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Einthoven and Electrical Risk: Value of the Electrocardiogram to Predict Sudden Cardiac Death

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Risk stratification; prediction; electrocardiogram; sudden cardiac death; cardiac arrest

The year was 1903, and Einthoven was a man well ahead of his time, but even he may not have realized the durable and lasting impact of his invention, the electrocardiogram (ECG). Over a century later, the ECG remains the most commonly utilized and broadly available cardiac test. The diagnostic utility of the ECG spans coronary disease manifestations, structural heart disease, conduction system disorders and cardiac arrhythmias. As a non-invasive measure of global cardiac electrical activity, this tool has special utility for prediction of lethal ventricular arrhythmias and sudden cardiac death (SCD).

In this issue of the Journal, Toukola and co-workers evaluated the potential significance of an abnormal ECG marker, fragmented QRS complex (fQRS), in the specific context of exercise-related SCD¹. Even though the overall benefits of exercise are undeniable and exercise-related SCD occurs in the small minority of patients², the paradox of transiently increased SCD risk during exercise is well documented. However, there are no methods of risk assessment that effectively identify high risk patients. From the analysis of archived resting 12-lead ECGs obtained on 276 SCD patients, they report that fQRS in at least two consecutive anterior leads was significantly more common in exercise-related SCD compared with both SCD at rest, and the general population. These are interesting findings, but there are some significant caveats that should be considered. The overall effect size of fQRS in the anterior leads on exercise-related SCD risk, is modest. ECGs from witnessed SCD cases were only available in a small subgroup (7%) of the overall FinGesture cohort, resulting in a large amount of missing data and creating potential for selection bias. It would be critical to validate these findings in a separate population. The manifestation of fQRS on the ECG may indicate discontinuous electrical conduction in larger areas of diseased myocardium and fibrosis³. However, a pathophysiological correlation with re-entrant arrhythmias would, at a minimum, require cardiac magnetic resonance imaging to be performed in the same patients. Finally, it is relevant to put these findings in the context of

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the larger problem that still awaits a solution. How do we identify the overall population of patients at highest risk of SCD, and can the ECG play an important role?

For the familial arrhythmia syndromes such as long QT and Brugada, the ECG is the main avenue for establishing the diagnosis but also provides prognostic information. For example, the absolute value of the corrected QT interval (QTc) and the type of spontaneous Brugada pattern are linked to risk of future arrhythmia. However, for the more common forms of SCD manifestation due to coronary disease or cardiomyopathies, assessment of risk is complex since it often represents the end result of multiple myocardial remodeling processes working together⁴. Different components of the surface ECG may potentially reflect distinct aspects of the SCD risk cascade. Therefore, a large body of investigative work has been dedicated to identification of potential markers from the ECG that may help identify the individual at highest risk of SCD. The current resurgence of interest in the ECG for this purpose is based on the diminishing returns from employing the left ventricular ejection fraction (LVEF) < 35% as the main clinically utilized predictor of SCD risk. Recent attempts to deploy combinations of a variety of clinical and plasma biomarkers as “SCD risk scores” have not gained traction since these appear to predict both SCD and overall cardiovascular mortality to equivalent extents. Today, the major gap in our knowledge vis a vis SCD risk stratification is the lack of predictors that will identify increased risk of sudden arrhythmic death. Could the ECG, assessor of electrical risk, step into this important role?

In recent years, investigations into electrical risk stratification using the 12-lead ECG fall into two broad categories, identification of individual risk markers and cumulative risk markers. There are multiple individual ECG markers that are independently associated with risk of SCD. Higher resting heart rate (HR) has been linked to SCD risk in several studies. In the Oregon Sudden Unexpected Death Study (SUDS) the HR-SCD association persisted even after accounting for common HR modulating drugs⁵. Various abnormalities related to the QRS complex, which reflects myocardial depolarization can help evaluate SCD risk in an individual. A longer QRS complex duration has been shown to be associated with risk of SCD even when controlled for presence of coronary artery disease⁶. Another often overlooked risk marker of SCD is the presence of left ventricular hypertrophy (LVH) on the ECG. While ECG LVH is associated with SCD risk⁷, conventional thinking has labelled it as an imperfect indicator of increased LV mass; thus being considered secondary in importance to the echocardiogram⁸. However ECG-LVH was independently associated with SCD risk even after adjustment for echo-LVH⁹. These findings suggest that increased myocardial voltage likely represents adverse “electrical” remodeling, conferring a risk that is distinct from the “anatomic” remodeling of echocardiographic LV hypertrophy¹⁰. Delayed intrinsicoid deflection (DID) of the QRS complex is an ECG marker that contributes to risk of arrhythmogenesis independent of anatomic increase in LV mass¹¹. Delayed QRS transition zone (R-wave transition at V5 or V6) is another abnormal ECG marker associated with increased SCD risk, a pathophysiology that extends beyond previous myocardial infarction and reduced LVEF¹². Manifestations of abnormal myocardial repolarization have also been linked to increased risk of SCD. In the general population, abnormal prolongation of the corrected QT interval (QTc) doubles the odds of SCD¹³. Another novel ECG marker is prolongation of the T-peak to T-end interval (Tpe)¹⁴ which may be more effective at extreme values of heart rate, when the QT interval cannot be corrected with accuracy¹⁵. An

