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Aldosterone-to-Renin Ratio Is Associated With Reduced 24-Hour Heart Rate Variability and QTc Prolongation in Hypertensive Patients

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Abstract: Aldosterone is considered to exert direct effects on the myocardium and the sympathetic nervous system. Both QT time and heart rate (HR) variability (HRV) are considered to be markers of arrhythmic risk and autonomous dysregulation. In this study, we investigated the associations between aldosterone, QT time, and HRV in patients with arterial hypertension.

We recruited 477 hypertensive patients (age: 60.2 ± 10.2 years; 52.3% females) with a mean systolic/diastolic 24-hour ambulatory blood pressure monitoring (ABPM) value of 128 ± 12.8/77.1 ± 9.2 mmHg and with a median of 2 (IQR: 1–3) antihypertensive agents. Patients were recruited from the outpatient clinic at the Department of Internal Medicine of the Medical University of Graz, Austria. Blood samples, 24-hour HRV derived from 24-hour blood pressure monitoring (ABPM) and ECG's were obtained. Plasma aldosterone and plasma renin concentrations were measured by means of a radioimmunoassay. Twenty-four-hour urine specimens were collected in parallel with ABPM.

Mean QTc was 423.3 ± 42.0 milliseconds for males and 434.7 ± 38.3 milliseconds for females. Mean 24H-HR and 24H-HRV was 71.9 ± 9.8 and 10.0 ± 3.6 bpm, respectively. In linear regression analyses adjusted for age, sex, body mass index, ABPM, and current medication, aldosterone to active renin ratio (AARR) was significantly associated with the QTc interval, a marker for cardiac repolarization abnormalities (mean = 426 ± 42.4 milliseconds; β-coefficient = 0.121; $P = 0.03$) as well as with the 24-hour heart rate variability a surrogate for autonomic dysfunction (median = 9.67 [IQR = 7.38–12.22 bpm]; β-coefficient = −0.133; $P = 0.01$).

In hypertensive patients, AARR is significantly related to QTc prolongation as well as HRV. Further studies investigating the effects of mineralocorticoid receptor blocker and aldosterone synthase inhibitors on QTc and HRV are warranted.

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Abbreviations: 24H-HRV = 24-hour heart rate variability, AARR = Aldosterone to active renin ratio, ABPM = 24-hour ambulatory blood pressure monitoring, ACE = angiotensin converting enzyme, AF = atrial fibrillation, AT1 = angiotensin II type one, BMI = body mass index, BP = blood pressure, CV = cardiovascular, eGFR = estimated glomerular filtration rate, HR = heart rate, HRV = heart rate variability, MDRD = Modification of Diet in Renal Disease, MR = mineralocorticoid receptor, MRA = mineralocorticoid receptor antagonist, PA = primary aldosteronism, PAC = plasma aldosterone concentrations, PRC = plasma renin concentration, RIA = radioimmunoassay.

INTRODUCTION

Aldosterone is secreted by the adrenal glands and is classically known to contribute to the regulation of salt and fluid homeostasis. It is further considered to assume functions of a growth factor,[1] that could potentially mediate actions of relevance to heart failure, myocardial infarction, and arterial hypertension.[2–4] Moreover, it is possibly involved in pathophysiological processes that lead to atherosclerosis, endothelial dysfunction, and ventricular remodeling.[5,6] In particular, the

