

# Drug-induced Brugada syndrome

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Brugada syndrome is an inherited cardiac arrhythmia condition characterized by (i) coved ST-elevation and J point elevation of at least 2 mm in at least two of the right precordial ECG leads (V1–V3) and (ii) ventricular arrhythmias, syncope, and sudden death. Patients with Brugada syndrome or suspected mutation carriers can have normal ECG recordings at other times. In these cases, a diagnostic challenge with a sodium channel blocker such as ajmaline, flecainide, or pilsicainide may induce the full-blown type 1 ECG pattern and support the diagnosis. However, recently, many other pharmacological agents not related to class I anti-arrhythmic agents have been reported to induce Brugada ECG patterns including tricyclic antidepressants, fluoxetine, lithium, trifluoperazine, antihistamines, and cocaine. As published reports of the drug-induced Brugada sign have become increasingly prevalent, there is growing interest in the mechanisms responsible for this acquired ECG pattern and its clinical significance. It is possible that drug-induced Brugada syndrome may be due to an individual susceptibility that favours drug-induced ECG abnormalities, possibly as a result of an increase in a latent ion channel dysfunction similar to that in drug-induced long QT syndrome. However, further evidence is needed to confirm this postulation. In this paper, we will review the cases and evidence of drug-induced Brugada syndrome reported in the literature.

**Keywords** Drug-induced Brugada syndrome • Sudden cardiac death

## Introduction

Brugada syndrome is an inherited cardiac arrhythmia condition, characterized by coved ST elevation and J point elevation of at least 2 mm in at least two of the right precordial ECG leads (V1–V3) that are unrelated to ischaemia, electrolyte disturbances, or obvious structural heart disease. It is also characterized by ventricular arrhythmias, atrial arrhythmias, syncope, and sudden death. The diagnosis in an individual requires the presence of the Brugada ECG pattern as described above (type 1) with at least one of the recognized diagnostic criteria: syncope, prior cardiac arrest, documented or inducible polymorphic ventricular tachycardia or ventricular fibrillation, a family history of sudden death <45 years old, or type 1 Brugada pattern and/or nocturnal agonal respiration.<sup>1</sup> It is a familial condition that displays an autosomal dominant mode of transmission, with incomplete penetrance and an incidence ranging between 5 and 66 per 10 000.<sup>2,3</sup> The majority of patients with Brugada syndrome are caused by mutations in the cardiac sodium channel gene *SCN5A*, the gene encoding for the  $\alpha$ -subunit of the sodium channel.<sup>4</sup> Recently, however, a subgroup of familial sudden cardiac death syndrome in which a Brugada syndrome phenotype is combined with short QT intervals (rate corrected QT interval  $\leq 360$  ms) has been identified. In these patients, loss-of-function missense mutations in *CACNA1C* (A39V and

G490R) and *CACNB2* (S481L) encoding the  $\alpha 1$ - and  $\beta 2$ -subunits of the L-type calcium channel have been found to be the underlying cause.<sup>5</sup> Similarly, a mutation in the glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) gene has also been identified as a less common cause of Brugada syndrome.<sup>6,7</sup> In these patients, the mutation in GPD1-L gene causes a decrease in the *SCN5A* surface membrane expression and a subsequent reduction in the inward sodium current across the cell membrane by as much as 50%, resulting in the phenotypical appearance of Brugada syndrome. The mechanism by which GPD1-L mutations alter the sodium channel membrane expression is currently unknown, although alteration in the cellular oxidative state has been suggested.<sup>6</sup>

Brugada phenotype is more prevalent in males and is a result of the presence of a more prominent  $I_{to}$  channels in males than females.<sup>8</sup> Carriers of the condition are at high risk of ventricular tachycardia, ventricular fibrillation, and sudden cardiac death. Syncope episodes and paroxysmal palpitations are the only symptoms the patient may have before sudden arrhythmic death occurs. Brugada syndrome is estimated to be responsible for at least 20% of sudden deaths in patients with structurally normal hearts.<sup>1</sup> In regions of Southeast Asia where it is endemic, the clinical presentation of Brugada syndrome is distinguished by a male predominance (8:1 ratio of male:female) and the appearance of

