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Cardiac heterogeneity in patients with chronic urticaria; A perusal of P wave and QT dispersions

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Abstract

Data on how the heart is affected in Chronic Urticaria (CU), a common annoying chronic dermatological disease, is quite limited. The electrocardiographic parameters; P wave dispersion (PWD) and QT dispersion (QTD) have been consistently reported to be predictive for cardiac arrhythmias and morbidity. We aimed to detect asymptomatic cardiovascular involvement in terms of predisposition to arrhythmias in chronic urticaria. This cross-sectional study included 128 individuals: 64 with CU and 64 healthy controls. 12-lead surface electrocardiogram and Doppler echocardiography were performed on patients and controls. All of the cardiologic parameters such as P wave, PWD, QTD and corrected QTD (QTDc) parameters were obtained from ECG measurements. Maximum P wave duration and PWD were found to be higher in CU patients than controls (P= 0.035 and P<0.001, resp). There were significant correlations between CU duration and PWD (r = 0.348, P = 0.005) and between Urticaria Activity Score and QTD and QTDc (r = 0.351, P = 0.004 and r = 0.361, P = 0.003 resp). Multiple linear regression analysis showed that; systolic blood pressure and CU duration are independently associated with PWD (β =0.344, p=0.003 and β=0.375, p=0.001 resp) and also that; diastolic blood pressure and disease activity (UAS7) are independently associated with both QTD (β=0.320, p=0.006 and β=0.377, p=0.001 resp) and QTDc (β=0.344, p=0.003 and β=0.389, p=0.001 resp). In patients suffering from Chronic Urticaria, PWD and QTD were significantly increased as compared to control group of healthy individuals. PWD was associated with disease duration while QTD and QTDc was associated with the disease activity.

Keywords: Arrhythmia, chronic urticaria, P wave dispersion, QT dispersion

Introduction

Urticaria is a dermatological disease characterized by pruritic wheals which are superficial red or pink colored swellings of the dermis [1]. Viral and parasitic infections, food and drug allergy, insect bites, cold, psychological stress are the precisely defined triggers whereas in more than half of the cases, the etiology remains unknown [2]. It is a common disease that affects about 20% of the general population. In acute urticaria wheals mostly resolve within a few days whereas in chronic spontaneous urticaria (CU), a rarer form that affects approximately 1-2% of the population, symptoms last more than six weeks. In addition to cutaneous manifestations, evidence of systemic effects of CU on the cardiac system as well as musculoskeletal, central nervous, respiratory and gastrointestinal systems has also been reported. [3]. CU patients were reported to have higher risk for hypertension. Also, HT was associated with prolonged duration of CU [4] and there are reported cases of Chronic urticaria presented with Kounis syndrome, an overlooked clinical entity in which mast cell activation due to allergy or hypersensitivity that provokes acute coronary syndrome [5]. Ventricular arrythmias and more often atrial fibrillation have been reported in Kounis syndrome likewise in anaphylaxis [6].

P wave dispersion (PWD is defined as the difference between maximum and minimum P wave durations and is a noninvasive electrocardiographic marker used to evaluate atrial remodeling. It has been defined as a predictor for atrial fibrillation [7]. QT dispersion (QTD)is simply defined as interlead QT interval differences within a 12 lead ECG and is a surrogate marker reflecting the homogeneity in ventricular myocardial refractoriness

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[8]. QTD analysis has been shown to be useful for predicting risk of sudden cardiac death due to ventricular arrhythmias [9].

Comprehensive clinical evaluations of PWD and QTD have been performed in the assessment of arrhythmia risk in patients not only with primary cardiac pathologies but also with rheumatological diseases, use of some medications and various conditions, but not yet in allergic diseases [7,10].

Though this, different forms of cardiac involvement have been demonstrated in allergic and hypersensitivity disorders. Higher incidence of abnormal ECG findings such as tachycardia, abnormal ST and T changes, abnormal QRS, premature ventricular complex and arrythmia is reported in patients with acute Urticaria [11]. However, the available data regarding cardiac involvement in patients with chronic urticaria –wouldn't be wrong to define as a prolonged allergic condition- is yet very limited. In this study we aimed to detect asymptomatic cardiovascular involvement in terms of predisposition to arrhythmias in chronic urticaria. Therefore, we sought to answer this issue by comparing the dispersion parameters of ECG in CU with the gender and age matched control group.

