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EDITORIAL COMMENT

From the boundaries of normality to the acknowledgment of a new nosological entity☆

Da delimitação do conceito de normalidade ao reconhecimento de uma nova entidade nosológica?

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The term 'fragmented QRS' (fQRS) was coined by Das et al. in 2006,[1] originally only for coronary patients. It was then extended to describe notching of the mid or terminal portions of the QRS complex lasting less than 120 ms, regardless of the underlying disease. It has been pointed out that fQRS can be a variant of normal[2,3] and is in fact found in 6-10% of apparently healthy individuals.[4,5]

The presence of fat on the epicardial surface of the heart, epicardial adipose tissue (EAT), is normal. However, its volume and/or thickness is increased in coronary patients and in a range of pathological conditions; the volume of EAT is related to the degree of underlying fibrosis.

Current knowledge of the significance of fQRS and of the pathophysiological relevance of EAT suggests that one or other of these factors is associated with the development and severity of coronary artery disease (CAD)[6,7] and the severity of left ventricular dysfunction in patients with dilated cardiomyopathy,[8,9] as well as with the development of rheumatoid arthritis[10,11] and psoriasis.[5,12] As the common denominator in these conditions is myocardial fibrosis associated with the underlying disease, this strongly suggests that there is a link between increased EAT thickness, the resulting development of myocardial fibrosis, and the subsequent occurrence of fQRS, in several other disorders in which there is also a chronic inflammatory state.

In this issue of the *Journal*, the article by Yaman et al.[13] analyzes the presence of EAT and assesses ventricular function in apparently healthy individuals, mostly middle-aged (mean age less than 60 years), divided into two groups, fQRS(+) with fQRS and fQRS(-) without fQRS, based on a routine electrocardiographic (ECG) study. Left ventricular function (systolic and diastolic) was assessed by conventional transthoracic, tissue Doppler and speckle-tracking echocardiography. The authors found that the fQRS(+) group had significantly greater EAT thickness than the control fQRS(-) group. Additionally, their left ventricular diastolic function was relatively impaired, and although ejection fraction was normal and similar in the two groups (around 62%), more detailed study by transthoracic speckle-tracking echocardiography revealed significant differences in global longitudinal strain (GLS) suggestive of impaired systolic function in the fQRS group. Lastly, multivariate analysis showed the number of ECG leads with fQRS to be an independent predictor of increased EAT thickness.

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So far as I am aware, this is the first study to show a direct relationship between increased EAT and fQRS; the association between increased EAT thickness and the number of ECG leads with fQRS was highly significant. Moreover, as fQRS in the absence of ischemic heart disease may be an at least moderately strong marker of myocardial fibrosis, we should perhaps question whether the group with fQRS studied by Yaman et al. can in fact be considered to be healthy.

Examination of the demographic characteristics of the study population reveals no data on how the individuals with fQRS were recruited (duration of the recruitment period, size of the population that underwent ECG screening, and whether or not most individuals were referred or whether specific geographic areas were involved) or on their overall ECG characteristics (there is no mention of mean duration of QRS complexes, P-wave duration and morphology, or mean duration of PQ and QT intervals). There is also no reference to waist circumference, although the fact that the standard deviation of mean body mass index was larger in the fQRS(+) group suggests that, even though overall they were not overweight, since most were male, a significant number of individuals may have had some degree of abdominal obesity. There is also no information on the subjects' blood uric acid levels.

I do not doubt that the mean duration of the QRS complex was greater in the group with fQRS, given the presence of notching. However, it would be interesting to know what percentage had a duration longer than 105 ms (and less than 120 ms), as this would already represent a marked intraventricular conduction disturbance and affected individuals could not strictly be considered free of cardiovascular disease.

Although the presence or onset of complete left bundle branch block is associated with varying but marked deterioration in GLS,[14,15] there are currently no data in the literature on alterations in GLS induced by other types of intraventricular block, such as left fascicular block or forms of parietal block.

Until recently, because of differences in equipment and software, there were no standardized normal values for GLS. The article by Yaman et al. makes no mention of the reference values for healthy adults used in their laboratory or of differences in normal values between genders. However, it is now established that systolic myocardial deformation is stronger in women, with significantly higher GLS values than in men.[16,17] Based on the recent guidelines of the European Association of Cardiovascular Imaging (EACVI),[17] a weighted analysis of the mean GLS values calculated in the fQRS(+) and fQRS(-) groups in Yaman et al.'s study strongly suggests that much of the difference between the groups is attributable to the predominance of men in the fQRS(+) group (57.8%). However, it should also be noted that the standard deviation of the mean GLS values in the fQRS(+) group is clearly larger than in the fQRS(-) group, which means the values in the former group are more heterogeneous and more widely dispersed than in the latter. As a result, while bearing in mind that differences in software and equipment could have affected the results, comparison of the means and standard deviations of each group with the lower limits of normal for each gender proposed by the EACVI[17] suggests that the majority of individuals in the fQRS(-) group would have normal values and a significant number (more than one third) in the fQRS(+) group would have abnormal values, below the newly established lower limits of normal. These low values are not explained by age, since the mean age in both groups was similar (between 55 and 60 years), and although the EACVI reference values were based on a population with a mean age of less than 50 years,[17] and GLS decreases with age, the difference is only apparent after the age of 55.[16]

We therefore have a group of individuals who at first sight appear normal and healthy, but in whom closer analysis shows an association between fQRS and increased EAT thickness (probably combined with varying degrees of myocardial fibrosis), and a significant number with mild abnormalities in left ventricular diastolic and systolic function (although with preserved ejection fraction). What does this mean? Do they have occult CAD, with an undetected initial acute coronary event? Do they have an early, subclinical form of dilated cardiomyopathy or a late preclinical form of hypertrophic cardiomyopathy? Or do they have some other condition at a subclinical stage? Is there a link with degenerative conduction system disease? Or, in fact, are they simply in a gray area, in the hazy transition between what is defined as normal and something that begins to look pathological? If individuals with fQRS are normal, are those without fQRS more normal than others? Or are we actually dealing with a new and previously unrecognized nosological entity?

It is thus clear that individuals in the fQRS(+) group should be thoroughly investigated. Their urate metabolism should be analyzed first of all, as hyperuricemia appears to be an independent risk factor for the development of intraventricular block in patients with degenerative conduction system disease, especially in those with severe CAD.[18] The extent of myocardial fibrosis should then be assessed by cardiac computed tomography or magnetic resonance imaging, and coronary artery angiography (either computed tomography or conventional) should be performed to exclude significant CAD. These individuals should be followed closely for two to five years in order to rule out currently subclinical forms of cardiomyopathy or other rare conditions that can accompany fQRS and increased EAT thickness. It will be important to continue periodic echocardiographic (with Doppler, transthoracic and speckle-tracking echocardiography) and electrocardiographic assessment over the next ten years (considering the mean age of the population) to monitor left ventricular systolic and diastolic function and to screen for the appearance of advanced intraventricular conduction defects.

If all other causes are excluded (and if the alterations described by Yaman et al. are shown to be gradually progressive), what I have suggested can then be confirmed: that we are dealing with a previously unrecognized nosological entity, which I shall call idiopathic lipogenic myocardial fibrosis, which is associated with increased visceral adiposity and may be genetically determined.

A new avenue of clinical research has opened up. Let us see where it leads.

Conflicts of interest

The author has no conflicts of interest to declare.

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