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Does pulmonary vein isolation prolong QT interval?

We read with great interest the article by Hermans *et al.*,¹ titled 'Pulmonary vein isolation in a real-world population does not influence QTc interval', where an automated measurement algorithm was used to analyse 12-lead electrocardiograms (ECGs) in a cohort of patients with atrial fibrillation taking antiarrhythmic drugs and the conclusion that pulmonary vein isolation (PVI) has no effect on QT or QTc.

Hermans *et al.*² used an automated algorithm, which provides a reliable QT-interval assessment compared to the manual measurement for long QT syndrome (LQTS). They found no significant prolongation of QTc after PVI, except Bazett's correction QTc at 1-day post-PVI, and concluded that there is no need to intensify post-PVI QT-interval monitoring. These findings are not consistent with our previous findings.³ In addition to differences in measurement methods and inclusion criteria (automatic or manual measurement, inclusion of patients taking antiarrhythmic drugs), the raw QT and RR intervals tended to be longer in this study compared to ours (baseline raw QT: 417 ± 36 ms vs. 392 ± 31 ms; Day 1 raw QT: 399 ± 37 ms vs. 376 ± 34 ms; baseline RR interval: 1025 ± 164 ms vs. 946 ± 158 ms; Day 1 RR interval: 870 ± 141 ms vs. 749 ± 128 ms, respectively). These differences may be explained by the use of antiarrhythmic drugs and different measurement methods, and it is possible that small QTc changes could not be detected in formulas other than Bazett's.

LQTS experts advocate for manual measurements because automated computer analysis of the ECG sometimes fails to identify LQTS.⁴ On the other hand, manual measurements are time and labour-intensive and not suitable for analysing a large number of cases. There is also risk of intra- and inter-measurement errors, especially in borderline cases.

Recently, the usefulness of heart rate-corrected QT interval assessment using artificial intelligence has also been reported.⁵ It would be desirable to establish and widely use a standardized algorithm for QTc assessment using automated measurements. Further studies with large number of patients, many time courses, and novel algorithms without bias from

antiarrhythmic drugs are needed to clarify whether PVI prolongs QTc.

Conflict of interest: none declared

References

1. Hermans BJM, Zink MD, Van Rosmalen F, Crijns HJGM, Vernooij K, Postema P *et al.* Pulmonary vein isolation in a real-world population does not influence QTc interval. *Europace* 2021;**23**:i48–i54.
2. Hermans BJM, Vink AS, Bennis FC, Filippini LH, Meijborg VMF, Wilde AAM *et al.* The development and validation of an easy to use automatic QT-interval algorithm. *PLoS One* 2017;**12**:e0184352.
3. Estes NA 3rd. Computerized interpretation of ECGs: supplement not a substitute. *Circ Arrhythm Electrophysiol* 2013;**6**:2–4.
4. Chikata A, Kato T, Usuda K, Fujita S, Maruyama M, Otowa KI *et al.* Prolongation of QT interval after pulmonary vein isolation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2020;**31**:2371–9.
5. Giudicessi JR, Schram M, Bos JM, Galloway CD, Shreibati JB, Johnson PW *et al.* Artificial intelligence-enabled assessment of the heart rate corrected QT interval using a mobile electrocardiogram device. *Circulation* 2021;**143**:1274–86.

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Does pulmonary vein isolation prolong QT-interval?— Authors' reply

We would like to thank you for the opportunity to respond to the issues raised in Dr Chikata's letter titled 'Does pulmonary vein isolation prolong QT-interval'.¹ In their letter to the editor, they raise three concerns regarding our study² which we will further discuss in this response: (1) the use of an automated algorithm to measure the QT-interval; (2) the use of antiarrhythmic drugs (AAD) in our study population, and (3) the heart rate correction methods for QT-intervals.¹

