Title: ‘To the editor: Reply to correspondence from Dr Martini (Nademanee K, Raju H, de Noronha SV, et al. Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome. J Am Coll Cardiol. 2015 Nov 3;66(18):1976-86.) and Dr Patanè (The complex network of the Brugada syndrome).’

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**To the editor:**

We thank Dr Patanè and Dr Martini for their letters in relation to our manuscript ‘Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome’ (1).

Dr Patanè points out the complexities underlying Connexin-43 expression including regulation by TBX linked transcription factors. Indeed work from our group and colleagues has associated common variation at the SCN5A-SCN10A locus with the risk for Brugada syndrome compared to 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 Brugada syndrome.

Dr Martini points out the absence of any ante-mortem ECGs that may support the diagnosis of the Brugada syndrome in the cases of sudden arrhythmic death syndrome (SADS) included in our study. We recognize this limitation but the diagnosis of Brugada syndrome in at least one first degree relative in all our cases makes any other aetiology extremely unlikely. This approach forms the basis of current diagnostic guidelines (4). In addition our own data in SADS 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 SADS cases in our cohort, i.e. ostensibly structurally normal hearts. The subsequent finding of subtle fibrosis in the right ventricular outflow tract in these cases represents one end of the spectrum of the Brugada syndrome phenotype, the other end being described by Nava.

Yours sincerely,

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On behalf of all authors.

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