

Iron overload and fragmented QRS in patients with Thalassemia major: Mechanisms, therapies, and new horizons

To the Editor,

We read with great interest the manuscript written by Bayar et al. (1) entitled "Assessment of the relationship between fragmented QRS and cardiac iron overload in patients with beta-thalassemia major," published in the February 2015 issue of the *Anatolian Journal of Cardiology*. In that study, they investigated the relationship between fragmented QRS (fQRS), which is a marker of depolarization abnormality, and the cardiac T2 value in magnetic resonance imaging (MRI) is used as a screening tool to evaluate the cardiac iron load in patients with beta thalassemia major. In this study, significant correlations were found between the presence of fQRS and cardiac iron overload detected by cardiac MRI. Furthermore, the effects of various chelating agents on the cardiac iron overload and the presence of fQRS were also evaluated and remarkable results have been achieved; however, we think that there are some confusing points in this respect. Firstly, in univariate analysis, it was shown in Table 2 that deferoxamine or deferasirox users compared with non-users had a low incidence of cardiac involvement. It could be true for deferasirox (OR 0.38 and $p=0.021$); however, it is not clear whether deferoxamine (OR 2.73 and $p=0.015$) was associated with cardiac involvement or not. Additionally, it was stated that in deferoxamine or deferasirox users, the cardiac iron overload was less than in non-users, and fQRS presence of these patients also were shown to be less in Tables 3 and 4. However, in deferoxamine users, both the cardiac iron overload and fQRS presence were observed more frequently. Another small detail about the results is that the age of the participants should be expressed as "mean" and not as "median."

fQRS represents a conduction delay from inhomogeneous activation of the ventricles due to a myocardial scar and is thought to be associated with ventricular tachyarrhythmias (2). Although this arrhythmic marker has long been evaluated mainly in ischemic etiologies, it has been frequently investigated in non-ischemic cardiac diseases, particularly in systemic diseases associated with cardiac involvement, such as sarcoidosis and rheumatoid arthritis (3, 4). Patchy-like inhomogeneous deposition, localized fibrous replacement, and oxidative mechanisms seem to be responsible for the electrical heterogeneity of the ventricular myocardium (5). Beyond this "iatrogenic iron exposure," toxic heavy metal and their chelation therapies that may have similar effects on myocardium may be considered to be a promising research subject.

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Author's Reply

To the Editor,

We would like to thank the authors for their comments and contributions towards our original research entitled "Assessment of the relationship between the fragmented QRS and cardiac iron overload in Patients with beta-thalassemia major" that was published in the February 2015 issue of the *Anatol J Cardiol* (1). As known, cardiac T2* values measured by cardiac MRI are used for the follow-up of cardiac iron overload in thalassemia major (TM) patients. In our study, 102 patients with TM using the same iron chelators for the last 2 years were enrolled. A significant relationship was found between the cardiac T2* values and the presence of the fragmented QRS complex on the surface electrocardiogram.

Although this was not the primary purpose of our study, the differences with respect to the T2* values and fragmented QRS presence were also assessed according to the use of iron chelators in the subgroup analysis. Thus, as noted by the authors, the univariate analysis in patients treated with deferasirox (OR=0.38; 95% CI 0.17–0.87, $p=0.021$) were lower than that in patients using deferoxamine (OR=2.73, 95% CI 1.2–6.14, $p=0.015$) for cardiac involvement. Similarly, cardiac involvement was detected in 56% of the patients using deferoxamine and 30% of deferasirox users ($p<0.005$). Consistent with these findings, the presence of fragmented QRS was found in 60% of deferoxamine users and 24% of deferasirox users ($p<0.001$). In the univariate analysis, we found that a less frequent presence of fragmented QRS was observed in deferasirox users; there was no significant association with the use of deferoxamine. In the light of these results, it can be thought that in patients with TM using deferasirox, cardiac involvement and the presence of fragmented QRS are less common. However, in our study, the recent T2* values at the time when the patients' electrocardiogram was taken were used. We have no datum of baseline T2* values before the start of the iron chelator regime used by the patients. Therefore, the limited number of our patients in each treatment group as well, both

because of the lack of our baseline T2* values, due to based on our study sub-analysis may not be appropriate to say that the more efficient use of deferasirox therapy.

