Unraveling Myocardial Mass
Using Classical ECG With Contemporary GWAS*

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I n the early 20th century, the Dutch physiologist Willen Einthoven stated “What you or I think is not important. What is important is the truth.” Today, this concept remains pertinent to our efforts to better understand myocardial mass complexity. Einthoven’s 1906 paper “Le télécardiogramme” presented the first collection of abnormal human electrocardiograms (ECGs) using the string galvanometer, which was the first published identification of abnormal ventricular cavity growth through cardiac signal recording (1). In 1914, Lewis investigated an autopsy series and reported the first use of bipolar leads voltage criteria to diagnose ventricular hypertrophy (2). His (RI – RIII) + (SI – SIII) index had a maximum normal value of 1.79 mV and primarily reflected axis deviation to the left.

In the mid-1940s, Wilson introduced precordial unipolar leads, enabling a better approach to estimating left ventricular mass on the basis of QRS voltage. In 1949, Sokolow and Lyon (3) published their famous summation voltage criteria (sum of R in V5 and S in V1 >3.5 mV), which were widely used over the following decades. The Romhilt-Estes criteria were published in 1968 but were less commonly employed, possibly due to their greater complexity, using a scoring system that considered QRS voltage data, ST-segment deviation, P-wave morphology, left axis deviation, and QRS duration (4). Utilization of voltage criteria peaked in 1982 with the paper by Siegel et al. (5) that proposed the use of the sum of the QRS amplitude of all 12 standard ECG leads.

In the 1980s and 1990s, the Cornell Medical Center group published several new sets of criteria. In 1985, Casale et al. (6) demonstrated the use of QRS voltage criteria in limb and precordial leads along with sex information (S in V3 + R in aVL >2 mV in men and >2.8 mV in women), improving the accuracy compared with previous criteria solely on the basis of voltage. The same paper also included a proposed scoring system that accounted for QRS voltage criteria, sex, age, and T-wave voltage in V1. In 1992, Molloy et al. (7), also from Cornell, used QRS duration in milliseconds to introduce the product of “voltage x duration,” with the voltage criteria being the so-called Cornell voltage (V3 and aVL leads) or the 12-lead voltage summation. More recently, in 2006, a new criterion solely on the basis of QRS duration was proposed (8).

Notably, the aforementioned studies exhibited heterogeneity of both the underlying cardiac disease and the methods used for ventricular hypertrophy detection (Table 1). The initial studies most commonly detected ventricular hypertrophy via direct measurement of ventricular mass at autopsy, whereas more modern studies employ image-based measurements (initially echocardiography, later cardiac magnetic resonance imaging). Some reports included no ventricular mass measurements, but rather compared cases and controls, with the cases being patients with heart diseases associated with ventricular hypertrophy.

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nder Harst et al. (9) report their commendable analysis of the genetic architecture of ventricular mass using ECG traits and a genome-wide association study (GWAS) approach, including data from 24 large international cohorts and more than 70,000 individuals. The authors report 52 loci that were associated with at least 1 of 4 ventricular mass-related ECG traits of interest. However, as highlighted in Table 1, the analysis of data from QRS traits alone lacks sensitivity and specificity. Additional analysis of the underlying predisposing factor for ventricular hypertrophy would have enabled a more refined interpretation of the presented data.

The authors have also used bioinformatics tools and performed experimental animal studies to further explore the identified loci of interest. They report that these loci are enriched for deoxyribonuclease hypersensitive and transcription factor binding sites that might regulate gene expression. Analyses of candidate genes further revealed that these loci are enriched in genes involved in cardiac and muscular development, some of which are already reportedly associated with cardiomyopathies, arrhythmias, and septal defects. Moreover, experimental results indicate that suppressing the expression of some of these genes caused severe cardiac defects in Drosophila models.

There are several issues related to this work that warrant specific comment. First, we must address the “complexity” of “complex” traits. Over the past decade, GWAS results have contributed to the identification of common genetic variants associated with complex cardiovascular traits (10). Although these studies provided reliable data and have dramatically advanced our knowledge of the genetic architecture of these traits, the explained variability remains small (11). van der Harst et al. (9) identified 52 loci that explained a variability ranging from 2.7% to 5.0% relative to the Sokolow-Lyon and QRS duration indexes, respectively. The missing heritability could be explained by: the existence of other common or rare variants; interactions among genetic variants or between genetic and environmental factors; or the

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### TABLE 1  ECG Scores Developed to Determine Ventricular Hypertrophy

