

# Ventricular arrhythmogenesis in the genetically-susceptible heart

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## VALORIZATION

The insights obtained in this thesis are highly suitable for valorization and will be described in three parts: EMW, Worm study, HeArt project.

### **SOCIO-ECONOMIC RELEVANCE**

Sudden cardiac death claims almost a million deaths annually in Western Europe and the United States. It accounts for one fifth of all natural deaths and up to 50% of all cardiovascular deaths.<sup>2, 3</sup> In the Netherlands, out-of-hospital SCD occurs with a yearly incidence of approximately 1 per 1,000 individuals,<sup>5</sup> with ~15 fatal cases per week in Limburg.<sup>6</sup> The most common cause of SCD is ventricular fibrillation secondary to acute coronary ischemia. Inherited primary electrical arrhythmia syndromes account for 5-10% of VF cases and occur often, but not exclusively, in the young.<sup>10</sup> In <5% of VF cases no cardiac structural or electrical abnormalities can be ascertained. It remains a challenge to adequately address the risk of apparently healthy, but genetically-susceptible, subjects for developing such life-threatening ventricular arrhythmias. It goes without saying that SCD imposes a substantial socio-economic burden, next to the devastating psychosocial impact on survivors of SCA and affected family members.

### **ELECTROMECHANICAL WINDOW**

First, risk stratification in patients with the long-QT syndrome traditionally relies on the determination of the QTc, besides assessing the occurrence of previous syncopal or arrhythmic events. It is well-known that the ubiquitously applied Bazett's formula to correct QT for the heart rate is less reliable at the higher or lower ends of cardiac cycle lengths. As is discussed in this PhD thesis, the noninvasive evaluation of the relation between the duration of the electrical and mechanical systole, notably the electromechanical window, is an easy-to-obtain parameter that improves risk stratification beyond QTc in patients with inherited repolarization defects. The EMW is not significantly affected by heart-rate variations.<sup>113</sup> Improved risk assessment will (re)classify LQTS patients in either low or high risk categories, leading to reduced overtreatment of medium-to-low-risk subjects, for example by reducing prophylactic pharmacological or interventional treatment, but it may also justify a more aggressive approach in EMW-based high-risk patients. In the former, subjects may be reassured, need less intensive follow-up and will not be subjected to unnecessary therapies, whereas in the latter intensified follow-up will result in psychological reassurance and, ideally, reduced mortality. In both circumstances, socio-economic and psychosocial benefit is evident. Clinicians or technicians can easily perform EMW measurements during a standard echocardiogram at relatively low cost.



### **WORM STUDY**

Secondly, through genealogical investigation the Worm study has identified a large familial population at increased risk of SCD in South Limburg and North Rhine-Westphalia. The total number of related individuals approaches 10,000. The striking phenotypic heterogeneity within mutation carriers and the genotype-negative phenotype-positive family members indicate the effect of modifier genes besides the familial SCN5A deletion, which has triggered in-depth genetic analyses. These genetic modifiers may have a nontrivial allelic frequency in the “general population”, and may add to the risk of SCD in non-related patients, for instance in the setting of acquired heart disease. As such, the potential outreach of our family-based results can be large. Future genetic risk profiling could identify patients with an increased arrhythmic risk, advocating more stringent cardiovascular risk management and lifestyle amendments. Furthermore, by cardiogenetic scrutiny we uncovered p.(Phe1617del)-specific arrhythmia patterns reminiscent of LQT1-/LQT2-like behavior with sympathetic (often auditory) triggering. This has led to mutation-specific patient counseling and therapy, aiming to reduce sympathetic triggering. The p.(Phe1617del)-related female proarrhythmic proclivity was surprising, but it primed increased clinical vigilance towards mutation-carrying women by initiating preventive antiarrhythmic measures at an earlier age.

