M U N I

COMMENTARY TO HABILITATION THESIS

Selected Aspects of Dynamic Electrocardiography

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Brief characteristic of the investigated matter

Despite substantial scientific progress over the past decades, sudden cardiac death (SCD) remains a high-priority public health problem with multifaceted treatment and prevention requirements. While automatic implantable cardioverters-defibrillators (ICD) offer a possibility of effective SCD prevention, identification of patients at increased SCD risk who might benefit from ICD prophylaxis represents a serious unmet clinical and healthcare need.

As SCD occurs in all population strata, a risk stratification strategy is needed that would be universally appropriate, and therefore not only effective but also inexpensive and broadly applicable. At present, however, no such risk stratification technique is available.

The requirement of a broad applicability of risk stratification techniques translates into the necessity of using multifactorial approaches that combine different risk markers into multivariable SCD-prediction risk scores. There are a number of characteristics that might be combined in such risk scores, but their mutual interactions and interdependencies have not been systematically investigated. In many cases, even the normal limits of the potential risk characteristics have not been fully established.

Objectives of the work

The most easily applicable cardiac investigations are based on electrocardiography (ECG). Thus, the analysis of ECG signals appears to be a primary candidate of examinations to consider when developing SCD screening tools. Contemporary technological advances permit collecting ECG signals digitally which allows the development of novel aspects of dynamic electrocardiography. These include both spatial- and time-domain signal evaluations. Although some of these dynamic techniques have already been, with some success, applied to recordings obtained in well-defined clinical populations, substantial unresolved uncertainties exist in terms of their normal physiologic levels and regulation processes.

The original articles included in and commented on in this thesis are devoted to several such uncertainties in dynamic electrocardiography. All studies described in these articles have been conducted with the aim of contributing to the development of strategies for effective SCD risk screening.

Employed methodologies

The investigated collections of ECG signals and of their physiologic and clinical covariates might broadly be divided into three areas.

The first of these comprised studies of data of patients with hereditary arrhythmic syndromes. The second area included investigations of long-term electrocardiographic characteristics in normal populations of both adult and paediatric subjects. The final area was devoted to the research of short-term electrocardiograms in clinically well-defined populations of cardiac patients and of representative sample of general unselected population.

Because of the obvious link between ventricular arrhythmias and cardiac repolarisation abnormalities, a number of the studies were devoted to the dynamics of electrocardiographic repolarisation parameters. These investigated, among others, heart rate dependency of repolarisation markers, the speed of the adaptation of such markers to the heart rate changes, and established distribution of values that defined normality standards of individual markers. The studies also investigated spatial dynamics of ventricular depolarisation and with the aim of proposing a novel risk stratification marker that could be derived from standard 10-second ECGs and that would thus make it applicable in a broad variety of clinical settings.

Obtained results

The first investigative area characterised families with long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia who were diagnosed, appropriately treated, and followed-up at our hospital. [1,2,3] The area also included identification of founder mutation of the *KCNQ1*[4] gene with a clear LQTS manifestation and demonstrated higher incidence of sequential variants in genes *KCNQ1, KCNH2, SCN5A, KCNE1* and *KCNE2* among ischaemic heart disease survivors of ventricular fibrillation.[5,6,7]

The second investigative area established inaccuracies of generic heart rate corrections of the QT interval when applied to normal adult population, and problems with the frequently used Bazett formula that are apparent especially when applied to children and adolescents in whom higher heart rates are commonly found in clinical ECG recordings.[8,10] Hormonal influence on appropriately corrected QTc interval was found during and post puberty in children of both sexes.[9] Normal limits and their statistical distributions, including sex differences and heart-rate dependency, were established for the speed of QT interval adaptation to heart rate changes, JT-peak, T-peak to T-end intervals, QT interval variability, and different expressions of spatial QRS-T angle.[11-15]

The final investigative area determined the normal limit of morphological abnormalities of multi-lead QRS complex[16] and showed, in three independent large clinical populations, that excess of such abnormalities is a very strong predictor of subsequent death which is

fully independent of other previously established risk predictors.[17] As these morphological abnormalities can be obtained from standard 10-second ECG recordings, the finding is of particular clinical importance.

Applicant's contribution

Of the 17 published articles included in the thesis, the applicant was the first and/or the corresponding author of 11 (65%). In the technically oriented articles where the first author was a biomedical engineering specialist, the applicant closely collaborated with the first author and provided physiologic and medical background to the developed technologies.

