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Letters Regarding Article by Coronel et al, "Right Ventricular Fibrosis and Conduction Delay in a Patient With Clinical Signs of Brugada Syndrome: A Combined Electrophysiological, Genetic, Histopathologic, and Computational Study"

Silvia G. Priori, Carlo Napolitano, Maurizio Gasparini, Guy Fontaine, Paul Fornes, Robert Frank, Ruben Coronel, Simona Casini, Tamara T. Koopmann, Arie O. Verkerk, Joris R. de Groot, Connie R. Bezzina, Marieke W. Veldkamp, André C. Linnenbank, Hanno L. Tan, Arthur A.M. Wilde, Jacques M.T. de Bakker, Francien J.G. Wilms-Schopman, Zahurul Bhuiyan, Allard C. van der Wal and Pedro Brugada

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Letters Regarding Article by Coronel et al, "Right Ventricular Fibrosis and Conduction Delay in a Patient With Clinical Signs of Brugada Syndrome: A Combined Electrophysiological, Genetic, Histopathologic, and Computational Study"

To the Editor:

We read with interest the report by Coronel et al[1] of a case of Brugada syndrome with structural abnormalities of the heart. We would like to comment on the ECG presentation of the patient, which, in our opinion, raises an important interpretation issue.

According to the criteria proposed by a group of experts that included 2 authors of the aforementioned report,[2] the ECG of the patient reported in the article by Coronel et al[1] does not appear to be diagnostic for Brugada syndrome. In fact, the Second Consensus Conference[2] states that only "type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST-segment elevation ≥2 mm, followed by a negative T wave, observed in >1 right precordial lead."

In the tracings of the patient presented by Coronel and colleagues,[1] the ST-segment elevation is present only in lead V_1, does not show a coved morphology in >1 lead, and has no negative T wave.

As the authors discuss in the article,[1] the presence of a mutation in the *SCN5A* gene is not univocally associated with Brugada syndrome. Therefore, to avoid overdiagnosis, its presence should not be considered diagnostic in the absence of a typical ECG.

Disclosures

None.

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To the Editor:

We read with great interest the article by Coronel et al[1] describing an apparent Brugada syndrome with the presence of structural abnormalities in the right ventricular infundibulum. The absence of genes related to arrhythmogenic right ventricular cardiomyopathy mutations does not allow us to rule out arrhythmogenic right ventricular dysplasia (ARVD) because of the large percentage of negative genetic tests in ARVD patients. The authors also indicate that the absence of transmural involvement of right ventricular myocardium rules out the diagnosis of the classic form of ARVD. However, it may represent a minor localized variant. The presence of subendocardial layers of seemingly normal cardiomyocytes is a frequent feature in ARVD. Increased thickness of the right ventricular free wall is not the result of myocyte hypertrophy but of the replacement of cardiomyocytes by adipocytes. In addition, the absence of signs of inflammation is not in favor of Brugada syndrome.[2] Dissociation of myocardium myocytes by adipose tissue is the only phenomenon explaining the beautifully demonstrated mechanism of reentry. However, nowadays, the mechanism of slow conduction, a prerequisite for reentry, has been shown to be due to the underexpression of gap junctions, which has not been tested in this myocardium. Evidence of such a phenomenon, already reported in Naxos disease, may provide a better understanding of the mechanism of slow conduction in ARVD.[3] This observation fits with our own observation of mediomural dissociation of myocytes by fat and fibrosis.[4] Finally, no data are provided on the possible role of apoptosis in this outstanding report.[5] In conclusion, the case reported by Coronel et al[1] seems to be a new example of a localized, albeit dangerous, form of ARVD mimicking the Brugada syndrome.

Disclosures

None.

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Response

In their letter, Dr Priori and colleagues refer to a 2005 consensus report on Brugada syndrome (BS).[1] The patient in our study[2] was diagnosed with BS 13 years earlier by Dr Brugada. The cardiac sodium channel (*SCN5A*) mutation did not contribute to the diagnosis. As we noted,[2] the patient does not entirely fit the recent criteria of BS, but there was clear ST-segment elevation in V_1 and V_2. We emphasize that provocation tests with procainamide are less sensitive than those with ajmaline and that the ST-segment elevation may have been underestimated. As with many syndromes, criteria tend to become more rigid in time, until pathophysiological mechanisms are defined and one eventually can speak of a disease and its markers rather than a

syndrome. We documented in a patient with right precordial ST elevation, recurrent ventricular fibrillation, and an *SCN5A* mutation (1) clinically undetected structural abnormalities, (2) the absence of transmural repolarization gradients, and (3) ventricular fibrillation caused by local conduction delay. Drs Priori and Napolitano and colleagues recently wrote an article[3] that confirmed our point[1] and remarkably concluded that right precordial ST elevation should not be considered a "marker" of a syndrome but a manifestation of structural right ventricular abnormalities. We concur with this view.

We agree with Dr Fontaine and colleagues that our patient is not representative of classic arrhythmogenic right ventricular dysplasia (ARVD) but may represent a localized variant, as we discussed.[2] Dr Fontaine and colleagues state that adipose tissue is the only reason for slow conduction in this patient. However, it is well established that other causes for conduction slowing exist that apply to our patient. Fibrosis and sodium channel dysfunction also may have played a role. In particular, interstitial fibrosis was abundant in the region of "origin" of ventricular fibrillation in our patient. Connexin43 downregulation is likely to be present also because connexin43 redistribution is common at the edges of fibrotic tissue.[4]

Dr Fontaine et al also state that increased thickness of the right ventricular free wall is the result of replacement of cardiomyocytes by adipose tissue. This may be the case in classic ARVD but certainly not in our patient. Although full fatty replacement was focally present, large parts of the right ventricular myocardium were composed almost entirely of hypertrophic myocyte bundles, leading to myocardial thickness of up to 12 mm (>4 times normal). This underscores the incomplete definition of the structural abnormalities in hearts of patients with ARVD variants or BS.

Disclosures

None.

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