Government of JERSEY

Health and Community Services

Ajmaline Challenge for detection of Brugada Syndrome

September 2021

DOCUMENT PROFILE

Document Registration	HSS-GD-CG-0408-06
Document Purpose	Policy and Procedure
Short Title	Ajmaline Challenge Protocol
Author	Angela Hall
Publication Date	September 2018, September 2021
Target Audience	Hospital based staff, In patient use only
Circulation List	Jersey General Hospital, via Intranet
Description	Drug challenge protocol for Brugada Syndrome
Linked Policies	Resuscitation Policy
Approval Route	Hospital Care Quality Group / Integrated Governance Committee
Review Date	3 years from approval
Contact Details	Sister Angela Hall

CONTENTS LIST:

1. INTRODUCTION

This updated (version 6) document represents changes as specified following contemporary evidence and information provided by specialist centres and at the Heart Rhythm UK conference 2014. For clarity of changes, previous information is faded and replaced by highlighted text.

1.1 Rationale

Brugada syndrome is a cause of sudden death due to ventricular arrhythmias in a structurally normal heart (Brugada, 1992). The disease is responsible for 4-12% of unexpected sudden deaths and for up to 50% of all sudden death in patients with an apparently normal heart (Brugada et al, 2000). First described in 1992 by the Brugada brothers, the disease has since had an exponential rise in the numbers of cases reported, to such an extent that the second consensus conference reported in 2005 that it was the second leading cause of death in males <40 (after trauma) (Antzelevitch et al, 2005).

The incidence may be even higher in the younger population and is the most common cause of sudden death in individuals younger than 50 years in South Asia with no underlying cardiac disease (Antzelevitch et al, 2005). The syndrome may be more prevalent but the magnitude is yet to be fully determined.

Intravenous Ajmaline (Gilurytmal) is the standard provocative test used to identify individuals with concealed forms of the disease and may reveal the characteristic ECG changes. Ajmaline is a class 1 antiarrhythmic drug with potent sodium channel blocking effects and a very short half-life. Brugada is a rare genetically conditioned anomaly of the cardiac sodium channels. The pharmacological test is so specific it is recommended in patients who present with ventricular fibrillation of unknown cause (Brugada, 2012).

Previously, Procainamide and Flecainide have been used in provocative testing for Brugada but Ajmaline elicits more sensitive results (Brugada et al, 2000, Obeyesekere et al, 2011, Wolpert et al 2005). By stressing the cardiac action potential, pharmacological testing can accentuate the desired abnormality or provoke a characteristic arrhythmia response and results in unmasking the cause of apparently unexplained aborted sudden cardiac death in >50% of patients. This is crucial when diagnosing genetically mediated arrhythmia syndromes (Obeyeskere et al, 2011 and Krahn et al, 2009).

Typically the patient exhibits ECG changes of right bundle branch block and ST segment elevation with a coved or saddle appearance in leads V1-V3. These clinical signs in association with a history of syncope are strong predictors of major arrhythmic events in patients (Obsyesekere et al, 2011). If positive for Brugada there is 1:100 risk of developing a cardiac arrhythmia (Spire policy, 2012).

If there is a family history of Brugada syndrome even in the absence of symptoms or ECG changes there may be a risk of arrhythmia. Brugada has a very poor prognosis if untreated. One third of patients having suffered syncopal attacks or resuscitated from near death develops a new episode of polymorphic ventricular tachycardia within two years. Because antiarrhythmic drugs (e.g. beta blockers, Amiodarone) do not protect against sudden cardiac death, the only available treatment is an implantable cardiac defibrillator (Brugada et al, 1992 and 2000, Antzelevitch et al, 2005).

1.2 Scope

This would apply to patients with a family history of Brugada or those with concealed forms of the disease, (the typical ECG features can be unmasked with sodium channel blockers).This test is recommended for all patients who present with ventricular fibrillation of unknown cause (Brugada, 2012).

An exclusion however would be children and therefore testing would not usually be performed on anyone under the age of 18 years.

The drug challenge will take place in the High Dependency Unit (HDU) where cardiac monitoring is available. Staffing present will include the Arrhythmia Nurse and either the Cardiology Consultant, Cardiac Registrar or Cardiac Fellow. In addition a staff nurse in HDU would be allocated to the patients care. A current advanced life support or intermediate life support qualification must exist and a defibrillator with emergency equipment at hand.

Prior to admission the patient will have been consulted by the Consultant Cardiologist and Arrhythmia Nurse for selection and advice respectively.
The patient would be electively admitted in the morning (beds permitting) and discharged home later the same day (typically 2-3 hours of bed usage).

1.3 Principles

Ajmaline is a class Ia anti-arrhythmic used as a diagnostic test for Brugada syndrome. Ajmaline blocks sodium channels and thus administration should exaggerate or unmask the ST-segment elevation aiding diagnosis in patients with concealed or intermittent forms of Brugada syndrome. This inhibits depolarisation in particular to the fast–conducting structures of the heart.

Half-life is 5-6 minutes; plasma elimination half-life is 95 minutes.

Patients with a positive Ajmaline challenge who are at high risk of developing arrhythmias / cardiac arrest will be considered for an implantable cardioverter defibrillator (ICD) and genetic screening (the latter off island).

Ajmaline challenge will be dictated by the Consultant Cardiologist and administration will be in accordance with the protocol and drug dosage calculation.
(The use of Ajmaline is preferred to Flecainide due to its much shorter half-life and increased safety as any pro-arrhythmic effects will wear off more quickly).

An accurate weight is essential. The dose is 1mg/kg. Administer by slow intravenous injection so that the total dose is given over 5 minutes. aiming for 5-10mg/min. Do not give faster than 10mg/min**. Ajmaline is presented as 50mg/10ml ampoule and depending on weight 1-2 ampoules may be required**.

See **Appendix 1** for cautions / contra-indications / complications / side effects of Ajmaline.

2. POLICY PURPOSE

The standard follows that of similar protocols used routinely in cardiac units nationally. Three specific policies have been used to inform local practice.
The purpose is to enable diagnosis and complete the management of patients locally, preventing further transfer to a UK centre for provocative drug testing.