Materials and Methods

Setting

This is a cross-sectional study conducted between October 2020 and January 2021. We included 64 chronic urticaria patients and 64 healthy individuals as control in the study. The patients underwent detailed dermatological and physical examinations by an experienced dermatologist. The urticaria durations of the patients and number of urticaria attacks per week were questioned in detail. Patients with urticaria lasting longer than 6 weeks were diagnosed with chronic urticaria and were included in our study group.

Control patients were recruited from the hospital staff. All participants provided written informed consent. The study complies with the Declaration of Helsinki. All procedures were approved by Ethics Committee with the approval number 2020 /9-22.

Patients with any conduction abnormality, dysrhythmia or on any antiarrhythmic therapy, and with atherosclerotic heart disease, valvular heart disease, pericardial disease, hypertension, history of pulmonary emboli or pulmonary hypertension were excluded. Presence of active infection and abnormal thyroid function were also in the exclusion criteria.

The BMI was computed as body weight divided by the square of height (kg/m^2). Smoking was considered if the participant was current smoker or quit smoking within the last one year with a smoking history of more than 5 pack year.

In the CU group, to increase the sensitivity of skin prick test, the tests were performed after a free period of steroid and antihistamine use for three days. Patients were advised not to take antihistamine therapy for 72 hours in order to perform a prick test applied to both arms and assessed by a clinical dermatologist. In order to eliminate any drug effect, ECGs, blood sampling and echocardiographic evaluations were also done on the appointment day of the skin prick test.

For evaluation of the disease activity Urticaria Activity Score (UAS) was used as recommended by EAACI/GA(2)LEN/EDF guidelines [12]. UAS, which includes the number of wheals and the intensity of itching, was filled daily by CU patients for consecutive 7 days. The UAS7 score (minimum 0-maximum 42) was calculated by summing up the Urticaria activity scores over seven days.

Blood samples were drawn after an overnight (8-12 hours) fasting to analyze for complete blood count and biochemical parameters by using Sysmex XT2000i analyzer and Roche Cobas C501 automatic photometric analyzer in accordance with the manufacturers' (Sysmex corporation, Kobe, Japan and Roche Diagnostics co., Ltd., Mannheim, Germany respectively) instructions.

Echocardiography

Echocardiographic examinations were performed (Vivid 7 pro, GE, Horten, Norway, 2-4-mHz phased array transducer) by the same cardiologist, who was blinded to the clinical details of the participants. All echocardiographic measurements were performed in accordance with the recommendations of European Association of Echocardiography [13].

Electrocardiography

A 12-lead surface ECG (ECG-1350K Cardiofax M, Nihon Kohden Corporation, Tokyo, Japan) recording was obtained from each participant in supine position following 10-min resting period with a 20 mm/mV amplitude and 50 mm/s paper speed. All of the ECG results were scanned, and images were converted to pdf file (Adobe Acrobat Reader DC (32-bit)) on a personal computer. ECG calculations were performed by using the measurement tool of the pdf file after the required calibrations were done for each ECG paper. Magnifier features were used to minimize the error rate. P wave was described as the duration between the point of first detectable atrial deflection from the isoelectric line and return of the deflection to the isoelectric line. P wave duration was measured in at least 10 leads on the surface ECG, the longest p wave in any of these leads was defined as P max, and the shortest P wave was defined as Pmin. The calculated difference between Pmax and Pmin was defined as PWD. QT interval was measured as the duration between the beginning of the Q wave and end of the T wave. QTD was calculated as the difference between the longest (QTmax) and the shortest (QTmin) QT intervals on a 12-lead ECG. As far as possible, at least ten of the twelve QT intervals were measured to determine these two extreme indices. Measured QT intervals were corrected by adjusting heart rate using Bazett's Formula ($QTC = QT / \sqrt{RR\ interval}$) to give rise to QTc intervals, and the difference between QTcmax and QTcmin was the corrected QTD (QTDc). All ECG calculations were performed by a cardiologist who was blinded to the clinical status of the subjects.