Bibliographic record of a published scientific results included in the habilitation thesis

Accessibility and Web of Science (WoS) classifications

[1] **Andrsova I**, Valaskova I, Kubus P, Vit P, Gaillyova R, Kadlecova J, Manouskova L, Novotny T. Clinical characteristics and mutational analysis of the *RyR2* gene in seven Czech families with catecholaminergic polymorphic ventricular tachycardia. Pacing Clin Electrophysiol 2012; 35:798-803.

Accessible at doi: 10.1111/j.1540-8159.2012.03399.x.

Original publication. WoS classification: Cardiac and Cardiovascular Systems Q3; Engineering – Biomedical Q2.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80	10	40	50

[2] **Andrsova I**, Novotny T, Kadlecova J, Bittnerova A, Vit P, Florianova A, Sisakova M, Gaillyova R, Manouskova L, Spinar J. Clinical characteristics of 30 Czech families with long QT syndrome and *KCNQ1* and *KCNH2* gene mutations: Importance of exercise testing. J Electrocardiol 2012; 45:746-751.

Accessible at doi: 10.1016/j.jelectrocard.2012.05.004.

Original publication. WoS classification: Cardiac and Cardiovascular Systems Q4.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
70	10	30	40

[3] Mazzanti A, Guz D, Trancuccio A, Pagan E, Kukavica D, Chargeishvili T, Olivetti N, Biernacka EK, Sacilotto L, Sarquella-Brugada G, Campuzano O, Nof E, Anastasakis A, Sansone VA, Jimenez-Jaimez J, Cruz F, Sánchez-Quiñones J, Hernandez-Afonso J, Fuentes ME, Średniawa B, Garoufi A, **Andršová I**, Izquierdo M, Marinov R, Danon A, Expósito-García V, Garcia-Fernandez A, Muñoz-Esparza C, Ortíz M, Zienciuk-Krajka A, Tavazzani E, Monteforte N, Bloise R, Marino M, Memmi M, Napolitano C, Zorio E, Monserrat L, Bagnardi V, Priori SG. Natural History and Risk Stratification in Andersen-Tawil Syndrome Type 1. J Am Coll Cardiol. 2020; 75:1772-1784.

Accessible at doi: 10.1016/j.jacc.2020.02.033

Original publication. WoS classification: Cardiac and Cardiovascular Systems Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
25	5	10	5

[4] Synková I, Bébarová M, **Andršová I**, Chmelikova L, Švecová O, Hošek J, Pásek M, Vít P, Valášková I, Gaillyová R, Navrátil R, Novotný T. Long-QT founder variant T309I-Kv7.1 with dominant negative pattern may predispose delayed afterdepolarizations under β-adrenergic stimulation. Scientific Reports 2021; 11:3573.

Accessible at doi: 10.1038/s41598-021-81670-1.

Original publication. WoS classification: Multidisciplinary Sciences Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	5	25	10

[5] Novotny T, Kadlecova J, Raudenska M, Bittnerova A, **Andrsova I**, Florianova A, Vasku A, Neugebauer P, Kozak M, Sepsi M, Krivan L, Gaillyova R, Spinar J. Mutation Analysis Ion Channel Genes Ventricular Fibrillation Survivors with Coronary Artery Disease . Pacing Clin Electrophysiol 2011;34:742-749.

Accessible at doi: 10.1111/j.1540-8159.2011.03045.x

Original publication. WoS classification: Cardiac and Cardiovascular Systems Q3; Engineering – Biomedical Q3.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	5	15	15

[6] **Andršová I**, Novotný T, Valášková I, Kadlecová J, Kuderová D, Sepši M, Kozák M, Křivan L, Gaillyová R, Špinar J. Mutation analysis of RyR2 gene in patients after arrhythmic storm Cor Vasa 2012;54:e84-e87.

Accessible at doi: 10.1016/j.crvasa.2012.03.003.

Original publication. WoS listing without impact factor.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	25	40	20

[7] Novotný T, Raudenská M, Kadlecová J, **Andršová I**, Floriánová A, Vašků A, Kozák M, Sepši M, Křivan L, Gaillyová R, Špinar J. Mutační analýza promotorů genů pro iontové kanály u pacientů s ischemickou chorobou srdeční, kteří přežili fi brilaci komor (Mutation analysis of ion channel genes promoters in ventricular fi brillation survivors with coronary artery disease) . Cor Vasa (2013) 06.009

Accessible at doi: 10.1016/j.crvasa.2013.06.009

Original publication. WoS listing without impact factor.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
25	5	15	30

[8] **Andršová I**, Hnatkova K, Šišáková M, Toman O, Smetana P, Huster KM, Barthel P, Novotný T, Schmidt G, Malik M. Influence of heart rate correction formulas on QTc interval stability. Scientific Reports 2021; 11:14269.