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arrhythmic events at an average age of 40 years (range: 1–77 years).<sup>9</sup>

## Patho-mechanism of Brugada syndrome

The exact electrophysiological mechanism of this syndrome has not yet been fully elucidated. Three mechanisms are proposed for ST-segment elevation in Brugada syndrome: local conduction abnormality, local ventricular depolarization, and early repolarization abnormality.<sup>10,11</sup> The latter hypothesis postulates an accentuation of the action potential notch in the right ventricular epicardium carried by the transient outward current ( $I_{to}$ ) via a reduction in the fast sodium inward current ( $I_{Na}$ ). In theory, a reduction in  $I_{Na}$  or L-type  $I_{Ca}$  or an increase in  $I_{to}$  (dominant at epicardium) would produce a striking abbreviation of the epicardial action potential, which would lead to an epicardial–endocardial heterogeneity of repolarization that would cause ST-segment elevation. Thus, a genetic defect in the cardiac sodium channel gene *SCN5A* may lead to a reduction in the transmural sodium voltage gradient, which is normally responsible for the inscription of the J wave, giving rise to a saddleback-form ST-segment elevation if the epicardial repolarization precedes repolarization in mid- and endocardial regions. Further accentuation of the notch accompanied by a prolongation of the epicardial action potential may lead to the development of a coved-type ST-segment elevation. Ultimately, a loss of the action potential dome at some epicardial sites may result. As a consequence, marked intramural dispersion of repolarization may be responsible for local re-excitation via phase 2 re-entry.<sup>10</sup> When coupled with extrasystoles capable of initiating circus movement, a re-entry arrhythmia can be triggered. Pharmacological agents that primarily block  $I_{Na}$  but not  $I_{to}$  (flecainide, ajmaline, and procainamide) can further diminish sodium current already reduced by the Brugada mutations. This hypothesis may explain the use of sodium channel blockers to unmask concealed forms of the Brugada syndrome and the potential pro-arrhythmic adverse effects of these and other pharmacological agents.

## Brugada syndrome mimicry

It is important to exclude other conditions that may mimic the Brugada ECG pattern. These include structural disease that may be hereditary (arrhythmogenic right ventricular cardiomyopathy) or acquired (e.g. acute myocardial infarction or ischaemia of the right heart, pulmonary embolism, or cardiac compression) and similar ECG patterns in normal hearts (e.g. early repolarization syndrome, electrolyte imbalance, or hypothermia). They are separate clinical entities and have different pathophysiologies and prognoses.<sup>1</sup>

## Drug-induced Brugada syndrome

Patients with proved Brugada syndrome can have normal ECG recordings at other times. Brugada syndrome can also be incompletely expressed in a family. Known or suspected mutation

carriers may display a normal ECG or a partial non-diagnostic Brugada pattern of a saddle-shaped ST segment with or without elevation: the type 2 and 3 ECG patterns, respectively. In these cases, a diagnostic challenge with a sodium channel blocker such as ajmaline, flecainide, or pilsicainide may induce the full-blown type 1 ECG pattern and support the diagnosis in a family member.<sup>1</sup>

On the other hand, the Brugada sign has been described in asymptomatic patients after exposure to various drugs.<sup>12</sup> These patients normally do not have any symptoms or history of ventricular arrhythmias. In these asymptomatic patients, the abnormal ECG often can be reproduced by class 1A and 1C antiarrhythmic drugs, such as flecainide, procainamide, or ajmaline, which block the sodium channel.<sup>13,14</sup> Autonomic influence is also important:  $\alpha$ -adrenergic blockade reduces the ST-segment elevation, whereas  $\alpha$ -adrenergic stimulation has the opposite effect.<sup>14</sup> It has become apparent subsequently that sporadic cases of the Brugada ECG pattern without a family history of the condition may be 'unconcealed' by exposure to drugs with sodium channel blocking effects.<sup>15,16</sup> Theoretically, therefore, an acquired intervention that causes a sufficient imbalance of inward and outward currents in the right ventricular outflow tract may induce the surface ECG pattern in an individual, although the likelihood of arrhythmias is unclear. Whether this requires an underlying genetic predisposition or represents latent Brugada syndrome has not been established.