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myocardium appears to be a target tissue for aldosterone, as animal studies and in vitro experiments have documented remodeling of cardiomyocytes when exposed to excessive aldosterone levels.[7–9] The proposed mechanisms mediating the link between aldosterone, the mineralocorticoid receptor (MR) and cardiovascular (CV) mortality involve genomic and nongenomic effects.[9–12] The latter fits with the observation that there is functional cross-talk between aldosterone and various growth factor receptor signaling pathways within cardiac tissue.[7–9,12–14] This is of particular importance given that the effects on cellular remodeling have been demonstrated to be a major underlying mechanism for the development of susceptibility to arrhythmias.[15] While the precise mechanisms are still largely unknown, it is possible that increased aldosterone might be directly related to negatively influencing myocardial inflammation and fibrosis.[3,11,16] Previous studies described an association between aldosterone and adrenergic tone.[17,18] Nevertheless, the association between aldosterone and surrogate markers of autonomic dysfunction and sudden cardiac death in patients with arterial hypertension remain to be fully elucidated. Both QTc and heart rate variability (HRV) are known to be associated with arrhythmic risk in patients with arterial hypertension.[19–24] In this study, we therefore aimed to examine the association between aldosterone (as a ratio to renin, as both represent 2 ends of a continuous spectrum)[25–27] and QTc interval as well as with 24-hour HRV (24H-HRV).

METHODS

Details of the Styrian Hypertension Study have been previously published.[28,29] We invited patients with a history of arterial hypertension, that is, either arterial hypertension according to medical records or according to patient interview. All study participants (age $\geq$18 years) were prospectively recruited at the Department of Internal Medicine at the Medical University of Graz, Austria and received 24-hour blood pressure monitoring (Figure 1). We examined 477 patients in total with a mean age of 60.9 ± 10.6 years (52.3% female). Exclusion criteria were stroke or myocardial infarction in the previous 4 weeks, pregnancy and lactation, and an estimated life expectancy of less than 1 year, as per assessment by a senior physician. Written informed consent was provided from all study participants. The Styrian Hypertension Study was approved by the ethics committee at the Medical University Graz, Austria. The study is compatible with the Declaration of Helsinki (October 2013) and the STROBE guidelines in regard to reporting cross-sectional studies.

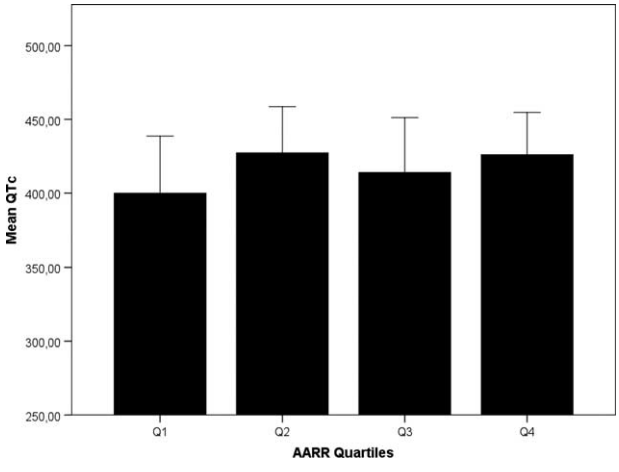

FIGURE 1. Consort 2010 Study flow chart describing the process of recruiting patients and their assessment.

Circumference of the upper arm was measured in all patients to select the appropriate cuff for blood pressure (BP) measurements. ABPM was performed with a SPACELABS 90217A device (firmware version: 03.02.16; Spacelabs Healthcare, Inc, Issaquah, WA) at 15-minute intervals during the day (06:00–22:00 AM) and every 30 minutes during the night (22:00–06:00 AM). In parallel, 24-hour urine specimens were obtained from the study participants. 24H-HRV was defined as the standard deviation of 24-hour heart rate obtained by ABPM measurement. This method can also be referred to as SDNN (standard deviation of normal to normal beats), measured every 15 minutes during the day and every 30 minutes during nighttime. QT time was measured on 50 and 100 mm/second ECG recordings by a single investigator masked to patient characteristics. The ECG was obtained in the morning between 7 and 11 PM at the beginning of the 24-hour period of ABPM measurement. An additional sample was recorded randomly by a second independent investigator for validation purposes. The corrected QT time was calculated according to Framingham: $QTc = QT + 0.154 \times (1 - RR)$.[30] All ECG measurements were performed by adhering to published guidelines.[31]

