EDITORIAL COMMENT

On the Intriguing Phenotypic Manifestations of Brugada Syndrome and the Diagnostic Value of the Electrocardiogram*

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In 1924, Willem Einthoven received the Nobel Prize for physiology or medicine “for his discovery of the mechanism of the electrocardiogram.” His colleague Sir Thomas Lewis, regarded by many as another father of clinical electrocardiography, was born in 1881, 21 years after Einthoven, and it is said that Lewis could not understand not being awarded the Nobel Prize together with Einthoven, or even alone. Such can be the greatness and the glory of one person, and so inane can be the stories of others. The reality is that thanks to electrocardiography, both physicians made superb contributions to what would later become the medical specialty of cardiology. Cardiology is unthinkable without electrocardiography, and these 2 men deserve a great deal of scientific respect, considering that 110 years later after its development, electrocardiography still contributes to our medical knowledge.

In this issue of the Journal, Chevallier et al. (1) bring us new scientific information derived from electrocardiographic (ECG) analysis. They compared the ECG findings of patients with incomplete right bundle branch block with those of patients with Brugada syndrome presenting with spontaneous type 2 or 3 ECG patterns that changed into a classic type 1 (coved) Brugada ECG pattern after pharmacologic challenge. The background for this study is clear: patients with incomplete right bundle branch block may be erroneously diagnosed as possibly having Brugada syndrome, and many patients do have incomplete right bundle branch block. However, there are many ECG patterns that are suspicious for Brugada syndrome, but in reality, they reveal only innocent incomplete right bundle branch block. Furthermore, types 2 and 3 of Brugada syndrome do resemble incomplete right bundle branch block.

Are there ECG markers that can differentiate between innocent incomplete right bundle branch block and a potentially threatening Brugada type 2 or 3 ECG pattern? the Chevallier et al. (1) study shows that there are significant differences in the configuration of the r'-wave in leads V1 and V2 between incomplete right bundle branch block and a type 2 or 3 Brugada syndrome pattern. Measuring 2 angles, α and β, in leads V1 and V2, Chevallier et al. (1) show that a reasonably good distinction can be made between incomplete right bundle branch block and a type 2 or 3 Brugada ECG pattern that will change into a type 1 ECG pattern after drug challenge. This is very important and clinically useful information. In simple terms, the r'-wave in incomplete right bundle branch block is taller and narrower than the r'-wave in patients with Brugada syndrome and type 2 or 3 ECG patterns.

Chevallier et al. (1) measured 2 angles to make the distinction: the α and β angles. The α angle was less accurate than the β angle in terms of positive and negative predictive values. However, the β angle was not 100% sensitive and specific. This is not a surprise when one correlates these data with present speculation on the potential pathophysiologic mechanisms involved in Brugada syndrome.

What do the α and β angles of Chevallier et al. (1) measure? The α angle clearly relates to repolarization. An incipient ST-segment elevation of Brugada syndrome simulating incomplete right bundle branch block results in an α angle that is wider and falls more slowly than with incomplete right bundle branch block (their Fig. 1B, bottom middle). The α angle is not influenced by the duration of the QRS complex (depolarization). In contrast, their β angle is related to both depolarization and repolarization: a wider QRS complex (slow conduction) and abnormal polarization both contribute to a wider β angle (their Fig. 1B, bottom middle). Why then is the β angle more sensitive and specific than the α angle but neither 100% sensitive nor 100% specific? It is because the ECG pattern is just the phenotype of the different possible electrophysiologic mechanisms underlying Brugada syndrome.

The pathophysiologic mechanisms of Brugada syndrome. There are at present 3 different hypotheses regarding the pathophysiologic mechanisms of Brugada syndrome. For the sake of simplicity (and because of the many scientific contributors), I will refer to them as the Amsterdam, New York, and Buenos Aires hypotheses.

The Amsterdam hypothesis was initially based on observations of a patient of mine who required cardiac transplantation because of physically and psychologically intolerable...
electrical storms, with hundreds of appropriate discharges of his implantable cardioverter-defibrillator. Slow conduction of the electrical impulse in the right ventricular outflow tract (RVOT) was present and was shown to be responsible for the initiation of ventricular fibrillation (2). This masterpiece of scientific research by Colonel et al. (2) should be obligatory reading in the curriculum of any cardiologist in training. The study is comparable only with a previous masterpiece of research by Durrer et al. (3), which in 1967 and also in Amsterdam mapped in a Langerdoff preparation the total electrical activation of the normal human heart, launching what would become the basis of modern cardiac electrophysiology.

The New York hypothesis is based on experimental models. Instead of slow conduction, the researchers in Utica proposed that gradients in repolarization between RVOT epicardium and endocardium result in the electrical heterogeneity that results in re-entry, based not on slow conduction (as in the Amsterdam hypothesis) but on phase 2 reentry (4). A mismatch in repolarization characteristics of adjacent cardiac cells or regions (phase 2 or phase 3 re-entry) was proposed as a possible mechanism of arrhythmias by my group as early as 1985. Although this was initially seen as an unrealistic hypothesis, multiple later studies proved it (5).

The Buenos Aires hypothesis is a fascinating one (6). It combines the 2 aforementioned mechanisms (slow conduction and abnormal repolarization) on the basis of the hypothesis that abnormal expression of cardiac neural crest cells leads to abnormal depolarization and repolarization of the RVOT (the “Achilles heel” of the heart, as the investigators called it). According to this hypothesis, abnormal expression of the cardiac neural crest cells would lead to abnormal connexin expression, particularly connexin 43, thereby creating the depolarization delay and heterogeneity in repolarization necessary to induce the Brugada ECG phenotype.

Are there any correlates for these 3 hypotheses? Indeed there are.

In agreement with the Amsterdam hypothesis, we know that the ECG pattern in Brugada syndrome shows not only ST-segment elevation (on the basis of conduction delay according to this hypothesis) but also true conduction delay, as shown by PR prolongation and right bundle branch block with a wide QRS complex. These findings fit with the mutations in the sodium channel gene SCN5A frequently found in these patients. However, mutations in the SCN5A gene account for no more than 25% to 30% of patients with Brugada syndrome.

In agreement with the New York hypothesis, we do observe patients with Brugada syndrome with only repolarization abnormalities and no conduction defects. These patients fit much better with the individuals in whom mutations are found in potassium or calcium channels. These represent a minority (<1 in 1,000) of patients with Brugada syndrome.

What about the Buenos Aires hypothesis? Why should cardiac neural crest cells behave abnormally and in such a specific area of the heart (the RVOT)? Does this hypothesis explain the remaining 70% of patients with Brugada syndrome in whom mutations in the germinal-derived deoxyribonucleic acid are not found? Do these patients carry mutations in the mitochondrial deoxyribonucleic acid or have somatic (nongerminal) cell-specific mutations? Somatic mutations have already been shown to be involved in RVOT ventricular tachycardia (6). As proposed by the Buenos Aires hypothesis, specific development abnormalities in the RVOT could also underlie not only Brugada syndrome but also other “idiopathic” arrhythmias from and around the RVOT area.

Chevallier et al. (1) bring us 1 major step further in the potential genotype-phenotype correlations in Brugada syndrome. From a practical point of view, an ECG pattern with incomplete right bundle branch block with a broad r′-wave should arouse suspicion of the possibility of an underlying channelopathy. If the β angle is 58° or more, a combined depolarization and repolarization abnormality should be suspected, probably related to a mutation in the cardiac sodium channel gene or to somatic mutations of the cardiac neural crest cells. When Brugada syndrome is suspected, confirmation or exclusion by means of a pharmacologic challenge should be done.

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