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Year</th>
<th>Ventricular Hypertrophy Detection</th>
<th>QRS Voltage</th>
<th>QRS Duration</th>
<th>Other Criteria</th>
<th>Sensitivity†</th>
<th>Correlation (Autopsy)‡</th>
<th>Correlation (CMR)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis (2)</td>
<td>1914</td>
<td>Autopsy</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sokolow-Lyon</td>
<td>1949</td>
<td>Cardiac disorder</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>24%</td>
<td>0.43</td>
<td>0.25</td>
</tr>
<tr>
<td>Romhilt-Estes</td>
<td>1968</td>
<td>Autopsy</td>
<td>Yes</td>
<td>No</td>
<td>Several ECG</td>
<td>27%</td>
<td>0.46</td>
<td>NA</td>
</tr>
<tr>
<td>12-lead QRS sum</td>
<td>1982</td>
<td>Aortic stenosis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>31%</td>
<td>0.50</td>
<td>0.49</td>
</tr>
<tr>
<td>Cornell voltage</td>
<td>1985</td>
<td>Echocardiography</td>
<td>Yes</td>
<td>No</td>
<td>Sex</td>
<td>36%</td>
<td>0.47</td>
<td>0.49</td>
</tr>
<tr>
<td>Cornell point score</td>
<td>1985</td>
<td>Echocardiography</td>
<td>Yes</td>
<td>No</td>
<td>Sex, age, T-wave</td>
<td>44%</td>
<td>0.60</td>
<td>NA</td>
</tr>
<tr>
<td>Cornell product</td>
<td>1992</td>
<td>Autopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>Sex, T-wave</td>
<td>51%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>QRS duration (8)</td>
<td>2006</td>
<td>CMR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>0.59</td>
</tr>
</tbody>
</table>

*The majority of early studies used QRS voltage, whereas QRS duration was more recently introduced. Some studies include other electrocardiographic (ECG) criteria (ST-segment deviation, P-wave morphology, ventricular axis, and T-wave voltage) or clinical variables (age, sex). †Sensitivity data according to Molloy et al. (7) performed at a matched specificity of 95% and on the basis of autopsy data. ‡Correlation with left ventricular mass in autopsy specimens according to Molloy et al. (7). §Correlation with left ventricular mass measured by CMR according to Carlsson et al. (7). ¶When using the Cornell leads voltage criterion.

CMR = cardiac magnetic resonance; NA = data not available.

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**FIGURE 1** Loci Overlap

There is varying overlap between the 52 loci associated with left ventricular (LV) mass (9) and other cardiovascular-related traits, on the basis of data from the catalog of published genome-wide association studies (10). ECG = electrocardiogram.
complex integration among genetics, epigenetics, transcriptomics, proteomics, and metabolomics.

Second, such studies necessitate the availability of public repositories of genomic data and bioinformatics tools to integrate these data. Most public funding agencies have adhered to the Fort Lauderdale Agreement, supporting the responsible, free, and unrestricted use of biological data by the scientific community, even before those data are published (12).

Advanced “-omics” methodologies and increasing availability of genomic data, as well as the associated clinical and epidemiological data, foster this type of research and shift the paradigm of the hypothesis-driven approach toward a hypothesis-free approach.

One major challenge in this type of study lies in determining how to handle, analyze, and integrate all of this information—and bioinformatics is emerging as a key discipline to address this issue. From 1995 to 1999, only 112 papers/year included the term “bioinformatics;” this term was used in 2,703 papers/year during the last 5 years (2011 to 2015), representing a 24-fold increase. These new endeavors heavily relied on collaborative and interdisciplinary teamwork.

Third, blood pressure is 1 determinant of ventricular mass (13), but due to the high prevalence of hypertension, we would have anticipated a significant overlap between the loci related to ventricular mass and those associated with blood pressure (14). However, only 3 of the identified loci were previously reported to be associated with blood pressure, although there was substantial overlap between loci related to obesity-glucose homeostasis and those related to ventricular mass (13 of 52 loci) (Figure 1, Online Table 1) (10). This finding suggests notable pleiotropy, a common genetic background between these 2 traits, and potentially, a common causal mechanistic pathway.

In summary, despite amazing advances in the field of molecular medicine and imaging in recent years, the nearly 120-year-old ECG technique remains the undisputed king of cardiovascular disease evaluation, at the forefront of every guideline algorithm. It is important to acknowledge its limitations and the necessity to properly use ECG data in combination with modern imaging techniques and -omics. As we move toward precision medicine, we must not forget the knowledge acquired by our predecessors (15). The combination of classical ECG with contemporary GWAS offers an attractive option that requires further exploration for use in cardiovascular pathology.

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**REFERENCES**

2. Lewis T. Observations upon ventricular hypertrophy, with especial reference to preponderance of one or the other chamber. Heart 1914;5:367-403.

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**APPENDIX** For a supplemental table, please see the online version of this article.