Laboratory Measurements

Blood samplings were performed in the morning (07:00–11:00 AM) after an overnight fast and after ten minutes of rest in the seated position. All blood samples were either measured at least within 4 hours after sampling or were immediately stored at -20°C until analysis. Plasma renin concentrations (PRC) were measured in EDTA plasma by a ''RENIN III GENERATION'' (GEN. III) radioimmunoassay (RIA) (Renin IRMA RIA-4541, DRG Instruments GmbH, Marburg, Germany). Plasma aldosterone concentrations (PAC) were also determined by means of a RIA (Aldosterone RIA DSL-8600, Diagnostic Systems Laboratories, Inc., Webster, TX). Aldosterone-to-active renin concentration was calculated as PAC divided by PRC (ng/dl divided by μU/ml). Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula. All other measurements (eg, sodium, potassium, calcium, c-reactive protein [CRP], etc.) were performed by routine laboratory procedures.

Statistical Methods

The distribution of continuous variables was evaluated and, where appropriate, nonnormally distributed variables were $\log_{10}$-transformed and indicated in the text with the prefix ''log.'' For baseline characteristics we formed quartiles according to the aldosterone to active renin ratio (AARR) values of the overall study cohort. There was no data imputation and patients with missing values were excluded from the main analysis. Group comparisons were performed either by Chi-square test, analyses of variance (ANOVA), or Kruskal–Wallis test, when appropriate. To test the assumption of a linear regression analysis between the dependent and independent variables of interest we plotted the residuals (observed vs. predicted values) and tested for colinearity for all included parameters (criteria were variance inflation factor $<$1.96 equivalent to tolerance $>$0.51). We performed linear regression analyses to evaluate the association between QTc or 24H-HRV (dependent variables) and AARR (independent variable). Cumulative adjustments were performed for various confounders that were prudently

selected based on their suspected interaction with the renin–angiotensin–aldosterone system, QT time, and 24H-HRV. Three models were built, based on increasing explanatory value. Model 1 included log age (years) and gender. Model 2 additionally included log body mass index (BMI) (kg/m^2), current smoking status (yes/no), eGFR-MDRD (ml/min/1.73 m^2), HbA1c (mmol/mol), systolic and diastolic 24-hour BP (mmHg), and urinary sodium/potassium (Na+/K+) ratio. In Model 3, treatment with binary variables for use of β-blockers (yes/no), angiotensin converting enzyme (ACE)-inhibitors (yes/no), angiotensin II type one (AT1) receptor blockers (yes/no), calcium channel blockers (yes/no), loop diuretics (yes/no) and thiazides (yes/no) were included. Patients under treatment with mineralocorticoid receptor antagonist (MRA) and atrial fibrillation (AF) on current ECG were excluded from the present analyses, as AF diminishes the interpretation of the QT interval.[31] In additional analysis, further adjustments for calcium (mmol/L), potassium (mmol/L), phosphate, 25-hydroxy-vitamin-D (ng/ml), nocturnal blood pressure (mmHg), and CRP (mg/L) were made. We repeated the analysis using a multiplicative interaction term of HR and HRV as well as including only those with an HR ranging between 60 and 70 bpm[32–34] in order to account for the fact that higher/lower HRs are intrinsically linked to changes in HRV.[32–34] In an effort to exclude the potential that our results may reflect changes typically known in patients with primary aldosteronism (PA), we repeated the analyses in patients with a negative screening result for PA (AARR $<$ 3.7 ng/dl/μU/ml). As a sensitivity check, participants with a renin level below 5 μU/ml (detection limit of the assay) were omitted in an attempt to control for flawed interpretations of the AARR as well as patients with low-renin hypertension, which is considered to resemble a mild form of PA. All statistical analyses were performed using SPSS 20 (SPSS, Inc., Chicago, IL) and a 2-sided *P*-value $<$ 0.05 was considered statistically significant.

