

Relationship between Fragmented QRS and Microvascular Dysfunction in Masked Hypertension

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Keywords

Fragmented QRS · Masked hypertension · Myocardial and microvascular dysfunction

Abstract

Aim: The aim of this study was to investigate the presence of fQRS and its association with subclinical systolic and microvascular dysfunction in patients with masked hypertension (MH). **Methods:** The study population consisted of 95 (mean age 48.9 ± 11.3 , 61% males) subjects with MH and 80 age- and gender-matched healthy individuals who served as a control group. Coronary flow reserve (CFR) using transthoracic echocardiography and for left ventricular global longitudinal strain (LVGLS) using speckle-tracking strain imaging were performed. Patients with MH were stratified into two groups according to the presence of fQRS on surface electrocardiogram. **Results:** Fragmented QRS was more common among MH patients compared with controls (38.9% vs. 6.25%, $p < 0.003$). CFR was significantly lower in patients with fQRS compared with those without fQRS and controls ($p < 0.001$). Likewise, LVGLS values were lower in MH patients with fQRS ($p < 0.001$) compared with subjects without fQRS and controls. Fragmented fQRS was significantly correlated with systolic blood pressure, CFR, and LVGLS. Multivariate analysis showed that the presence of fQRS, number of leads,

and CFR were independent predictors of subclinical systolic dysfunction. With ROC curve analysis, number of leads with fQRS ≥ 4 was the optimal value for predicting the presence of subclinical systolic dysfunction in subjects with MH. **Conclusions:** Fragmented QRS is more frequent among subjects with MH compared with controls. The presence of fQRS is related with pronounced subclinical left ventricular systolic dysfunction. Furthermore, CFR was significantly reduced in subjects with MH, a finding supposed that microvascular dysfunction to be a mechanistic link.

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Introduction

Masked hypertension (MH) is considered when the subject is normotensive at the office with conventional blood pressure measurements and out-of-office hypertensive without any antihypertensive medications [1]. MH patients have the same cardiovascular adverse effects similar to those with sustained hypertension. Furthermore, earlier studies have demonstrated that the risk of having sustained hypertension is significantly high in MH subjects [2].

Fragmented QRS (fQRS) on electrocardiography (ECG) is well defined by the existence of *notches in the R*

or S wave in two contiguous leads in one of the major coronary artery territories without a classic bundle branch block and with QRS duration of less than 120 ms [3]. It is considered a sign of inhomogeneous and delayed ventricular conduction and is usually associated with myocardial fibrosis or scarring and could be associated with adverse outcomes in many cardiac diseases [4–6].

Nevertheless, the significance of fQRS in subjects with MH is uncertain. Hence, we aimed to explore any relation between the presence of fQRS on surface ECG and subclinical systolic dysfunction in subjects with MH and to investigate their association with microvascular function.

Methods

One hundred subjects were identified to have MH were recruited for the study, from January 2019 to September 2020. Five subjects were excluded due to difficulty of coronary flow reserve (CFR) assessment for them. So, the study cohort constituted 95 (mean age 45 ± 11 years) patients with MH. Eighty normotensive controls, matched with cases for sex, age, were randomly selected from the hypertensive clinic in our department. Patients with diabetes, ischemic heart disease; patients with left ventricular hypertrophy, arrhythmia, systemic disease; poor echocardiographic image quality; and patient unwillingness were excluded.

Electrocardiogram and fQRS

At a paper speed of 25 mm/s and a voltage of 10 mm/1 mV in the supine position, 12-lead ECG was recorded for every subject. The fQRS pattern is ECGs with various morphologies of the QRS interval. fQRS was defined as the presence of an additional R wave (R') or notching in the S wave or >1 R' in two contiguous leads with a QRS duration of <120 ms [7]. Patients with complete or incomplete bundle branch block were excluded.

