EDITORIAL

Asymptomatic Brugada syndrome: a cardiac ticking time-bomb?

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‘You have a ticking time-bomb in your body’ is an expression too commonly used by cardiovascular surgeons when counseling patients with asymptomatic aortic aneurysm. Such patients find it difficult to cope with their ‘ticking-bomb’ dilemma—which sooner or later may blow-out their aorta—and often opt for invasive therapy before the ‘risk-vs.-benefits’ section of the discussion is over. Based on the growing number of patients undergoing cardioverter defibrillator (ICD) implantation because of ‘asymptomatic Brugada syndrome with inducible ventricular fibrillation (VF),’ it appears that many cardiologists have adopted a ticking-bomb approach. Such aggressive approach was driven by studies by Brugada et al.2–4 convincingly showing (i) that a high percentage of asymptomatic patients with Brugada syndrome develop spontaneous VF within 3 years of diagnosis and (ii) that electrophysiologic studies (EPS) identify patients at risk for this potentially lethal outcome.2–4 More recent studies, however, do not confirm these observations.5,6 In this issue of the European Heart Journal, Paul et al.1 report a meta-analysis of Brugada syndrome that will force clinicians to pause and reevaluate the evidence supporting current practices.

Paul et al.1 carefully reviewed the literature and painstakingly contacted the authors of every study reporting on EPS in Brugada syndrome. They were able to compare data from >400 patients included in the ‘Brugada Series’ (which is the largest data-base reported by Brugada et al.),3 with data from >700 patients included in 15 different studies, referred to here as ‘the other studies.’ The main findings of Paul’s analysis1 are: (i) patients included in the Brugada Series have higher inducibility rates during EPS than patients included in all ‘the other studies’ (Figure 1); (ii) the high rate of spontaneous arrhythmic events reported in the Brugada Series was not observed in the other studies, explaining why other studies failed to reproduce the high positive predictive value for EPS (Figure 2).

How can we explain the higher inducibility rate reported in the Brugada Series?

One possible explanation is that patients in the Brugada Series have a worse disease and are therefore more inducible during EPS. The second possibility is that Brugada et al. achieve higher inducibility rates by using more aggressive EPS protocols. However, in the data compiled by Paul, the difference in inducibility cannot be credited to different patient characteristics or EPS protocols.1

Patient characteristics

The two patient characteristics consistently associated with higher inducibility rates (and worse prognosis) are ‘male gender’3,5,7 and ‘presence of coved ST segment elevation in the resting electrocardiogram (ECG)’ (as opposed to its appearance after challenge with a sodium channel blocker).3,5,7 However, according to Paul, the percentage of males included in the Brugada Series and in the other studies is similar.1 The same is true for the percentage of patients with spontaneous coved-type ST-elevation.1 Thus the higher inducibility rates achieved in the Brugada Series cannot be attributed to easily identifiable patient characteristics.

Electrophysiologic studies protocols

Brugada et al.3 stimulate only from the right ventricular apex (RVA), whereas other authors attempted to induce VF both from the RVA and the right ventricular outflow tract (RVOT).1 Even if one assumes that both sites are equally arrhythmogenic, simply by sequentially stimulating from two sites one would double the odds for inducing VF. In fact, two lines of evidence suggest that the RVOT is more...
arrhythmogenic. First, review of the studies\textsuperscript{8-14} reporting the contribution of each stimulating site to VF induction shows that 43 and 57\% of VF episodes were induced from the RVA and from the RVOT, respectively. This difference is meaningful because, generally, only patients who are non-inducible from the RVA undergo RVOT stimulation. Secondly, in one study meticulously comparing pacing sites, VF was always induced from the RVOT but was induced from the RVA in only 12\% of patients and was never induced from the left ventricle.\textsuperscript{13}

Studies also differ in the minimal coupling interval of the extrastimuli, whereas Brugada et al.\textsuperscript{3,4} limit the coupling interval of the ventricular extrastimuli to $\geq$200 ms, others limit the coupling interval only by ventricular refractoriness. This is important because the odds of inducing VF increase as the coupling interval is shortened $<200$ ms.\textsuperscript{15} Thus, the higher inducibility rate in the Brugada Series cannot be ascribed to more aggressive EPS protocols since the protocol used by Brugada is definitively less aggressive than protocols used by others.