The purpose for developing the guideline is:

- to set standards of performance for the Ajmaline drug challenge
- to guide pre, peri and post procedural care
- to ensure all correct equipment is available
- to ensure all staff are aware of their role and the procedure
- to act as a resource for advice and theoretical training

The guideline follows up to date evidence from the Burgada association, along with evidenced contemporary literature, referenced throughout this document.

In normal subjects Ajmaline produces slight widening of the QRS complex. In people with Brugada, Ajmaline will result in the appearance of a Brugada pattern on the ECG (see page 21-24).

3. SERVICE DESIGN – Medical and Nursing Responsibility

This service is designed as an Arrhythmia Nurse and Consultant Cardiologist joint service. This facilitates the Arrhythmia Nurse to follow the patients' journey from pre-assessment through to discharge.

3.1 Clinical Lead

The clinical lead is the Consultant Cardiologist.

3.2 Operational Lead

The operational lead responsibility for the service lies with the Consultant Cardiologist and Arrhythmia Nurse Specialist with overall nursing management from Head of Ambulatory Care. Studies will not take place in the event of the aforementioned cardiology staff absence. All policies, protocols and guidelines must be agreed with the clinical lead.

The Arrhythmia Nurse provides education for the users of the service as well as conducting clinical audit.

4. ASSESSMENT

4.1 Pre-Assessment

Patients will be seen by the Arrhythmia Nurse following the arrangement of an appointment to attend pre-assessment (typically on a Tuesday afternoon). Clinic slots to be fully utilised. Document 'did not attend' if no response. If pre-assessment cannot be attended, an

alternative appointment will be arranged. It is crucial direct contact is made to gather patient information, detailed history and advice.

Blood results will be checked, ECG taken and vital signs recorded to include blood pressure, pulse, oxygen saturations, respirations, height and weight and to be swabbed for MRSA. Patient notes will be available at this time and updated. Computerised records (TrakCare) will be updated accordingly.

Pharmacy will be made aware of the impending admission and prescription at this point, to ensure Ajmaline is available. An accurate weight is essential. Ajmaline is an unlicensed product but can be prescribed under the Consultant Cardiologist guidance.

4.2 Patient Assessment

Patient assessment includes:

- History taking and checking Cardiologist notes for patient screening for inclusion
- Check risk factors including all blood results, echocardiogram and baseline ECG
- Determine need for further / repeat investigations and discuss with cardiologist
- Give patient detailed information regarding the study to include written information

If at any point the patient becomes unwell, the cardiology doctor will be called for review (if absent once testing complete but still an in patient). Normal procedures will then take place for admission if necessary.

Reassure patients and families and answer questions.

5. PROCEDURE (HOW)

5.1 Preparation

The test will be carried out in the High Dependency Unit where cardiac monitoring and an external defibrillator is available.

See **Appendix 2** for equipment list and general preparation checklist.

- Ajmaline dose must be calculated according to weight (1mg/kg) and drawn up into a 20ml luer lock syringe. Prime the IV giving set with the drug (expel any excess so the syringe contains the correct dose).
- Ajmaline is supplied in 10ml ampoules. The strength is 5mg/ml.
- Double check with second staff member, as per IV drug administration policy. Connect in syringe pump. Set the rate to infuse the total dose over 5 minutes (Imperial College, Antzelevitch et al, 2005)120mls/hr (10mg/min) (Arnalsteen-Dassonvalle et al, 2010). Never give by hand or bolus injection.
- Apply cardiac monitoring, BP cuff and oxygen saturation probe. The defibrillator must be close to the patient but not necessarily attached.
- Record baseline observations and a 12 lead ECG with leads V1 and V2 in the conventional 4th intercostal space. 15 lead ECG's should then be recorded every minute

(see **Appendix 4 and 5**). then repeat the ECG with leads V1 and V2 in the 3rd intercostal space (as alternative placement for increased sensitivity). Mark the ECG with the time it was taken and the lead position (Antzelevitch et al, 2005) (see **Appendix 4 and 5**).

- Using the ANTT (aseptic non-touch) technique flush the line with 0.9% saline and connect the infusion.
- Dr or nurse 1 – Cannula and resuscitation trolley side
- Dr or nurse 2 – ECG machine side

5.2 Procedure

- Start the infusion and stopwatch.
- Monitoring will be continuous but observations will be recorded at the same time as the ECG is recorded. At each interval the ECG should be recorded every minute in the 15 lead position (**Appendix 4**). must be recorded twice with leads V1 and V2 in the conventional and then 3rd intercostal space (Antzelevitch et al, 2005) (see **page 21**).
- Intervals for recording are at 5 minutes, 10 minutes, 15 minutes, 20 minutes 30 minutes, 40 minutes, 50 minutes and 60 minutes.
- Mark each ECG with the timing and the V1 and V2 lead position (Antzelevitch et al, 2005).
- If the patient develops symptoms of concern whether ECG related or not, then stop the infusion and seek assistance if necessary.
- Stop the infusion if an obvious *Type 1* Brugada pattern appears (see **Appendix 6**), ventricular arrhythmias or ventricular ectopics or QRS width widening of >30% of baseline are seen. (Rolf et al, 2003). (Ajmaline is quickly deactivated and effects wear off after a few minutes).
- Continue monitoring until the ECG has returned to baseline.

5.3 Positive Ajmaline test

- *Type 1* (coved ST segment elevation >2mm in >1 of V1-V3 followed by a negative T wave) is potentially diagnostic (referred to as 'Brugada sign', Littmann et al, 2003, Antzelevitch et al, 2005).
- Brugada is definitively diagnosed when a *Type 1* ST-segment elevation is observed in >1 right precordial lead (V1-3) in the presence or absence of a sodium channel blocking agent and in conjunction with one of the following:
- Documented VF, polymorphic VT, a family history of sudden cardiac death at <45 years old, coved-type ECG's in family members, inducibility of VT with programmed electrical stimulation, syncope or nocturnal agonal respiration. (The ECG manifestations of Bruaga when concealed can be unmasked primarily by sodium channel blockers; also documented when in febrile state) (Antzelevitch et al, 2005 and 2002 and Brugada et al, 2000).
- *Type 2* and *3* Brugada are non-diagnostic but may warrant further investigations. *Type 2* has >2mm of saddleback shaped high take off ST elevation then either a positive or biphasic T wave (**Appendix 6**).

