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Letters to the Editor

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Brugada by any other name?

The article by Remme *et al.*[1], and the editorial comment by Antzelevitch[2], fortuitously again forgot that the syndrome known worldwide as the Brugada syndrome had been described by Nava, Martini and Thiene more than 4 years before Brugada[3–5].

There is autoptical evidence in the medical literature that this syndrome is related to some form of right heart disease (which does not mean typical right ventricular cardiomyopathy/ dysplasia), and to organic conduction disturbance[3,6,7]. Despite this evidence, these authors insist that their patients are affected only by a functional disorder related to mutant *SCN5A* genes, the prevalence of which is very low in this syndrome despite the initial enthusiasm (and does not exclude an associated organic heart disease).

These authors presumed to have identified 37 patients with ventricular fibrillation not related to organic heart disease, according to their extensive and rigorous investigations[1]. They failed, however, to make a diagnosis of dilated cardiomyopathy and right ventricular cardiomyopathy/dysplasia in two patients submitted to autopsy. It is reasonable to assume that other patients in this series will have similar pathological substrates. This reported evidence demonstrates the problem of the sensitivity and specificity of invasive and non-invasive investigations, and of inter-observer variability and experience in the diagnosis of heart disease.

We need more than the ECG (and other available diagnostic tools) to make a diagnosis of this complex syndrome, as well as of the underlying pathology and electrophysiological mechanisms[8].

It must be emphasized that there is no simple single feature typical of the syndrome and no typical ECG[3]. Different degrees of right bundle branch block, left axis deviation, and prolonged PR interval, have so often been described in this disease[4], as demonstrated by Brugada. A prolonged HV interval and late potentials are common, and an organic substrate has been detected in all autopsy cases. These findings fit well with an organic heart disease which causes a conduction disturbance at the right ventricular outflow tract[3,6,7]. A functional disorder of repolarization has never before produced right bundle branch block, left axis deviation, prolonged PR and HV intervals, and late potentials, and as reported previously, a normal necropsy study has never been documented in this syndrome[6,12,13].

The functional theory is partially derived from the excellent Antzelevitch experiments[9,10], but the clinical conclusions are often speculative. As far as it is known, not a single Antzelevitch experiment has induced the typical ECG pattern in V_1[9,10], despite beautiful drawings published worldwide[2,11]. It must be remembered that Antzelevitch initially wanted[9] to explain the typical J wave frequently seen in left precordial ECG leads (which is a true repolarization abnormality), and not to speculate on the late r1 seen in the syndrome in V_1, V_2 (pseudo J wave), or to explain the ST elevation, which both represent a strange conduction delay at the right ventricular outflow tract and not a repolarization abnormality[3,7,12,13].

Antzelevitch had demonstrated in an arterially perfused left ventricle[9], that in pathophysiological conditions which enhance It_o, there is a prominent notch in the left epicardial AP, which produces a J wave on the surface ECG (in II, III, aVF and left lateral precordial leads). The It_o current is absent in endocardial cells but appears to be more pronounced in M cells, and even more in right ventricular epicardial cells[9,10] (a genetic abnormality of the It_o channel has indeed been excluded in the syndrome!). The larger notch in right ventricular myocardium (as demonstrated in a recent article using perfused RV wedge preparations), in Antzelevitch's opinion, gives only a minor contribution to the J wave seen at left precordial leads, because the right ventricular epicardial activation precedes left ventricular activation, and the right notch occurs inside the QRS[10]. Antzelevitch could demonstrate a surface right precordial J wave only in isolated right ventricle (not the whole heart!) wedge preparations[9,10]. Thus according to his theories, in a whole heart wedge preparation, a J wave in V_1, might be seen only in the presence of a conduction delay in the right ventricle. Only in this case could a right epicardial AP be activated after a left epicardial AP producing a J wave in V_1[12,13].