RESULTS

Mean QTc corrected by the Framingham equation was 423.3 ± 42.0 milliseconds for males and 434.7 ± 38.3 millise-milliseconds for females (Table 1, showing the baseline

TABLE 1. The Baseline Characteristics According to Aldosterone–Renin Ratio Quartiles

Variable	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	*P*
Aldosterone range, ng/dl	0.03–0.3	0.32–0.83	0.85–1.72	1.73–13.26	
Number of patients (total = 477)	116	123	122	116	
Age, yr	62.0 ± 11.65	61.3 ± 8.1	57.0 ± 10.0	60.0 ± 11.0	**0.04**
BMI, kg/m^2	30.9 ± 4.6	30.0 ± 4.7	29.8 ± 4.6	28.6 ± 5.1	**0.03**
QTc Framingham, ms	419 ± 34	429 ± 39	416 ± 37	440 ± 48	**0.02**
Mean 24-h heart rate variability, bpm	9.79 ± 3.48	10.0 ± 3.59	10.30 ± 3.53	9.64 ± 3.73	0.45
Mean 24-h heart rate, bpm	70.8 ± 14.4	69.7 ± 8.8	71.8 ± 9.2	70.8 ± 9.7	0.57
Heart rate during nighttime, bpm	63.1 ± 12.7	62.5 ± 8.2	64.5 ± 9.1	63.6 ± 8.8	0.69
Heart rate variability during nighttime, bpm	4.10 (2.70–5.17)	3.80 (3.08–5.20)	3.87 (2.83–5.34)	3.69 (2.83–5.63)	0.97
Blood pressure					
Daytime systolic BP, mmHg	129.9 ± 11.4	127.5 ± 13.9	134.4 ± 14.2	132.6 ± 12.9	**0.04**
Nighttime systolic BP, mmHg	115.9 ± 13.5	116.0 ± 15.0	119.2 ± 16.0	119.0 ± 13.6	**<0.01**
Daytime diastolic BP, mmHg	75.7 ± 8.5	78.8 ± 8.4	81.5 ± 8.1	81.4 ± 11.0	0.49
Nighttime diastolic BP, mmHg	65.3 ± 7.6	68.5 ± 8.4	69.1 ± 8.13	70.6 ± 8.1	**0.01**
24 h urinary sodium, mmol/24 h	165.0 (116.0–217.5)	139.0 (108.0–192.0)	152.0 (107.0–193.0)	136.0 (97.6–198.8)	0.26
C-reactive protein, mg/dl	2.37 ± 3.01	3.26 ± 4.29	2.55 ± 2.83	3.31 ± 3.78	**0.03**
Serum potassium, mmol/L	4.12 ± 0.39	4.04 ± 0.30	3.99 ± 0.34	4.02 ± 0.32	**0.02**
Serum calcium, mmol/L	2.39 ± 0.12	2.37 ± 0.11	2.38 ± 0.11	2.38 ± 0.09	0.30
Serum phosphate, mg/dl	2.97 ± 0.48	2.97 ± 0.49	2.95 ± 0.50	3.03 ± 0.52	0.59
25-Hydroxyvitamin D, ng/ml	26.91 ± 11.45	29.05 ± 12.04	28.38 ± 11.81	28.73 ± 10.97	0.52
GFR-MDRD, ml/min/1.73 m^2	71.2 ± 19.8	72.4 ± 13.6	78.6 ± 18.7	79.2 ± 17.5	**0.04**
Diabetes mellitus, %	34.0	22.6	17.0	15.4	0.09
Active smokers, %	3.7	9.4	20.8	25.0	**<0.01**
Medication					
Number of different antihypertensive drugs	2 (1–3)	2 (1–3)	1 (1–3)	2 (1–3)	0.08
ACE-I, %	49.0	43.4	34.0	40.4	0.46
AT1 blocker, %	39.2	35.9	18.9	17.3	**0.01**
β-blocker, %	45.3	54.7	50.9	63.5	0.29
Calcium channel blockers, %	30.2	21.1	27.1	19.8	0.33
Thiazide diuretics, %	50.8	38.6	37.0	36.2	0.06
Loop diuretics, %	13.3	3.9	2.4	0.8	n.p.
MRA, %	1.9	3.9	0.0	0.0	n.p.