### **HEART PROJECT**

Thirdly, we describe the synergy between art and science. Besides personal satisfaction for the artist or scientist, this venture may serve as an inspiring example for future academic entrepreneurs, clinicians, and patients. We are faced with an increasingly shallow patient-doctor relationship, as the current trend of health-care organizations is to constrain patient-doctor time slots, for financial reasons. Despite the availability of sophisticated communication tools, doctors often fail to be good conversationalists. High-standard patient care anno 2020 mandates careful communication with a clear definition of the patient’s expectations, knowledge sharing, advising on test results and treatment options, and shared-decision making. Art can facilitate this communicative process by stimulating empathy, insight, creativity and shift in motivation.

### **TARGET GROUPS**

These three major valorization topics target different populations. Enhanced risk prediction using the EMW is relevant for patients with inherited or acquired repolarization prolongation worldwide, and this non-invasive tool is cheap and easy to measure. Genealogical and cardiogenetic profiling of the Worm population affects subjects in the larger Euregio. Moreover, we anticipate that the discovery of modifier genes could be of great importance for the general population, to screen out patients at risk for severe arrhythmias. The HeArt project targets academic entrepreneurs, clinicians, PhD candidates, residents, scientists, artists, and patients.

## ACTIVITIES, PRODUCTS AND INNOVATION

The mechanical part of determining the EMW is usually performed by continuous-wave Doppler imaging of the aortic-valve outflow. Attempts have been made to develop hand-held devices that assess electromechanical coupling using phonocardiography. This will allow bedside risk evaluation and guidance of therapy. Future incorporation of phonocardiography (or techniques alike) into ICDs could enable diurnal EMW monitoring, alerting physicians to treat patients in case of a significant drop.

The Worm project has a strong impact on the (eu)regional cardiac and psychosocial health. In anticipation, we have informed the local community through articles in local news media (de Limburger, Nummer 1, Gezond Idee, Observant), a Belgian (Belang van Limburg) and a German newspaper (die Aachener Zeitung). Furthermore, we have developed a website for interested individuals who wish to receive additional information on the (cardiac) consequences of this *SCN5A* founder mutation, and the Worm study in general ([www.hartenvaatcentrum.mumc.nl/de-worm-studie](http://www.hartenvaatcentrum.mumc.nl/de-worm-studie)). Specific questions related to the Worm study can be asked directly by telephone or by mail at [wormstudie@mumc.nl](mailto:wormstudie@mumc.nl). In April 2015, we organized the first Worm Information Day for family members, where patients were informed about the latest scientific progress, but also were given a platform to meet distant family members and to share experiences. Finally, we currently face a situation of knowing thousands of names of relatives within the large Worm pedigree, but are unable to reach out to individuals because of privacy laws. This raises ethical challenges. To solve these matters, we will contact Dutch and German ethical and legal experts.

We plan to offer art-based interventions (preferably in a randomized fashion) to current PhD candidates at the Cardiology department, aiming to increase creativity, stimulate out-of-the-box thinking and facilitate communication. Output variables like creativity, out-of-the-box thinking and communication skills will be measured, for instance by using the Torrance Tests of Creative Thinking, which assesses fluency, flexibility, originality, and elaboration. Originality can be graded using the taxonomy of creative design (<http://www.senseandsensation.com/2012/03/assessing-creativity.html>). Finally, in my personal HeArt project, I have been involved in creating art objects that will be exhibited at the Heart+Vascular Center outpatient clinic from March 2018. In this innovative and unprecedented way, patients waiting for the consultation with their cardiovascular specialist will learn about the values of combining art and science, in this case through the HeArt project, and about the scientific findings of the Worm study. Also, they can actively participate in the creation of patient-scientist mindmaps displayed on hospital tables, in order to stimulate patient-scientist communication and get feedback (**Figure A**). This feedback will serve as a tool to improve patient-centered health care. This exhibition will travel fourth to the Main Building of Maastricht University at the Minderbroedersberg, and onward to Zuyderland Medical Centre later in 2018, aiming to reach as many patients and family members in the region as possible. Finally, we plan to further expand this art-based patient communication to other Dutch and European medical facilities.





**Figure A.** Complex scientific information, artistic objects and patient's response to stimulate patient-doctor interaction, opening eyes in both of them.