The Electrocardiogram: *From Einthoven to Molecular Genetics*

Arthur J. Moss, M.D.

From the Heart Research Follow-up Program, University of Rochester Medical Center, Rochester, New York

It is just 100 years since Willem Einthoven published his landmark article on the modification of the string galvenometer for recording the electrocardiogram.[1] The background leading up to Einthoven's contribution is a fascinating story in and of itself, and now a century later the molecular genetic insights into the ionic currents responsible for generation and configuration of the repolarization T wave have enhanced our understanding of the electrocardiogram.

We need to go back more than 200 years when studies of electricity produced by animals were investigated. In 1791, Galvani used the electrical organ of the torpedo-fish to stimulate not only the muscles and nerves of the frog, but also of the heart itself. In the mid-1800s, it was appreciated that when the frog's heart contracted it produced an electric current. For many years, the heart current of laboratory animals was studied with the crude apparatus that was available at that time. A major technical advance was made in 1875 with the invention of the mercury capillary electrometer by Gabriel Lippmann.[2] Augustus Waller applied this new technique to record the electromotive changes accompanying the heart beat of the human heart in 1889.[3] The recordings were barely adequate because of the inertia of the mercury column. It was about this time that Ader invented a new type of galvanometer known as the string galvenometer based on the principle that a current in a wire generates a magnetic field that can be influenced by a second magnetic field in its vicinity. Ader's string galvenometer was used in the transatlantic cable for transmission of electric signals.

Einthoven modified the string galvenometer and applied this electrical measuring device to record the human electrocardiogram. Einhoven's electrocardiographic galvenometer became the practical tool for electocardiography, and its evolutionary use during the twentieth century is well known to all of us. It is of interest that Einthoven recognized early on that each individual had his own characteristic electrocardiogram. Of course, we now have a reasonable understanding why this is the case.

The electrical activity of the heart as well as the morphology of the heart's structure, the related mechanical contraction pattern of individual cardiac myofibers, and the heart's function as an intact organ are influenced in large part by the genetic determinants of the cardiac ion channels, the contractile proteins, and architectural growth factors. Of course, disease and other environmental factors influence the genetic expression. If we focus on the electrical activity of the heart and the characteristic P, Q, R, S, and T waves of each individual as first enunciated by Einthoven, we can appreciate from our current knowledge of the genetic determinants of proteins why an individual's electrocardiogram is like a fingerprint.

Genetic mutations involving the KVLQT1, HERG, SCN5A, KCNE1, and KCNE2 ion-channel genes result in altered ion-channel currents responsible for prolonged ventricular repolarization and the long QT syndrome (LQTS). The different phenotypic repolarization T-wave patterns in LQT1, LQT2, and LQT3 reflect the genetically distinct forms of the hereditary long QT syndrome.[5] But this is the tip of the iceberg. We know from the

Address for reprints: Dr. Arthur J. Moss, M.D., Heart Research Follow-up Program, Box 653, University of Rochester Medical Center, Rochester, NY 14642. Fax: (716)273-5284. E-mail: heartajm@heart.rochester.edu

recently completed genome project that among unrelated individuals there is, on average, one base alteration in every 1,000 bases of the DNA sequence. Thus, there are approximately 3 million sequence variations scattered over 3 billion bases that make up the human genome. These sequence variations are referred to as single nucleotide polymorphisms (SNPs) and account for our individual characteristics. If we apply this genetic knowledge to the five known ion-channel genes, it is easy to understand that even in normal individuals without LQTS gene mutations, the SNPs may contribute to the various fingerprint T-wave patterns first recognized by Einthoven.

But this is only the beginning. If the morphology of the T wave and the duration of the QT interval can vary from individual to individual as a result of SNP variations in the human genome, then some of these variations may make some individuals more susceptible to the QT-prolonging effect of certain drugs that affect ion-channel currents. This problem first surfaced in 1990 with the new nonsedating antihistamine terfenadine,[4] especially when coadministered with an azole antifungal agent. Investigations revealed that at high blood concentrations resulting from conazole inhibition of terfenadine metabolism by the CYP3A4-P450 liver enzyme system, terfenadine blocks the HERG potassium channel with resultant QT prolongation, malignant torsades de pointes arrhythmia, and sudden death. This problem surfaced in only a handful of patients receiving terfenadine despite millions of prescriptions. Similar rare adverse-effect problems have been recognized with many marketed drugs including antiarrhythmic, antihistamine, antimicrobial, psychotropic, and gastrointestinal agents.

Einthoven's appreciation that each individual had a characteristic electrocardiographic pattern has a molecular genetic underpinning. Variations in ion-channel genes (polymorphisms) determine the unique depolarization and repolarization wave patterns seen on the electrocardiogram as well as the unique sensitivity of some individuals to the QT prolonging effects of commonly prescribed medications.

REFERENCES

1. Einthoven W. Un nouveau galvanometer. Arch neerl Sci 1901(II);6:625.
2. Lippmann G. Relations entre les phenomenes electriques et capillaries. Ann Chim (Phys) 1875;5:494.
3. Waller A. On the electromotive changes connected with the beat of the mammalian heart, and of the human heart in particular. Phil Trans B 1889;180:169.
4. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsades des pointes occurring in association with terfenadine use. JAMA 1990;264:2788-2790.
5. Moss AJ, Zareba W, Benhorin J, et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 1995;92:2929-2934.