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HYPERTENSION AND THE HEART (B UPADHYA, SECTION EDITOR)

Fragmented QRS as a Marker of Myocardial Fibrosis in Hypertension: a Systematic Review

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Abstract

Purpose of Review Hypertension cause damage in cardiac structure and induce pathological myocardial fibrosis that leads to hypertensive cardiomyopathy. A narrow fragmented QRS complex (fQRS) is associated with myocardial fibrosis and scar tissue in various cardiovascular diseases. It is also associated with myocardial fibrosis in hypertensive patients even in the absence of any structural heart diseases. This article aimed to demonstrate importance and usefulness of fQRS in hypertensive patients.

Recent Findings Current evidence suggest that the frequency of fQRS is significantly higher in hypertensive patients compared to normotensives. Also, fQRS seems to be a predictor of left ventricular hypertrophy, increased systolic blood pressure, non-dipping, deterioration of the left ventricular geometry, and worse systolic and diastolic functions in hypertensive patients.

Summary As a simple and easy detectable electrocardiographic finding, fQRS may indicate myocardial fibrosis, uncontrolled blood pressure, and deteriorated cardiac structure in hypertensive patients even in the absence of other structural heart diseases, and may also be useful to predict high-risk hypertensives.

Keywords Hypertension · Fibrosis · Fragmented QRS · Electrocardiography · Left ventricular hypertrophy

Introduction

Hypertension is a leading cause of morbidity and mortality around the globe and is a global health problem affecting approximately one third of general population and is strongly associated with major adverse cardiovascular events (MACE) [1, 2]. Increased blood pressure is associated with numerous abnormalities on electrocardiography (ECG) mainly due to increased left ventricular mass (LVM) and left ventricular hypertrophy (LVH) as a result of chronic pressure overload [3]. As a sign of myocardial fibrosis and scar tissue, recent studies demonstrated that the frequency of a narrow fragmented QRS complex (fQRS) on ECG is significantly higher in hypertensive patients compared to normotensives even in the absence of LVH, indicating the fQRS as a marker of higher myocardial fibrotic burden in hypertensive patients [4••]. This review is focused to describe the importance and usefulness of fQRS as a novel fibrotic ECG marker in hypertensive patients, in particular, in the absence of LVH.

Methods

A comprehensive search of several medical databases (Pubmed and EMBASE) was performed for all the English written articles in the fields of hypertension and fQRS until May 2019 using the following keywords: "hypertension" and "blood pressure" combined with "fragmented QRS" and "QRS fragmentation." This review article focused on review of all the relevant articles investigating the relationship of fQRS with hypertension.

All the English written articles were included if all of the following criteria were met: (a) diagnosis of hypertension in patients aged 18 years or older, (b) reported a relationship between fQRS and increased blood pressure levels, (c) reported a relationship between fQRS and hypertension-related disorders or target organ damage. All study designs (prospective, cross-sectional, and retrospective) were included. Following the initial screening by titles and abstracts, full-text articles were examined in detail for their eligibility. Importantly, no

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articles which investigated the importance and usefulness of fQRS in hypertensive patients were excluded. A flowchart for the search strategy and article selection is shown in Fig. 1. The studies which investigated the fQRS in hypertensive patients are summarized in Table 1.

Hypertension and Electrocardiography

Hypertension is generally defined as office systolic blood pressure (SBP) of ≥ 140 mmHg and diastolic blood pressure (DBP) of ≥ 90 mmHg. Based on new evidence, recent guidelines recommended lower target blood pressure levels, mainly office blood pressure levels of less than 130/80 mmHg to reduce MACE [16, 17]. However, the method of blood pressure measurement has a significant effect on measured blood pressure levels and this situation creates an important difficulty in the diagnosis of hypertension in clinical practice. Nevertheless, ambulatory blood pressure monitoring (ABPM) provides a better cardiovascular risk prediction than office blood pressure measurements, and ABPM values predict MACE more accurately than office blood pressure values [18, 19]. The diagnosis of hypertension is made by ABPM when recordings indicate a 24-h mean SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg, daytime mean SBP ≥ 135 mmHg and/or DBP ≥ 85 mmHg, or nighttime mean SBP ≥ 120 mmHg and/or DBP ≥ 70 mmHg [16, 19]. Hence, the studies that diagnosed the hypertension by ABPM recordings were clearly stated in this review.

