and Lung Institute. Considerable clinical research collaboration is needed to identify the population most likely to respond favourably to a training programme in order to permit efficient resource utilization. The results of the Harrington paper suggest that the greatest benefit would be observed in deconditioned, well-motivated patients with symptomatic heart failure. This potential treatment deserves to be explored further. Our traditional focus on pharmacological intervention and central haemodynamics is clearly too narrow.

K. DICKSTEIN
Cardiology Division,
Central Hospital in Rogaland,
Stavanger, Norway

References
The electrocardiographic signature of the Brugada syndrome is dynamic and often concealed, but can be unmasked by potent sodium channel blockers such as flecainide, ajmaline and procainamide. Although intravenous administration of these drugs is most effective in unmasking the syndrome, oral formulations of flecainide have been reported to be effective as well. The specificity of the effect of sodium channel blockade in uncovering the syndrome and the prognostic significance of this finding remain to be fully elucidated.

Because of various ambiguities concerning the diagnostic criteria for the Brugada syndrome, the incidence remains poorly defined. For these same reasons, it has been difficult to establish what fraction of idiopathic ventricular fibrillation cases may be attributable to the Brugada syndrome. In this issue, Remme et al. report the results of a single-centre study designed to assess the prevalence of the Brugada syndrome among 37 patients diagnosed with idiopathic ventricular fibrillation. All are survivors of sudden death in whom structural disease, acute myocardial infarction, pre-excitation and the long QT syndrome were ruled out with a battery of invasive and non-invasive tests. Depending on the diagnostic criteria applied (complete or incomplete right bundle branch block and ST segment elevation [1 or 2 mm] in the absence or presence of sodium channel blockers), the incidence of the Brugada syndrome in this cohort of idiopathic ventricular fibrillation patients ranged between 3 and 24%. The larger figure is similar to that recently reported by Viskin and coworkers (21%) but is considerably below the 40–60% value initially conjured by Chen et al. in 1997. Taking into consideration the fact that the study by Remme et al., like the study by Viskin et al., did not test the effects of sodium blockers in all patients, it is possible that the true incidence may lie somewhere between these two ranges (24–40%).

The report by Remme et al. raises a critically important issue in demonstrating the sensitivity of the outcome on the diagnostic criteria applied. What are the proper diagnostic criteria to be used in identifying the Brugada syndrome? A definitive answer to this question is currently out of reach but will no doubt evolve with time as clinical data become available and as our understanding of the underlying mechanisms advances. The priority that we assign current diagnostic parameters is predicated on our limited clinical knowledge and understanding of the cellular mechanisms responsible for the unique ECG features and arrhythmogenicity of the Brugada syndrome which we discuss below.

Proposed cellular and ionic mechanisms underlying the Brugada syndrome

The cellular basis for the Brugada syndrome is thought to be due to an outward shift in the ionic current active during phase 1 of the right ventricular epicardial action potential. A rebalancing of the currents contributing to the early phases of the action potential can accentuate the action potential notch or lead to all-or-none repolarization at the end of phase 1, causing loss of the epicardial action potential dome and marked abbreviation of the action potential at that site. A variety of pathophysiological conditions (e.g. ischaemia, metabolic inhibition, hypothermia, pressure) and some pharmacological interventions are known to effect these changes in canine and feline ventricular cells in which Ito is prominent. Under these pathophysiological conditions or in response to agents that reduce INa or ICa, or agents that activate IK-ATP or augment IKr, ICa(Ca) or Ito, canine ventricular epicardial cells exhibit an accentuation of the spike and dome morphology of the action potential, resulting in a delay in the development of the dome, secondary to widening of the action potential notch. A further shift in the balance of current leads to loss of the action potential dome and marked abbreviation of the epicardial response. The dome fails to develop because the outward currents flowing at the end of phase 1 overwhelm the inward currents that normally give rise to the secondary upstroke and action potential plateau.