Ambulatory Blood Pressure Measurements

At first, arterial blood pressure readings were recorded in the morning hours using mercury sphygmomanometer. The averages of three consecutive measurements were taken at a 5-min interval in the sitting position. The averaged values were used for analysis. With the use of TM-2430 device (A & D Co., Ltd., Tokyo, Japan), all subjects underwent a 24-h BP monitoring. We programmed the device to obtain blood pressure readings at 30-min intervals during the day (7:00 a.m. to 11:00 p.m.) and at 60-min intervals during the night (11:00 p.m. to 7:00 a.m.). The cuff was placed on the non-dominant arm, and all through the monitoring period, subjects were informed to attain their usual activities. Pre-established quality control criteria including a successful recording of $\geq 80\%$ of BP measurements during both the daytime and nocturnal periods should be fulfilled. Systolic blood pressure readings outside the range of 70 mm Hg (60 mm Hg during sleep) to 250 mm Hg and diastolic readings outside the range of 40 mm Hg (30 mm Hg during sleep) to 150 mm Hg were regarded as errors and excluded [8]. The patients with office blood pressure (average of three readings) $<140/90$ mm Hg and average BP $\geq 130/80$ mm Hg at 24-h ambulatory BP monitoring records were evaluated as the masked HT [9].

Transthoracic Echocardiographic Measurements and Evaluation

All participants underwent echocardiographic assessment with a commercial ultrasound system (a Vivid E9 system; GE Healthcare, Horten, Norway), equipped with a multifrequency transducer (M3S1.7/3.4 MHz), according to the standard echocardiographic guideline recommendations [10]. Focused left ventricular views were obtained from the apical four-, two-, and three-chambers, as well as parasternal short-axis views at the papillary muscle level. All studies were digitally stored and analyzed off-line. Left ventricular wall thickness and left ventricular mass were measured. The left ventricular mass index (g/m^2) was calculated by dividing the LV mass by the body surface area. Relative wall thickness was expressed as the ratio of $2 \times \text{PWT}/\text{LVEDV}$. Left ventricular ejection fraction (%) was estimated using biplane modified Simpson's method. Left atrial volume was estimated using the modified biplane Simpson's method and the left atrial volume index (mL/m^2) was calculated by dividing the left atrial volume by body surface area. The longitudinal left ventricular systolic function was evaluated by assessment of mitral annular plane excursion (MAPSE) with an M-mode line positioned through the mitral annulus. From pulsed-wave Doppler mode positioned at the tip of the mitral valve, the peak early (E) and late (A) diastolic mitral inflow velocities were obtained. The mean early (e') and late (a') diastolic mitral annular tissue velocities were measured at the medial and lateral mitral annulus from the apical 4-chamber view using pulsed-wave tissue Doppler imaging. Then the E/e' ratio was estimated as a surrogate parameter of left ventricular filling pressure. Each measurement including Doppler data was performed over at least 5 consecutive beats, and the average was obtained.

Two-Dimensional Strain Imaging by Speckle Tracking

Myocardial strain parameters were assessed by blinded off-line speckle-tracking analysis on a GE[®] EchoPAC workstation. A semiautomatic myocardial tracking system was used, with manual demarcation of the endocardial border in end-systole and manual adjustment of the region of interest. Left ventricular apical 4-chamber, 2-chamber, and 3-chamber views were attained in grayscale with a frame rate of 60–100 frames per second. Three consecutive cardiac cycles at end-expiration breath holding were obtained and averaged. Only myocardial segments considered to be of adequate quality by both the automatic system and the operator were included in the analysis. Left ventricular global longitudinal strain and strain rate were calculated by taking the average values of all of the segments. Systolic function was assessed by measurement of global longitudinal peak systolic strain (%) [11].

CFR Assessment

Participants underwent transthoracic echocardiographic evaluation of CFR. With a high frequency transducer (5–7 MHz) and the guidance of color Doppler flow mapping, the distal portion of the left anterior descending artery was imaged at modified apical 4-chamber view. A 2.5-mm sample volume was placed on the left anterior descending coronary artery color-flow signal to obtain coronary flow spectral tracing. A Doppler signal was obtained at rest, and the peak diastolic velocity was recorded. Then, IV adenosine was administered (0.14 mg/kg/min) to record the hyperemic peak diastolic velocity. The average of three peak diastolic velocities was obtained of both at baseline and hyperemia. After that, we calculate the CFR as the ratio of peak hyperemic diastolic