- *Type 3* can be the morphology of *Type 1 or 2* (saddleback or coved) but with <1mm of ST elevation.
- *Type 2* is also considered positive (saddleback) or *Type 3* when ST elevation is observed in >1 right precordial lead under baseline conditions and conversion to diagnostic *type 1* occurs after sodium channel blocker administration (ST elevation >2mm). One or more of the clinical criteria above should be present.
- Drug conversion from *Type 3* to *Type 2* ST elevation is considered inconclusive for a diagnosis of Brugada (Antzelevitch et al, 2005).
- In the case of a negative baseline ECG, a J-wave amplitude of >2mm in lead V1 and/or V2 and/or V3 with or without RBBB is considered positive (Rolf et al, 2003).
- Conversion of a *Type 2* or *3* (**Appendix 6**) ECG to a *Type 1* is considered positive.
- An increase in the J wave amplitude of more than 2mm without the development of a *Type 1* configuration is also considered significant, but is rarely observed.
- If ventricular arrhythmias are observed and the patient is haemodynamically compromised, treat accordingly. (This may be with electrical cardioversion or IV Isoprenaline and IV Magnesium under cardiologist guidance) (See **Appendix 7**).
- If cardiac arrest occurs follow ALS procedures.

See flow chart – **Appendix 3.**

Ensure the Consultant Cardiologist is available to interpret the results once the test is complete

5.4 End points

The study should complete when the following occurs:

- Target dose reached
- QRS widens to ≥ 30% of baseline (Rolf et al, 2003)
- ST segment elevation in *Type 2* ECG increases by ≥ 2mm in at least one right precordial lead
- Presence of typical Brugada ECG
- Premature ventricular beats / VT, sinus arrest or AV block (Type II or III)
- If the patient develops symptoms of concern whether ECG related or not
- Stop the infusion if an obvious *Type 1* Brugada pattern appears (see **Appendix 6**)

Ajmaline is quickly deactivated and effects wear off after a few minutes. Half-life is 5-6 minutes and plasma elimination half-life is 95 minutes. Continue monitoring until ECG returns to baseline.

6. AUDIT

Audit will be ongoing but with a summary of findings reviewed after the first six patients have undergone drug challenge. Key performance indicators will include:

- waiting time from referral to admission
- hours of bed occupancy time

- diagnostic ECG's for Brugada
- *type 1, 2 and 3* patterns on administration of Ajmaline
- arrhythmias during administration / haemodynamic compromise
- patient satisfaction
- any other complications requiring medical assistance

7. DEVELOPMENT AND CONSULTATION PROCESS

Consultation Schedule

Name and Title of Individual	Date Consulted
Dr Andrew Mitchell, Consultant Cardiologist	26.02.2013, first draft 19.03.2013, second draft
Dr Ranji Thomas, Cardiology Registrar	03.07.2013
Geoff Benning, Practice Development	19.03.2013
Sister Dorothy Perks, CCU Manager	19.03.2013
Sister Jackie Tardivel, Head of Ambulatory Care	19.03.2013
Adam North, Senior Pharmacist	19.03.2013
Jessica Le Marquand, Clinical Pharmacist	20.06.2013

Reviewed June 2017 and 2021

Name and Title of Individual	Date Consulted
Dr Andrew Mitchell, Consultant Cardiologist	18.05.2015, 14.06.2017, 16.9.21
Dr Ranji Thomas, Cardiology Registrar	18.05.2015
Jessica Le Marquand, Clinical Pharmacist	18.05.2015

8. REFERENCE DOCUMENTS

- Antzelevitch C, Brugada R (2002) Fever and Brugada syndrome. Pacing Clinical Electrophysiology. 25. 1537-1539.

- Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. (2005) Brugada Syndrome: Report of the Second Consensus Conference. Circulation.111. 659-670.

- Arnalsteen-Dassonvalle E, Hermida J, Kubala M, Six I, Quenum S, Leborgne L, Jarry G. (2010) Ajmaline challenge for the diagnosis of Brugada syndrome: which protocol? Archives of Cardiovascular Disease. 103 (11-12). 570-578.

- Brugada P, Brugada J, (1992) Right bundle branch block, persistent ST elevation and sudden cardiac death: a multicentre report. Journal of American Coll Cardiology. 20. 1391-1396.

- Brugada R, Brugada J, Antzelevitch C, Kirsch G, Potenza D, Towbin J, Brugada P. (2000) Sodium channel blockers identify risk for sudden death in patients with ST segment elevation and right bundle branch block but structurally normal hearts. Circulation. 101. 510-515.

- Essington-Boulton M, Rajappan K, Hailey V, Titchener R (2011) Drug Challenges for the diagnosis of Cardiac Arrhythmias. Oxford: John Radcliffe Hospitals NHS Trust.

- Jongman J, Jepkes-Bruin N, Ramdat A, Beukema W, Delnoy P, Oude H, Dambrink J, Hoorntje J, Elvan H. (2007) Electrical storms in Brugada syndrome successfully treated with isoproterenol infusion and quinidine orally. Netherlands Heart Journal. 15 (4). 151-154.

- Krahn A, Healey J, Chauhan V, Birnie D, Simpson C, Champagne J, Gardner M, Sanatani S, Exner D, Klein G, Yee R, Skanes A, Gula L and Gollob M. (2009) Obeyesekere M, Klein G, Modi S, Leong-Sit P, Gula L, Yee R, Skanes A, Krahn A (2011) How to perform and Interpret Provocative Testing for the Diagnosis of Brugada Syndrome, Long QT Syndrome, and Catecholaminergic Polymorphic Ventricular Tachycardia. Circulation Arrhythmia Electrophysiology. 4. 958-964.

- Littmann L, Monroe M, Kerns W, Svenson R, Gallagher J. (2003) Brugada syndrome and ‘’Brugada sign’’: clinical spectrum with a guide for the clinician. American Heart Journal. 145 (5) 768-778.

