The paper by Nademanee et al. (1) is so excellent—it demonstrated that the proposed diagnosis of idiopathic origin for the so-called Brugada syndrome must be dismissed.

There are 2 minor criticisms: one is that not one of the patients submitted to necropsy had an electrocardiogram (ECG) performed during life, so it is possibly but not definitely sure that they have the complete phenotypic traits. It is also confusing why, because this lethal syndrome has been proposed to be the “mother” of a relevant number of sudden deaths, it has been so difficult to perform detailed necropsy studies in patients who have died because of the syndrome, and why those published have been so rarely discussed (see Table 1 of Martini et al. [2]).

As a second comment, I find it unfair in this paper that the humble but first discoverer of the syndrome (and its underlying structural abnormalities), Professor Andrea Nava from Padova, was not even cited. Nava described the complete syndrome in 1987/1998 (1-3) and by a simple analysis of the ECG demonstrated that the ECG pattern was due to a right ventricular conduction disturbance linked to a structural abnormality of the right ventricle. These evidence-based theories received a lot of heavy criticism (and other unfair definitions and boycott), because experts have insisted the syndrome was idiopathic, linked to ion channel abnormalities in a totally normal heart. The unjustified abuse of this non-evidence-based assumption has led to devastating (and high-cost) therapy in asymptomatic and healthy young people (4), which could have been avoided if the structural heart abnormalities underlying the true patients described 30 years ago had been heeded, and not the functional phantoms and the genetic purgatory had been investigated (5). I hope that starting from now efforts will be made to improve the knowledge of what is evidence based rather than to search different confusing pathways that slow the correct identification and risk stratification of the syndrome and its underlying disease.

Search for Evidence-Based Medicine for Brugada Syndrome

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The Complex Network of the Brugada Syndrome

I read the paper by Nademanee et al. (1) with great interest and congratulate the authors on their excellent work. As the authors correctly state, Brugada
syndrome is associated with epicardial surface and interstitial fibrosis and reduced gap junction expression in the right ventricular outflow tract. However, I would like to call attention to a point that needs further clarification. The development and function of the heart components is driven by a set of chromatin remodeling proteins and interacting specific noncoding regulatory DNA sequences binding transcription factors to activate or repress their activity (2). These same transcription factors (including NKX2-5 and members of the T-box family) play essential roles in regulating regionized expression of ion channel (including the clustered sodium channel genes Scn5a) and gap junction genes (e.g., for heart connexins), affecting cardiac electrophysiology and that, when mutated, can bring about electrical abnormalities (2). Several factors are involved in the regulation of Connexin-43. Research has reported relationships among Connexin-43 levels, NKX2.5 (2), abnormalities (2). Several factors are involved in and that, when mutated, can bring about electrical abnormalities in the Brugada syndrome. J Am Coll Cardiol 2015; 86:1976–86. 

Dr. Patanè points out the complexities underlying Connexin-43 expression including regulation by T-box (TBX)-linked transcription factors. Indeed, work from our group and colleagues has associated common variation at the SCN5A-SCN10A locus with the risk for the Brugada syndrome compared with healthy controls (2,3). This locus is associated with a TBX3/5 binding site thought to regulate SCN5A transcription. It is therefore appealing to investigate how TBX3/5 may influence Connexin-43 expression and in turn influence the phenotype of the Brugada syndrome.

Dr. Martini points out the absence of any ante mortem electrocardiographic studies (ECGs) that may support the diagnosis of the Brugada syndrome in the cases of sudden arrhythmic death syndrome included in our study. We recognize this limitation, but a diagnosis of the Brugada syndrome in at least 1 first-degree relative in all our cases makes any other etiology extremely unlikely. This approach forms the basis of current diagnostic guidelines (4). In addition, our own data in sudden arrhythmic death syndrome cases with a familial diagnosis of Brugada syndrome who underwent ECGs ante mortem indicate that a type 1 ECG pattern is usually absent (5).

Dr. Martini also points out work by Nava describing an overt right ventricular structural disorder associated with ECG abnormalities, including the subsequently termed type 1 ECG Brugada pattern. Limitations on reference numbers meant that we were unable to refer to all manuscripts worthy of inclusion. We included only sudden arrhythmic death syndrome cases in our cohort, that is, ostensibly inclusion. We included only sudden arrhythmic death syndrome cases in our cohort, that is, ostensibly normal hearts. The subsequent finding of subtle fibrosis in the right ventricular outflow tract in these cases represents 1 end of the spectrum of the Brugada syndrome phenotype, the other end being described by Nava.