Table 1. Baseline characteristics of the study population

Variable	fQRS (+) MH (n = 37)	fQRS (-) MH (n = 58)	Control (n = 80)
Age, years	49.8±10.5 ^a	48.7±12.3	47.9±11.5
Male, n (%)	23 (62.2) ^a	35 (60.3)	19 (63.3)
BMI, kg/m ²	23.8±2.7 ^a	24.1±2.6	24.3±2.5
Smoking, n (%)	12 (32.4) ^a	17 (29.3)	26 (32.5)
Total cholesterol, mmol/L	5.8±0.9 ^a	5.6±1.1	5.7±0.9
LDL cholesterol, mmol/L	3.4±0.7 ^a	3.5±0.7	3.3±0.6
Triglyceride, mmol/L	1.09±0.57 ^a	1.13±0.61	1.13±0.52
Creatinine, mg/dL	0.92±0.13 ^a	0.90±0.13	0.89±0.15
hs-C reactive protein, mg/L	3.9±0.75 ^b	1.3±0.21	1.1±0.09
Heart rate	78±11 ^a	79±11	77±9
Office SBP, mm Hg	129±110 ^a	127±7	125±8
Office DBP, mm Hg	76±6 ^a	75±7	73±5
24-h SBP, mm Hg	136±11 ^b	128±9 ^c	120±7
24-h DBP, mm Hg	85±6 ^b	81±6	76±5
Daytime SBP, mm Hg	139±9 ^b	125±12	121±10
Daytime DBP, mm Hg	78±7 ^a	78±8	75±5
Nighttime SBP, mm Hg	129±10 ^b	122±10 ^c	115±8
Nighttime DBP, mm Hg	78±6 ^a	76±6	75±4

LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index. ^a Nonsignificant difference between the fQRS (+) group and both fQRS (-) group and controls. ^b Significant difference between the fQRS (+) group and both fQRS (-) group and controls. ^c Significant difference between the fQRS (-) group and controls.

velocity over baseline peak diastolic velocity. CFR ≤ 2.5 was considered a microvascular dysfunction [12].

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation according to normality and distribution characteristics and were compared using one-way ANOVA, independent samples *t* test, or Mann-Whitney U-test, according to group number and distribution characteristics. Categorical variables were expressed as number and percentage (%) and were compared using the χ^2 test or the Fisher's exact test. Multivariate logistic regression analysis was used to assess the correlation between fQRS and the studied variables. Univariate and multivariate analyses were used to assess various independent variables associated with subclinical systolic dysfunction. Impact significance was reported as odds ratio and corresponding 95% confidence interval. *p* < 0.05 was considered significant in all statistical analyses. All statistical analyses were performed using SPSS Statistics for Windows SPSS version 22.0 (SPSS Inc, Chicago, IL, USA).

Results

fQRS was detected in 37 (38.9%) in MH patients and in 5 (6.25%) in the control subjects. Subjects with MH were stratified into two groups based on the presence of fQRS. The fQRS (+) group included 37 (38.9%) subjects,

and the fQRS (-) group included 58 (61.1%) patients. Table 1 depicts the baseline data of all study population. There was no statistical difference as regards age, sex, risk factors, and laboratory data except hs-C reactive protein which was higher in MH subjects with fQRS, compared to MH subjects without fQRS and controls (*p* < 0.01). With respect to ambulatory blood pressure measurement data, 24-h SBP (*p* < 0.001), daytime SBP (*p* < 0.05), nighttime SBP (*p* < 0.05) were higher in MH patients with fQRS compared with both MH without fQRS and controls.

All echocardiographic data of the study participants are presented in Table 2. With respect to LV diastolic function, our results revealed that mitral annulus *e'* was decreased significantly (*p* < 0.05) in MH patients with fQRS compared to MH patients without fQRS and controls, while the *E/e'* ratio was significantly increased (*p* < 0.01). In addition, the left atrial volume index tended to be higher in the MH group with fQRS than the group without fQRS and healthy subjects (*p* < 0.03).