The characteristic ECG pattern of ST-segment elevation in V1 and V2 in the Brugada syndrome is dynamic; it is often intermittently present in affected individuals and can be unmasked by sodium channel blockers as mentioned above.<sup>15,17–26</sup> However, recently, many other pharmacological agents not related to class I antiarrhythmic agents have been reported to induce Brugada ECG pattern including tricyclic antidepressants (TCAs), fluoxetine, lithium, trifluoperazine, antihistamines, and cocaine. In a survey of 1000 normal subjects in whom two ECGs were systematically recorded, the prevalence of drug-induced Brugada syndrome (confirmed on a sodium channel blockade challenge) was reported to be 5 out of 1000.<sup>16</sup>

As published reports of the drug-induced Brugada sign have become increasingly prevalent, there is growing interest in the mechanisms responsible for this acquired ECG pattern and its clinical significance. It is possible that drug-induced Brugada syndrome may be due to an individual susceptibility that favours drug-induced ECG abnormalities, possibly as a result of an increase in a latent ion channel dysfunction similar to that in drug-induced long QT syndrome. However, further evidence is needed to confirm this postulation. In this paper, we will review the cases and evidence of drug-induced Brugada syndrome reported in the literatures.

## Tricyclic antidepressants

Tricyclic antidepressants exhibit a dose-related risk of sudden cardiac death, with a relative risk (RR) of 2.5 at maximal doses of amitriptyline compared with control subjects.<sup>27</sup> At or just above therapeutic levels, TCAs also have a quinidine-like antiarrhythmic action, with effects on repolarization. Hence, fatalities due to TCA overdose may be a result of QT prolongation and torsades de pointes.<sup>28</sup> The most common adverse cardiovascular

effects of TCAs, however, are slowing of intraventricular conduction, manifested by prolongation of the PR and QRS intervals QT prolongation, torsades de pointes, and postural hypotension.<sup>27,28</sup> In addition, there have been reports of patients exhibiting transient Brugada type 1 ECG in the right precordial leads and marked QRS widening following therapeutic dosing and overdose of amitriptyline.<sup>29,30</sup> In two cases of overdose, nortriptyline has been reported to induce the type 1 ECG pattern associated with ventricular fibrillation and cardiac arrest.<sup>31,32</sup> In a series of 95 cases of cyclic antidepressant overdoses,<sup>33</sup> 10 (10.5%) presented with the Brugada ECG, 1 of whom died of recurrent ventricular fibrillation compared with 1 death among those without the Brugada ECG.

In a recently published series, however, 65 young patients without a history of cardiovascular disease who had taken intentional overdoses of either amitriptyline or clomipramine, 15% exhibited the type 1 Brugada pattern.<sup>34</sup> Although ventricular arrhythmia or cardiac arrest was not reported in this series, a case of cardiac arrest associated with a type 1 pattern following high-dose amitriptyline intoxication has been described elsewhere.<sup>35</sup>

In another series of 402 patients, the incidence of a type 1 Brugada ECG pattern was reported to be only 2.3%.<sup>36</sup> Interestingly, these patients had an increased incidence of non-cardiac adverse outcomes including seizures (RR: 4; 95% CI: 1.5–10.8) and hypotension (RR: 3.9; 95% CI: 2.1–7.4). A widened QRS interval was also present (RR: 4.8; 95% CI: 1.8–12.9) but there were no deaths or ventricular arrhythmias. Thus, TCA-induced Brugada syndrome (type 1 ECG and sudden death or arrhythmias) appears rare.