Statistics

The data obtained for the study were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, v. 22.0. In the analysis of data, number, percentage, mean and standard deviation values were used as descriptive statistic methods. The

normality of data distribution was determined using a histogram and/or the Kolmogorov-Smirnov/Shapiro-Wilk test. The paired-samples t-test was used to compare quantitative normally distributed continuous data between the two groups. Non-normal distributed data were analyzed by using the Mann Whitney U test. Correlations between all variables were calculated with Pearson correlation test. Multiple linear regression analysis was utilized to identify the factors related to PWD, QTD and QTDc. P-value below 0.05 was considered statistically significant

Results

The demographic characteristics and laboratory findings of the CU patients and the control group are summarized in table 1. There was no significant difference between groups in terms of age, sex and other demographic parameters. Among laboratory findings, HDL was lower and CRP was higher in the CU group. No statistically significant difference was observed in other laboratory findings. Echocardiographic and ECG results were listed in table 2. LVESD was slightly and LVEDD and LVMI were significantly increased in the CU group.

Maximum QTc was slightly increased in CU while Pmax, PWD, QTD and QTDc parameters were significantly higher in the CU group compared to healthy controls.

In order to explore further the association between the relevant clinical factors and ECG parameters, we performed correlation analysis. Among significantly associated factors, listed in table 3, multiple linear regression analysis showed that; systolic blood pressure and CU duration are independently associated with PWD (β =0.344, p=0.003 and β=0.375, p=0.001 resp) and also that; diastolic blood pressure and disease activity (UAS7) are independently associated with both QTD (β=0.320, p=0.006 and β=0.377, p=0.001 resp) and QTDc (β=0.344, p=0.003 and β=0.389, p=0.001 resp). The significant correlations between CU duration and PWD (r = 0.348, P = 0.005) and between disease activity (UAS7) with QTD and QTDc (r = 0.351, P = 0.004 and r = 0.361, P = 0.003 resp) are depicted as scatterplots in figure 1.

Table 1. Demographic and laboratory findings of the CU patients and the control group

	CU (n=64)	Control (n=64)	P value
Age(years)	41.4±17.1	39.3±10.9	0.42[a]
Female, male (n,%)	34 female (53.1%) 30 male (46.9%)	37 female (57.8%) 27 male (42.2%)	0.59[a]
BMI (kg/m²)	25.0±2.5	24.8±2.6	0.67[b]
Smoking (n,%)	8(12.5%)	7(10.9%)	0.78[a]
SBP (mm Hg)	121.0(96-140)	120.5(92-138)	0.80[c]
DBP (mm Hg)	75.0(62-90)	76.5(63-89)	0.72[c]
CU duration (months)	8.12±6.69	-	-
CU Activity Score	25.5±8.2	-	-
Angioedema (n)	10 (15.6%)	-	-
Positive prick test (n)	14(21.9%)	-	-
Fasting Blood Glucose(mg/dL)	95.5(74±229)	93.5(78-167)	0.68[c]
Total Cholesterol (mg/dL)	182.9±32.8	180.9±31.5	0.72[b]
Triglyceride (mg/dL)	150.5±70.2	149.6±54.9	0.93[b]
LDL (mg/dL)	106.1±25.7	101.8±29.3	0.38[b]
HDL (mg/dL)	45.0(29-83)	47.5(33-81)	0.096[c]
Creatinine (mg/dL)	0.75(0.54-1.82)	0.76(0.51-1.18)	0.35[c]
Calcium	9.4(8.3-10.6)	9.4(8.0-11.1)	0.92[c]
Potassium	4.3(2.2-5.5)	4.4(3.7-5.3)	0.57[c]
Magnesium	2.0(1.8-2.5)	2.1(1.7-2.6)	0.65[c]
CRP	0.41(0.10-2.5)	0.32(0.001-1.51)	0.068[c]
TSH	1.4(0.2-6.7)	1.66(0.42-5.6)	0.32[c]
fT4	0.87(0.64-1.89)	0.89(0.64-1.68)	0.64[c]

BMI; body mass index, CRP; C-reactive protein, CU; chronic urticaria, DBP; diastolic blood pressure, fT4; free thyroxine, HDL; high density lipoprotein, LDL; low density lipoprotein, SBP; systolic blood pressure, TSH; thyroid stimulating hormone.
[a]; analyzed by qi-square test.
[b]; Mean±SD in cases where the data were distributed normally, analyzed by student's t test.
[c]; median (minimum-maximum) values were presented in cases where the data were not normally distributed, analyzed by Mann-Whitney U test.