interesting ECG parameter involving both depolarization and repolarization is the frontal QRS-T angle, representing the difference between the net directions of depolarization and repolarization in the ventricular myocardium. In population-based studies, an increased QRS-T angle higher than 90 degrees has been associated with increased SCD risk, independent of the LV ejection fraction¹⁶.

While there are other examples of individual ECG markers that predict SCD risk, none of these have had a meaningful impact on the risk stratification process, due to the relatively small magnitude (1.5 to 3-fold) of the individual effect sizes on risk. This phenomenon has led to a paradigm shift in the assessment of electrical risk from the 12-lead ECG. We have recently assessed the cumulative effects of a panel of ECG markers on assessment of SCD risk. In the Oregon SUDS (catchment population $\approx$ 1 million), archived ECGs performed prior and unrelated to the SCD event were analyzed. A total of 522 SCD cases (65.3 ± 14.5 years, 66% male) were compared with 736 geographical controls to assess the incremental value of multiple ECG parameters in SCD prediction. Resting heart rate, LV hypertrophy, QRS transition zone, QRS-T angle, QTc, and Tpe interval were combined in an electrical risk score (Figure) which was externally validated in the Atherosclerosis Risk in Communities (ARIC) Study. After adjusting for multiple clinical factors and LVEF, patients with 4 ECG abnormalities had an odds ratio (OR) of 21.2 for SCD (95% confidence interval [CI] 9.4–47.7; $P < 0.001$). In the LVEF $>35\%$ subgroup, the OR was 26.1 (95% CI 9.9–68.5; $P < 0.001$). The ECG risk score improved the C-statistic from 0.625 to 0.753 ($P < 0.001$), with net reclassification improvement of 0.319 ($P < 0.001$). In the ARIC validation cohort, risk of SCD associated with 4 ECG abnormalities remained significant after multivariable adjustment (hazard ratio 4.84; 95% CI 2.34–9.99; $P < 0.001$; C-statistic improvement 0.759–0.774; $P = 0.019$). Therefore, this novel cumulative ECG risk score was independently predictive of SCD with a significantly larger effect size compared to individual ECG markers. The attenuation of effect observed in the ARIC validation study is due to the overall low risk nature of this cohort that enrolled patients who were apparently free of heart disease. While this is proof of concept, now this electrical risk score should be evaluated in large cohorts that have enrolled subjects who are at intermediate risk of SCD. It is conceivable that larger combinations of the ECG score, possibly in concert with other clinical, plasma and genetic risk markers may further enhance methodology for SCD risk stratification.

Toukola and colleagues from the FinGesture group are to be congratulated for their careful work on an individual ECG risk marker in the sub-population of patients that suffer exercise-related SCD. For assessing overall risk of SCD, recent findings suggest that the cumulative effect of several ECG risk markers has a significantly larger effect size and may be much more effective as a risk stratification tool. More prospective evaluations are needed, especially in cohorts of patients that are at intermediate risk of SCD. Einthoven's original contribution has evolved into a ubiquitous, non-invasive, digital test for electrical risk, that may yet lend itself to user-friendly SCD risk stratification methodology.