The primary mechanism of these ECG changes is likely to be sodium channel antagonism. TCAs cause a decrease in the maximum rate of rise ( $V_{\max}$ ) of phase 0 of the action potential in canine Purkinje fibres. This confirms that these drugs possess effects similar to Class I antiarrhythmics.<sup>37</sup> Amitriptyline, however, not only acts in this manner<sup>38</sup> but also reduces  $I_{\text{to}}$  activation.<sup>39</sup>

The type 1 Brugada ECG has also been reported following ingestion of TCAs at therapeutic levels in patients who had normal ECG when medication exposure was removed: for example, nortriptyline<sup>40</sup> and desipramine.<sup>41,42</sup> In both desipramine-related cases, the Brugada ECG pattern manifested itself after the dosage was increased. One patient developed recurrent but successfully resuscitated ventricular fibrillation and was subsequently found to have the His558Arg SCN5A polymorphism.<sup>42</sup> Its relevance in this context is unclear, although polymorphisms have been identified in other drug-associated ventricular arrhythmias. Thus, it is possible that TCA-induced Brugada syndrome is related to the genetic susceptibility of an individual.

Rare reports of similar cardiotoxicity with other psychotropic medications have also been described but their true significance is unclear: maprotiline (heterocyclic antidepressant), fluoxetine (selective serotonin reuptake inhibitor), and trifluoperazine (phenothiazine).<sup>29,30</sup> Nonetheless, fluoxetine, similar to amitriptyline, depresses sodium and calcium channel activation in cardiac myocytes and induces significant shortening of the action potential duration (APD) in guinea pig, rabbit, and canine ventricular myocytes.<sup>43</sup> Similarly, phenothiazines decrease the  $V_{\max}$  and

amplitude of phase 2.<sup>44,45</sup> The shortened APD may therefore induce an intramyocardial electrical gradient, the Brugada ECG pattern, and possibly the substrate for re-entry.

## Lithium

Lithium is a commonly used drug in the treatment of depressive and bipolar affective disorders. Cardiac side effects have been described at both therapeutic and toxic serum levels in adult patients. Lithium has been associated with non-specific T wave abnormalities (inverted, flattened, or bifid T waves) without QT prolongation.<sup>46</sup> Other conduction defects and rhythm disturbances have also been reported, including sinus node dysfunction, atrial flutter, atrioventricular block, right bundle-branch block, left anterior hemiblock, ventricular tachycardia, and ventricular fibrillation.<sup>47,48</sup>

Recently, two cases of lithium therapy unmasking the type 1 Brugada ECG pattern have been reported, both with other features suggestive of the Brugada syndrome.<sup>49</sup> In one of the patients, the type 1 pattern occurred when lithium levels were therapeutic. Lithium withdrawal in both patients resulted in resolution of ECG abnormalities. In Chinese hamster ovary cells transfected with SCN5A, which encodes the cardiac sodium channel, lithium chloride caused potent cardiac sodium channel blockade in a concentration-dependent manner at levels well below the therapeutic range (IC<sub>50</sub> of  $6.8 \pm 0.4 \mu\text{mol/L}$ ). This is the probable mechanism of action in unmasking patients with underlying Brugada syndrome.<sup>49</sup> Whether the induction of the type 1 ECG pattern in patients without other features of Brugada syndrome indicates an increased risk for sudden cardiac death is unclear.

## Antihistamines

The Brugada type 1 ECG has been elicited in patients treated with first-generation antihistamines. One patient, receiving an intravenous infusion of dimenhydrinate for the treatment of labyrinthopathy, developed transient coved-like ST elevation in the right-sided precordial leads. Although the patient had no history of syncope and no family history of cardiac disease or sudden death, the ECG abnormality was reproduced with intravenous flecainide and asymptomatic Brugada syndrome was diagnosed.<sup>50</sup>

In another case report, a 39-year-old patient with an overdose of diphenhydramine became unconscious and hypotensive and subsequently developed the type 1 ECG pattern.<sup>51</sup> His serum potassium concentration was 8.3 mEq/L but the ECG abnormalities failed to settle despite correction of the hyperkalaemia and an intravenous infusion of isoproterenol. They subsequently normalized spontaneously. A negative flecainide test suggested that these transient ECG abnormalities were the consequence of the drug overdose and not the unmasking of an underlying Brugada syndrome by diphenhydramine.