Chronic and continuous pressure overload induce and accelerate the excessive accumulation of collagen fibers and connective tissue matrix within the myocardium of hypertensive patients that leads pathological fibrosis and subsequently proceeds to LVH [20]. ECG abnormalities are highly prevalent in hypertensive individuals, mainly driven by LVH and secondary ST/T changes [21]. However, LVH is not a common finding and only a small proportion of hypertensive patients have a diagnosis of LVH [22]. Therefore, novel and simple ECG markers indicating myocardial fibrosis like fQRS may be helpful in terms of risk stratification of the majority of hypertensive patients, particularly in the early phase of the disease and before the development of LVH.

Fragmented QRS on Electrocardiography

fQRS is defined as presence of various RSR′ patterns or notching in the nadir of the S wave in the original QRS complex, in two contiguous leads corresponding to a major coronary artery territory with a QRS duration of < 120 ms and in the absence of typical bundle branch block [23]. Figures 2 and 3 show the examples of different morphologies of the fQRS.

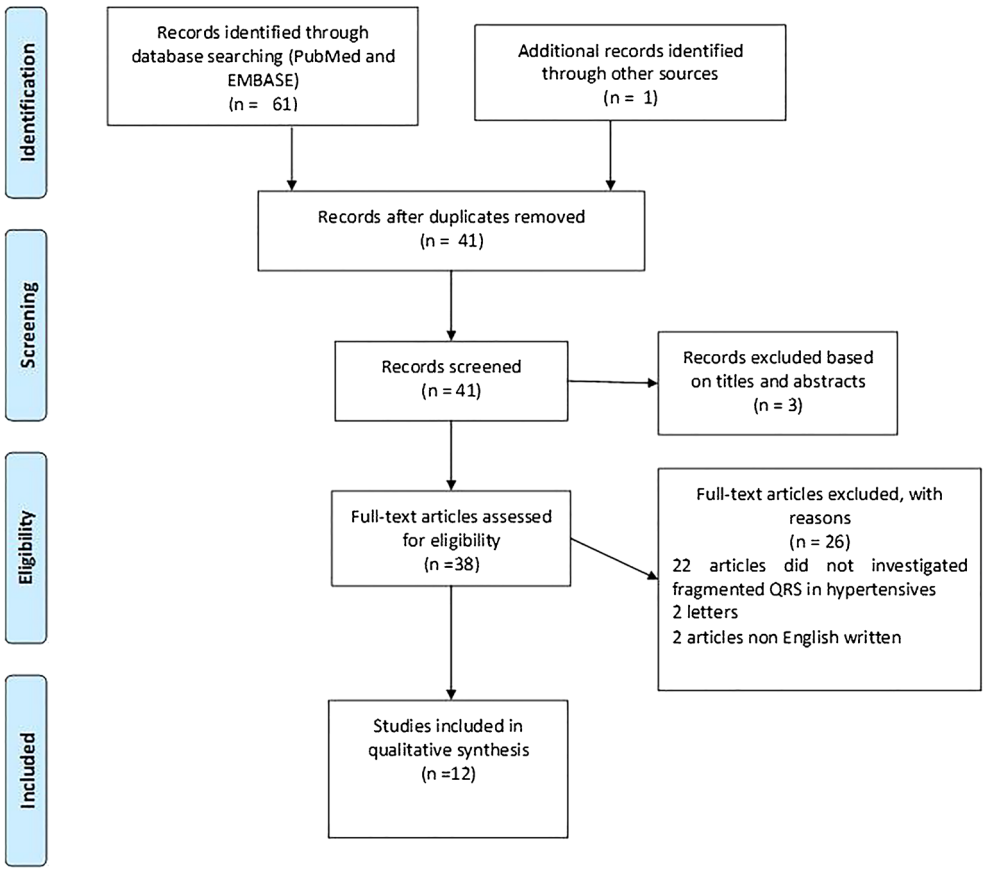

Fig. 1 Flowchart of the search strategy and article selection

Table 1 Studies investigated the fragmented QRS in hypertensive patients

Authors, *n*	Study design	Year	Diagnosis of hypertension	Findings
Eyuboglu et al. [4] (*n* = 548)	Cross-sectional	2017	ABPM	Frequency of fQRS was found to be significantly higher in hypertensive patients compared to normotensives even in the absence of LVH, and SBP was found to be an independent predictor of fQRS in hypertensives
Bekar et al. [5] (*n* = 90)	Cross-sectional	2016	Office measurement or ABPM	As a marker of fibrosis, serum PCIP levels were found to be an independent predictor of fQRS in hypertensive patients
Kadı et al. [6] (*n* = 90)	Prospective	2013	Office measurement	fQRS was found to be significantly associated with LVH and LVMI in hypertensive patients with normal coronary angiogram
Zhang et al. [7] (*n* = 236)	Retrospective	2015	Office measurement	fQRS was found to be an independent predictor of LVH and severity of LVH in hypertensive patients with normal coronary angiogram
Tanriverdi et al. [8] (*n* = 106)	Retrospective	2017	ABPM	fQRS was found to be an independent predictor of non-dipper status in hypertensive patients without LVH
Eyuboglu et al. [9] (*n* = 338)	Cross-sectional	2017	ABPM	Nighttime SBP was found to be an independent predictor of fQRS in hypertensive patients without LVH
Bekar et al. [10] (*n* = 200)	Cross-sectional	2019	Office measurement or ABPM	Presence of fQRS was found to be independently associated with the complex ventricular arrhythmias in hypertensive patients.
Kadı et al. [11] (*n* = 72)	Prospective case control	2015	Office measurement	Presence of fQRS was associated with more severe diastolic dysfunction in patients with hypertension