Table 2. Echocardiographic and ECG findings of the CU patients and the control group

	CU (n=64)	Control (n=64)	P value
LVEF (Simpson), %	61.8±4.4	61.2±4.3	0.44[b]
LVEDD, mm	46.8±3.9	45.1±3.8	0.018[b]
LVESD, mm	32.2± 3.1	31.3±3.0	0.08[b]
LA, mm	34.0±3.6	33.7±3.3	0.63[b]
IVS, mm	9.2(8.0-12.0)	9.5(8.0-11.0)	0.74[c]
PW, mm	8.5±0.8	8.3±1.2	0.28[b]
LVMI, g/m²	81.2±16.5	75.7±13.2	0.038[b]
E velocity	90.0(60-150)	90.0(70-130)	0.90[c]
A velocity	70.0(45-150)	70.0(40-140)	0.95[c]
E/A	1.37(0.69-1.85)	1.33(0.75-1.85)	0.78[c]
EDT, ms	200.0(150-280)	210(160-260)	0.52[c]
Heart rate, beats/min	80.3±11.8	78.0±9.5	0.23[b]
Pmax, ms	112.23±10.37	108.09±11.6	0.035[b]
Pmin, ms	75.53±9.95	76.89±9.58	0.43[b]
PWD, ms	36.61±7.89	31.13±8.27	<0.01[b]
Maximum QT, ms	383.0(318-480)	378.5(314-464)	0.47[c]
Minimum QT, ms	339.65±34.04	341.66±29.59	0.72[b]
QTD, ms	42.85(16-84)	37.0(12-78)	0.016[c]
Maximum QTc, ms	443.01±36.19	432.65±33.76	0.09[b]
Minimum QTc, ms	390.35±34.56	387.74±33.52	0.66[b]
QTDc, ms	48.82(18-103)	42.5(13-87)	0.012[c]

A velocity; peak atrial mitral inflow velocity E velocity; peak early mitral inflow velocity, E/A; E velocity /A velocity , EDT; early wave deceleration time, IVS; interventricular septum thickness, LA; left atrium diameter, LVEDD; left ventricular end-diastolic diameter, LVESD; left ventricular end-systolic diameter, LVEF; left ventricular ejection fraction, LVMI; left ventricular mass index, QTD; dispersion of QT interval, QTDc; dispersion of corrected QT wave, PW; posterior wall thickness, Pmax: maximum P wave duration, Pmin: minimum P wave duration, PWD; dispersion of P wave.
[a]; analyzed by qi-square test.
[b]; Mean ± SD in cases where the data were distributed normally, analyzed by student's t test.
[c]; median (minimum-maximum) values were presented in cases where the data were not normally distributed, analyzed by Mann-Whitney U test.

Table 3. Correlations of patient variables with PWD, QTD and QTDc

PWD		
	R	p value
BMI	0.368**	0.003
Duration of Urticaria	0.348**	0.005
Systolic blood pressure	0.341**	0.006
Left atrium diameter	0.402**	0.001
Serum Creatinine	0.268*	0.032
QTD		
	R	p value
Diastolic blood pressure	0.290*	0.020
Age	0.258*	0.039
Urticaria activity score	0.351**	0.004
Serum Magnesium	0.251*	0.045
Serum CRP	0.267*	0.033
QTDc		
	R	p value
Diastolic blood pressure	0.313*	0.012
Urticaria activity score	0.361**	0.003
CRP	0.269*	0.032

BMI: body mass index, CRP: C reactive protein, PWD: P wave dispersion, QTD: QT dispersion, QTDc: corrected QT dispersion, R: Pearson correlation coefficient