- Maury P, CoudercP, Delay M, Boveda S, Brugada J. (2004) Electrical storms in Brugada syndrome successfully treated using isoprenaline. Europace. 27. 821-823.

- Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. (1996) Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. Journal of American Coll Cardiology. 27. 1061-1070.

- Veltman et al (2011)

- Watanabe A, Fukushima F, Morita H, Miura D, Sumida W, Hiramatsu S. (2006) Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. European Heart Journal. 27. 1579-1583.

- Wolpert C, Echternach C, Veltmann C, Antzelevitch C, Thomas G, Spehl S, Streitner F, Kuschyk J, Schimpf R, Haasek, Borggrefe M (2005) Intravenous drug challenge using Flecainide and Ajmaline in patients with Brugada syndrome. Systematic assessment of

patients with unexplained cardiac arrest: cardiac arrest survivors with preserved ejection fraction registry (CASPER). Circulation. 120. 278-285.

9. BIBLIOGRAPHY

- Imperial College London NHS Hospitals, Ajmaline Challenge Protocol
- St Georges Hospital Policy on Ajmaline Drug Challenge
- Spire / Southampton University Hospital Ajmaline Drug Challenge
- Southampton University Hospitals NHS Trust Ajmaline Injection for Investigation of Brugada Syndrome

10. GLOSSARY OF TERMS / KEYWORDS AND PHRASES

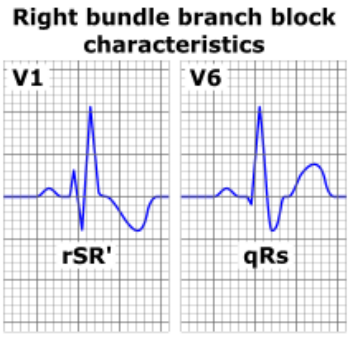
Action potential	Action potentials are generated by the movement of ions through the transmembrane ion channels in the cardiac cells. Rate dependence of action potential repolarization is a fundamental property of cardiac cells, and its modification by disease or drugs can bring about fatal arrhythmias.
Ajmaline	Class Ia antiarrhythmic agent and sodium channel blocker
Antiarrhythmic	Antiarrhythmics are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.
Amiodarone	Amiodarone is a class III antiarrhythmic agent used for various types of cardiac dysrhythmias, both ventricular and atrial.
Flecainide	Flecainide acetate is a class Ic antiarrhythmic agent used to prevent and treat tachyarrhythmias
ICD	An implantable cardioverter-defibrillator (ICD) is a small battery-powered electrical impulse generator that is implanted in patients who are at risk of sudden cardiac death due to ventricular fibrillation and ventricular tachycardia. The device is programmed to detect cardiac arrhythmia and correct it by delivering a jolt of electricity.
Isoprenaline	Its primary use is for bradycardia or heart block. By activating β_1-receptors on the heart, it induces positive chronotropic, dromotropic, and inotropic effects
Procainamide	Procainamide antiarrhythmic agent used for treatment of cardiac arrhythmias, classified as class Ia.

QRS complex

The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram (ECG). It corresponds to the depolarization of the right and left ventricles. In adults, it normally lasts 0.06 - 0.10 s

Right bundle branch block

The right ventricle is not directly activated by impulses travelling through the right bundle branch. The left ventricle is still normally activated by the left bundle branch. These impulses are then able to travel through the myocardium of the left ventricle to the right ventricle and depolarise the right ventricle this way. As conduction through the myocardium is slower than through the Bundle of His - Purkinje fibres, the QRS is seen to be widened.



Sodium channel blocker

Sodium channel blockers are agents that impair conduction of sodium ions (Na^+) through sodium channels; blocking from the intracellular side of the channel include class 1 antiarrhythmics

Syncope

The medical term for fainting, is precisely defined as a transient loss of consciousness and postural tone, characterised by rapid onset, short duration, and spontaneous recovery, due to global cerebral hypoperfusion (low blood flow to the brain) that most often results from hypotension (low blood pressure).

Polymorphic VT

Polymorphic ventricular tachycardia has beat-to-beat variations in morphology.

11. APPENDICES

Appendix 1: Cautions and contraindications

Concomittant antiarrhythmic drugs or drugs known to provoke Brugada ECG to be discontinued for at least five half-lives prior to challenge.

Drugs known to prolong QT interval (and hence concurrent administration is not recommended) are:

- Class 1a antiarrhythmics – Disopyramide, Procainamide, Quinidin
- Class 1c antiarrhythmics – Flecainide
- Class III antiarrhythmics – Amiodarone, Sotalol, Bretylium, Dofetilide
- Cardiac glycosides – Digoxin
- Tricyclic antidepressants and Antipsychotics e.g. Amitryptylline, Clozapine, Olanzipine, Risperidone

Other drugs such as Levofloxacine, Erythromycin, Sulphamethoxazole

<table>
<tr><th colspan="2">Contraindications</th><th>Cautions</th></tr>
<tr><td colspan="2">Arrhythmias including:
▪ 2nd and 3rd degree AV block
▪ Existing atrial and / or ventricular conduction disorder
▪ Widening of QRS or P waves, PR prolongation (avoid risk of precipitating CHB)
▪ QT prolongation
▪ Tachycardia due to cardiac decompensation
▪ Bradycardia or Digitalis toxicity</td><td>▪ Bundle branch block, Sick sinus syndrome or 1st degree AV block
▪ Non-rhythmogenic hypotension (<90mmHg)
▪ Cholestatic jaundice
▪ AF and atrial flutter (ventricular rate may increase dramatically)</td></tr>
<tr><td>▪ Hypertrophic cardiomyopathy</td><td>▪ Pregnancy</td><td rowspan="4"></td></tr>
<tr><td>▪ Ajmaline Hypersensitivity</td><td>▪ Myasthenia gravis</td></tr>
<tr><td>▪ Heart Failure with LVEF <35%</td><td>▪ MI within 3/12</td></tr>
<tr><td>▪ Bacterial endocarditis</td><td>▪ Liver disease</td></tr>
</table>

Higher risk patients for drug induced AV block include older adults with syncope – this may necessitate drug challenge being performed with temporary pacing.