Genetic mutations that affect these same currents are capable of producing the Brugada syndrome. The only gene thus far linked to the syndrome is the a subunit of the cardiac sodium channel gene, SCN5A, the same gene implicated in the LQT3 form of the long QT syndrome. In fact, Bezzina and co-workers recently reported a mutation in SCN5A (1795InsD) capable of producing both the Brugada and LQT3 phenotypes. Three types of mutations in SCN5A have been uncovered thus far, and shown to result in: (1) failure of the sodium channel to express; (2) reduced current due to a shift in the voltage- and time-dependence of INa activation, inactivation or reactivation; and (3) reduced contribution of INa during the early phases of the action potential due to accelerated inactivation of the sodium channel. Insertion of two nucleotides (AA) at the 5' end, deletion of a single nucleotide (A) at codon 1397 leading to an in-frame stop codon and some missense mutations (R1432G) result in disruption of protein formation and failure of channel expression. Other insertion mutations (1795InsD) cause a positive shift of activation and negative shift
of inactivation curves, resulting in a reduction of \( I_{\text{Na}} \). In the case of the T1620M missense mutation, inactivation of \( I_{\text{Na}} \) is accelerated such that \( I_{\text{to}} \) is left unopposed during phase 1 of the action potential, resulting in a strong predominance of the outward repolarizing current at the end of phase 1, thus providing the substrate for the Brugada syndrome.

This change in the function of the sodium channel is observed at physiological temperatures, but not at room temperature, typically used in studies of function involving heterologous expression systems. It is interesting that this characteristic of the mutant channel is exaggerated at temperatures above the physiological range, pointing to the possibility that patients with the Brugada syndrome may be at more risk during a febrile state. Several Brugada patients displaying fever-induced polymorphic ventricular tachycardia have been identified since the publication of this report. Other mutations such as L567Q, reported by Priori et al. to be responsible for the Brugada syndrome in children, also act by importantly accelerating inactivation of \( I_{\text{Na}} \). In comparison with T1620M, the dysfunction of the sodium channel with this missense mutation located in the DI-DII linker of \( SCN5A \) is less temperature sensitive (Dumaine, Priori and Antzelevitch, unpublished data). The temperature dependence of most mutations thus far described for the Brugada syndrome is not known because most are expressed in Xenopus oocytes and studied at room temperature.

Two other missense mutations, R1512W and A1924T, linked to the Brugada syndrome produce negative shifts of either activation (−5.1 and −9 mV, respectively) and/or inactivation (−3.8 and 0 mV, respectively) curves. The voltage shifts and other relatively minor effects of these missense mutations on the biophysical properties of \( SCN5A \) (measured at room temperature) appear inadequate to explain the electrocardiographic manifestation of the Brugada syndrome.

In addition to \( SCN5A \), gene mutations that alter the intensity or kinetics of either \( I_{\text{to}} \), \( I_{\text{Kr}} \), \( I_{\text{K,ATP}} \), \( I_{\text{Ca}} \) or \( I_{\text{Cl(Ca)}} \) so as to increase the activity of the outward currents and/or diminish that of the inward currents are candidates for the Brugada syndrome. Other candidate genes include those encoding for autonomic receptors which directly modulate ion current density and/or alter the expression of channels in the membrane (e.g., sympathetic control of \( I_{\text{to}} \)).

The cellular changes believed to underlie the Brugada phenotype are shown in Fig. 1. The presence of an \( I_{\text{to}} \)-mediated spike and dome morphology or notch in the ventricular epicardium, but not endocardium, of larger mammals creates a transmural voltage gradient responsible for the inscription of the electrocardiographic J wave (Osborn wave). Under normal conditions, the J wave is relatively small, in large part reflecting the left ventricular action potential notch, since that of the right ventricular epicardium is usually buried in the QRS. The ST segment is isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau (Fig. 1(a)). Accentuation of the right ventricular notch under pathophysiological conditions is attended by exaggeration of transmural voltage gradients and thus exaggeration of the J wave or J point elevation and/or the appearance of a saddleback configuration of the repolarization waves (Fig. 1(b)). The development of a prominent J wave can also be construed as ST segment elevation. Under these conditions, the T wave remains positive because epicardial repolarization precedes repolarization of the cells in the M and endocardial regions. Further accentuation of the notch may be accompanied by prolongation of the epicardial action potential such that the direction of repolarization across the right ventricular wall and transmural voltage gradients are reversed, thus leading to the development of a coved-type of ST segment elevation and inversion of the T wave (Fig. 1(c)), typically observed in the ECG of Brugada patients. A delay in epicardial activation may also contribute to inversion of the T wave.

