

# Vectorcardiographic evaluation of ventricular repolarization in healthy individuals and LQTS mutation carriers

Akademisk avhandling

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Av

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Avhandlingen baseras på följande delarbeten:

I. Vahedi F, Haney MF, Jensen SM, Näslund U, Bergfeldt L: **Effect of heart rate on ventricular repolarization in healthy individuals applying vectorcardiographic T vector and T vector loop analysis.** Ann Noninvasive Electrocardiol. 2011; 16:287-294.

II. Vahedi F, Odenstedt J, Hartford M, Gilljam T, Bergfeldt L: **Vectorcardiography analysis of the repolarization response to pharmacologically induced autonomic nervous system modulation in healthy subjects.** J Appl Physiol 2012; 113:368-76.

III. Diamant UB\*, Vahedi F\*, Winbo A, Rydberg A, Stattin EL, Jensen SM, Bergfeldt L: **Electrophysiological Phenotype in the LQTS Mutations Y111C and R518X in the KCNQ1 Gene.** In manuscript

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IV. Vahedi F, Diamant UB, Lundahl G, Bergqvist G, Gransberg L, Jensen SM, Bergfeldt L: **Instability of repolarization in LQTS mutation carriers compared to healthy control subjects assessed by vectorcardiography.** Heart Rhythm 2013; 10:1169–1175.



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## Abstract

Ventricular arrhythmia is a well-known cause of syncopal attacks and sudden cardiac death in humans. Ventricular repolarization (VR) is the most unstable phase in cardiac electrical activity and its regulation depends on the coordinated activity in multiple ion channels. Several physiological factors such as heart rate (HR), autonomic nervous system (ANS) activity, gender and age influence the function of these ion channels. Meanwhile there are some genetic disorders e.g. the long QT syndrome (LQTS), which by changing (increase or decrease) the function of the ion channels can cause an imbalance in ion currents and subsequently increase the propensity for ventricular arrhythmias. Evaluation of VR in response to both physiological and pathophysiological factors is of great importance for understanding the mechanism of ventricular arrhythmias. Vectorcardiography (VCG) as a noninvasive tool in evaluation of global VR has proven superior to scalar ECG and, therefore, been used in this project.

### Aims

To apply VCG as a noninvasive tool in VR analysis in order to:

1. Evaluate the influences of important physiological determinants for VR such as increase in HR, pharmacological modulations of ANS activity, and gender in healthy individuals.
2. Study the phenotypes in carriers of two common LQT1 mutations (R518X and Y111C in the *KCNQ1* gene) with biophysically different properties and also compare the LQT1 mutation carriers with age and sex matched healthy control subjects as well as with a group of LQT2 mutation carriers.
3. Evaluate VR instability by calculating the beat to beat variability of VR measures in groups of LQTS mutation carriers and compare them with age and sex matched healthy control subjects.

### Results and Conclusions

1. In healthy individuals the pure HR increase by atrial pacing decreased the heterogeneity of action potential (AP) morphology and VR, while similar increase in HR by  $\beta$ -adrenoceptor stimulation or vagal withdrawal had different effects on VR and resulted in changes that could increase arrhythmia risk.
2. At supine rest there was a modest but significant difference in QTcB but otherwise no difference in VR measures between carriers of two LQT1 mutations with in vitro different biophysical effects on potassium channel function.
3. There were no signs of increased VR dispersion in LQT1 and LQT2 mutation carriers at rest. In fact, there was an inverse relation between QTcB and measures of global heterogeneity of AP morphology and VR in both controls and LQT mutation carriers.
4. Although LQTS mutation carriers did not show any sign of increased heterogeneity of VR at rest compared to healthy controls, they had higher instability of VR duration and heterogeneity at beat to beat analysis. A greater instability of most aspects of VR already at rest thus seems to be a salient feature in both LQT1 and LQT2, which might pave the way for afterdepolarizations and ventricular arrhythmias.

**Keywords:** Vectorcardiography; Repolarization; T-wave vector; Tarea;  $T_{\text{peak-end}}$ ; Ventricular gradient; Short-term variability;  $\beta$ -adrenoceptors; Long QT syndrome.