The ‘founders’ effect’

Initial descriptions of hypertrophic cardiomyopathy from tertiary centres portrayed a very grim prognosis.\textsuperscript{16} As newer community-based studies appeared, a more balanced and less ominous picture was recognized.\textsuperscript{16} We may now be observing a similar phenomenon in Brugada syndrome. As shown in Figure 1 of Paul’s paper,\textsuperscript{1} the percentage of asymptomatic patients who went on to develop spontaneous VF during follow-up decreased in successive reports of the Brugada Series (from 27\% in their initial publication\textsuperscript{2} to 8\% in their second report\textsuperscript{17} and to only 5\% in their most recent publication\textsuperscript{3}). Patients included in the first report\textsuperscript{1} also appeared in subsequent publications,\textsuperscript{3,17} and apparently contributed the majority of arrhythmic events.

Induction of ventricular fibrillation in asymptomatic patients: what does it mean?

The odds of inducing VF in patients with Brugada syndrome are highest for cardiac arrest survivors, intermediate for patients with syncope and lowest for asymptomatic patients.\textsuperscript{1,3,6,17} This association between the vulnerability to spontaneous and induced ventricular arrhythmias suggests that EPS is of diagnostic value.\textsuperscript{18} It does not necessarily mean that the prognostic value of EPS is robust enough for clinical-decision making.

Two decades ago, debates similar to those now surrounding Brugada syndrome were held about the role of EPS in patients with heart disease.\textsuperscript{19} Animal data had shown that 40\% of healthy dogs have inducible VF with double extrastimulation and that the inducibility rate increases to 100\% when triple extrastimulation is performed from multiple ventricular sites.\textsuperscript{20} Thus, to establish the specificity of inducible ventricular arrhythmias, a few studies included patients considered to be at no risk for spontaneous arrhythmias as controls.\textsuperscript{21-25} It became evident that up to 6\% of controls have inducible VF with protocols using up to three extrastimuli (Table 1). This 6\% figure, however, underestimates the risk for ‘false positive’ (i.e. accidental) induction of VF because, to avoid the need for DC shock defibrillation in controls, the EPS protocol was prematurely terminated (when inductions of non-sustained polymorphic VT occurred) in $<45\%$ of controls (Table 1). Of note, the odds for inducing VF raise as the number of extrastimuli increases and their coupling interval is shortened. Unfortunately, this holds true both for ‘false positive’ VF inductions (i.e. the accidental provocation of VF in controls)\textsuperscript{15} and for ‘true positive’ VF inductions (i.e. in patients prone to develop spontaneous VF).\textsuperscript{16} Consequently, understanding the clinical significance of VF induction in asymptomatic patients, especially when the arrhythmia is induced with triple extrastimulation and short coupling intervals, is problematic.

Figure 2 shows the predictive value of EPS in patients with asymptomatic Brugada syndrome. The figure includes data for 263 patients included in the Brugada Series\textsuperscript{1} and 441
Table 1 Electrophysiologic studies that included patients at low risk for spontaneous arrhythmias as controls to evaluate the specificity of programmed stimulation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Controls</th>
<th>Pacing sites, BCL; output</th>
<th>Inducible NSPVT</th>
<th>Inducible VF</th>
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<td>Double VES</td>
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<tr>
<td>Brugada et al.</td>
<td>35 NHD ± SVT</td>
<td>RVA, 1 BCL; 2DT</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>Morady et al.</td>
<td>52 NHD = 16</td>
<td>RVA, 2 BCL; 5 mA</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Buxton et al.</td>
<td>28 NHD</td>
<td>RVA, 2 BCL; 2DT</td>
<td>NA</td>
<td>4%</td>
</tr>
<tr>
<td>Stevenson et al.</td>
<td>32 NHD + SVT</td>
<td>RVA, 3 BCL; 2DT</td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td>Belhassen et al.</td>
<td>30 NHD + VE</td>
<td>RVA + RVOT, 3 BCL; 3 mA</td>
<td>10%</td>
<td>7%</td>
</tr>
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In all these studies, the coupling interval of the extrastimuli was shortened until ventricular refractoriness was reached. Controls: NHD + SVT, NHD + VE = Patients with no heart disease evaluated for supraventricular tachycardia (SVT) or for ventricular extrasystoles (VE). RVA, RVOT = right ventricular apex and outflow tract.