The downsloping ST segment elevation or accentuated J wave observed in the experimental wedge models often appears as an R′, suggesting that the right bundle branch block morphology often encountered in the Brugada ECG may be due to early repolarization of the right ventricular epicardium and not to conduction block in the right bundle. Indeed, rigorous application of right bundle branch block criteria reveals that a large majority of right bundle branch block-like morphologies encountered in cases of the Brugada syndrome do not fit the criteria. Moreover, attempts by Miyazaki and co-workers to record delayed activation of the right ventricle in Brugada patients met with failure.

It is interesting to note that although the typical Brugada morphology is present in Figs 1(b) and (c), the substrate for reentry is not. A further shift in the balance of current, leads to loss of the action potential dome at some epicardial sites, which would manifest in the ECG as a further ST segment elevation (Fig. 1(d)). The loss of the action potential dome in epicardium but not endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window during
Figure 1  Schematic showing right ventricular epicardial action potential changes thought to underlie the electrocardiographic phenotype of the Brugada syndrome.
which a premature impulse or extrasystole can induce a reentrant arrhythmia. Because loss of the action potential dome in the epicardium is generally not spatially uniform, we see the development of a striking epicardial dispersion of repolarization (Fig. 1(d)). Support for these hypotheses derives from experiments involving the arterially perfused right ventricular wedge preparation[13].

Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local reexcitation via a phase 2 reentry mechanism, leading to the development of a closely coupled extrasystole, capable of triggering circus movement reentry (Figs 1(e) and 2)[13,22]. The phase 2 reentrant beat fuses with the negative T wave of the basic response. Because the extrasystole originates in the epicardium the QRS is largely comprised of a Q wave, which serves to accentuate the negative deflection of the inverted T wave, thus giving the ECG a more symmetrical appearance. This morphology is often observed in the clinic preceding the onset of polymorphic ventricular tachycardia.

Phase 2 reentry is observed in canine epicardium exposed to: (1) K+ channel openers; (2) sodium channel blockers; (3) increased [Ca2+]o; (4) metabolic inhibition; (5) simulated ischaemia and (6) local pressure applied to the right ventricular epicardium (see[23] for references). Phase 2 reentry has been shown to trigger circus movement reentry in isolated sheets of the right ventricular epicardium[22] as well as in the intact wall of the canine right ventricle[19,24]. The arrhythmia commonly takes the form of polymorphic ventricular tachycardia, resembling a rapid torsade de pointes, often indistinguishable from...
ventricular fibrillation. In other cases, the experimental model displays monomorphic ventricular tachycardia. Both are observed in patients with the Brugada syndrome, although the polymorphic form is much more common.

Local pressure alone applied to a discrete right ventricular site can also produce loss of the action potential, ST segment elevation, phase 2 reentry and ventricular tachycardia/ventricular fibrillation in the arterially-perfused right ventricular wedge preparation\[13\]. This mechanism may be responsible for the Brugada-like syndrome caused by a mediastinal tumour compressing the right ventricular outflow tract\[25\].

The mechanism proposed to underlie the Brugada syndrome is one that provides the substrate for the development of circus movement reentry in the form of epicardial and transmural dispersion of repolarization, as well as the trigger for ventricular tachycardia/ventricular fibrillation in the form of a phase 2 reentrant extrasystole.

