European Review for Medical and Pharmacological Sciences 2021; 25: 6333-6338

Screening of QTc interval and global autonomic activity in autosomal dominant polycystic kidney disease and atherosclerotic renal artery stenosis hypertensive patients

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Abstract. – OBJECTIVE: Arterial hypertension (AH) represents a major risk factor for cardiovascular disease and is associated to several complications, such as prolonged corrected QT (QTc) interval and impaired heart rate variability (HRV). Secondary causes of AH include autosomal dominant polycystic kidney disease (ADPKD) and atherosclerotic renal artery stenosis (ARAS), both known to be related to arrhythmic risk and autonomic imbalance.

The aim of the study is to evaluate whether global autonomic activity and QTc interval differently affect ADPKD and ARAS hypertensive patients.

PATIENTS AND METHODS: An observational study was performed on 59 patients: 16 ADPKD patients and 19 diagnosed with ARAS, compared to 24 healthy controls (HC). All patients underwent clinical evaluation, biochemical lab tests, 24-hour electrocardiogram (ECG) and renal Doppler ultrasound. HRV was assessed through the analysis of 24-hour ECG to detect standard deviation of normal-to-normal RR intervals (SDNN). QTc interval was defined as prolonged when > 440 msec.

RESULTS: SDNN was significantly lower in ADPKD and ARAS patients than HC ($p < 0.0001$) and no significant differences were found between ADPKD and ARAS patients ($p > 0.05$). QTc was found significantly higher in ARAS patients than HC ($p = 0.001$) and in ARAS patients than ADPKD patients ($p = 0.004$).

CONCLUSIONS: The pathogenesis of hypertension in ADPKD and ARAS patients is related to the activation of the renin angiotensin aldosterone system (RAAS). In ADPKD, cyst enlargement leads to kidney ischemia and renin release, associated to endothelial dysfunction, low nitric oxide and sympathetic tone activation. Differently, reduction in renal perfusion pressure activates RAAS and renal adrenergic nerves in ARAS patients. We can speculate that prolonged QTc interval is more present in ARAS vs. ADPKD hypertensive patients due to a greater activation of RAAS. We suggest adding 24-hour HRV evaluation in association with traditional risk factors in course of ADPKD and ARAS hypertension to better stratify cardiovascular risk in these groups of patients.

Key Words:
Atherosclerotic renal artery stenosis, Autosomal dominant polycystic kidney disease, Hypertension, Heart rate variability, QTc prolongation.

Introduction

Arterial hypertension (AH) is one of the leading causes of cardiovascular death worldwide. Among other complications, both prolonged corrected QT interval (QTc) and impaired heart rate variability (HRV) are associated with arrhythmic risk in AH patients[1]. Autosomal dominant polycystic kidney disease (ADPKD) and atherosclerotic renal artery stenosis (ARAS) are well-known secondary causes of AH. Furthermore, these conditions are also related with kidney failure and accelerated cardiovascular disease[2,3]. In particular, ADPKD patients show increased incidence of early onset hypertension, which occurs in 50-70% of patients with normal kidney function and is associated to left ventricular hypertrophy and cardiovascular abnormalities. In a large study on 419 ADPKD patients, Helal et al[4] showed that arrhythmias were the most prevalent cardiovascu-

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lar events, observed in 25.9% of cases. Grubler et al[5] showed an association between reduced HRV, QTc prolongation and aldosterone to renin ratio in 477 AH patients, considering both prolonged QTc and HRV as markers of arrhythmic risk and autonomic dysfunction. The prevalence of AH due to ARAS ranges from 1% to 5% among secondary causes of hypertension. Clinical complications include renovascular hypertension, ischemic nephropathy and cardiac destabilization syndrome[6]. In a pilot study, dysfunction of global autonomic activity was lower in ARAS patients than in healthy controls (HC) and QTc prolongation was significantly higher in ARAS patients than HC[3].

The aim of our study is to evaluate the differences in global autonomic activity and QTc between ADPKD and ARAS hypertensive patients.

Patients and Methods

An observational study was performed on 59 patients: 16 patients diagnosed with ADPKD, and 19 patients diagnosed with ARAS who were compared with 24 HC. All patients underwent clinical evaluation, biochemical lab tests, 24-hour electrocardiogram (24h ECG) recording and renal Doppler ultrasound (RDU) at the University Hospital "Policlinico Umberto I" in Rome, Sapienza University, Italy. Patients were enrolled from March 2020 to December 2020. Patients with heart disease, electrolyte disturbances, diabetes mellitus, fibromuscular dysplasia, glomerulonephritis and other kidney diseases were excluded. Patients were not taking any anti-arrhythmic and QTc prolonging drugs. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the Local Clinical Research Ethics Committee of the University Hospital "Policlinico Umberto I", Sapienza University in Rome with protocol number 302/17, 4465.