Korkmaz et al. [12] (*n* = 150)	Cross-sectional	2015	Office measurement	fQRS was found to be associated with increased arterial stiffness in asymptomatic hypertensive patients
Mahfouz et al. [13] (*n* = 120)	Cross-sectional	2019	Office measurement	fQRS was found to be associated with exercise intolerance and reduced coronary flow reserve
Bekar et al. [14] (*n* = 114)	Cross-sectional	2019	Office measurement or ABPM	fQRS was found to be associated with increased epicardial adipose tissue thickness in hypertensive patients
Bekar et al. [15] (*n* = 90)	Cross-sectional	2019	Office measurement or ABPM	A significant association was found between an inflammatory marker serum ICAM-1 levels and the presence of fQRS in hypertensive patients

ABPM ambulatory blood pressure monitoring, *fQRS* fragmented QRS, *LVH* left ventricular hypertrophy, *SBP* systolic blood pressure, *PCIP* carboxy-terminal propeptide of type 1 procollagen, *LVMI* left ventricular mass index, *ICAM-1* intercellular adhesion molecule-1

fQRS is not an uncommon finding in general population. Terho et al. [24] reported that the frequency of fQRS was 19.7% among 10,904 middle-age subjects. However, the frequency of fQRS seems to be significantly higher in hypertensive patients compared to general population and approximately one third of hypertensive patients have fQRS on ECG [4••]. Recent studies demonstrated that it is a sign of an inhomogeneous ventricular activation, and as a ventricular conduction abnormality due to myocardial fibrosis and/or scar tissue, it is associated with MACE in various cardiovascular diseases, in particular, in patients with coronary artery disease (CAD) [25, 26]. Although single lead fQRS has been studied in patients with CAD in small studies [27], its prognostic and clinical importance is not well described in cardiovascular diseases. Another topic may be the localization of fQRS on ECG. Although presence of fQRS on anterior leads compared to fQRS in inferior leads seems to be associated with more severe CAD [24, 28], the importance of localization of fQRS on ECG has not been yet studied in patients with hypertension. Moreover, presence of fQRS on ECG also seems to be associated with myocardial fibrosis in hypertensive patients indicating hypertensive heart disease [5]. Bekar et al. [5] found that, as a marker of fibrosis, serum carboxy-terminal propeptide of type 1 procollagen (PICP) level was a strong and independent predictor of presence of fQRS on ECG in hypertensive patients.

Fragmented QRS and Left Ventricular Hypertrophy

Chronic and continuos pressure overload leads to pathological fibrosis, thickening, and LVH in the hearts of hypertensive patients due to excessive accumulation of collagen fibers and connective tissue matrix within the myocardium [20, 29]. Kadı et al. [6•] demonstrated that LVM and left ventricular mass index (LVMI) of the hypertensive patients who had fQRS on their ECGs was significantly higher than the LVM