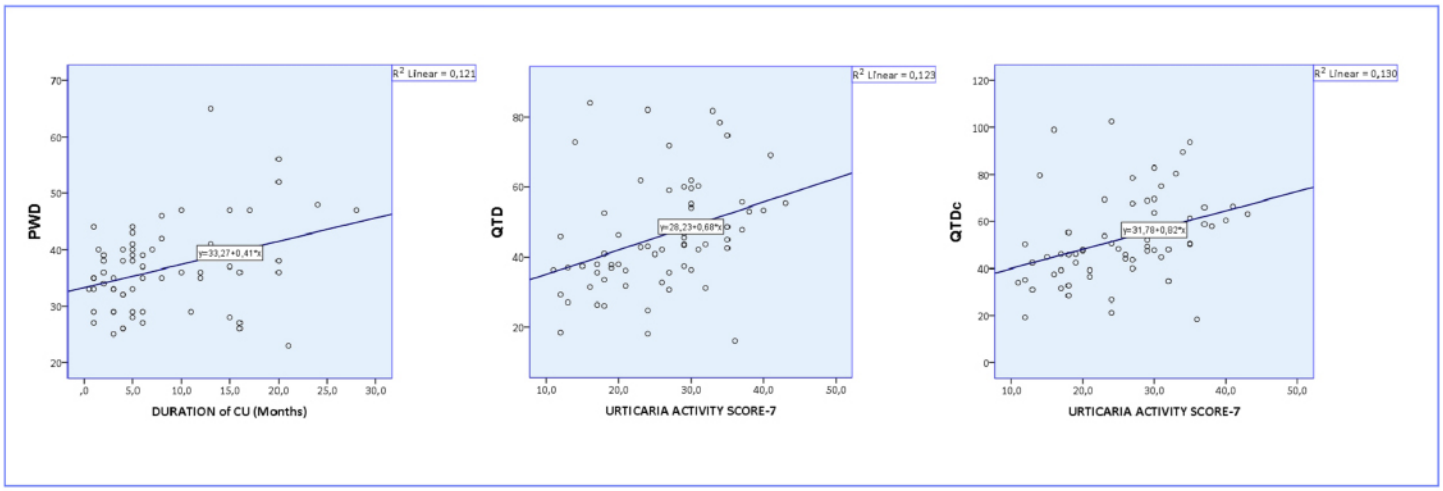

Figure 1: Scatterplots of the linear regression models relating duration of CU with PWD, and Urticaria activity score-7 with QTD and QTDc.

PWD; dispersion of P wave, QTD; dispersion of QT interval, QTDc; dispersion of corrected QT interval.

Discussion

In this study, we found higher values of PWD and QTD values on the surface ECG of patients with chronic urticaria compared to otherwise healthy control individuals. To the best of our knowledge, this is the first study in chronic urticaria patients to evaluate these parameters which predict potential predisposition to arrythmias. Frankly, we were surprised to not met any study conducted on this domain in patients with chronic urticaria, although considerable number of studies on cardiovascular involvement are present in allergic and inflammatory diseases.

CIU is a chronic immune disorder that can be classified under the umbrella of mast cell activation disorders. The mast cells are long-lived tissue-resident granulocytes with an important role in the allergic response. They also have vital roles in immune response, angiogenesis, lymph angiogenesis and tissue remodeling besides many inflammatory settings [14]. Mast cells contain various substances (serine proteases, such as tryptase and chymase, histamine, serotonin, heparin, lysosomal enzymes, eicosanoids (thromboxane, LT C4, platelet activating factor), cytokines (including TNF-α, VEGF, basic fibroblast growth factor, interleukin-4) and reactive oxygen species in their granules [14].

Presence of mast cells, the well-known primary effector cells of urticaria, has been documented in the human heart as well [15]. They are usually located in the interstitial space between cardiomyocytes and are very close to the nerves which may be related to the development and progression of arrhythmia in CU. Mast cells can be activated to degranulate by binding of allergens to receptor bound specific IgE or by multiple other non-specific stimuli. Once they degranulate, all the substances aforesaid, especially histamine play a role in the formation of the clinical picture of urticaria depending on the tissue they reside.

Histamine is a well-known mediator in immuno-inflammatory and allergic conditions and has been known to regulate various cardiovascular and endothelial functions with arrhythmogenic potential [6]. Role of histamine in the modification of cardiac rhythm has been noticed almost since its first isolation [16]. Histamine enhances arrhythmia by delaying atrioventricular (AV) conduction through the H1 receptors in the left atrium and by increasing sinus rate and ventricular automaticity via the H2 receptors in the right atrium [16].

Highest concentrations of cardiac histamine have been found in the right atrium, and with smaller amounts in the left atrium, right ventricle, and left ventricle respectively [17]. The distribution pattern of histamine within the heart is remarkably correlated to of mast cells which suggests that most of the cardiac histamine is mast cell originated.

The Ca2+-activated K+ channel modulates the influx of extracellular Ca2+ which is essential for degranulation of a mast cell [18]. By allergic stimuli, alterations of these ionic interactions in interstitial space, cause polarization changes at microcellular level. We claim that the differences in the spatial distribution of mast cells in the myocardium and related variations of ionic and cytokine burden in the interstitial space may lead to variations in de- and repolarization durations at different leads reflecting different regions of the heart, which are presented as increased PWD and/or QTD on a surface ECG.