Renal Doppler Ultrasound

RDU was performed by a single expert investigator who was blinded to the clinical features of patients using Aplio Ultrasound System SSA-790 with a convex 3.5-MHz probe (Toshiba, Tokyo, Japan). RDU was performed targeting the arcuate arteries at corticomedullary junction, as well as the interlobar arteries at the border of medullary pyramids. The exam was conducted by placing the probe at three different positions over both kidneys, under the guidance of colour-flow mapping. The gain was set so that background echoes were visible. Anterior approach was used to scan the origin of renal arteries while oblique-lateral approach was adopted to scan the intermediate tract and intra-renal blood vessels. The presence of ARAS and its grade were evaluated by measuring proximal parameters, renal-aortic ratio and parenchymal parameters. Renal stenosis was diagnosed when the systolic peak velocity was found > 200 cm/s. In all ARAS patients included in the study, a degree of stenosis > 60% was detected.

Heart Rate Variability

Global autonomic activity was performed by HRV analysis during 24h ECG recording to detect standard deviation of normal-to-normal RR intervals (SDNN)[7]. QTc was defined as prolonged when > 440 ms, assessed by 24-hour Holter electrocardiogram recording[8].

Statistical Analysis

Data management and analysis were performed using IBM® SPSS® Statistics 25 for Windows® software (IBM Corporation, Armonk, NY, USA). The normality of the variables was tested using the Shapiro-Wilk method for normal distributions. All continuous variables were expressed as means ± standard deviation and categorical variables were expressed as numbers (percentages). Kruskal-Wallis test with Bonferroni adjustment was performed to determine differences between groups. The χ^2 test was used for comparison of categorical data. A probability value of $p < 0.05$ was considered statistically significant.

Results

Characteristics of patients are shown in Table I. A total of 59 patients were enrolled: 16 ADPKD (7 males) patients with a mean age of 41.56 ± 9.6 years and 19 diagnosed with ARAS (6 males) with a mean age of 64.16 ± 7.3 years. These groups of patients were compared with 24 HC (10 males) with a mean age of 48.92 ± 6.1 years. All patients with ARAS received pharmacological treatment with angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARBs). 9 patients were treated in association with dihydropyridine calcium channel blockers while 6 patients were treated with diuretics. All ADPKD patients received pharmacological treatment with ACEi and/or ARBs, while 11 patients were treated in associations with dihydropyridine calcium channel blockers. SDNN was sig-

nificantly lower in ADPKD (109.32 ± 17.90) and ARAS patients (115.05 ± 20.99) than HC (147.55 ± 35.62) ($p < 0.0001$). No significant differences were found between ADPKD and ARAS patients ($p > 0.05$) (Figure 1). QTc was found significantly higher in ARAS patients (432.94 ± 29.11) than HC (388.37 ± 28.73) ($p = 0.001$) (Figure 2) and in ARAS patients than ADPKD patients (391.37 ± 19.45) ($p = 0.004$) (Figure 2). We did not find a significant correlation between QTc and carotid intima-media thickness (CIMT).

Discussion

In our study, global autonomic activity was found to be impaired in both ADPKD and in ARAS hypertensive patients when compared with HC. ADPKD is a systemic disease and is characterized by elevated cardiovascular morbidity and mortality. Main cardiac manifestations, such as left ventricular hypertrophy, pericardial effusions and cardiac valvular abnormalities, may be present before the development of renal failure and even before the onset of hypertension[9]. The present investigation supports and extends results of other studies, based almost exclusively on patients with essential AH[5]. It demonstrates that autonomic dysfunction is triggered by AH regardless of the underlying causes. It is well established[10] that low SDNN is associated with an increased cardiovascular and sudden cardiac death risk. In the present study, prolonged QTc was higher in ARAS patients than in those with ADPKD. To our knowledge, there are not previous studies which investigated prolonged QTc in ADPKD patients. Furthermore, many factors, including sex, age, electrolyte disturbances, thyroid disease, cardiac disease, gene mutations, autonomic dysfunction, use of QT-prolonging drugs and AH itself are related to QT prolongation[11].

Festa et al[12] were the first to report a positive association of HR-corrected QT interval with sub-clinical carotid atherosclerosis association of HR-corrected QT interval with sub-clinical carotid atherosclerosis in nondiabetic subjects without clinically overt coronary artery.

In the past, Festa et al[12] documented an association between subclinical carotid atherosclerosis and prolonged QTc in nondiabetic patients using CIMT detection. Also, a positive association was found between coronary artery disease (histologically diagnosed) and prolonged QT, confirming that QTc represents a marker for both carotid and coronary atherosclerosis amongst the many physiological and pathological factors that contribute to the QT interval, the HR and the autonomic tone play a major role.