## Cocaine

Sudden unexpected death due to cocaine in young otherwise healthy individuals occurs in an idiosyncratic manner and is commonly felt to be arrhythmogenic in nature, although the exact

cause of death is rarely documented. In addition to indirect sympathomimetic actions, cocaine has a potent sodium channel blocking effect resembling that of flecainide.<sup>52</sup> The sodium channel blocking property of cocaine is now thought to be a major mechanism behind cocaine-induced sudden cardiac death.

A case of transient Brugada type 1 ECG pattern provoked by recreational cocaine use has been reported in an individual with a normal baseline ECG.<sup>53</sup> An electrophysiological study performed in the presence of these changes was unremarkable and challenge with procainamide, propranolol, and noradrenaline failed to re-induce the pattern. Its clinical importance is unclear.

More commonly, cocaine-induced Brugada syndrome has been reported following overdose with the drug. In one case, a patient with massive cocaine ingestion complicated by generalized seizures, an asystolic cardiac arrest and severe metabolic acidosis, developed right bundle branch block, left anterior fascicular block, QRS and QT prolongation, and coved ST-segment elevation in leads V1 and V2. Sodium bicarbonate administration rapidly normalized cardiac conduction and the Brugada pattern settled slowly. Subsequent flecainide challenge was unremarkable.<sup>54</sup> Several similar cases of drug-induced Brugada syndrome following cocaine overdose have also been reported.<sup>55–57</sup> Cocaine significantly prolonged the PR, QRS, QTc, AH, and HV intervals in a canine model.<sup>58</sup> During cocaine toxicity, myocardial depression, malignant arrhythmias, and sudden death could relate in part to its potent sodium channel blockade<sup>59,60</sup> resembling flecainide.<sup>52</sup>

Interestingly, the class IB antiarrhythmic lidocaine, much like cocaine, inhibits the voltage-gated cardiac sodium channels but has an antiarrhythmic effect, whereas cocaine may be pro-arrhythmic. This may be explained by lidocaine's other actions on  $I_{Na}$  that are not shared with cocaine: a strong voltage-dependence of  $I_{Na}$  inhibition; and a large leftward shift of the steady-state inactivation to hyperpolarized potentials which appeared to be very important in the prevention of fatal arrhythmias by lidocaine.<sup>61</sup>

## Bupivacaine

Although class 1A and 1C antiarrhythmic agents have been used to identify concealed Brugada syndrome, lidocaine, also used as a local anaesthetic, does not.<sup>14</sup> Similarly, Mexiletine, a class 1B sodium channel blocker, has not been reported to induce Brugada ECG.<sup>24</sup> On the other hand, exposure to the long-acting local anaesthetic, bupivacaine, has been reported to induce the ECG manifestations of Brugada syndrome and ventricular tachycardia in an otherwise silent carrier of an SCN5A mutation. The mutation was shown to reduce the sodium current on whole-cell patch-clamping.<sup>62</sup> In another report, a patient developed the type 1 ECG pattern after receiving a continuous epidural bupivacaine infusion. After withdrawal of bupivacaine, the ECG changes reverted back to baseline.<sup>63</sup>

Unlike lidocaine, bupivacaine causes greater depression of the rapid phase of depolarization in Purkinje fibres and ventricular muscle<sup>64</sup> and remains bound to the sodium channels for a longer period of time. This may explain its ability to induce arrhythmia in patients with concealed Brugada syndrome.

## Calcium channel blockers

Although there has only been one report of verapamil-induced Brugada syndrome among all the calcium channel blockers,<sup>65</sup> co-administration of diltiazem and isosorbide-5-mononitrate had also been reported to induce the Brugada ECG pattern and ventricular tachycardia in the patient aforementioned.