Histamine impact in arrhythmia generation has become more elicited with a recent study [19]. Increased histamine levels detected in a population of 10 patients with new onset AF, led the authors to recommend focusing on any recent allergic reaction or underlying IgE-mediated disease in the clinical history of these patients. Cardiac arrest following ventricular fibrillation was reported in a case with systemic mastocytosis who had hyperhistaminemia and urticaria pigmentosa [20]. Considering the studies showing the association of histamine with arrhythmias including atrial tachycardia, atrial fibrillation and ventricular fibrillation, increased PWD and QWD values in a chronic state

of histamine release should not be surprising, since both are proven predictive markers for mentioned arrhythmias. However, we hypothesize that mechanisms other than histamine may also contribute to these ECG changes in chronic urticaria.

Emerging evidence has revealed that inflammation extends duration of action potential thereby increase QT durations as a consequence of various impacts over electrophysiological properties of cardiomyocytes [10]. Population based studies of patients with rheumatoid arthritis, metabolic syndrome, psoriasis and similar inflammatory conditions showed an association of CRP with QT time. Ylber Jani et al [21] showed high C-reactive protein levels were associated with increased QTDc. A large cohort study conducted by G.L. Erre et al [10] showed that long-standing and moderately active rheumatoid arthritis patients had longer QTc and a 1.8-fold higher prevalence of increased QTD compared to control population. Systemic inflammation increases AF risk by atrial electrical remodeling, in line with this, significant correlation between CRP and high PWD has been attested multiple times [22,23].

CU has also an inflammatory process in its pathogenesis. Besides an increased number of mast cells, contributions of inflammatory cells like CD 4+ lymphocytes, monocytes, neutrophils, eosinophils, and basophils were demonstrated in biopsies from urticarial wheals. Cytokines like IL-4, IL-5, IL-6 and interferon-γ (IFN-γ), growth factors, matrix metalloproteinases are also shown to be involved in the pathogenesis of the disease [2,24]. Proinflammatory mediators are not merely elevated in the skin, increased levels of these cytokines have been noticed also in the circulation of CU patients. Elevated IL-6 levels have been detected in the plasma of CU patients, moreover this, IL-6 levels were found to be correlated with the disease activity [25]. High levels of C-reactive protein, a sensitive marker of inflammation, has also been linked to disease activity and response to treatment in CU [26]. A marginally significant association between CRP and CU was present in our study, but regression analyses showed that the associations between CU and the PWD and QTD were independent from CRP levels. Then it should be reasonable to look for other possible relations between increased levels of these parameters and CU.

Following an extensive literature search, we could not encounter a study that clearly elicited the role of autonomic regulation over dermal inflammation. The autonomic nervous system (ANS) has control over vascular and glandular structures in the skin. Meanwhile, in inflammatory conditions, ANS may have effect on the skin through immune cells and primary afferent neurons [27]. Degranulated mast cells release not only histamine but also various proteases and cytokines causing various degrees of inflammation. Control of the chronic inflammation has many actors including autonomic nervous system [28]. It has been suggested that both sympathetic and parasympathetic efferent fibers affect immune cells and inflammatory responses. The sympathetic system interferes in the earlier stages of the inflammatory process, while the latter is important in chronic processes. Cytokines released by activated immune cells including mast cells are detected via different types of cutaneous C nociceptors in the skin, some of which are responsible for itching sensation [29]. In the case of chronic hives, once the dermal afferent sensory fibers are stimulated, revealing proinflammatory properties of autonomic nervous system, thus in turn results signaling to brainstem nuclei and sending vagal and cholinergic efferents to the periphery including heart. Vagus nerve is well known to play a critical role in the control of heart rate, and some of the indicators of cardio autonomic control on ECG are PR and QT intervals [8,30]. Our results may hint to the altered autonomic balance in CU.

Not only the cutaneous sensory fibers take role in the modulation of ANS in CU, it is highly possible that the Vagus is also involved. About 40% of CU patients presents with gastrointestinal symptoms [3]. Moreover, Minnei et al [31] have revealed that CU patients had significantly increased number of mast cells in their gastrointestinal mucosa even if they did not have any gastrointestinal symptoms. A direct neural communication between the afferent vagal nerve fibers and the mast cells in the gastrointestinal mucosa has been affirmed previously [32]. As an inference, we think that in some of the CU patients, gastrointestinal tract may contribute to modulation of ANS via the Vagus nerve.