Electro-mechanical dissociation has been encountered in isolated cases. Isoprenaline and sodium lactate may be effective antidotes in this setting.

Complications

The main potential complications are VT or VF but other pro-arrhythmic effects (similar to all Class I anti-arrhythmics) include sinus bradycardia, sino-atrial block, AV block and widening of the QRS complex. Rapid delivery can lead to arrhythmias.

Electromechanical disassociation has been encountered in isolated cases. Isoprenaline and sodium lactate are effective antidotes (necvn.nhs.uk, 2006).

In extreme overdose, can cause respiratory depression, hypotension, coma, cardiac arrest and development of heart failure or angina.

Expected side effects

Sensation of visual disturbance, metallic taste, heat, flushing, paraesthesia and GI disturbances.

Appendix 2: Preparation before cardiac drug challenge

The patient will have been seen by the Consultant Cardiologist and the decision made to proceed for drug challenge.

Informed consent will be obtained.

Patients will be admitted electively to the High Dependency Unit. Usual admission procedures will apply.

The patient will have been seen also by the Arrhythmia Nurse and information provided. Treatment plans will also be outlined.

On admission

- Ensure consent has been obtained
- Cannula inserted and flushed
- A venous blood sample obtained for potassium level (target >4mmols) and imbalance corrected prior to infusion
- Clear fluids only for 2 hours preceding administration
- Document weight and baseline observations
- A 12 lead ECG recorded
- The correct doses and drugs must be prepared
- An external defibrillator and crash trolley must be close to hand ensuring checks of the emergency equipment are complete (Antzelevitch et al, 2005, Obeyeskere et al, 2011, Firman 2006)

Equipment

Syringe pump and IV line
20ml and 50ml luer lock syringe
Relevant drug to be used
Documentation
External defibrillator
Crash trolley
Stop watch
ECG machine
Monitoring equipment
IV Atropine, Isoprenaline, Magnesium and Metoprolol

Appendix 3: Procedure flow chart

SIMPLIFIED FLOW CHART FOR AJMALINE CHALLENGE

- Patient consent obtained
- Patient weighed (in kg) and cannula inserted
- Patient admitted to High Dependency Unit
- Baseline observations and 12 15 lead ECGs (normal and high V1/V2)
- Ensure all resuscitation equipment is present, particularly a defibrillator
- Continuous heart rate, SpO2, and BP recording equipment attached to patient

↓

- Ajmaline is supplied in 10ml ampoules; the strength is **5mg/ml**.
- The dose of the drug is 1mg/kg (rounded to the nearest 5mg). Maximum total dose 100mg.
- Draw up dose into a 20ml luer lock syringe.
- A double check by a second qualified member of staff is required
- Apply a green label to the syringe and place in the syringe pump
- Set the rate of the syringe pump to infuse the total dose over 5 minutes. 120mls/hr (10mg/min) maximum (acceptable range is 5-10mg/min)
- To ensure the correct dose is administered at the correct rate, Ajmaline must **NEVER** be given by hand injection.

↓

- Start the infusion pump and the stopwatch
- Record ECGs in both normal and high V1/V2 positions at the following time points: 5, 10, 15, 20, 30, 40, 50 and 60 minutes (or at any time that ECG changes are seen). Record 15 lead ECG's every minute.
- Mark each ECG with the timing and the V1/V2 lead position

↓

AT THE END OF THE TEST DISCUSS THE RESULTS WITH THE CONSULTANT CARDIOLOGIST AND INFORM THE PATIENT

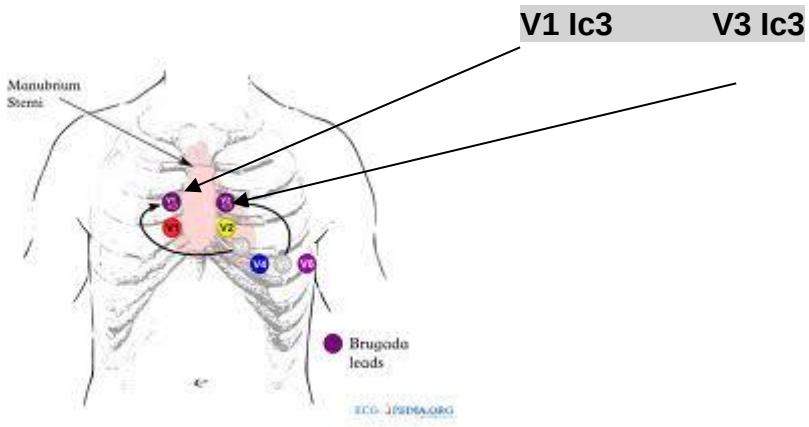
WHEN TO STOP THE INFUSION BEFORE THE END OF THE TEST:

- If an obvious Type-1 Brugada pattern appears
- If ventricular arrhythmias (including any ventricular ectopics) are seen
- With QRS width widening of >30% of baseline

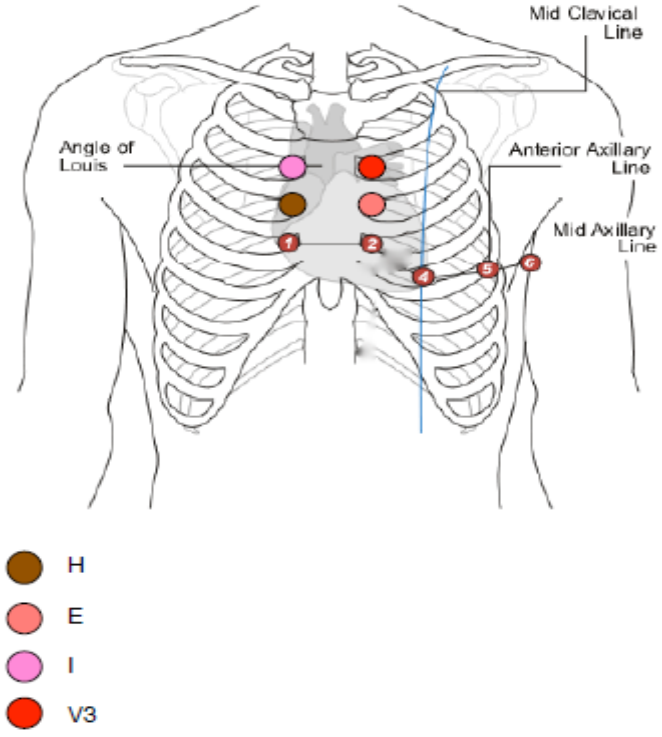
PERFORM CPR IF NECESSARY, BUT MINIMISE SHOCKS IF PATIENT CONSCIOUS, CONSIDER EARLY INTUBATION, & GIVE IV SODIUM CHLORIDE 0.9%, MAGNESIUM, AND POSSIBLY ISOPRENALINE
KEEP PATIENT MONITORED UNTIL ECG RETURNS TO BASELINE