Regarding systolic function, we found that parameters of left ventricular systolic function with conventional study (EF%, MAPSE) were similar among the three groups (*p* > 0.05). On the other hand, 2D-STE-derived LV global longitudinal strain was significantly lower in MH

Table 2. Echocardiographic data of control subjects compared with MH patients with and without fQRS

Variable	fQRS (+) MH (n = 37)	fQRS (-) MH (n = 58)	Control (n = 80)
<i>Conventional parameters</i>			
Ejection fraction, %	63±5 ^a	63±3	64±5
LVMI, g/m ²	80.9±14.9 ^a	80.1±11.8	78.4±12.3
Relative wall thickness	0.371±0.048 ^a	0.365±0.062	0.353±0.056
E/A	0.74±0.24 ^b	0.85±0.13	1.17±0.21
LAVI, mL/m ²	31±3 ^b	25±2	23±3
e' wave velocity, cm/s	8.1±1.2 ^b	11.3±1.9	13.5±1.8
E/e' ratio	9.2±1.5 ^b	6.5±1.0	6.1±0.9
MAPSE, mm	16.3±2.0 ^a	16.9±1.9	17.9±2.1
<i>LV systolic mechanical parameters</i>			
GLS, %	-13.5±1.5 ^b	-20.5±1.9	-21.7±1.8
Systolic longitudinal strain rate, S ⁻¹	-0.97±0.1 ^b	-1.15±0.1	-1.17±0.1
<i>Coronary flow</i>			
Baseline SFV, cm/s	20.6±2.5 ^a	19.2±2.3	19.3±2.9
Baseline DFV, cm/s	30.7±5.8 ^a	29.3±5.1	29.5±5.2
Hyperemic SFV, cm/s	55.2±9.7 ^a	53.8±9.5	52.5±9.1
Hyperemic DFV, cm/s	49.5±6.1 ^b	82.5±10.5	91.5±11.5
CFR	1.65±0.35 ^b	2.91±0.51	3.25±0.73

MAPSE, mitral annular plane systolic excursion; SFV, systolic flow velocity; DFV, diastolic flow velocity; LVMI, left ventricular mass index; LAVI, left atrial volume index. ^aNonsignificant difference between the fQRS (+) group and both fQRS (-) group and controls. ^bSignificant difference between the fQRS (+) group and both fQRS (-) group and controls.

Table 3. Correlation analysis to assess the association between blood pressure and echo parameters in patients with MH

fQRS	r	p value
Office SBP, mm Hg	0.135	0.09
Office DBP, mm Hg	0.186	0.06
Daytime SBP, mm Hg	0.251	<0.05
Nighttime SBP, mm Hg	0.385	<0.01
E/e'	0.117	0.23
LAVI, mL/m ²	0.149	0.10
GLS%	-0.320	<0.01
CFR	-0.493	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; LAVI, left atrial volume index; GLS, global longitudinal strain.

subjects, who had fQRS (Fig. 1) than in both MH without fQRS and controls (Fig. 2). Likewise, the strain rate was significantly decreased in fQRS (+) subjects compared with both those without fQRS and controls ($p < 0.001$ and < 0.05 , respectively). Although the conventional systolic function indicator was normal, the left ventricular systolic function index and strain rate decreased in MH patients, indicating subclinical left ventricular systolic dys-

function. Moreover, Table 2 revealed that the fQRS (+) group had significantly reduced CFR, compared to the fQRS (-) group and healthy subjects (1.65 ± 0.35 ; 2.91 ± 0.51 and 3.25 ± 0.73 , respectively; $p < 0.001$).

Univariate Spearman's rank correlation analysis revealed that fQRS was correlated with LVGLS ($p < 0.001$) and CFR ($p < 0.001$). In addition, it was correlated with daytime and nighttime SBP ($p < 0.05$ and < 0.01) in subjects with MH (Table 3).

Table 4 shows the results of the univariate and multivariate logistic regression analyses to detect subclinical systolic dysfunction in subjects with MH. It is notable that left ventricular global longitudinal strain was independently associated with the presence and number of leads with fQRS, reduced CFR, in addition to daytime and nighttime SBP.