- (1) Indeed, long QT syndrome experts have advocated manual QT-interval assessment

because of erroneous QT-interval measurements determined by available algorithms. This was the reason why we developed and validated our own QT-interval algorithm which was also used in this study. We validated our algorithm by comparing the QT-intervals with the mean QT-interval measured by three independent observers.³ This resulted in an intra-class coefficient of 0.981 and a mean difference in a Bland–Altman analysis of –0.38 ms with limits of agreement of –25.41:24.65 ms. The inter-observer variability of the three observers showed very similar results. Based on these results we concluded that our algorithm is as accurate in determining QT-intervals as manual observers are and, hence, we believe that the use of our algorithm to study QT-interval changes after pulmonary vein isolation (PVI) is justified and that the use of our methodology does not explain differences in raw RR- and QT-interval between their and our study.

- (2) We do agree with Dr Chikata *et al.* that AAD might affect both the RR- and QT-interval in our study and could be an explanation for the differences in raw RR- and QT-intervals between their and our study. However, as we already mentioned in the discussion of our original paper,² we believe that our study population better reflects the real-world population of patients undergoing pulmonary vein isolation since these patients are frequently treated with AAD before ablation. Therefore, we believe we induce a bias if we would only include patients without AAD.
- (3) Finally, Dr Chikata *et al.*¹ suggest that Bazett's formula is superior in detecting small QTc changes. In our opinion, however, our reported QTc prolongation 1 day after PVI when using Bazett's formula is most likely caused by the well-known over- and underestimation of QTc at RR <1000 ms and >1000 ms, respectively.⁴ Furthermore, we would like to highlight that in the original paper by Chikata *et al.*⁵ the average QTc Bazett increased only mildly from 404.9 ± 25.2 ms at baseline to 420.1 ± 21.8 ms at 3 months post-PVI. Therefore, although the increase in QTc Bazett was significant, this does not automatically imply it is clinically relevant since the average QTc Bazett remains well within the normal range.

Recently, Chikata *et al.*⁶ published an interesting case report of Torsade de Pointes due to QT prolongation after PVI. Clearly, we have different

experiences and therefore endorse their¹ suggestion to perform multi-centre studies with large number of patients and many time courses to clarify the influence of PVI on the QT-interval. However, we do not agree that only patients off antiarrhythmic drugs should be included but think the inclusion criteria should meet daily practice.

Conflict of interest: none declared.

References

- Chikata A, Kato T, Usuda K, Hayashi K, Takamura M. Does pulmonary vein isolation prolong QT interval? *Europace* 2021;**23**:2046.
- Hermans BJM, Zink MD, van Rosmalen F, Crijns HJGM, Vernoooy K, Postema P et al. Pulmonary vein isolation in a real-world population does not influence QTc interval. *Europace* 2021;**23**:i48–i54.
- Hermans BJM, Vink AS, Bennis FC, Filippini LH, Meijborg VMF, Wilde AAM et al. The development and validation of an easy to use automatic QT-interval algorithm. *PLoS One* 2017;**12**:e0184352.
- Vandenberk B, Vandaal E, Robyns T, Vandenbergh J, Maruyama M et al. Prolongation of QT interval after pulmonary vein isolation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2020;**31**:2371–9.
- Chikata A, Kato T, Usuda K, Fujita S, Maruyama M, Otowa KI et al. Prolongation of QT interval after pulmonary vein isolation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2020;**31**:2371–9.
- Chikata A, Kato T, Usuda K, Fujita S, Otowa KI, Maruyama M et al. Torsade de pointes due to QT prolongation after pulmonary vein isolation for persistent atrial fibrillation. *Intern Med* 2021. doi: 10.2169/INTERNALMEDICINE.6627-20.

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Corrected QT interval prolongation after ganglionated plexus ablation: myth or reality?