Continuous data are presented as means ± standard deviation or as medians with interquartile range. Categorical data are shown as percentages. ANOVA with *P* for trend, Kruskal–Wallis and Chi-square test were used. n.p. indicates insufficient cell size to reliable test all quartiles.

ACE = angiotensin converting enzyme, AT1 = angiotensin II type one, BMI = body mass index, BP = blood pressure, GFR = glomerular filtration rate, MDRD = Modification of Diet in Renal Disease, MRA = mineralocorticoid receptor antagonist.

TABLE 2. Linear Regression Modeling

	24 h Heart Rate Variability		QTc	
	β-Coefficient	*P*	β-Coefficient	*P*
Model 1	−070	**0.11**	0.144	**<0.01**
Model 2	−153	**<0.01**	0.119	**0.02**
Model 3	−133	**0.01**	0.121	**0.03**
+ CRP	−128	**0.01**	0.116	0.05
+ Serum potassium	−133	**0.01**	0.115	0.05
+ Serum phosphate	−134	**0.01**	0.113	**0.04**
+ Serum calcium	−131	**0.01**	0.120	0.05
+ 25-hydroxy Vit D	−134	**0.01**	0.129	**0.04**
+ Nocturnal systolic BP	−131	**0.01**	0.118	**0.03**
Model 3 using an interaction term of heart rate and heart rate variability	−0.142	0.063	—	—
Model 3 in patients with heart rate 60–70/min	−0.074	0.36	0.238	**<0.01**

Model 1 included age (years) and gender. Model 2 additionally included log body mass index (BMI) (kg/m^2), current smoking status (yes/no), eGFR-MDRD (ml/min/1.73 m^2), HbA1c (mmol/mol), systolic and diastolic 24-h BP (mmHg), and urinary sodium/potassium (Na+/K+) ratio. In Model 3, treatment with binary variables for use of β-blockers (yes/no), angiotensin converting enzyme (ACE)-inhibitors (yes/no), angiotensin II type one (AT1) receptor blockers (yes/no), calcium channel blockers (yes/no), loop diuretics (yes/no) and thiazides (yes/no) were included. A *P* values <0.05 is considered statistically significant.

BP = blood pressure, CRP = C-reactive protein, Vit D = vitamin D.

Bold letters indicate a *P*-value of less than 0.05 and thus indicates statistical significance.

characteristics according to aldosterone–renin ratio quartiles). Mean 24H-HR and 24H-HRV was 71.9 ± 9.8 and 10.0 ± 3.6 bpm, respectively (Table 2).

Heart Rate Variability

The mean 24H-HRV was not statistically significant different between the quartiles (Figure 2) in the unadjusted ANOVA. AARR associations between 24H-HRV and AARR according to the different regression models are reported in Table 2 (Model 3: β-coefficient = −0.133; $P = 0.01$). Using renin alone we observed a borderline statistically significant association (β-coefficient = 0.102; $P = 0.05$), but not for aldosterone (β-coefficient = −0.029; $P = 0.53$).

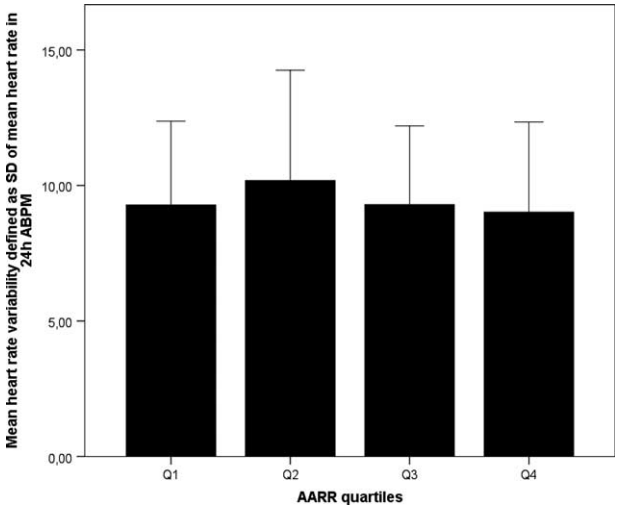

FIGURE 2. Mean 24-hour heart rate variability in each aldosterone to active renin ratio quartile. Error bars indicate 1 standard deviation.