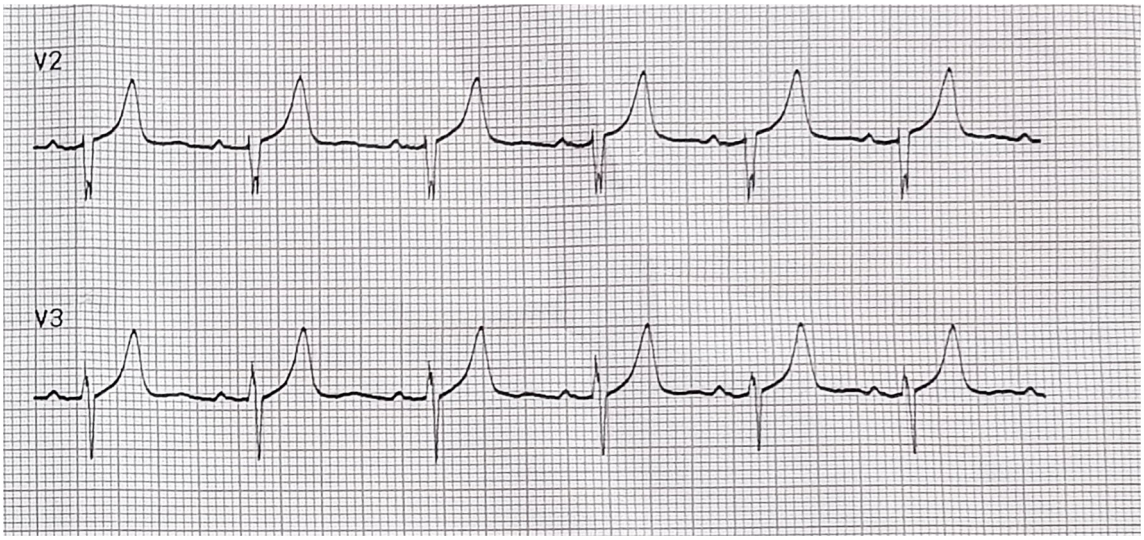

Fig. 2 An example of fragmented QRS in anterior leads

and LVMI of those who did not have. Despite the small number of the study population, this study was a prospective study and included only hypertensive patients with normal coronary arteries. Hence, it seems reasonable to interpret the fQRS as a reflection of higher myocardial fibrotic burden on ECG in hypertensive patients with LVH. Another study by Zhang et al. [7] demonstrated that fQRS was an independent predictor of LVH and may be useful to assess the severity of LVH in hypertensive patients with normal coronary angiogram. However, this was a retrospective analysis and diagnostic value of fQRS was limited.

LVH is the most important finding of hypertensive heart disease and reflects to changes in the composition of cardiac tissue and structural remodeling of the myocardium mostly driven by collagen accumulation [20]. Current data suggest that fQRS may be a sign of fibrosis and myocardial damage due to LVH in hypertensive patients. It seems reasonable to conclude that fQRS is an ECG sign of increased LVM, LVMI, and LVH in hypertensive hearts.

Blood Pressure and Fragmented QRS in the Absence of Left Ventricular Hypertrophy

Although LVH is one of the most important prognostic end-organ damage and is the cornerstone of the cardiovascular risk assessment in patients with hypertension, development of LVH is a long process and the vast majority of hypertensive patients will not have a diagnosis of LVH during their clinical evaluation [16, 22]. Therefore, further ECG interpretation and definition of novel ECG findings for hypertensive patients may be useful for clinical evaluation of hypertensive patients. Eyuboglu et al. [4••] studied the usefulness of fQRS in hypertensive patients without LVH. In their analysis, the authors found that the frequency of fQRS was significantly higher in hypertensive patients compared to normotensives even in the absence of LVH. Furthermore, they reported that increased SBP was independently associated with presence of fQRS on ECG in these patients. The findings of the study by Eyuboglu et al. [4••] may indicate that fQRS may be a sign