Differences in segment-specific atherosclerosis in both carotid and coronary arteries in relation to

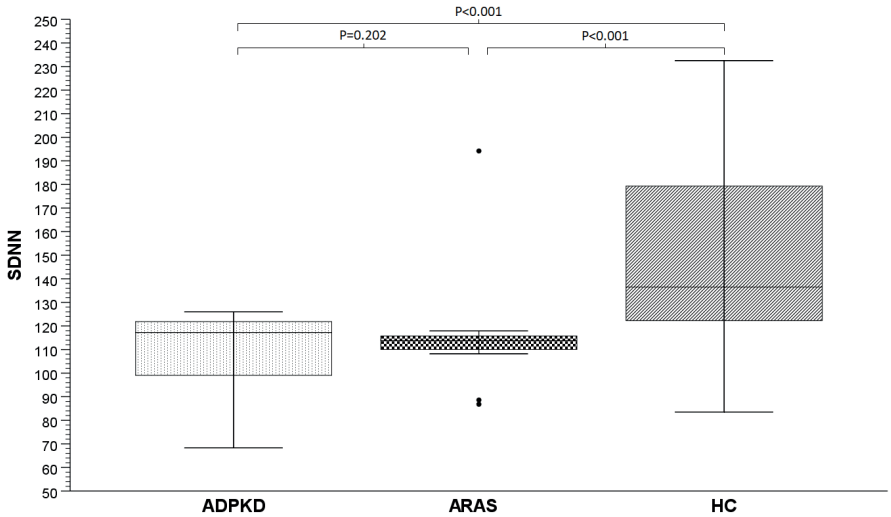

Figure 1. Box-and-whisker plot. SDNN in ADPKD, ARAS and HC groups. Median value of SDNN is statistically significant different in HC group compared with ARAS (136.5 *vs.* 113.9, $p < 0.001$) and ADPKD groups (136.5 *vs.* 117.2, $p < 0.001$). There is not statistically significant difference in median value of SDNN in ARAS group *vs.* ADPKD group (113.9 *vs.* 117.2 $p = 0.202$). • = Outliers. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARAS, atherosclerotic renal artery stenosis; HC, healthy controls; SDNN, standard deviation of normal-to-normal RR intervals.