*Data for NSVT inducibility available for 52 patients considered to be at low risk for arrhythmias, including 35 patients with no heart disease.24

*In these studies, induction of NSPVT, of 6 beats or more, led to premature ending of the pacing protocol.

In this study, 14 patients also underwent left ventricular stimulation.

6% of patients with no heart disease had inducible VF with double extrastimulation.

In this study, repetition of extrastimulation at the shortest coupling interval capturing the ventricle was performed 10 times.

2DT, pacing output was twice the diastolic pacing threshold; BCL, basic cycle lengths; VF, ventricular fibrillation. NSPVT, non-sustained polymorphic ventricular tachycardia; Double VES and triple VES, double and triple ventricular extrastimulation, respectively; NA, data not available; ND, not done.

patients from the other studies. The last group includes data carefully collected by Paul1 for 351 patients from 10 studies reporting EPS results and follow-up events, as well as data from 90 asymptomatic patients (including 52 patients with inducible VF) participating in a Japanese Registry that has not been published (data kindly provided by Drs Kamakura and Shimizu). There is universal agreement on the excellent negative predictive value of EPS (Figure 2). However, disagreement surrounds the positive predictive value of EPS. In the Brugada Series, 34% of asymptomatic patients had inducible VF and 12% of the latter developed spontaneous VF. These numbers are the basis for the recommending prophylactic ICD implantation when the EPS is positive. Yet, in the other studies only 9 (3.6%) of 254 asymptomatic patients with inducible VF developed spontaneous VF (with follow-up periods approaching 3 years in the larger studies). Information about the presence of spontaneous ‘coved-type’ ST-segment elevation was available for only 136 patients. For these patients, the risk for spontaneous VF—if the EPS was positive—was 5.1%.

Conclusion, limitations and clinical implications

The meta-analysis by Paul et al.1 shows that patients in the Brugada Series have high inducibility rate at EPS and high risk for subsequent spontaneous arrhythmias. Neither of these findings was substantiated by the other studies. As discussed above, it appears that the first patients recognized by Brugada et al. contributed an extraordinary number of spontaneous arrhythmic events, which in turn translated into better predictive accuracy for the EPS.

Reaching conclusions based on meta-analysis is risky. If one employs the meta-analysis approach, the pooled random effect of the vent rate in the other studies is 5.6% (95% confidence intervals 3.2–9.6%) compared to point estimation of 12% (95% confidence intervals 6.8–20.5%) in the ‘Brugada series’. The fact that the confidence intervals overlap suggests that the ‘true risk’ is somewhere in between.

The critical question is what to do until definitive data with longer follow-up periods are available. Prophylactic ICD implantation in Brugada syndrome is accompanied by high rates of complications.27,28 Infection after ICD replacement, as well as inappropriate ICD shocks (due to T-wave over-sensing, atrial arrhythmias, or lead fractures) are common in young patients.27,28 A recent European study reported serious complications in 28% of patients undergoing ICD implantation, whereas the odds for life-saving ICD therapy were only 1% per year for initially asymptomatic patients. Thus, it is morally justifiable to consider alternative approaches even if they are not entirely risk-free. Patients with Brugada syndrome may be ideal candidates for the extra-cardiac subcutaneous ICD (S-ICD) because they need only shock therapy. Patients should know that it may be in their best interest not to undergo ICD implantation now, but wait for the S-ICD, which may soon be available. In the meantime, patients and their relatives should master cardiopulmonary resuscitation and should learn about the advances in home-monitoring of arrhythmias and external automatic defibrillators. Finally, patients should be given the option of prophylactic drug therapy. Beta-blockers are the first-line of therapy for low- and medium-risk patients with congenital long QT syndrome and many enjoy years of safety with beta-blockers as their only therapy. The irony is that most of them would have undergone ICD implantation if the device had been available when the long-QT syndrome was described (as happened for Brugada syndrome). Quinidine appears to be a suitable therapy for this disease because of the following: (i) quinidine prevents phase-II reentry and VF in the wedge preparation of Antzelevitch;29 (ii) fully 76%–88%30 of patients who have inducible VF at baseline EPS are rendered non-inducible by quinidine therapy; (iii) quinidine is effective for aborting VF-storms;31 (iv) limited clinical data (from work pioneered by Belhassen)32 suggests that quinidine prevents spontaneous arrhythmias in high-risk patients with Brugada syndrome.8,30

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References