Appendix 4: ECG lead positioning

ECG electrode placement during Brugada testing (note this is now replaced by the 15 lead ECG at the bottom of this page)



Brugada ECG diagnosis made from right precordial leads
Sensitivity can be increased with alternative placement to the intercostal space above V1 and V2 (as above).
Changed lead positions if leads V3 and V5 to increase the sensitivity to 'catch' a Burgada pattern on the ECG



15 lead ECG placement

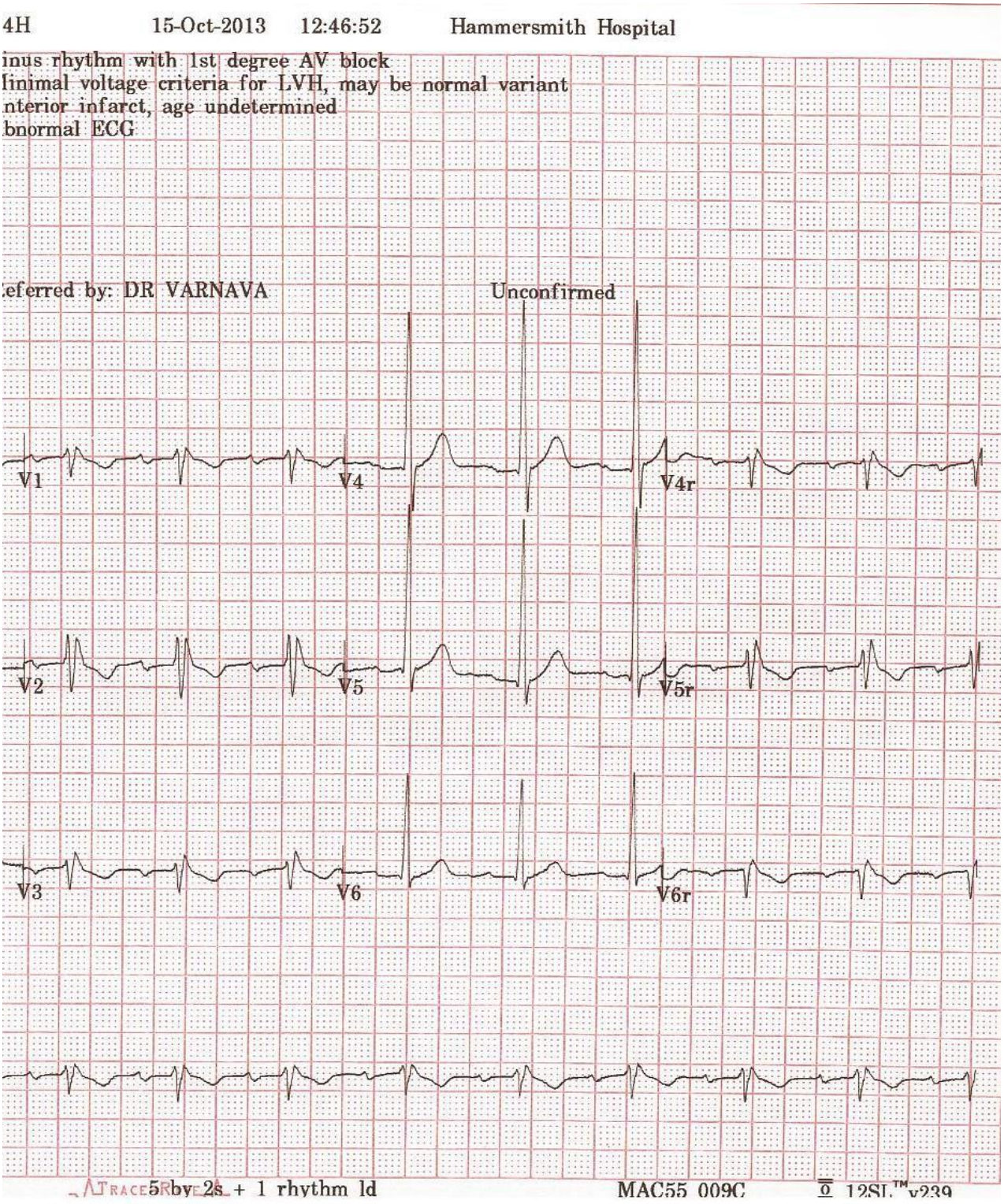
As per Imperial College London Healthcare NHS Ajmaline Protocol

Increased sensitivity over maximal RVOT area, coinciding with maximal ST elevation (Veltman et al, 2011)