As regards ST elevation, this was explained experimentally by Antzelevitch as a marked increase in heterogeneity of action potential duration across the wall of the heart. In the presence of pinacidil, the It_o current becomes so prominent that it interferes with the Ca^{2+} current of epicardial AP, producing an absence of the dome in these cells. Loss of the dome produces a marked abbreviation of the AP in the epicardium but not in the endocardium. The resultant transmural voltage gradient leads to the development of an elevated ST segment. However, from the published experiments of Antzelevitch, it has been demonstrated that when an ST elevation is induced, the J wave disappears (and vice-versa), thus totally contradicting clinical and ECG observations[10]. Strong support for the functional theory had also come from the discovery of an Na+ channel gene (*SCN5A*) abnormality in some (very few) patients with the syndrome. The initial paper described a 50% prevalence of the abnormality, but recent reports describe positive results of only 10%–20%. The linkage between *SCN5A* abnormalities and the ECG pattern has never been clarified, and the presence of this genetic abnormality does not exclude an associated organic heart disease.

The last point to be clarified is the significance of the typical ECG pattern unmasked by Class 1C drugs, which Brugada maintains is specific for the syndrome, and a clear documentation of a repolarization abnormality, with shortening of right epicardial action potential (AP) because of drug-induced alterations in the Na+ channels. This hypothesis has recently been described in a drawing by Roden[14], but the experiments of Antzelevitch with flecainide documented the exact contrary[10]. In the perfused RV wedge, Antzelevitch demonstrated that flecainide and ajmaline reduced the notch, and increased the dome, without any J wave or ST elevation[10]. This latter abnormality could be produced only by adding acetylcholine but we know however that the clinical ECG pattern is only incidentally dependent on vagal drive[7,12,13]. Thus the hypothesis that flecainide induces a repolarization abnormality is far

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from being elucidated, whilst it is well demonstrated that the drug induces an intra-ventricular conduction disturbance. This is easily demonstrable by inducing recordable late potentials after injection of the drug, which confirms that flecainide induces major depolarization and not repolarization abnormalities[13].

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Variations in approach to the same disease

It was with great interest that I read the paper by Fox[1] on the causes of heart failure in a population-based coronary angiography study. Their major finding was that in patients monitored for admission to the hospital or through a rapid access heart failure clinic, the final aetiology of heart failure was coronary heart disease in 52% of cases.

This carefully performed study supports using coronary angiography in the great majority of cases who present for the first time with heart failure, at least if the patients are in a reasonable age range. This policy has not yet been adopted in all countries, whereas it is standard practice in most hospitals in our country. It is important to be aware of such differences in national approaches to the same disease. Despite international communication, such differences in routine patient management obviously exist. Among the reasons for this might be historical differences in clinical practice and teaching which might have been influenced by different ease of access to invasive techniques due to economic restraints.

Obviously, as shown by European morbidity and mortality statistics[2] and the results of the EuroHeartSurvey Programme of the European Society of Cardiology, important differences in the number of diagnostic and interventional procedures performed in the various European countries exist. This was also shown in multicentre international trials. In the ATLAS trial[3], an international heart failure trial, important differences in patient characteristics and use of medications and coronary revascularization were evident. With respect to the large number of heart failure patients, different management strategies may finally contribute to the differences in the number of procedures.

In the 1995 Guidelines of the European Society of Cardiology on the diagnosis of heart failure[4], it was stated 'Invasive investigation is generally not required to establish the presence of coronary heart failure but may be important in elucidating the cause. . . . coronary angiography is required to exclude coronary disease when a diagnosis of dilated cardiomyopathy is being considered. In patients with heart failure and evidence of myocardial ischemia, coronary angiography will be required if revascularization is considered as treatment option'. Overall, this is quite a soft statement and had already raised comments when these Guidelines underwent review. Now, national differences in the way cases are managed have become apparent. The paper by Fox *et al*. clearly shows that the diagnosis of underlying coronary artery disease in heart failure patients can only be made with certainty by coronary angiography. It is now time to revise the proposal made in the 1995 Guidelines.

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