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References

1. Junttila J, Holmström LTA, Haukilahti MA, Tikkanen JT, Terho H, Kenttä TV, Aro AL, Anttonen O, Kerola T, Pakanen L, Kortelainen M-L, Kiviniemi A, Huikuri HV. Fragmented QRS complex as a predictor of exercise-related sudden cardiac death. *J Cardiovasc Electrophysiol*. 2017; 28doi: 10.1111/jce.13341
2. Marijon E, Uy-Evanado A, Reinier K, Teodorescu C, Narayanan K, Jouven X, Gunson K, Jui J, Chugh SS. Sudden cardiac arrest during sports activity in middle age. *Circulation*. 2015; 131:1384–91. [PubMed: 25847988]
3. Das MK, Saha C, El Masry H, Peng J, Dandamudi G, Mahenthiran J, McHenry P, Zipes DP. Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. *Heart Rhythm*. 2007; 4:1385–92. [PubMed: 17954396]
4. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J. Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis*. 2008; 51:213–28. [PubMed: 19026856]
5. Teodorescu C, Reinier K, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Resting heart rate and risk of sudden cardiac death in the general population: influence of left ventricular systolic dysfunction and heart rate-modulating drugs. *Heart Rhythm*. 2013; 10:1153–8. [PubMed: 23680897]
6. Teodorescu C, Reinier K, Uy-Evanado A, Navarro J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged QRS duration on the resting ECG is associated with sudden death risk in coronary disease, independent of prolonged ventricular repolarization. *Heart Rhythm*. 2011; 8:1562–7. [PubMed: 21699869]
7. Wachtell K, Okin PM, Olsen MH, Dahlöf B, Devereux RB, Ibsen H, Kjeldsen SE, Lindholm LH, Nieminen MS, Thygesen K. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE Study. *Circulation*. 2007; 116:700–5. [PubMed: 17664372]
8. Devereux RB, Casale PN, Wallerson DC, Kligfield P, Hammond IW, Liebson PR, Campo E, Alonso DR, Laragh JH. Cost-effectiveness of echocardiography and electrocardiography for detection of left ventricular hypertrophy in patients with systemic hypertension. *Hypertension*. 1987; 9:II69–76. [PubMed: 2948913]
9. Narayanan K, Reinier K, Teodorescu C, Uy-Evanado A, Chugh H, Gunson K, Jui J, Chugh SS. Electrocardiographic versus echocardiographic left ventricular hypertrophy and sudden cardiac arrest in the community. *Heart Rhythm*. 2014; 11:1040–6. [PubMed: 24657425]
10. Aro AL, Chugh SS. Clinical Diagnosis of Electrical Versus Anatomic Left Ventricular Hypertrophy: Prognostic and Therapeutic Implications. *Circ Arrhythm Electrophysiol*. 2016; 9:e003629. [PubMed: 27009417]
11. Darouian N, Narayanan K, Aro AL, Reinier K, Uy-Evanado A, Teodorescu C, Gunson K, Jui J, Chugh SS. Delayed intrinsicoid deflection of the QRS complex is associated with sudden cardiac arrest. *Heart Rhythm*. 2016; 13:927–32. [PubMed: 26699237]
12. Aro AL, Phan D, Teodorescu C, Uy-Evanado A, Reinier K, Gunson K, Jui J, Huikuri HV, Chugh SS. Cardiac structural and functional profile of patients with delayed QRS transition zone and sudden cardiac death. *Europace*. 2017; 19:629–635. [PubMed: 28431059]
13. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, Mariani R, Gunson K, Jui J. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. *Circulation*. 2009; 119:663–70. [PubMed: 19171855]
14. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2011; 4:441–7. [PubMed: 21593198]

15. Chua KC, Rusinaru C, Reinier K, Uy-Evanado A, Chugh H, Gunson K, Jui J, Chugh SS. Tpeak-to-Tend interval corrected for heart rate: A more precise measure of increased sudden death risk? *Heart Rhythm*. 2016; 13:2181–2185. [PubMed: 27523774]
16. Chua KC, Teodorescu C, Reinier K, Uy-Evanado A, Aro AL, Nair SG, Chugh H, Jui J, Chugh SS. Wide QRS-T Angle on the 12-Lead ECG as a Predictor of Sudden Death Beyond the LV Ejection Fraction. *J Cardiovasc Electrophysiol*. 2016; 27:833–9. [PubMed: 27094232]
17. Aro AL, Reinier K, Rusinaru C, et al. Electrical risk score beyond the left ventricular ejection fraction: Prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. *Eur Heart J*. 2017 Jun 26. [Epub ahead of print]. doi: 10.1093/eurheartj/ehx331

Figure.

Components of a multi-marker, cumulative electrocardiographic risk score for prediction of sudden cardiac death. Reprinted with permission from Aro et al¹⁷.