**Clinical correlation**

The experimental findings suggest that a depressed right ventricular epicardial action potential dome is the basis for the accentuated J wave or ST segment elevation, and that phase 2 reentry is a trigger for episodes of circus movement reentry that are responsible for ventricular tachycardia and ventricular fibrillation in Brugada patients. There are a number of similarities between the conditions that give rise to ST segment elevation and phase 2 reentry in the experimental models and those that attend the appearance of the Brugada syndrome. Accentuation of the action potential notch or loss of the action potential dome in epicardium but not endocardium leads to elevation of the ST segment, with either a saddleback or coved appearance, similar to those recorded in patients with the Brugada syndrome\[19–21\]. In Brugada patients, as in the wedge preparation, ventricular tachycardia/ventricular fibrillation is inducible in the majority of cases. In the study by Remme et al.\[10\] ventricular tachycardia/ventricular fibrillation could be induced in 67% and 54% of Brugada and non-Brugada ventricular fibrillation patients, respectively. In the wedge preparation, ventricular tachycardia/ventricular fibrillation is most easily induced by the application of an extrastimulus to the site of briefest refractoriness, always located on the epicardial side. In the clinic, programmed stimulation is most commonly applied to right ventricular endocardium. An epicardial approach is possible via the coronary sinus and it is of interest that in a recent case report ventricular tachycardia/ventricular fibrillation was shown to be non-inducible with endocardial extrastimulation, but readily inducible using an electrode placed deep within the coronary sinus\[26\]. Is it possible that a larger fraction of idiopathic ventricular fibrillation patients would be determined to be inducible using programmed electrical stimulation via a coronary sinus approach? If this was a criterion for the diagnosis of the Brugada syndrome, could failure to use this approach lead to under-estimation of risk or prevalence of the syndrome?

In isolated epicardial tissues as well as in wedge preparations, loss of the action potential dome and phase 2 reentry are readily induced in right ventricular preparations, but are more difficult to induce in the left ventricle. These findings are due to the presence of a much more prominent I_{to} in right vs left ventricular epicardium and are consistent with the appearance of ST segment elevation only in right precordial leads in patients with the Brugada syndrome. Normalization of the ST segment in response to an increase in rate is observed in the wedge model as well as in some Brugada patients\[21\], and is consistent with a decreased availability of I_{to} (due to relatively slow recovery from inactivation) which diminishes the notched configuration of the epicardial action potential. Not all Brugada patients display rate-dependent changes in ST. With some mutations, such as those involving a slowing of reactivation of the sodium channel, or in the presence of sodium channel blockers with strong use-dependence, acceleration may be attended by ST segment elevation.

Because accentuation of the notch and/or loss of the dome are caused by an outward shift in the balance of currents active at the end of phase 1 (principally I_{to} and I_{Ca}), autonomic neurotransmitters like acetylcholine facilitate these changes in the action potential\[27\] by suppressing I_{Ca} and/or augmenting potassium current, whereas beta-adrenergic agonists restore the dome by augmenting I_{Ca}. As a consequence, in the arterially perfused wedge, vagal and sympathetic influences exaggerate and reduce ST segment elevation, respectively\[19\]. Accentuation of ST segment elevation in patients with the Brugada syndrome following vagal manoeuvres and normalization of the ST segment following beta-adrenergic agents are consistent with these findings\[21\].

The effect of sodium channel blockers to facilitate loss of the right ventricular epicardial action potential dome in the wedge and in isolated tissues\[28\] is consistent with their ability to\[19\] unmask the Brugada syndrome in the clinic\[9\]. Moreover, linkage of the Brugada syndrome to mutations in SCN5A is consistent with conduction disturbances that sometimes accompany the Brugada syndrome\[29\].

