



## A step forward parameter for the effects of transcatheter aortic valve implantation: transmural dispersion of repolarization

Mehmet Tezcan<sup>1</sup>, Ömer Yiğiner<sup>2</sup>, Mehmet Doğan<sup>2</sup>, Gökhan Değirmencioğlu<sup>2</sup>

<sup>1</sup>Department of Cardiology, Gumussuyu Military Hospital, Beyoglu, Istanbul, Turkey

<sup>2</sup>Department of Cardiology, Gulhane Military Medical Academy Haydarpasa Hospital, Istanbul, Turkey. Email: drmehmettezcan@gmail.com (Tezcan M)

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### To the Editor

We read the article “Effect of transcatheter aortic valve implantation on QT dispersion in patients with aortic stenosis” by Erkan, *et al.*<sup>[1]</sup> with great interest. In this study, they investigated the effect of transcatheter aortic valve implantation (TAVI) on QT dispersion (QTd) in patients with symptomatic severe aortic stenosis. They reported that left ventricular mass index (LVMI) and associated QTd were both reduced by the TAVI procedure. Given the correlation of QTd with the incidence of ventricular tachyarrhythmias and sudden death, it was concluded that the TAVI procedure might have potential beneficial effects on reducing such arrhythmias beyond relieving symptoms of these patients.

As mentioned by authors, it has long been known that QTd reflects inhomogeneity of ventricular repolarization which serves as a prognostic tool in the detection of future ventricular tachyarrhythmias and sudden death.<sup>[2–4]</sup> This electrical instability can be measured in the electrophysiologic laboratory via monophasic action potential mapping method.<sup>[5]</sup> Meanwhile, QTd is the most frequently used non-invasive method to reveal electrical regional heterogeneity of the myocardium. However, in the literature, there are varying results due to the technical limitations of QT interval (QTI) measurement.<sup>[6]</sup> The reproducibility of QTI measurements is low both in manual and automatic measurement techniques.<sup>[5,6]</sup> Moreover, in manual measurements, inter- and intra-observer variability of QTd is very high.<sup>[6]</sup> In this study, the measurements have been performed by two independent cardiologists manually, without transferring the data to the digital platform. Additionally, standard 12-lead ECG recordings were done with a paper speed of 25 mm/ms. In order to obtain more accurate data, the measurements were recommended to be performed in digital platform.<sup>[5,6]</sup> Also, the accuracy of the measurements could be increased

by recording the ECGs with the paper speed of 50 mm/ms and amplitude of 20 mm/mV. Determination of the end of the T wave is one of the technical challenges of the QTI measurements.<sup>[7]</sup> Tangential, differential threshold and visual methods may be used to determine the end of the T-wave.<sup>[7]</sup> Despite all efforts, the end of the T-wave can't be determined in some leads and the number of measurable leads in the standard ECG have been shown to influence the range of QTI durations. As the number of the leads in which QTI can't be measured increases, accuracy of the QTd decreases. In order to overcome this limitation, different methods (standard deviation of the QTI, relative QTd, adjusted QTd) have been proposed by some investigators instead of QTd.<sup>[6]</sup>

In order to quantify the inhomogeneity of the myocardium, in addition to QTd, transmural dispersion of repolarization (TDR) was introduced as an index of arrhythmogenesis in the beginning of the 2000's.<sup>[8]</sup> Isolated cells from different layers of the myocardium exhibited that myocardium comprise of 3 distinct myocyte types- namely, endocardial, epicardial, and midmyocardial M cells.<sup>[9]</sup> Despite the fact that these myocytes are morphologically similar, they exhibit different electrophysiological characteristics. Midmyocardial M cells have typically the longest action potential duration. Furthermore, when myocardium is exposed to the conditions prolonging repolarization phase such as agents or bradycardia, action potential duration of the M cells are more prolonged than the other cell types.<sup>[9]</sup> This electrical heterogeneity seems to be caused by varying responses of the distinct cell types in the different myocardial layers. ECG may reflect these discrepancies. While repolarization phase of the epicardial region ends at the peak of the T-wave, repolarization phase of the M cells continues until the end of the T wave.<sup>[9]</sup> Therefore, the time between the peak and end of the T wave is entitled as Tp-e interval, as an index of