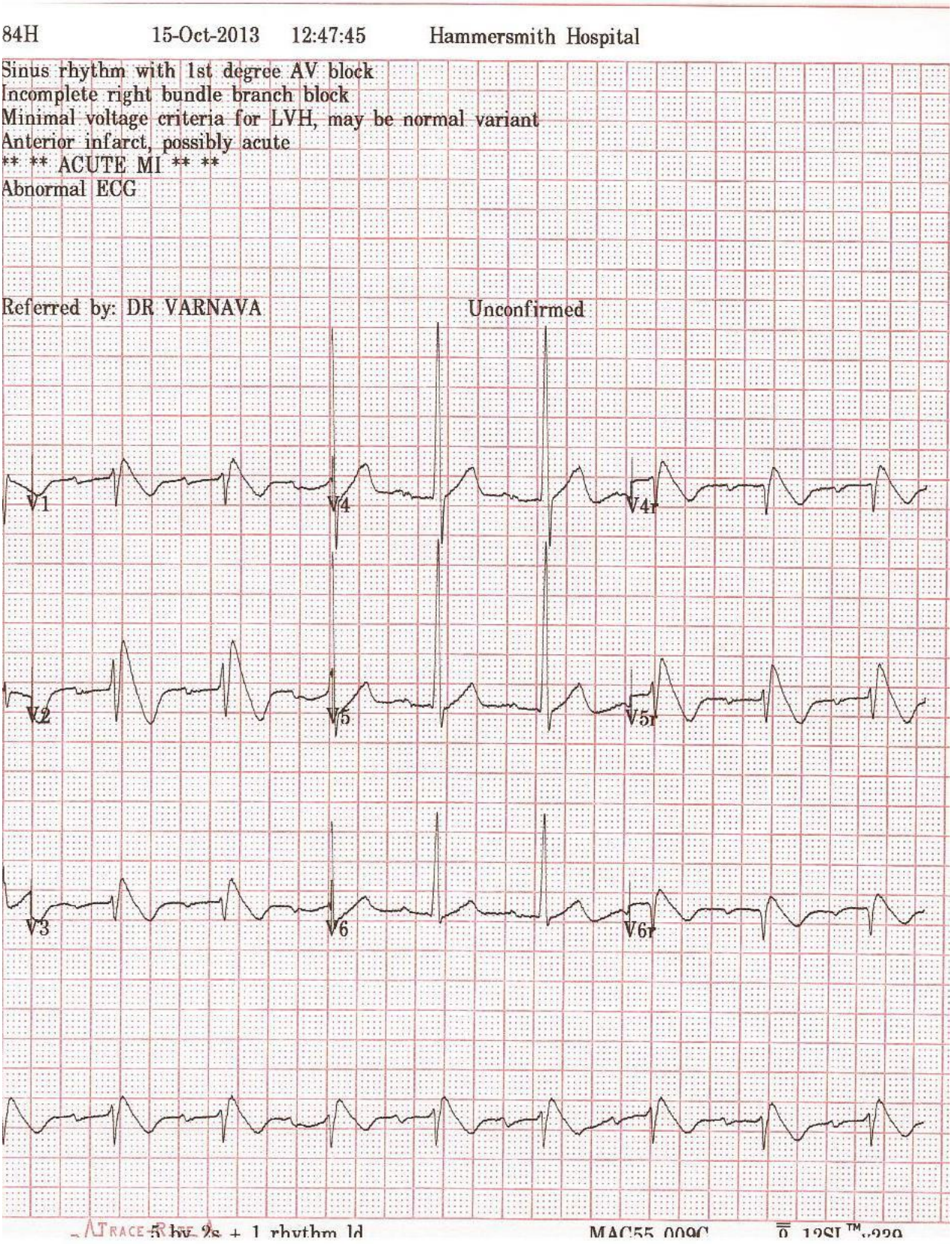
Appendix 5: ECG examples (at one minute intervals)

ECG examples evident by performing at one minute intervals (note previous recommendations were 5 minute intervals)

Note time (12.46)



Note time (12.47)



Appendix 6: Brugada ECG examples

Brugada ECG patterns

Type 1
Pronounced elevation
J point (arrow), a coved
Type ST segment and inverted
T wave in V1 and V2
Type 1 suggestive of Brugada

Type I Brugada
Appearance of type 1 Brugada pattern in more than one right precordial lead (V1-V3) in the presence or absence of a sodium channel blocker, **and *at least one*** of the following:

1) Documented ventricular fibrillation
2) Self-terminating polymorphic ventricular tachycardia (VT)
3) Family history of sudden cardiac death at <45 years
4) Type 1 ST segment elevation in family members
5) Electrophysiological inducibility of VT
6) Unexplained syncope suggestive of a tachyarrhythmia
7) Nocturnal agonal respiration

