.9±36	187.7±40.4	190.3±45.2
Beta-blockers (yes/no)	31.3/68.7	34.2/65.8	34.4/65.6
Alphabeta-blockers (yes/no)	10.4/89.6	11.7/88.3	3.1/96.9
Alpha-blockers (yes/no)	6.3/93.7	6.7/93.3	15.6/84.4
Diuretics[a] (yes/no)	35.4/64.6	40.8/59.2	62.5/37.5
ACE inhibitor (yes/no)	33.3/66.7	40/60	31.3/68.7
Dihydropyridine (yes/no)	25/75	25/75	31.3/68.7
IMT max	1.8±0.76 [a]	2.23±1.21	2.9±2.85
LVMi	124.3±25.9	132.8±32.1	128.9±30.9

a. p-value less than 0.05

We found low LF/HF was associated with patient with moderate GFR, the highest grade of kidney involvement considered in this study. This association remained significant after adjustment for other factors known to contribute to the development of renal failure, including diabetes, hypertension, lipid variables. Our results were consistent with two recent studies[27, 28] investigating HRV and kidney disease, which concluded that lower HRV (particularly, frequency domain measures) was associated with higher risk of progression to end-stage renal disease and suggested that autonomic imbalance may lead to kidney damage. However, the plausible mechanisms by which abnormal autonomic balance may lead to kidney damage are not clearly known.

TABLE III. COMPARISONS OF HRV MEASUREMENT IN THE GROUP OF PATIENTS STRATIFIED BY GFR

Indexes	*Group 1 (MDRD > 90)*			*Group 2 (60 <MDRD < 90)*			*Group 3 (MDRD < 60)*			*p-value*
	Median	*25th*	*75th*	*Median*	*25th*	*75th*	*Median*	*25th*	*75th*	
AVNN	848.931	784.875	915.911	852.402	772.551	953.323	875.997	806.343	963.397	0.358
SDNN	119.542	102.303	145.981	111.134	92.211	141.291	113.797	98.261	141.068	0.309
SDANN	108.585	90.246	137.020	99.823	78.398	129.377	105.624	86.031	132.446	0.331
SDNN IDX	51.430	43.872	58.769	47.101	40.778	61.044	45.040	36.859	58.248	0.244
RMSSD	30.060	24.496	37.738	30.525	22.410	42.082	33.665	24.671	42.061	0.501
pNN50	7.678	3.942	11.742	7.884	2.732	17.711	10.063	4.069	12.851	0.661
TOTPWR	16124.3	11012.10	23626.20	13783.60	9042.49	21606.80	15175.15	10303.48	24712.60	0.355
ULF	12378.5	8864.23	18678.70	10707.80	7102.66	18480.05	12001.30	8215.47	20216.80	0.359
VLF	1592.02	1195.17	2367.55	1421.585	961.295	2404.685	1259.530	812.876	1958.985	0.110
LF	711.187	485.837	1102.005	600.558	370.216	916.729	577.239	373.462	925.431	0.154
HF	471.256	298.766	724.492	493.440	201.829	801.501	549.748	288.798	1230.165	0.436
LF/HF	1.439	1.168	2.099	1.253	0.910	1.751	0.867	0.724	1.251	<0.001

The methods of computation of HRV measures were different between the studies. For these reasons, further research is needed to define the role of sympatho-vagal imbalance in the development of renal disease and to define the role of HRV as a diagnostic or prognostic maker of kidney disease in hypertensive patient.

TABLE IV. ADJUSTED MODEL FOR ALL THE VARIABLES IN TABLE I FOR THE RELATIONSHIP BETWEEN LF/HF AND THE GROUPS ACCORDING TO MDRD; THE GROUP 3 (MDRD < 60) IS THE REFERENCE IN THIS MODEL

Measures	β	Std error	p-value	e^{β} Odd ratio	95% CI for Odd ratio	
					Low	Upp
1. Intercept	5.856	2.512	.020			
LF/HF	.977	.459	.033	2.655	1.079	6.531
Systolic BP	-.005	.011	.645	.995	.973	1.017
Age	-.104	.028	.000	.901	.854	.951
Absence of familiy history of hypertension	1.153	.536	.031	3.168	1.109	9.050
2. Intercept	.322	2.225	.885			
LF/HF	.993	.436	.023	2.699	1.149	6.341
Systolic BP	.021	.010	.040	1.021	1.001	1.042
Age	-.051	.024	.034	.950	.906	.996
Absence of familiy history of hypertension	.758	.448	.091	2.134	.887	5.138

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