TDR. Additionally, Tp-e/QT ratio has also been used as an index of TDR. The role of TDR in the prediction of life treating arrhythmic events has been demonstrated in the Brugada, short QT and long QT syndromes, as well as in acute ST-elevation myocardial infarction.<sup>[9]</sup> Previously, we showed that TDR was increased in patients with obstructive sleep apnea and chronic arsenic exposure via drinking water.<sup>[10,11]</sup> Additionally, increased TDR has also been demonstrated in subjects with hypertension, obesity and in animal models of ventricular hypertrophy.<sup>[12-14]</sup>

In this study, the authors put forward the effect of TAVI on QTd to be due to the reduction of LVMI. Microvascular dysfunction and myocardial interstitial fibrosis were discussed as responsible abnormalities in left ventricular hypertrophy causing impaired repolarization and inhomogeneity of intraventricular conduction. In the light of above mentioned explanations, different electrophysiological characteristics of myocyte cell types in the different myocardial layers should be taken into account. Thus, it would be wise adding the transmural dispersion data to the study which would completely reveal the effect of TAVI procedure on electrical heterogeneity of the myocardium.

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## Authors' reply

We have recently reported a potential beneficial effect of transcatheter aortic valve implantation (TAVI) on reducing ventricular arrhythmias beyond relieving symptoms in patients with symptomatic severe aortic stenosis.<sup>[1]</sup> Basically, we showed a reduction in myocardial repolarization dispersion evaluated by QT dispersion (QTd) after TAVI in this population.

QTd is the most frequently used non-invasive method to assess the myocardial repolarization abnormalities in many diseases in literature. It has been well known that QTd may provide prognostic data for future ventricular tachyarrhyth-

mias and sudden death.<sup>[2-4]</sup> However, 'achilles heel' of this method is the reproducibility of QTd measurements. In general, it is low in both manual and automatic measurement techniques and inter- and intraobserver variability is especially high in manual measurements of QTd.<sup>[5,6]</sup> This situation was chiefly caused by using insufficient quality of electrocardiography (ECG) samples to measurement of QTd. Such ECG's do not reflect the end of T wave with sufficient certainty. Therefore, using the appropriate ECG samples is essential to obtain the reliable data on myocardial dispersion abnormalities by QTd. In our study, we used only ECG

samples which have high quality. And, we believe that our results are reliable and have future perspectives on the effects of TAVI beyond relieving symptoms in patients with symptomatic severe aortic stenosis.

On the other hand, the notion of ‘transmural dispersion’ has emerged in early last decade and has led to a new perception on the understanding of myocardial repolarization. According to this model, it has been accepted that three layer of myocardium including endocardium, epicardium and mid myocardial M cells have different electrophysiological features which represents a repolarization heterogeneity in basal situation.<sup>[7]</sup> Conditions affecting the myocardial repolarization such as heart rate, blood electrolyte status and drugs have a different effects on these myocardial layers which can increase the basal repolarization heterogeneity and can cause ventricular arrhythmia. On ECG, the peak of T-wave represents the epicardial repolarization while the end of T-wave suggests the repolarization of midmyocardial M-cells. The time between the peak and end of the T wave is called ‘Tp-e interval’ and its ratio with QTd (Tp-e/QTd) were defined as indexes of transmural dispersion of repolarization which can predict life treating arrhythmias in different populations.<sup>[8,9]</sup>

We evaluated the Tp-e interval and Tp-e/QTd ratio on ECG of patients in our study group to comply with the author's suggestions. Both Tp-e interval and Tp-e/QTd ratio were significantly reduced after TAVI procedure in patients with severe aortic stenosis ( $80.1 \pm 3.5$  vs.  $78.5 \pm 2.6$  ms;  $P = 0.008$  and  $0.20 \pm 0.1$  vs.  $0.19 \pm 0.1$ ;  $P = 0.001$ , respectively). We agree with the authors that the results might be useful to

completely reveal of effect of TAVI procedure on electrical heterogeneity of the myocardium.

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