Eur Heart J, Vol. 22, issue 5, March 2001
While augmentation of $I_{to}$ may precipitate phase 2 reentry and the Brugada syndrome, it is not a prerequisite. However, the presence of a prominent $I_{to}$ is essential. Because of the pivotal role of $I_{to}$, agents that inhibit $I_{to}$, including 4-aminopyridine and quinidine, restore the action potential dome and electrical homogeneity, thus suppressing all arrhythmic activity. Agents that potently block $I_{Na}$ but not $I_{to}$ (flecainide, ajmaline and procainamide), exacerbate or unmask the Brugada syndrome, whereas those with actions to block both $I_{Na}$ and $I_{to}$ (e.g. quinidine and disopyramide) may exert an ameliorative effect. The anticholinergic effects of quinidine and disopyramide may also contribute to their effectiveness. An experimental drug that may be useful in the treatment of the Brugada syndrome and other syndromes associated with an ST segment elevation is tedisamil, an agent that blocks a variety of outward potassium currents, including $I_{to}$.

Because the syndrome has come to the forefront only recently, there is relatively little information about pharmacological interactions and conditions that exacerbate the Brugada syndrome. From our limited knowledge, there is reason to be wary of agents or agencies that significantly reduce sodium or calcium channel current and/or augment outward potassium or chloride currents during the early phases of the action potential. In addition to those agents already discussed, possible culprits include fatty acids, which are known to reduce $I_{Na}$, agents that augment cGMP, including nitrates, as well as conditions that reduce $I_{Na}$ and $I_{ca}$ while augmenting $I_{to}$, such as chronic iron overload. The superimposition of mild ischaemia or of a pharmacological intervention on the existing intrinsic anomalies may suffice to shift the balance of current so as to create an arrhythmogenic substrate.

On the other side of the spectrum are patients who present with an apparently normal ECG but are prone to develop ventricular fibrillation. To what extent may these be representative of the Brugada population? While genetic data are available for individuals with the Brugada phenotype, none are available for the ‘idiopathic ventricular fibrillation’ group. It is noteworthy that the two groups have previously been shown to be of similar age at time of presentation and to exhibit similar spontaneous and inducible arrhythmias. These findings are reasserted in the study by Remme et al. In that study, the two groups were also found to have similar (uncommon) familial involvement. In contrast, Viskin et al. reported that the two groups differ significantly with respect to familial involvement, it being relatively common in the Brugada group, but largely absent in the idiopathic ventricular fibrillation group.

To what extent should ST segment elevation be manifest in the ECG of patients diagnosed as Brugada? The extent to which ST segment elevation is observed depends on the specific site affected relative to the position of the precordial electrodes and the extent to which right ventricular epicardium is affected. When the region is limited in area, the ST segment may not be as readily apparent when recorded with normal precordial leads, although the substrate may be no less arrhythmogenic. Displacement of the right precordial leads from their standard positions may be helpful in revealing the affected regions, as recently demonstrated by Shimizu et al. using body surface potential mapping techniques. In the idiopathic ventricular fibrillation population this may prove to be a valuable criterion for diagnosing the Brugada syndrome and failure to do so may result in under-diagnosis of the disease.

C. ANTZELEVITCH
Masonic Medical Research Laboratory,
Utica, New York, U.S.A.

References
Screening for drug-induced (acquired) long QT syndrome: is it time to apply new methods?

See page 410 for the article to which this Editorial refers

Lande et al.\textsuperscript{[1]} have performed a nice investigation, throwing new light onto the diagnostic criteria of the long QT syndrome by exploring a large French family with the Romano–Ward syndrome followed-up for 25 years. In this family, as expected\textsuperscript{[3]}, the electrocardiographic QT interval normalized when the males grew-up. In adulthood, however, the corrected QT


\textsuperscript{[6]} Carlson J, Erdogan A, Schulte B et al. Possible role of left ventricular programmed stimulation in Brugada syndrome. PACE 2000; (In Press).


\textsuperscript{[10]} Xiao YF, Wright SN, Wang GK et al. Coexpression with beta(1)-subunit modifies the kinetics and fatty acid block of hH1(alpha) Na(+) channels [In Process Citation]. Am J Physiol Heart Circ Physiol 2000; 279: H35–H46.