QTc Interval

The mean QTc was statistically significant different between the quartiles (Figure 3) in the unadjusted ANOVA. QTc Framingham prolongation was significantly associated

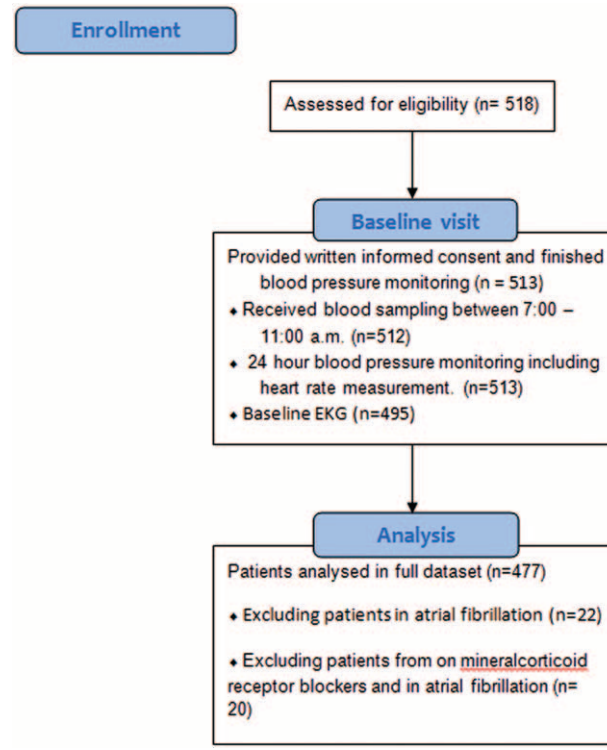

FIGURE 3. Mean QTc time in each aldosterone to active renin ratio quartile. Error bars indicate 1 standard deviation.

with AARR irrespective of adjustment (Model 3: β-coefficient = 0.121; $P = 0.03$). Considering renin and aldosterone separately, we did not observe a statistically significant association for 24H-HRV (β-coefficient = −0.067; $P = 0.25$ and β-coefficient = −0.029; $P = 0.53$, respectively).

Sensitivity Analysis

The main results were similar when including only patients with an AARR below 3.7 ng/dl/μU/ml or when excluding patients with a renin level below the detection threshold (5 μU/ml, n = 42 patients). Repeating the analysis for HRV using a multiplicative interaction term of HR × HRV yielded similar results as well as when only participants with an HR between 60 and 70 bpm were included (Table 2).