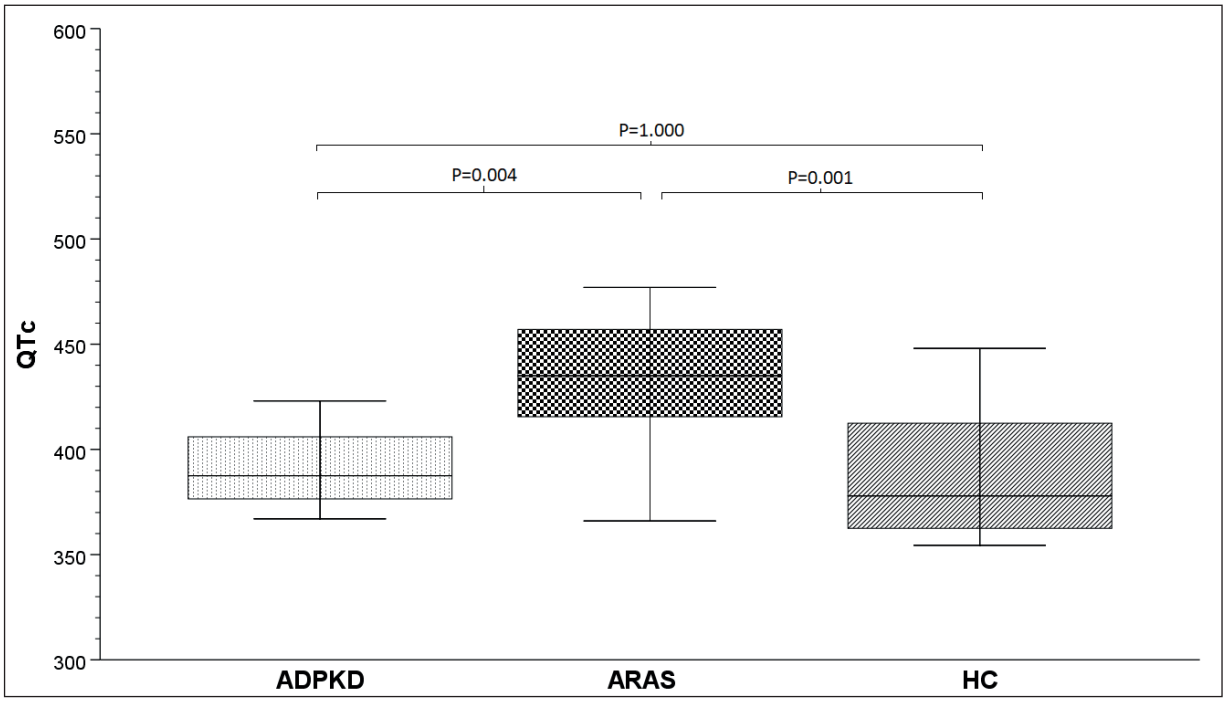

Figure 2. Box-and-whisker plot. QTc ADPKD, ARAS and HC groups. Median value of QTc is statistically significant different in ARAS group compared with ADPKD (435.0 *vs.* 387.5, $p = 0.004$) and HC groups (435.0 *vs.* 377.9, $p < 0.001$). There is not statistically significant difference in median value of QTc in ADPKD group *vs.* HC group (387.5 *vs.* 377.9, $p = 1.000$). Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARAS, atherosclerotic renal artery stenosis; HC, healthy controls; QTc, corrected QT interval.

prolonged QTc have been reported[13,14] but, to our knowledge, only a previous study by our group described the relation with renal atherosclerosis. Prolonged QTc was observed in course of ARAS *vs.* HC, and we assumed that the *primum movens* was the presence of atherosclerosis with the activation of pro-inflammatory and pro-fibrotic pathways, endothelial dysfunction, chronic ischaemia and reduced bioavailability of nitric oxide (NO). NO reduction may alter cytosolic free calcium with subsequent prolongation of myocardial repolarization, likely sustained by parenchymal ischemia[3]. Although the exact mechanism behind QTc prolongation in AH is not well understood, some authors[5] suggested that aldosterone to active renin ratio is related to autonomic tone and arrhythmic risk in hypertensive patients. In particular, elevated aldosterone levels are associated with repolarization abnormalities due to the increased density of myocardial capillaries, abnor-

Table I. Patient's characteristics at baseline. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARAS, atherosclerotic renal artery stenosis; HC, healthy controls; PAS, systolic blood pressure; PAD, diastolic blood pressure; QTc corrected QT; SDNN, standard deviation of normal-to-normal RR intervals.

Parameters	ADPKD N:16	ARAS N:19	HC N:24
Females	9 (56%)	13 (68%)	14 (58%)
Age (years)	41.5 ± 9.6	64.1 ± 7.3	48.9 ± 6.1
PAS	130.45 ± 18.03	130.42 ± 8.58	130.32 ± 9.34
PAD	82.27 ± 9.04	78.47 ± 6.834	79.45 ± 5.98
QTc	391.37 ± 19.45	432.94 ± 29.11	388.37 ± 28.73
SDNN	109.32 ± 17.90	115.05 ± 20.99	147.55 ± 35.62

APSGN, acute post-streptococcal glomerulonephritis; CVA tenderness, costovertebral angle tenderness.

mal matrix proteins and high levels of superoxide within mitochondria[15].

The pathogenesis of hypertension in ADPKD and ARAS patients is characterized by the activation of renin angiotensin aldosterone system (RAAS). Moreover, hypertension is very common in ADPKD patients, and it is diagnosed even before the onset of renal failure in 50% to 75% of cases. The pathogenesis of hypertension in ADPKD has not been fully elucidated yet, but some mechanisms have been revealed. Among these, activation of RAAS could be due to cyst enlargement which leads to kidney ischaemia with renin release, impaired NO-related vasorelaxation, increased sympathetic activity, increased endothelin-1 serum level and insulin resistance[2]. Similarly, the reduction in renal perfusion pressure activates RAAS and renal adrenergic nerves in ARAS patients. Therefore, we can speculate that prolonged QTc is present in ARAS *vs.* ADPKD hypertensive patients due to a greater activation of RAAS.

Limitations of the Study

The limitations of our study are the relatively small cohort of hypertensive ARAS and ADPKD patients as well as the cross-sectional, single-centre design. Larger studies are needed to confirm the reported data.

Conclusions

Autonomic dysfunction and prolonged QTc are associated with cardiovascular events, life-threatening arrhythmias and sudden cardiac death. In our study we showed global autonomic activity to be impaired in both ADPKD and in ARAS hypertensive patients when compared with HC. The 24h ECG is a non-invasive tool to determine autonomic activity (HRV) and QTc, which are both extremely helpful in predicting cardiovascular and fatal arrhythmic events. Therefore, we suggest adding these assessments in association with the evaluation of traditional risk factors in course of ADPKD and ARAS hypertension. This approach could allow a better stratification of cardiovascular risk in these groups of patients.

Conflicts of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. The manuscript has been seen and approved by all authors. This study was not funded. The manuscript is not under consideration for publication elsewhere.

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