With ROC curve analysis, our data revealed that the presence of fQRS (2 leads or more) had an AUC (0.73) with 74% sensitivity and 71% specificity for detecting subclinical systolic dysfunction. The specificity was increased with the increased number of fQRS leads. A number of ECG leads ≥ 4 was the optimal number of leads which predicted subclinical left ventricular dysfunction as evaluated with 2D speckle-tracking echo (AUC 0.89, $p < 0.001$, with sensitivity of 93% and specificity of 85%) (Fig. 3).

Fig. 1. Illustrative strain tracings of patient with MH. Upper left (four-chamber), upper right (two-chamber), and lower left (apical long-axis). Lower right is the resulting “bull’s-eye” plot. In this example, segmental strain values are decreased and represented by shades of red in the bull’s-eye plot. Global longitudinal strain was -11.9% .

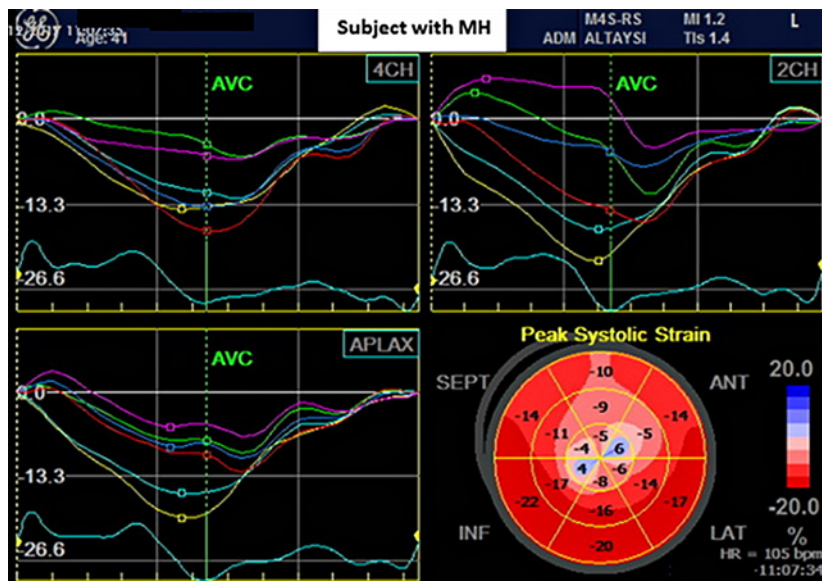
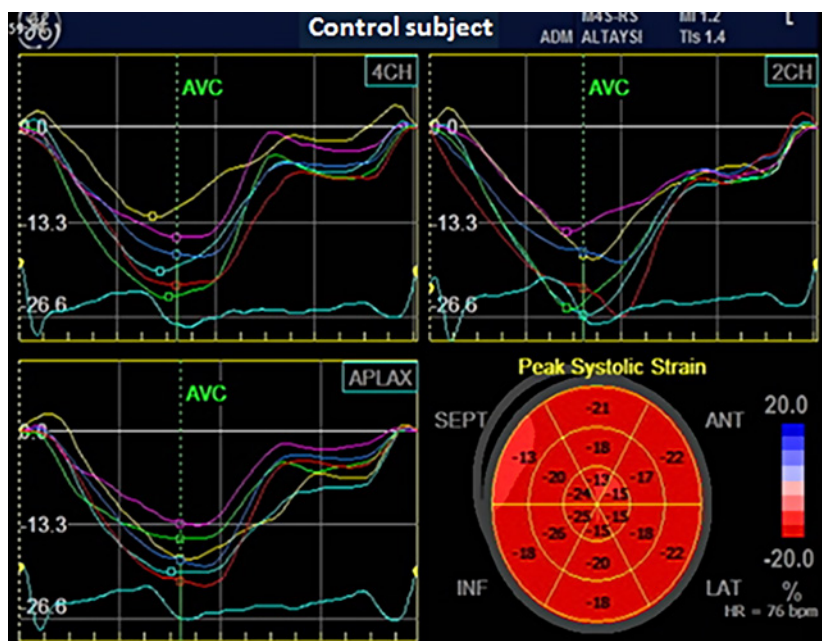


Fig. 2. Illustrative strain tracings of the healthy control subject. Upper left (four-chamber), upper right (two-chamber), and lower left (apical long-axis). Lower right is the resulting “bull’s-eye” plot. In this example, segmental strain values are all normal and represented by shades of red in the bull’s-eye plot. Global longitudinal strain was -19% .