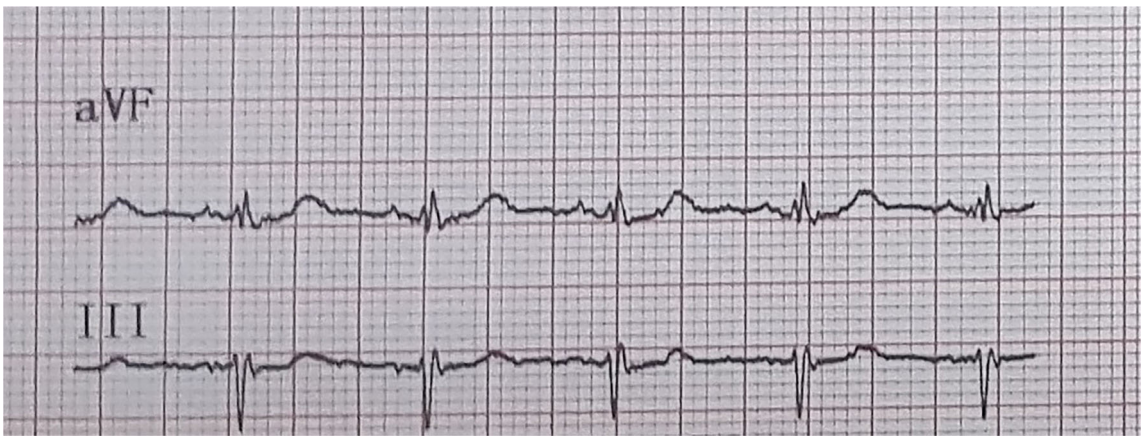

Fig. 3 An example of fragmented QRS in inferior leads

of chronic and continuous pressure overload, in particular, due to increased SBP that leads to pathological fibrosis in hypertensive hearts even in the absence of LVH. Hence, it may be reasonable to evaluate fQRS as a sign of higher myocardial fibrotic burden in hypertensive patients without LVH.

Fragmented QRS and Deteriorated Circadian Blood Pressure Variability

ABPM provides a better cardiovascular risk prediction than office blood pressure measurements and is a better predictor of hypertension-related target organ damage compared to office measurements [18, 30]. The natural circadian blood pressure variability includes a morning surge with higher levels during daytime and subsequently reduction during the rest of the day with a 10–20% decline during nighttime, and this phenomenon is known as "dipping" [19]. However, non-dipping which is defined as less than 10% decline in blood pressure levels in sleep is associated with worse adverse outcomes compared to daytime blood pressure levels [31]. Non-dipping is also associated with autonomic nervous system dysfunction, increased sympathetic activity, and metabolic abnormalities that may accelerate the hypertension-induced target organ damage independent of average 24-h blood pressure levels [30–32]. Also, recent studies demonstrated that non-dipping pattern may induce interstitial myocardial fibrosis independent of 24-h mean blood pressure levels [33]. Tanriverdi et al. [8] aimed to investigate the relationship between fQRS and non-dipper status in hypertensive patients without LVH. The authors reported that patients with non-dipping blood pressure pattern had significantly higher frequency of fQRS on ECG compared to dippers. Also, they found that fQRS was an independent predictor of non-dipping in hypertensive patients in the absence of LVH. Interestingly, the authors also reported that higher number of leads with fQRS was significantly associated with higher nighttime blood pressure levels; however, importance of number of leads with fQRS is not well described in hypertensive patients. A larger study conducted by Eyuboglu et al. [9•] also aimed to investigate the effect of deteriorated circadian blood pressure variability on presence of fQRS on ECG. In their study, the authors reported that the frequency of fQRS was significantly higher in reverse dippers, which is defined as higher nocturnal average blood pressure levels than daytime blood pressure levels, compared to dippers in hypertensive patients without LVH. Also, daytime DBP and nighttime SBP were found to be independent predictors of presence of fQRS on ECG. Both studies excluded the patients with LVH and the diagnosis of hypertension was made by ABPM. Hence, it may be reasonable to claim a relationship between deteriorated circadian blood pressure variability and increased myocardial fibrosis that may seen on ECG as QRS fragmentation.

Fragmented QRS and Arrhythmic Events in Hypertensive Patients

fQRS predicts arrhythmic events in various cardiovascular diseases including CAD, heart failure, cardiomyopathies, and inherited arrhythmogenic syndromes such as Brugada syndrome [34–37]. However, its predictive value for arrhythmias in hypertensive patients is not well described. Although the incidence of complex arrhythmias is not frequent in patients with hypertension, hypertensive heart disease may manifest atrial and ventricular arrhythmias, most commonly being atrial fibrillation particularly due to LVH and myocardial fibrosis [38]. Bekar et al. [10••] investigated the association between the presence of fQRS on ECG and ventricular arrhythmias in patients with essential hypertension and without other structural heart diseases. The authors reported that ventricular arrhythmias defined as ventricular ectopic beats, couplets, triplets, and ventricular tachycardia were significantly higher in patients with fQRS compared to those without fQRS. Furthermore, they found that presence of fQRS on ECG was independently associated with the complex ventricular arrhythmias in hypertensive patients. These findings point out the utility of fQRS in hypertensive patients in terms of risk stratification for ventricular arrhythmias even in the absence of structural heart disease such as coronary artery disease, cardiomyopathy, and heart failure. The relationship of fQRS with atrial arrhythmias was not studied in detail in isolated hypertensive patients. Nevertheless, given the impaired cardiac structure and increased myocardial fibrosis in hypertensive patients, the relationship of fQRS with atrial arrhythmias is worth further investigation.