CU is also classified under psycho-dermatological disorders since chronic stress is a common undesired problem that almost always accompany with chronic urticaria and often leaves patients to seek psychiatric support [33]. In addition to stress-related exacerbations in CU, itching itself can also cause stress. Since the ANS has prominent role in stress response, chronic stress is another mechanism that can be proposed to contribute to the occurrence of depolarization abnormalities, by causing neuroautonomic imbalance. Association between anxiety and stress disorders with QTD and PWD have been demonstrated previously [34]. In addition, insomnia, a frequent symptom in CU due to chronic itch, may contribute to the cardiovascular system being affected through cardio-autonomic control [35]. Severe skin lesions led by itching may also share in the process by causing exacerbations of both local inflammatory and neurologic responses [36].

Some limitations should be considered while interpreting the present study. Modest sample size and lack of a long-term follow-up are the major shortfalls of our study. Automated ECG measurements were not accessible so second point that might be criticized is manual calculation of parameters related to P wave and QT interval. Whether increased PWD and QTDc in patients with CU carries risk of any poor outcomes or mandates any special treatment requires further studies. The fact that these arrhythmia predictors are high in patients does not mean that these arrhythmias will develop. So, lack of long-term follow-ups or 24-48 hour Holter recordings is another major limitation of the study.

In the present study, we have confirmed that Pmax, PWD, QTD and QTDc indices derived from the ECGs of patients with CU are increased compared to otherwise healthy controls. ECG pathologies described in acute urticaria have not been reported with the same frequency in CU presumably due to the relatively low burden and the localization of inflammation in chronic urticaria. The ECG changes we have defined in CU seems to be the first to indicate potential cardiac electrical heterogeneity in these patients. Moreover, mild but significant correlations between PWD and the duration of urticaria and between disease activity with QTD and QTDc were firstly observed.

Considering the added potential negative CV system side effects

of antihistamines and steroids used in CU treatment, we hope that our research will be beneficial for clinicians to be more cautious in follow up of CU patients. The propounded arrhythmogenic alterations in cardiac tissue of CU patients are yet to be specifically investigated via further randomized prospective follow-up studies.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
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Ethical approval
All procedures were approved by Local Ethics Committee with the approval number 2020 /9-22.