We read the article with a great interest by Hermans et al.¹ published recently in *Europace* Journal entitled ‘Pulmonary vein isolation in a real-world population does not influence QTc interval’. In this study, the authors evaluated whether routine pulmonary vein isolation (PVI) induces significant corrected QT interval (QTc) changes. Twelve-lead electrocardiograms were recorded at hospital’s admission (T – 1d), 1 day after the PVI-procedure (T + 1d) and at 3 months post-procedure (T + 3m). QTc was calculated using Bazett’s, Fridericia’s, Framingham’s, and Hodges’ formulas. There was no statistically significant within-subject difference in QTc Fridericia, QTc Hodges, and QTc Framingham between the recordings. QTc Bazett was significantly prolonged at T + 1d but recovered at T + 3m.

In a recently published study, Chikata et al.² found that both QTc Fridericia and QTc Bazett are significantly prolonged after PVI. An unintentional modulation of the atrial ganglionated plexuses (GPs) during PVI has been suggested as the possible explanation for this QTc prolongation by the authors. On contrary to this hypothesis, we found significant and durable shortening of QTc after GP ablation in patients with normal QTc range and long QT syndrome.^{3,4} A similar QTc shortening effect was confirmed after GP ablation plus PVI in our following work.⁵ Shortening of QTc was attributed to the additional sympathetic effect of GP ablation.

Although earlier reports suggested that only the second parasympathetic neurons exist in the GPs, it is well known that epicardial ganglia contain both efferent parasympathetic and sympathetic neuronal somata and presumably local circuit neurons/interneurons.^{3–5} Considering a similar distribution of sympathetic innervation, the achievement of similar and durable denervation on the sympathetic system might be possible after GP ablation. The difference between our experience and prior data may have several explanations. In our current approach, GPs were ablated with bi-atrial ablation approach. Considering the largest number of epicardial ganglia demonstrated intramural clustering between right and left atrial structures, this anatomy may enable bi-atrial endocardial GP ablation to eliminate a significant number of post-ganglionic sympathetic neurons

rather than PVI or surgical GP ablation. Whilst it is possible to access substantial part of epicardial ganglia solely through the left atrium, to prevent re-innervation as has been described for the sympathetic fibres after cardiac transplantation, comprehensive coverage may be more likely through bi-atrial ablation. QTc effects of PVI vs. GP ablation plus PVI have not been studied, yet. We therefore cannot conclude how PVI only strategy modulates GPs. We can, however, conclude that GP ablation cannot be associated with QTc prolongation.

Conflict of interest: none declared.

References

- Hermans BJM, Zink MD, Van Rosmalen F, Crijns HJGM, Vernoooy K, Postema P et al. Pulmonary vein isolation in a real-world population does not influence QTc interval. *Europace* 2021;**23**:48–54.
- Chikata A, Kato T, Usuda K, Fujita S, Maruyama M, Ichi OK et al. Prolongation of QT interval after pulmonary vein isolation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2020;**31**:2371–9.
- Aksu T, Guler TE, Bozyel S, Yalin K, Lakkireddy D et al. Medium-term results of cardioneuroablation for clinical bradyarrhythmias and vasovagal syncope: effects on QT interval and heart rate. *J Interv Card Electrophysiol* 2021;**60**:57–68.
- Aksu T, Guler TE, Bozyel S, Yalin K, Gopinathannair R. Potential therapeutic effects of electrogram-guided cardioneuroablation in long QT syndrome: case series. *J Interv Card Electrophysiol*. 2020; doi:10.1007/s10840-020-00831-w.
- Aksu T, Bozyel S, Yalin K, Tanboga IH, Gopinathannair R. QTc shortening effect of ganglionated plexi ablation. *J Cardiovasc Electrophysiol* 2021;**32**:1161–5.

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Corrected QT interval prolongation after ganglionated plexus ablation: myth or reality?—Authors’ reply

We thank Prof. Aksu for this valuable and well-balanced discussion on the possible effect of ablation of atrial ganglionated plexuses (GPs) on the QT interval.¹ Their comments are in line with our statement that from our study² we neither can conclude that pulmonary vein isolation (PVI) does not modulate GP nor that GP modulation leads to changes in QTc. We can, however, conclude