Fish and Antzelevitch proposed a cellular mechanism for the Brugada syndrome in which accentuation of the epicardial action potential notch and eventual loss of the epicardial action potential dome results in ST-segment elevation, phase 2 re-entry, and polymorphic VT/VF.<sup>11</sup> The proposed mechanism involves a rebalancing of the currents available at the end of phase 1 of the epicardial action potential. Diminution of inward currents ( $I_{Na}$  and  $I_{Ca}$ ) or enhancement of outward currents ( $I_{to}$  and  $I_{K-ATP}$ ) results in a slowing of the second upstroke of the epicardial action potential, eventually leading to loss of the action potential dome as a consequence of all-or-none repolarization at the end of phase 1. Thus, mechanistically, the pro-arrhythmic action of calcium channel blockers could be explained by the additional  $I_{Ca}$  block by calcium channel blockers a situation with pre-existing defective  $I_{Na}$  channel resulting in a synergistic loss of the epicardial action potential dome and precipitates the syndrome.

## Propofol

Propofol is the commonest anaesthetic used in modern medicine. It generally has few significant side effects. However, high doses of propofol infusion given for several days to patients with severe head injury had been reported to be associated with sudden death, a condition termed 'propofol infusion syndrome'.<sup>66,67</sup> The pathophysiological mechanism underlying this lethal effect remains unclear. In a retrospective study of 67 patients with head injury that received prolonged propofol infusion, seven had been identified as having propofol infusion syndrome.<sup>68</sup> Six of the propofol infusion syndrome patients developed the Brugada-like ECG and died within hours of irrecoverable electrical storm, whereas none of the 60 other patients developed ventricular arrhythmias, suggesting that the mechanism underlying the arrhythmogenesis in propofol infusion syndrome is similar to that responsible for ventricular arrhythmias in the Brugada syndrome.

Recently, an article by Junttila et al.<sup>69</sup> describing the poor prognosis associated with the acute induction of the Brugada type 1 ECG pattern. In particular, 11 of 26 patients with drug-induced changes suffered sudden and/or resuscitated cardiac death with the majority of these life-threatening cases being related to propofol infusion, whereas the rest were secondary to use of sodium channel blockers (antiarrhythmics and local anaesthetics). However, this series of patients probably represents a selected group and may not indicate the true spectrum and prognosis of the drug-induced Brugada ECG pattern. As discussed above, anti-depressant overdoses appear to be the most commonly reported cause of the drug-induced Brugada ECG pattern, usually with an unremarkable event rate. A systematic, population-based, observational study of the condition will be necessary to understand the true significance of this presentation.



## Miscellaneous

Other isolated cases of drugs reported to induce Brugada-like ECG pattern include  $\beta$ -blockers and nitrates. However, the significance of these isolated cases remained unclear.<sup>1,63</sup>

## Conclusions

In summary, it appears that potent sodium channel blockers and selected non-cardiac drugs may induce the type 1 Brugada ECG even in patients without any other features of the syndrome such as history of syncope or ventricular tachyarrhythmias. In some cases, the abnormal ECG appeared in some individuals only during the administration of a sodium channel blocker used to identify carriers of the disease within a family with a history of sudden death or Brugada syndrome. In other individuals, the diagnostic ECG was seen when the patients were exposed to the offending drugs for other medical reasons. In such patients, it is not clear whether or to what extent a genetic predisposition may be involved. The prognosis appears to be good provided the full-blown Brugada syndrome is not uncovered. Thus, in asymptomatic patients without a family history of sudden death, drug-induced Brugada sign is likely to be benign once the offending agent is discontinued.<sup>12</sup> Existing data in Brugada syndrome support this approach. For example, a registry study of patients with type 1 Brugada ECG pattern found that asymptomatic patients who developed the Brugada sign only after pharmacological challenge had no arrhythmic events at  $27 \pm 29$  months.<sup>70</sup> These findings have been replicated by other groups. Once the offending agent has been removed, it is therefore reasonable to then treat the patient utilizing existing algorithms from the Second Consensus Conference of the Heart Rhythm Society and the European Heart Rhythm Association.<sup>1</sup> Canine ventricular wedge studies suggested that a flecainide-induced Brugada phenotype does not necessarily indicate the presence of an arrhythmic substrate; it does denote the ability of sodium channel block to create the conditions under which the arrhythmic substrate may readily develop.<sup>71</sup>

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