Relationship of Fragmented QRS with Impaired Cardiac Structure and Inflammation in Hypertensive Patients

Chronic and continuous pressure overload is an important risk factor for myocardial damage and systolic and diastolic dysfunction [16]. It is reasonable to predict more severe damage in cardiac structure in hypertensive patients with fQRS due to higher myocardial fibrotic burden in these patients. Zhang et al. [7] reported that hypertensive patients with fQRS had higher levels of interventricular septal thickness, left ventricular end diastolic and end systolic dimensions, left atrium diameter, and LVM compared to those without fQRS. Also, the authors reported that hypertensive patients with fQRS had lower levels of left ventricular ejection fraction compared to patients without fQRS. The findings of the study by Zhang et al. [7] suggest that hypertensive patients with fQRS have worse systolic and diastolic cardiac function than patients

without fQRS. Kadı et al. [11] studied the association of fQRS on ECG with left ventricular diastolic functions in hypertensive patients. The authors found that presence of fQRS was associated with more severe diastolic dysfunction detected by two-dimension and Doppler echocardiography compared to those without fQRS. Also, Korkmaz et al. [12] studied the association of fQRS with arterial stiffness in asymptomatic hypertensive patients. The authors reported that the presence of fQRS was associated significantly and independently with increased arterial stiffness in asymptomatic hypertensive patients. Hence, current data suggest that presence of fQRS on ECG in hypertensive patients is associated with impaired cardiac structure, deterioration of the left ventricular geometry, and worse systolic and diastolic functions.

A recent study by Mahfouz et al. [13] studied the association between fragmented QRS and symptoms in hypertensive patients. The authors reported that fQRS was an independent predictor of reduced exercise tolerance defined by 6-min walk test in hypertensive patients. The diagnosis of hypertension was made based on office measurements in this study; however, it was the first to report the relationship between fQRS and functional status in hypertensive patients in the absence of other structural heart diseases. Additionally, Bekar et al. [14] recently reported that increased epicardial adipose tissue (EAT) thickness was found to be associated with the presence of fQRS in hypertensive patients. In this study, EAT was found to be an independent predictor of fQRS that may favor the causative role of EAT in cardiovascular pathophysiology and myocardial fibrosis.

Moreover, a recent study by Bekar et al. [15•] aimed to investigate the association of fQRS with inflammation in hypertensive patients. The authors studied an inflammatory marker intercellular adhesion molecule-1 (ICAM-1) in 90 hypertensive patients and found a significant association between serum ICAM-1 levels and the presence of fQRS in hypertensive patients. More than half of the patients with fQRS had LVH in this study suggesting the causative role of both fibrosis and inflammation in the pathogenesis of LVH and hypertensive heart disease.

Fragmented QRS and Prehypertension

Although the relationship between fQRS and prehypertension is not the subject of this review, a recent published article points out important findings that are worthy to be discussed. Prehypertension consists a group of high-risk patients for future adverse events, indicates future hypertension, and is generally defined as office SBP of 120–139 mmHg and/or office DBP of 80–89 mmHg [16]. Eyuboglu and Akdeniz [39] investigated the usefulness of fQRS in prehypertensive patients. This was an ABPM study, and although definition of prehypertension based on ABPM recordings is not well described, the authors assigned the patients with non-hypertensive elevated blood pressure levels as prehypertensives. As a result, the authors reported that there was no difference regarding incidence of fQRS in dipper prehypertensives compared to normotensives; however, non-dipper prehypertensives had significantly higher frequency of fQRS on ECG compared to normotensives. Furthermore, they found that presence of fQRS on ECG was an independent predictor of non-dipping blood pressure pattern in prehypertensive patients. Hence, fQRS may also be associated with higher myocardial fibrotic burden in non-dipper prehypertensives and may be useful to identify high-risk prehypertensive patients. However, further studies are necessary to determine the importance of fQRS in prehypertensive patients.

