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Diagnosing Long-QT Syndrome, Simple but not easy

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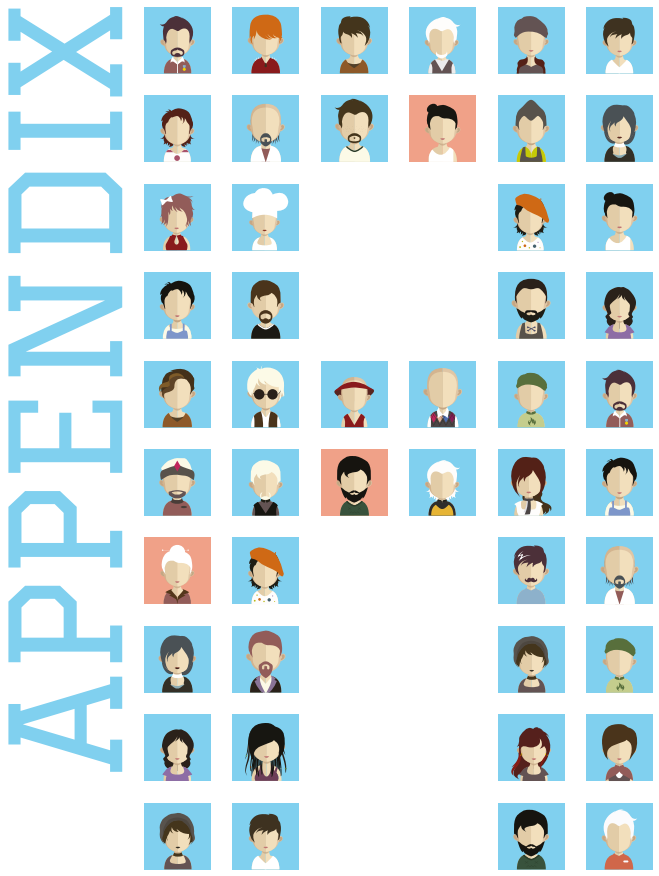

APPENDIX A

SUMMARY

The congenital long-QT syndrome (LQTS) is an inherited condition in which the ventricular cardiac action potential can be prolonged due to an altered repolarization. The underlying mechanism of the altered repolarization is a mutation in genes encoding ventricular ion channels involved in the repolarization phase of the action potential. The prolonged action potential duration and altered repolarization is typically characterized by an increased QT-interval and/or an abnormal T-wave morphology on the electrocardiogram (ECG). LQTS patients have an increased risk on potentially lethal ventricular arrhythmias such as Torsades de Pointes. An early diagnosis is crucial since current treatments are well able to reduce the risk on a cardiac event.

Since LQTS owes its name to a prolonged QT-interval, it seems obvious to diagnose LQTS based on the QT-interval. However, diagnosing LQTS solely based on the QT-interval comes with serious limitations. First of all, manual assessment of the QT-interval is subjective and may lead to erroneous measurements. Besides that, two often used methods to manually measure the QT-interval (the threshold and tangent method) result in different QT-intervals while all maintaining the same cut-off for a prolonged QT-interval. The sensitivity and specificity for the currently used cut-offs therefore differ per method. Secondly, an existing considerable overlap in QT-intervals at rest between LQTS patients and healthy individuals hampers the diagnosis of LQTS. Therefore, the diagnostic accuracy of a QT-interval driven diagnosis is poor.

Apart from the diagnostic limitations of the QT-interval, DNA testing for known LQTS mutations also has limitations. Other (unknown) genetic factors like mutations or variants distinct from the LQTS mutation can influence the expression of the LQTS mutation or affect the repolarization via other pathways. As a result, approximately 20% of phenotype-positive LQTS patients remain genetically elusive whereas on the other hand, genotype-positive LQTS patients can be phenotype-negative. Therefore, classification and reporting of potentially malign genetic variants might currently be incomplete and misleading.

In this thesis we addressed several of the above-mentioned limitations to improve the diagnosis of LQTS.

In **Chapter 2**, we developed and validated a QT-interval algorithm robust to heart axis orientation and T-wave morphology that can be applied on a beat-to-beat basis. The algorithm not only uses the standard 12 ECG leads, but also a root mean square, standard deviation and vectorcardiogram to measure the QT-interval from. Whereas the QRS-onset is taken from the root mean square, the end of the T-wave is defined per individual lead and per reconstructed scalar ECG leads by an automated tangent approach. The median of all T-wave ends is finally used as the general T-wave end for the particular complex. To validate the algorithm, QT-intervals measured using the algorithm were compared with the QT-intervals manually measured by three observers. Measuring errors between our algorithm and manual measurements were similar or even smaller than inter-observer measuring errors and therefore we concluded that the algorithm was a good objective alternative for manual QT-interval measurements.

In **Chapter 3** we investigated whether genotype-negative individuals from LQTS families have a prolonged QT-interval with respect to healthy controls. We hypothesized that, due to modifier genes, there would be a graded increase in QTc from shortest in healthy non-family members, intermediate in genotype-negative individuals from LQTS families and finally longest in genotype-positive LQTS patients. To study this hypothesis, we applied our QT-interval algorithm as described in chapter 2 to standard 10-second twelve-lead ECGs obtained from healthy subjects, genotype-negative individuals from LQTS families

and genotype-positive LQTS patients. A multilevel linear regression analysis with QTc as the dependent variable and sex, age, and LQTS-family vs no-family and LQTS vs no-LQTS as independent variables showed that there was no difference between genotype-negative individuals from LQTS families and healthy control subjects.