Accessible at doi: 10.1038/s41598-021-93774-9.

Original publication. WoS classification: Multidisciplinary Sciences Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	20	60	30

[9] **Andršová I**, Hnatkova K, Helánová K, Šišáková M, Novotný T, Kala P, Malik M. Individually rate corrected QTc intervals in children and adolescents. Front Physiol 2019; 10:994.

Accessible at doi: 10.3389/fphys.2019.00994.

Original publication. WoS classification: Physiology Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
85	60	60	40

[10] **Andršová I**, Hnatkova K, Helánová K, Šišáková M, Novotný T, Kala P, Malik M. Problems with Bazett QTc correction in paediatric screening of prolonged QTc interval. BMC Pediatrics 2020; 20:558.

Accessible at doi: 10.1186/s12887-020-02460-8.

Original publication. WoS classification: Pediatrics Q3.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
85	60	60	40

[11] **Andršová I**, Hnatkova K, Šišáková M, Toman O, Smetana P, Huster KM, Barthel P, Novotný T, Schmidt G. Malik M. Sex and rate change differences in QT/RR hysteresis in healthy subjects. Front Physiol 2022; 12:814542.

Accessible at doi: 10.3389/fphys.2021.814542.

Original publication. WoS classification: Physiology Q2.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	10	50	45

[12] **Andršová I**, Hnatkova K, Toman O, Šišáková M, Smetana P, Huster KM, Barthel P, Novotný T, Schmidt G and Malik M. Intra-subject stability of different expressions of spatial QRS-T angle and their relationship to heart rate. Front. Physiol 2022; 13:939633.

Accessible at doi: 10.3389/fphys.2022.939633.

Original publication. WoS classification: Physiology Q2.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	10	50	45

[13] **Andršová I**, Hnatkova K, Šišáková M, Toman O, Smetana P, Huster KM, Barthel P, Novotny T, Schmidt G, Malik M. Heart rate dependency and interlead variability of the T peak - T end intervals. Front Physiol 2020; 11:595815.

Accessible at doi: 10.3389/fphys.2020.595815.

Original publication. WoS classification: Physiology Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	10	50	50

[14] **Andršová I**, Hnatkova K, Šišáková M, Toman O, Smetana P, Huster KM, Barthel P, Novotný T, Schmidt G, Malik M. Heart rate influence on the QT variability risk factors. Diagnostics 2020; 10:1096;

Accessible at doi:10.3390/diagnostics10121096.

Original publication. WoS Classification: Medicine, General & Internal Q2.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	20	60	45

[15] Toman O, Hnatkova K, Šišáková M, Smetana P, Huster KM, Barthel P, Novotný T, **Andršová I**, Schmidt G, Malik M. Short-term beat-to-beat QT variability appears influenced more strongly by recording quality than by beat-to-beat RR variability. Front Physiol 2022; 12: 863873.

Accessible at doi: 10.3389/fphys.2022.863873.

Original publication. WoS classification: Physiology Q2.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	70	25	60

[16] Hnatkova K, **Andršová I**, Toman O, Smetana P, Huster KM, Šišáková, Barthel P, Novotný T, Schmidt G, Malik M. Spatial distribution of physiologic 12-lead QRS complex. Scientific Reports 2021; 11:4289.

Accessible at doi: 10.1038/s41598-021-83378-8.

Original publication. WoS classification: Multidisciplinary Sciences Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	45	50

[17] Hnatkova K, **Andršová I**, Novotný T, Britton A, Shipley M, Vandenberk B, Sprenkeler DJ, Junttila J, Reichlin T, Schlögl S, Vos MA, Friede T, Bauer A, Huikuri HV, Willems R, Schmidt G, Franz MR, Sticherling C, Zabel M, Malik M. QRS micro-fragmentation as a mortality predictor. Eur Heart J 2022; 43:4177-4191.

Accessible at doi: 10.1093/eurheartj/ehac085.

Original publication. WoS classification: Cardiac and Cardiovascular Systems Q1.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	10	30	35