DISCUSSION

In the present analysis we demonstrated an association between reduced 24H-HRV, QTc prolongation, and aldosterone to renin ratio (ie, relative aldosterone excess) in patients with arterial hypertension. These findings remained significant after adjusting for a broad panel of confounders. The present investigation supports and extends results of prior studies by demonstrating a linear association between PAC with QTc times as well as 24H-HRV. Our study is consistent with previous investigations which point toward aldosterone mediated proarrhythmic properties that might contribute to CV morbidity and mortality in patients with hypertension and is a therapeutic target.[2,35] Intriguingly, both QTc and 24H-HRV are significantly associated with aldosterone plasma levels, possibly due to an interaction with autonomic tone and consequently with arrhythmic risk.[17,20,36–39] Ouvrard-Pascaud et al[40] published a transgenic mouse model suggesting a role of MR activation in intrinsic rate and rhythm control. Aldosterone mediated disorders of collagen turn-over might represent one potential mechanism underlying MR-related arrhythmic properties.[41] The basic mechanism linking elevated aldosterone levels to repolarization abnormalities might be associated with increased myocardial capillary density, increased accumulation of matrix proteins and higher mitochondrial levels of superoxide.[7] Further, evidence from basic research indicates interplay between MR activation and protein expression of the NADPH oxidase subunits Nox2 and Nox4 as well as changes in stress-induced NF-κB activation and thus apoptosis in cardiomyocytes.[3,7] There seem to be also changes in calcium and potassium channel activity be involved.[42,43] Interestingly, Santulli et al[44] described in an animal model a mutation of the ryanodine receptor (RyR), an important cause of ventricular arrhythmias, is also associated with metabolic alterations. In patients with heart failure, MRAs have been shown to reduce the amount of premature ventricular beats, QT interval, ventricular tachycardia, and ventricular fibrillation,[45–47] which may be the case in arterial hypertension as well.[2,48,49] Matsumura et al[50] previously described QTc prolongation in 69 patients with PA. Another study comprising 186 patients demonstrated longer QTc in those with PA (434 ± 23 milliseconds) and low renin hypertension (430 ± 18 milliseconds) as compared with essential hypertension (419 ± 22 milliseconds).[51] This study further supports our use of the AARR instead of aldosterone or renin alone, especially as in both groups (PA and low renin hypertension) the QT was similarly prolonged compared to essential hypertension.[51] Albeit, these studies[50–52] were limited by the relatively small sample sizes. Further, most prior studies used QTc corrected by Bazett, which is known to be limited due to over and under-correction depending on HR.[30,31,53] Our findings are further strengthened by the use of 24-hour BP measurement and by considering dietary salt intake, which strongly interferes with the renin–aldosterone system.[54] We used AARR instead of plasma aldosterone or renin concentrations alone as high aldosterone and low-renin status are 2 ends of a continuous spectrum of relative and absolute aldosterone excess and should not be investigated separately.[25] Additionally, we omitted patients with a renin level below the detection limit (<5 μU/ml) and with a positive screening result for PA, which suggests that the findings are not mainly driven by patients with Conn syndrome[25,55] or due to a denominator phenomenon. We therefore were able to demonstrate for the first time a continuous association between aldosterone to renin ratio and prolonged QTc as well as reduced HRV in patients with arterial hypertension.

LIMITATIONS

Our study consists of a group of hypertensive patients recruited from outpatient clinics at a tertiary care hospital, thus the current findings may not be applicable to the general population. More so, the large majority of our patients were under treatment with antihypertensive medication known to interfere with the RAAS. To minimize the confounding, the patients had to be on stable treatment for at least four weeks to be included in the study. Though, it bears mentioning that our cohort reflects patients typically seen in clinical practice. Further, the lack of a normotensive control group limits the present findings to patients with arterial hypertension. The diurnal variation of aldosterone was not considered appropriately by use of an 1-time measurement of morning plasma concentrations. Nevertheless, previous studies demonstrated that the overall 24-hour variation in aldosterone is low, especially compared with the suppression seen by high salt intake.[56] In an effort to improve comparability, blood sampling was scheduled during the morning hours.[57] Both outcome parameters (ie, QTc and 24H-HRV) might not necessarily reflect risk for hard clinical endpoints (eg, mortality) and are not able to completely measure autonomic nervous system dysregulation and intrinsic cardiac automaticity.[33,34,58,59] More so, we used the SD of ABPM based 24-hour heart rate as a measure of 24H-HRV, which differs according to ECG based HRV.[33,34,58–60] Nevertheless HRV measured by ABPM (standard deviation of normal to normal beats) has turned out to be a valid predictor of clinical outcomes.[61,62]

CONCLUSIONS

We investigated the association of aldosterone to renin ratio with surrogate markers of autonomous dysfunction and sudden cardiac death, namely reduced heart rate variability and prolonged QTc. In this study, AARR was found to be a strong predictor of both prolonged QTc time and reduced 24H-HRV. Considering that these associations may reflect a causal relationship, we speculate that there might be a more favorable effect (eg, arrhythmic risk reduction) of aldosterone blockade beyond antihypertensive effects in patients with arterial hypertension. From a clinical point of view QTc and 24H-HRV may help risk stratification in patients with arterial hypertension and may be considered as an underlying rational when choosing specific antihypertensive agents and/or combination therapies, such as MRAs. Though clearly, further studies are needed to test this hypothesis.

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