Discussion

Our study revealed that 38.9% of MH subjects had fQRS. Furthermore, the presence of fQRS on ECG was found to be associated with subclinical left ventricular dysfunction as well as diastolic dysfunction in the absence of left ventricular hypertrophy.

The Masked Hypertension Study reported that tissue Doppler-derived diastolic function parameters, specifically e' wave and E/e' ration, were similarly impaired in

subjects with masked and sustained hypertension [13]. Contrary, no data reported with respect to systolic dysfunction. We investigated the usefulness of fQRS in predicting subclinical left ventricular systolic dysfunction using 2D speckle-tracking echo.

Left ventricular strain was significantly decreased in the fQRS-positive group, in spite of normal ejection fraction, MAPSE, and S' , providing a clue for subclinical left ventricular systolic dysfunction. In multivariate logistic regression analysis, daytime/nighttime SBP, the

Fig. 3. ROC for the presence (a) and the number (b) of leads with fQRS for predicting subclinical left ventricular systolic dysfunction in masked hypertensive subjects.

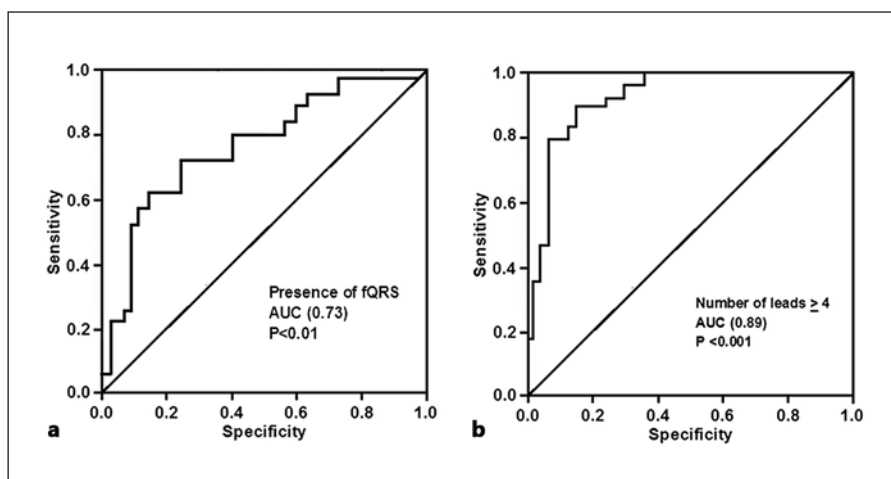


Table 4. Univariate and multivariate logistic regression analyses to identify subclinical systolic dysfunction (reduced LVGLS) in subjects with MH

Variable	Univariate		Multivariate	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.17 (0.81–1.29)	0.28	–	–
Sex	0.93 (0.85–1.01)	0.22	–	–
BMI, kg/m ²	1.14 (0.99–1.28)	0.33	–	–
Smoking	1.49 (0.98–1.99)	0.09	–	–
Total cholesterol, mmol/L	1.03 (1.00–1.05)	0.15	–	–
hs-C reactive protein, mg/L	1.39 (0.96–1.83)	0.08	–	–
Office SBP, mm Hg	1.07 (0.98–1.16)	0.19	–	–
Office DBP, mm Hg	1.02 (0.46–1.57)	0.41	–	–
Daytime SBP, mm Hg	2.61 (0.51–4.92)	<0.01	1.72 (1.21–2.19)	<0.05
Nighttime SBP, mm Hg	3.40 (1.09–5.72)	0.01	2.10 (1.18–3.01)	<0.03
E/e'	1.52 (0.45–2.63)	0.09	–	–
LAVI, mL/m ²	1.60 (1.05–2.14)	<0.05	–	–
The presence of fQRS	5.04 (1.90–8.15)	<0.001	3.28 (1.35–5.23)	<0.003
Number of fQRS on ECG	6.36 (2.09–10.62)	<0.001	4.16 (2.35–5.95)	<0.001
Microvascular dysfunction (reduced CFR)	7.13 (4.21–11.67)	<0.001	4.71 (1.25–8.19)	<0.001

CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; fQRS, fragmented QRS; E/e', early mitral flow (E)/early mitral annular wave (e'); LAVI, left atrial volume index; ECG, electrocardiography; CFR, coronary flow reserve; LVGLS, left ventricular global longitudinal strain; OR, odds ratio.

presence and number of leads with fQRS, and CFR were independent determinants of the presence of subclinical LV systolic dysfunction. In light of these findings, we suppose that microvascular dysfunction with the impact of MH results in left ventricular systolic dysfunction.

Accordingly, we supposed that the presence of fQRS on surface ECG is an indicator of paramount subclinical left ventricular systolic dysfunction in subjects with MH. Our results revealed that the MH with fQRS subjects had

reduced longitudinal LV deformations, despite normal left ventricular ejection fraction and MAPSE, indicating subclinical LV systolic dysfunction. This is consistent with the results of Tadic et al. [14] who found that left ventricular deformation was significantly impaired in subjects with MH.

Nonetheless, the novelty of our results is that this subclinical LV systolic dysfunction is significantly correlated with the presence of fQRS and reduced CFR (a marker of microvascular dysfunction) and constituted that micro-

vascular dysfunction could be an important mechanistic link between fQRS and subclinical left ventricular dysfunction. Furthermore, this finding indicates the impact of microvascular dysfunction as a contributing factor for higher fibrotic burden within the myocardium and the importance of electrocardiographic risk assessment of subjects with MH despite the absence of LVH.

Several clinical and experimental studies have demonstrated that the microcirculation has a considerable role in the pathophysiology of hypertension [15, 16]. One study detected that left ventricular diastolic dysfunction was more obvious in hypertensive subjects with modest retinal arteries atherosclerosis (*Scheie stage II*) than subjects with *Scheie stage I* [17].

Although the key causal pathophysiologic relation between fQRS and microvascular dysfunction was not explained previously, inflammatory and ischemic burden, which may result in unusual depolarization of the myocardium at the cellular level, could be an explanation. Microvascular dysfunction is responsible for morbidity and mortality in many different cardiovascular diseases. Fibrosis is caused by irreversible damage to the cellular elements of the microvascular bed that feed the myocardium. This leads to delays in interventricular conduction. Thus, it may cause fQRS formation.

Implication

The presence of fQRS is of value in the identification of high-risk patients with MH in the absence of left ventricular hypertrophy. Routine ECG may be helpful in identifying MH patients with microvascular and myocardial dysfunction. Future studies should be able to determine the prognostic value of fQRS in subjects with MH.

Limitation

First, a relatively small study sample size. Second, the absence of data regarding confirmation of fibrosis within the myocardium by magnetic resonance imaging is another limitation.

Conclusions

We found that fQRS was a valuable indicator of subclinical myocardial in subjects with MH even in the absence of LVH. Furthermore, we supposed that microvascular dysfunction could be the mechanistic link between fQRS and myocardial dysfunction. Hence, it can be thought that the detection of fQRS on ECG may be used to risk stratify and monitoring of subjects with MH.

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Statement of Ethics

All participants have given an informed written consent, and the study protocol has been approved by the ethical and scientific committee (IRB: 03189), faculty of medicine, Zagazig University Hospital. The study complied with internationally accepted standards for research practice and reporting.

Conflict of Interest Statement

Authors declared that they have no conflict of interest.

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There are no funding sources to declare.

Author Contributions

Ragab A. Mahfouz: idea and design of the work and writing and submission of the manuscript as a corresponding author. Mohamed Mesbah: collection of data, drafting the paper, and revising it critically. Marwa M. Gad: analysis and interpretation of data and shared in writing the paper. Moheye Abulfotouh: collection of data, analysis of data, writing and drafting the paper, and revising it critically. Mohamed Arab: collection of data, writing and drafting the paper, and revising it critically.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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