In **Chapters 4 and 5** we studied the brisk standing test that has been presented as a promising bed-side provocation test that could aid in the diagnosis of LQTS. The so far promising results of the brisk standing test rely on manually assessed QT-intervals of several predefined complexes. In Chapters 4 and 5 we examine the diagnostic value of the QT-intervals of these complexes as well as the dynamic behaviour of the QT-intervals of all complexes in adult (Chapter 4) and paediatric (Chapter 5) LQTS patients and controls. For both the adult and the paediatric cohort, the brisk standing provocation did not result in a better classification of LQTS patients. The diagnostic accuracy of QT-intervals measured during provocation did not significantly improve compared to the diagnostic accuracy of QT-intervals during baseline (i.e. QT-intervals at rest). The reasons why our results differ from previous studies remain unknown. Assuming that the analysis protocol and the use of our QT-interval instead of manual assessment of the QT-interval did not cause these differences, inequalities in our cohort compared with the previously used cohorts might explain the differences. The data used in our study is more a reflection of a 'real-world-population' than the data used in the previous studies. For example, the control groups of the previous studies largely consisted of healthy volunteers whereas we included patients suspect for LQTS as controls.

Apart from a prolongation of the QT-interval, T-wave morphology variations are also seen in LQTS patients. In **Chapters 6 and 7** we investigate the added value of T-wave morphology markers obtained from standard 10-second 12-lead ECGs in the diagnosis of LQTS. In Chapter 6 we trained and tested two models: a baseline model with age, sex, heart rate, QT-interval and QT-interval corrected for heart rate (QTc) as inputs and an extended model including several known T-wave morphology-features next to the baseline model parameters. The extended model resulted in a major rise in sensitivity and specificity compared to the baseline model. From this, we concluded that T-wave morphology does have an added value in the diagnosis of LQTS. Although the model described in Chapter 6 already increased the diagnostic accuracy, a downside of the morphology features used in this chapter is that they describe altered LQTS T-wave morphology characteristics known so far. Unrecognized altered LQTS T-wave morphology characteristics might therefore not lead to an abnormal morphology characterisation. Therefore, in Chapter 7 we developed an objective method to characterize T-wave morphology based on Hermite-Gauss polynomials. The diagnostic accuracy was again compared with a baseline model containing age, sex and QT-intervals. The extended model again had a better overall accuracy compared to the baseline model and could, based on the T-wave morphology characterization and in contrast to the baseline model, also accurately diagnose LQTS patients with a QTc down to 400ms.

Other pathologies or treatments can also lead to a prolonged QT-interval. In **Chapters 8 and 9** we studied two interventions that might lead to a prolonged QT-interval. In Chapter 8 we studied the effect of a pulmonary vein isolation (PVI) on QTc. PVI has become the cornerstone treatment for atrial fibrillation but unintentional modulation of the ganglionated plexi by PVI might affect ventricular electrophysiology. Recently, an experimental study in canine hearts showed an increased ventricular action potential duration after ablating the ganglionated plexi. To investigate whether PVI induces a prolongation of QTc, we compared QTc's obtained one day before, one day after and three months after PVI in 279 patients. No statistically significant within-subject difference in QTc was found between the recordings indicating that PVI on average does not prolong QTc. Whether this is because a standard PVI does not modulate the ganglionated plexi (enough) or whether the gaglionated plexi modulation does not prolong QTc cannot be concluded from this study. In Chapter 9 we study the effect of various calcium concentrations in dialysates on the QT-interval. A low dialysate calcium concentration may positively affect the calcification tendency in serum of haemodialysis patients. However, calcium is an important electrolyte in the repolarization of cardiac myocytes and a lower calcium concentration in the dialysate, and subsequently in the blood, might lead to a prolonged cardiac action potential and thus a prolonged QT-interval. In Chapter 9 we analysed ECGs recorded in a four-week multicentre randomized cross-over trial in which 13 patients received different dialysates during their thrice weekly haemodialysis sessions. The results of this study showed that QTc significantly increases during haemodialysis session with an acetic-acid dialysate with calcium concentration of 1.25mmol/L and a citric-acid dialysate with a calcium concentration of 1.50mmol/L whereas the QTc did not significantly increase during sessions with an acetic-acid dialysate with a calcium concentration of 1.50mmol/L. Benefits of the lower calcium concentration might therefore not be worthy in all haemodialysis patients and, hence, dialysate concentrations should be personalized for each patient.

In **Chapter 10**, all findings of the various chapters as well as all currently known limitations of the diagnosis of LQTS were put into broader perspective. The main conclusions of this thesis that could improve LQTS diagnostics are:

- The automatic QT-interval algorithm described in **Chapter 2** is as accurate as instructed manual observers are.
- QT-intervals at rest do not differ between healthy subjects and genotype-negative individuals from LQTS families (**Chapter 3**).
- Contradictory with earlier studies, we could not replicate earlier documented added diagnostic value of brisk standing tests for the diagnosis of LQTS in an adult and paediatric cohort (**Chapter 4 and 5**)
- T-wave morphology contains additional diagnostic information that can be useful to diagnose LQTS. (**Chapter 6 and 7**)
- Pulmonary vein isolation, on average, does not induce a prolongation of QTc (**Chapter 8**)
- QTc significantly increases during haemodialysis with an acetic-acid dialysate with calcium concentration of 1.25mmol/L as well as with a citric-acid dialysate with a calcium concentration of 1.50mmol/L (**Chapter 9**)