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 regionalized 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), sodium channel Nav1.5, calcium-dependent phosphatase calcineurin A (3), L-type calcium channel (4), microRNA, type β transforming growth factor superfamily (3), T-box (2,5), and fibrosis (2,3). The findings of Nademanee and colleagues add significant information to previously published data, but evaluating the real effect of the factors involved in the regulation of Connexin-43 would be useful for better understanding of the complex network of the Brugada syndrome.

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REPLY: Search for Evidence-Based Medicine for Brugada Syndrome

The Complex Network of the Brugada Syndrome

We thank Drs. Patanè and Martini for their letters in relation to our paper (1).

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 structurally 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.

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