Conclusion

Fibrosis within myocardium is one of the leading causes of MACE in patients with elevated blood pressure. Presence of fQRS seems to be associated with LVH in hypertensive patients. Although LVH is the cornerstone in the risk stratification of hypertensive patients for MACE, only a small proportion of hypertensive patients have the diagnosis of LVH. However, approximately one third of hypertensive patients have fQRS on ECG. Recent data suggest that fQRS may be associated with myocardial fibrosis in hypertensive patients even in the absence of LVH, in particular, in patients with elevated SBP and deteriorated circadian blood pressure variability. It also seems to be associated with impaired cardiac structure, deterioration of the left ventricular geometry, and worse systolic and diastolic functions in hypertensive patients even in the absence of other structural cardiac diseases. Therefore, as a simple and easy detectable ECG finding, fQRS may also be useful to define high-risk hypertensive patients even in the absence of LVH. The main limitation is the lack of the prospective randomized trials. The majority of articles investigating fQRS in hypertensives are cross-sectional studies with relatively small number of patients. Hence, further larger scale studies are necessary to identify the prognostic value of fQRS in hypertensive patients.

Compliance with Ethical Standards

Conflict of Interest I have no commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360:1903–13.
2. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. PURE study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310:959–68.
3. Bacharova L, Schocken D, Estes EH, Strauss D. The role of ECG in the diagnosis of left ventricular hypertrophy. Curr Cardiol Rev. 2014;10:257–61.
4.•• Eyuboglu M, Karabag Y, Karakoyun S, Senarslan O, Tanriverdi Z, Akdeniz B. Usefulness of fragmented QRS in hypertensive patients in the absence of left ventricular hypertrophy. J Clin Hypertens (Greenwich). 2017;19:861–5 **This study was the first study to report an association between increased blood pressure and presence of fragmented QRS in the absence of left ventricular hypertrophy. Systolic blood pressure was reported to be independently associated with presence of fragmented QRS**.
5. Bekar L, Katar M, Yetim M, Çelik O, Kilci H, Önalan O. Fragmented QRS complexes are a marker of myocardial fibrosis in hypertensive heart disease. Turk Kardiyol Dern Ars. 2016;44:554–60.
6.• Kadi H, Kevser A, Ozturk A, Koc F, Ceyhan K. Fragmented QRS complexes are associated with increased left ventricular mass in patients with essential hypertension. Ann Noninvasive Electrocardiol. 2013;18:547–54 **This study demonstrated that left ventricular hypertrophy-related myocardial fibrosis is associated with presence of fragmented QRS independent of coronary artery disease**.
7. Zhang B, Zhen Y, Shen D, Zhang G. Significance of fragmented QRS complexes for identifying left ventricular hypertrophy in patients with hypertension. Ann Noninvasive Electrocardiol. 2015;20:175–80.
8. Tanriverdi Z, Eyuboglu M, Bingol Tanriverdi T, Nurdag A, Demirbag R. The relationship between fragmented QRS and non-dipper status in hypertensive patients without left ventricular hypertrophy. Clin Exp Hypertens. 2017;39:680–4.
9.• Eyuboglu M, Karabag Y, Karakoyun S, Akdeniz B. The effect of circadian blood pressure pattern on presence of fragmented QRS complexes in hypertensive subjects. J Am Soc Hypertens. 2017;11:513–8 **This study demonstrated that deteriorated circadian blood pressure variability was associated with presence of fragmented QRS on electrocardiography in hypertensive patients**.
10.•• Bekar L, Kalçık M, Kilci H, Çelik O, Yetim M, Doğan T, et al. Presence of fragmented QRS may be associated with complex ventricular arrhythmias in patients with essential hypertension. J Electrocardiol. 2019;55:20–5 **This study reported that presence of fragmented QRS on electrocardiography may be associated with complex ventricular arrhythmias in hypertensive patients**.
11. Kadı H, Demir AK, Ceyhan K, Damar İH, Karaman K, Zorlu Ç. Association of fragmented QRS complexes on ECG with left ventricular diastolic function in hypertensive patients. Turk Kardiyol Dern Ars. 2015;43:149–56.
12. Korkmaz L, Hatem E, Erkan H, Ata Korkmaz A, Dursun I. Fragmented QRS may predict increased arterial stiffness in asymptomatic hypertensive patients. Blood Press Monit. 2015;20:16–9.
13. Mahfouz RA, Gouda M, Ghareb MS, Galal I. Association between fragmented QRS and exercise intolerance in hypertensive patients: the relation with coronary flow. Blood Press. 2019;28:124–30.
14. Bekar L, Kalçık M, Çelik O, Alp Ç, Yetim M, Doğan T, et al. Presence of fragmented QRS is associated with increased epicardial adipose tissue thickness in hypertensive patients. J Clin Ultrasound. 2019;47:345–50. https://doi.org/10.1002/jcu.22683.
15.• Bekar L, Kalçık M, Katar M, Yetim M, Çelik O, Doğan T, et al. Investigation of ICAM-1 levels in hypertensive patients with fragmented QRS complexes. Acta Cardiol. 2019:1–7. doi: https://doi.org/10.1080/00015385.2018.1555200. **This study reported a significant association between serum ICAM-1 levels and presence of fragmented QRS on electrocardiography, that points out the importance of inflammation in the pathogenesis of myocardial fibrosis in hypertensive patients.**
16. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953–2041.
17. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:e13–e115.
18. Verdecchia P. Prognostic value of ambulatory blood pressure : current evidence and clinical implications. Hypertension. 2000;35:844–51.
19. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31:1731–68.
20. Díez J. Mechanisms of cardiac fibrosis in hypertension. J Clin Hypertens (Greenwich). 2007;9:546–50.
21. Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS, et al. Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. J Hypertens. 2016;34:959–66.
22. Cuspidi C, Rescaldani M, Sala C, Negri F, Grassi G, Mancia G. Prevalence of electrocardiographic left ventricular hypertrophy in human hypertension: an updated review. J Hypertens. 2012;30:2066–73.
23. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. Circulation. 2006;113:2495–501.
24. Terho HK, Tikkanen JT, Junttila JM, Anttonen O, Kenttä TV, Aro AL, et al. Prevalence and prognostic significance of fragmented QRS complex in middle-aged subjects with and without clinical or electrocardiographic evidence of cardiac disease. Am J Cardiol. 2014;114:141–7.
25. Pietrasik G, Zareba W. QRS fragmentation: diagnostic and prognostic significance. Cardiol J. 2012;19:114–21.
26. Das MK, Saha C, El Masry H, Peng J, Dandamudi G, Mahenthiran J, et al. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. Heart Rhythm. 2007;4:1385–92.
27. Tanriverdi Z, Dursun H, Colluoglu T, Kaya D. Single derivation fragmented QRS can predict poor prognosis in successfully