In the literature, there are studies that have found more effective iron chelators that are available for use in TM patients. In a research conducted by Pather et al. (2), a significant increase of T2* values in deferasirox users was reported in a 18-month follow-up for 19 patients with cardiac iron loading and T2* values of 6–20 ms. Similarly, in the study by Pennel et al. (3), an increase in T2* values were detected with deferasirox in the 3-year follow-up of 71 patients with T2* values of 5–20 ms. In the CORDELIA study that compared the deferoxamine treatment with deferasirox, in deferasirox group, also not reach statistical significance, better results in myocardial iron removal was determined (4). Also, in the study conducted by Pepe et al. (5), the difference between the baseline and follow-up T2* values of 164 TM patients was investigated to study the effectiveness of the iron chelators that were used. According to this research, initially in patients with non-iron load combined treatment with deferiprone+deferoxamine were similar with the use of each drug as monotherapy in terms of the maintenance of normal T2* values. However, in this group of patients, deferiprone monotherapy was found to be superior to monotherapy with deferoxamine and combination therapy in the maintenance of normal left ventricular ejection function. Initially, in patients with iron overload, with respect to the elevation of T2* values, combination therapy has been reported to be similar with deferiprone treatment but superior to treatment with deferoxamine (5). Therefore, knowledge of baseline T2* values are important in the evaluation of drug efficacy. Currently, ongoing large-scale studies will guide our treatment selection.

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Apical transverse motion is associated with speckle-tracking radial dyssynchrony in patients with non-ischemic dilated cardiomyopathy

To the Editor,

We have read with great interest the article in press entitled "Apical transverse motion is associated with speckle-tracking radial dyssynchrony in patients with non-ischemic dilated cardiomyopathy" by Gürel et al. (1), published in the latest issue of *Anatol J Cardiol*. The study demonstrated that the patient's selection for cardiac resynchronization therapy and follow-up of echocardiographic parameters for those who received this therapy is a problem that concerns both echocardiographers and electrophysiologists.

The authors proposed an original comparison of two methods to assess the presence of ventricular dyssynchrony in patients with non-ischemic dilated cardiomyopathy. Mainly, the study population of patients with an ejection fraction below 40% and no evidence of ischemic disease was divided in two groups based on the presence or absence of radial dyssynchrony as assessed by speckle tracking. Speckle-tracking analysis, including global radial and circumferential strain and myocardial rotation, twist and torsion, apical transverse motion analysis, and noting the main direction and amplitude of the curves, were performed. At first glance, it may seem that the small number of patients (n=35) would make the analysis easy, but the authors had to assess a tremendous number of regional strain curves (n=1050). Statistical analysis revealed that even though the two groups were similar regarding clinical characteristics, three out of four parameters reflecting apical transverse motion (ATM loop, ATM4CV, and ATM3CV) were higher in patients with radial dyssynchrony, as well as end-systolic and end-diastolic diameters, while left ventricle torsion and twist were significantly lower for this group. This clearly showed a correlation of these parameters with radial dyssynchrony assessed by speckle-tracking. For distinguishing between patients with and without radial dyssynchrony, the authors found a cut-off value for ATM loop, with a high grade of sensitivity and specificity. It is our belief that such measurements would make the difference between the visual assessments of apical rocking, that is clearly subjective, and a method capable of a precise evaluation for radial dyssynchrony because it has been shown that apical motion is a surrogate parameter comprising information on both regional myocardial function and temporal inhomogeneities of myocardial contraction. In this perspective, a relation between ATM and the extent and location of myocardial scar tissue may be expected (2), making possible the evaluation of patients with ischemic dilated cardiomyopathy also. Although in the present study the follow-up of patients could not be performed, we think that along with other methods capable of detecting not only intraventricular dyssynchrony but also disturbed atrioventricular coupling and interactions between the right and left ventricle (3), assessing ATM may be a useful tool in selecting candidates for CRT as well as in device optimization using echocardiographic methods.

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