References

1. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, et al. Urticaria and Angioedema: an Update on Classification and Pathogenesis. Clin Rev Allergy Immunol. 2018;54:88-101.
2. Jafilan L, James C. Urticaria and Allergy-Mediated Conditions. Prim Care. 2015;42:473-83.
3. Kocaturk E, Grattan C. Is chronic urticaria more than skin deep? Clin Transl Allergy. 2019;9:48.
4. Chang HW, Cheng HM, Yen HR, et al. Association between chronic idiopathic urticaria and hypertension: A population-based retrospective cohort study. Ann Allergy Asthma Immunol. 2016;116:554-8.
5. Erxun K, Wei L, Shuying Q. Kounis Syndrome Caused by Chronic Autoimmune Urticaria: A Case Report. J Emerg Med. 2016;50:37-40.
6. Kounis NG, Koniari I, Tzanis G, et al. Anaphylaxis-induced atrial fibrillation and anesthesia: Pathophysiologic and therapeutic considerations. Ann Card Anaesth. 2020;23:1-6.
7. Okutucu S, Aytemir K, Oto A. P-wave dispersion: What we know till now? JRSM Cardiovasc Dis. 2016;5:2048004016639443.
8. Baumert M, Porta A, Vos MA, et al. QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology. Europace. 2016;18:925-44.
9. Atiga WL, Calkins H, Lawrence JH, et al. Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death. J Cardiovasc Electrophysiol. 1998;9:899-908.
10. Erre GL, Piras A, Piga M, et al. QT and QT dispersion intervals in long-standing and moderately active rheumatoid arthritis: results from a multicentre cross-sectional study. Clin Exp Rheumatol. 2020;38:516-22.
11. Zhan X, Li C, Wu Q. Cardiac urticaria caused by eucleid allergen. Int J Clin Exp Med. 2015;8:21659-63.
12. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018;73:1393-414.
13. Galderisi M, Cosyns B, Edvardsen T, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18:1301-10.
14. Akin C. Mast cell activation disorders. J Allergy Clin Immunol Pract. 2014;2:252-7.e1;quiz 258.
15. Janicki JS, Brower GL, Levick SP. The emerging prominence of the cardiac mast cell as a potent mediator of adverse myocardial remodeling. Methods Mol Biol. 2015;1220:121-39.
16. Wolff AA, Levi R. Histamine and cardiac arrhythmias. Circ Res. 1986;58:1-16.
17. Zdravkovic V, Pantovic S, Rosic G, et al. Histamine blood concentration in ischemic heart disease patients. J Biomed Biotechnol. 2011;2011:315709.
18. Ma HT, Beaven MA. Regulation of Ca2+ signaling with particular focus on mast cells. Crit Rev Immunol. 2009;29:155-86.
19. Layritz CM, Hagel AF, Graf V, et al. Histamine in atrial fibrillation (AF)--is there any connection? Results from an unselected population. Int J Cardiol. 2014;172:e432-e433.
20. Rohr SM, Rich MW, Silver KH. Shortness of breath, syncope, and cardiac arrest caused by systemic mastocytosis. Ann Emerg Med. 2005;45:592-4.
21. Jani Y, Rexhepi A, PocestaBKamberi A, et al. C-reactive protein is associated with ventricular repolarization dispersion among patients with metabolic syndrome. J Cardiol Cardiovasc Med. 2019;2:043-052.
22. Zheng LH, Yao Y, Wu LM, et al. Relationships of High-sensitive C-reactive Protein and P-wave Dispersion in Lone Atrial Fibrillation. Chin Med J (Engl). 2015;128:1450-4.
23. Lazzerini PE, Laghi-Pasini F, Acampa M, et al. Systemic Inflammation Rapidly Induces Reversible Atrial Electrical Remodeling: The Role of Interleukin-6-Mediated Changes in Connexin Expression. J Am Heart Assoc. 2019;8:e011006.
24. Puxeddu I, Pratesi F, Ribatti D, et al. Mediators of Inflammation and Angiogenesis in Chronic Spontaneous Urticaria: Are They Potential Biomarkers of the Disease? Mediators Inflamm. 2017;2017:4123694.
25. Kasperska-Zajac A, Sztylc J, Machura E, et al. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. Clin Exp Allergy. 201;41:1386-91.
26. Kolkhir P, Altrichter S, Hawro T, et al. C-reactive protein is linked to disease activity, impact, and response to treatment in patients with chronic spontaneous urticaria. Allergy. 2018;73:940-8.
27. Birklein F, Schlereth T. Autonomic Effects on the Skin. In: Granstein R.D., Luger T.A. (eds) Neuroimmunology of the Skin. Springer, Berlin, Heidelberg, 2009;23-32.
28. Leal Â, Carvalho M, Rocha I, et al. H.Inflammation and autonomic function. In: Autonomic nervous system. InTech, 2018.
29. Mano T, Iwase S, Toma S. Microneurography as a tool in clinical neurophysiology to investigate peripheral neural traffic in humans. Clin Neurophysiol. 2006;117:2357-84.
30. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res. 2014;114:1004-21.
31. Minnei F, Wetzels C, De Hertogh, G et al. Chronic urticaria is associated with mast cell infiltration in the gastroduodenal mucosa. Virchows Arch. 2006;448:262-8.
32. Williams RM, Berthoud HR, Stead RH. Vagal afferent nerve fibres contact mast cells in rat small intestinal mucosa. Neuroimmunomodulation. 1997;4:266-70.
33. Konstantinou GN, Konstantinou GN. Psychological Stress and Chronic Urticaria: A Neuro-immuno-cutaneous Crosstalk. A Systematic Review of the Existing Evidence. Clin Ther. 2020;42:771-82.
34. Buckley U, Shivkumar K. Stress-induced cardiac arrhythmias: The heart-brain interaction. Trends Cardiovasc Med. 2016;26:78-80.
35. Yang HY, Sun CC, Wu YC, et al. Stress, insomnia, and chronic idiopathic urticaria--a case-control study. J Formos Med Assoc. 2005;104:254-63.
36. Kini SP, DeLong LK, Veledar E, et al. The impact of pruritus on quality of life: the skin equivalent of pain. Arch Dermatol. 2011;147:1153-6.