revascularized acute STEMI patients. Arq Bras Cardiol. 2017;109: 213–21.
28. Eyuboglu M, Kucuk U, Senarslan O, Akdeniz B. Comparison of the presence of fragmented QRS complexes in the inferior versus the anterior leads for predicting coronary artery disease severity. Rev Port Cardiol. 2017;36:89–93.
29. Rossi MA. Pathologic fibrosis and connective tissue matrix in left ventricular hypertrophy due to chronic arterial hypertension in humans. J Hypertens. 1998;16:1031–41.
30. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, et al. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the ambulatory blood pressure collaboration in patients with hypertension (ABC-H) meta-analysis. Hypertension. 2016;67:693–700.
31. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension. 2011;57:3–10.
32. Sherwood A, Steffen PR, Blumenthal JA, Kuhn C, Hinderliter AL. Nighttime blood pressure dipping: the role of the sympathetic nervous system. Am J Hypertens. 2002;15:111–8.
33. Yokota H, Imai Y, Tsuboko Y, Tokumaru AM, Fujimoto H, Harada K. Nocturnal blood pressure pattern affects left ventricular remodeling and late gadolinium enhancement in patients with hypertension and left ventricular hypertrophy. PLoS One. 2013;8:e67825.
34. Jain R, Singh R, Yamini S, Das MK. Fragmented ECG as a risk marker in cardiovascular diseases. Curr Cardiol Rev. 2014;10:277–86.
35. Rattanawong P, Riangwiwat T, Prasitlumkum N, Limpruttidham N, Kanjanahattakij N, Chongsathidkiet P, et al. Baseline fragmented QRS increases the risk of major arrhythmic events in Brugada syndrome: systematic review and meta-analysis. Ann Noninvasive Electrocardiol. 2018;23:e12507.
36. Femenía F, Arce M, Van Grieken J, Trucco E, Mont L, Abello M, et al. Fragmented QRS as a predictor of arrhythmic events in patients with hypertrophic obstructive cardiomyopathy. J Interv Card Electrophysiol. 2013;38:159–65.
37. Das MK, Maskoun W, Shen C, Michael MA, Suradi H, Desai M, et al. Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm. 2010;7:74–80.
38. Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH, et al. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace. 2017;19:891–911.
39. Eyuboglu M, Akdeniz B. Association between non-dipping and fragmented QRS complexes in prehypertensive patients. Arq Bras Cardiol. 2019;112:59–64.