Type 2
Saddle back ST segment elevated by >1mm

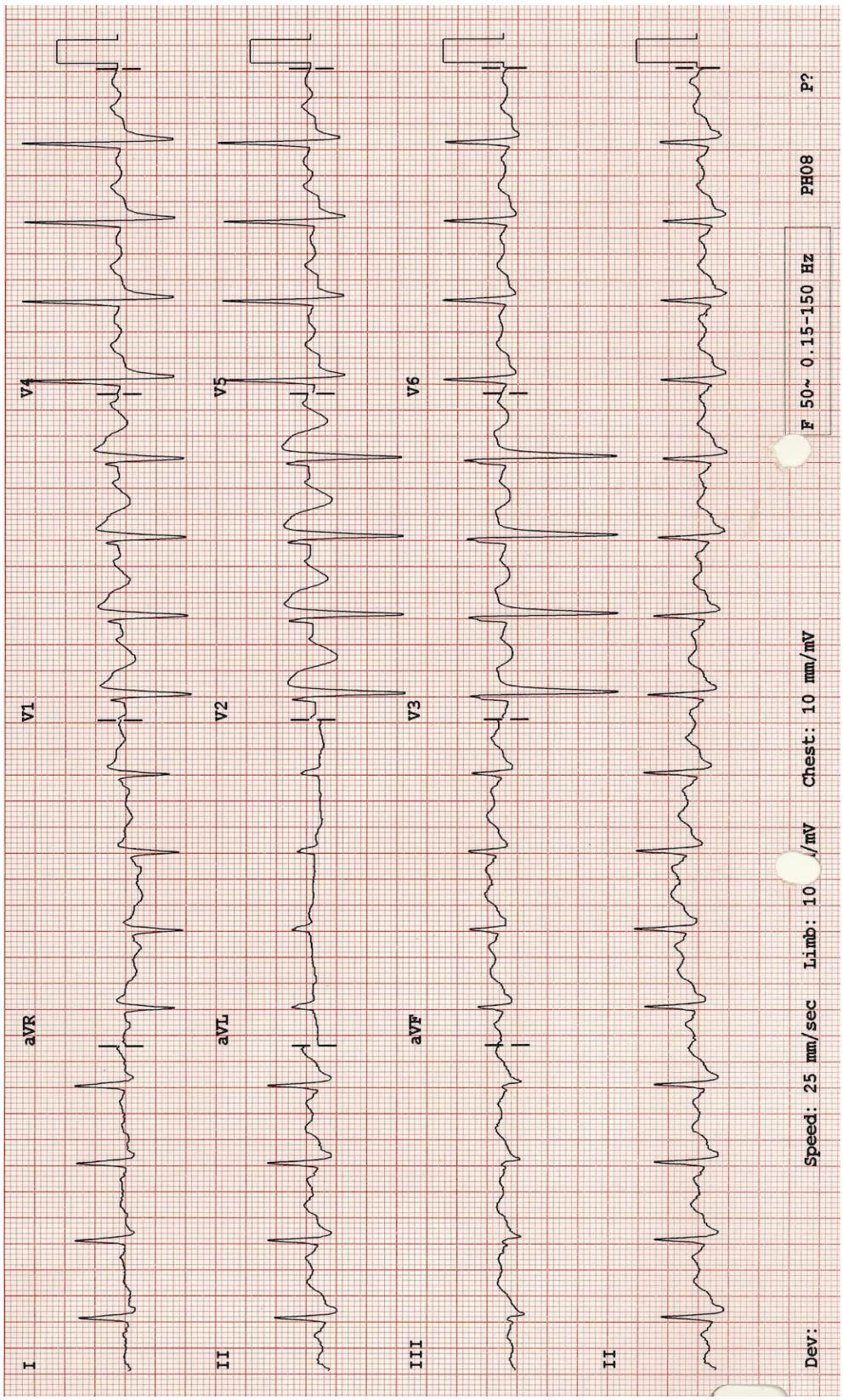
Type 3
ST segment elevated <1mm

Type 2 and type 3 Brugada — a type 2 or type 3 Brugada ECG who meet both of the following criteria:

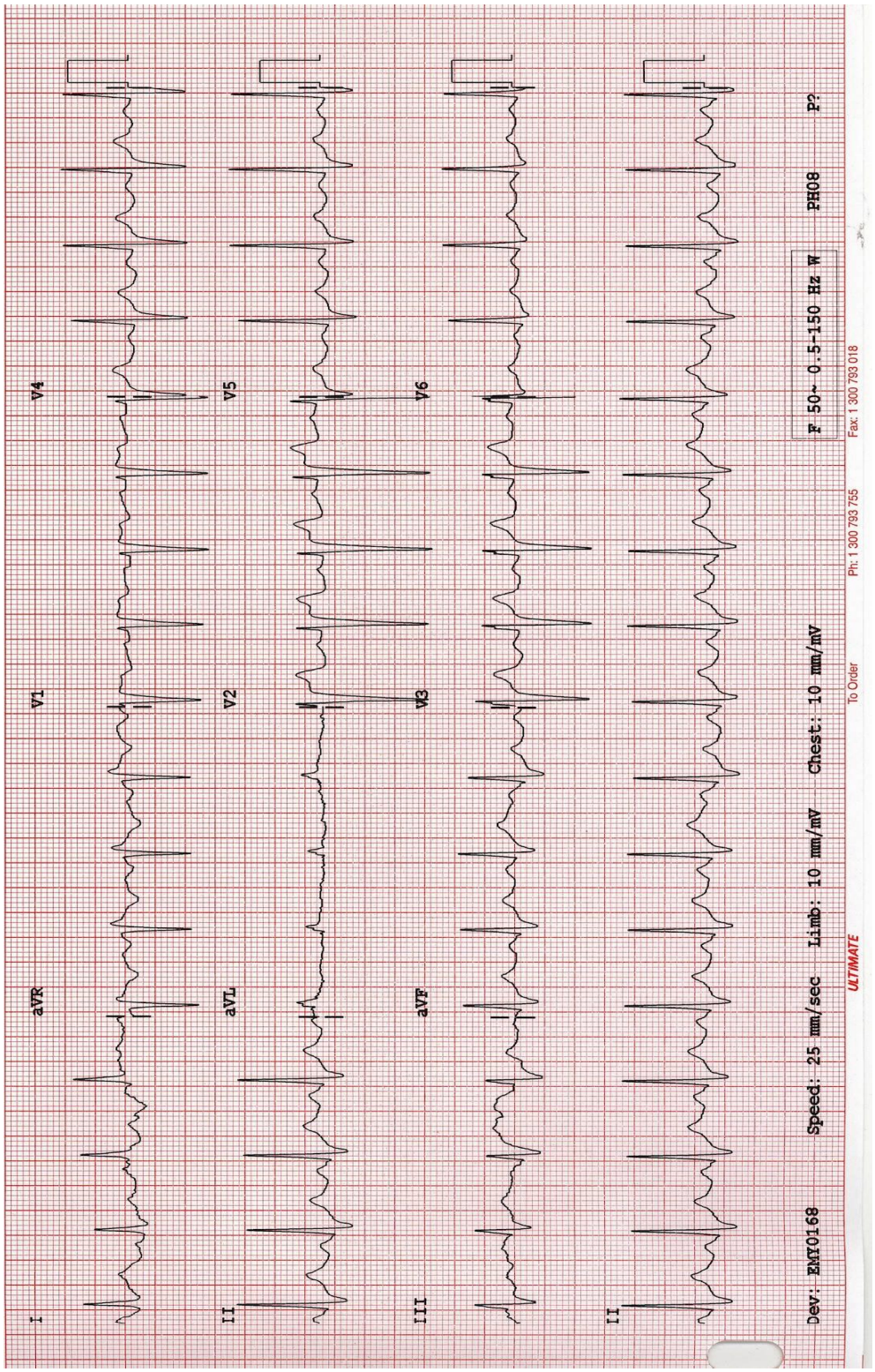
1) Appearance of type 2 or type 3 ST segment elevation (saddle-back type) **in more than one right precordial lead** under baseline conditions, with conversion to type 1 following challenge with a sodium channel blocker.

2) One of (1-7) above.

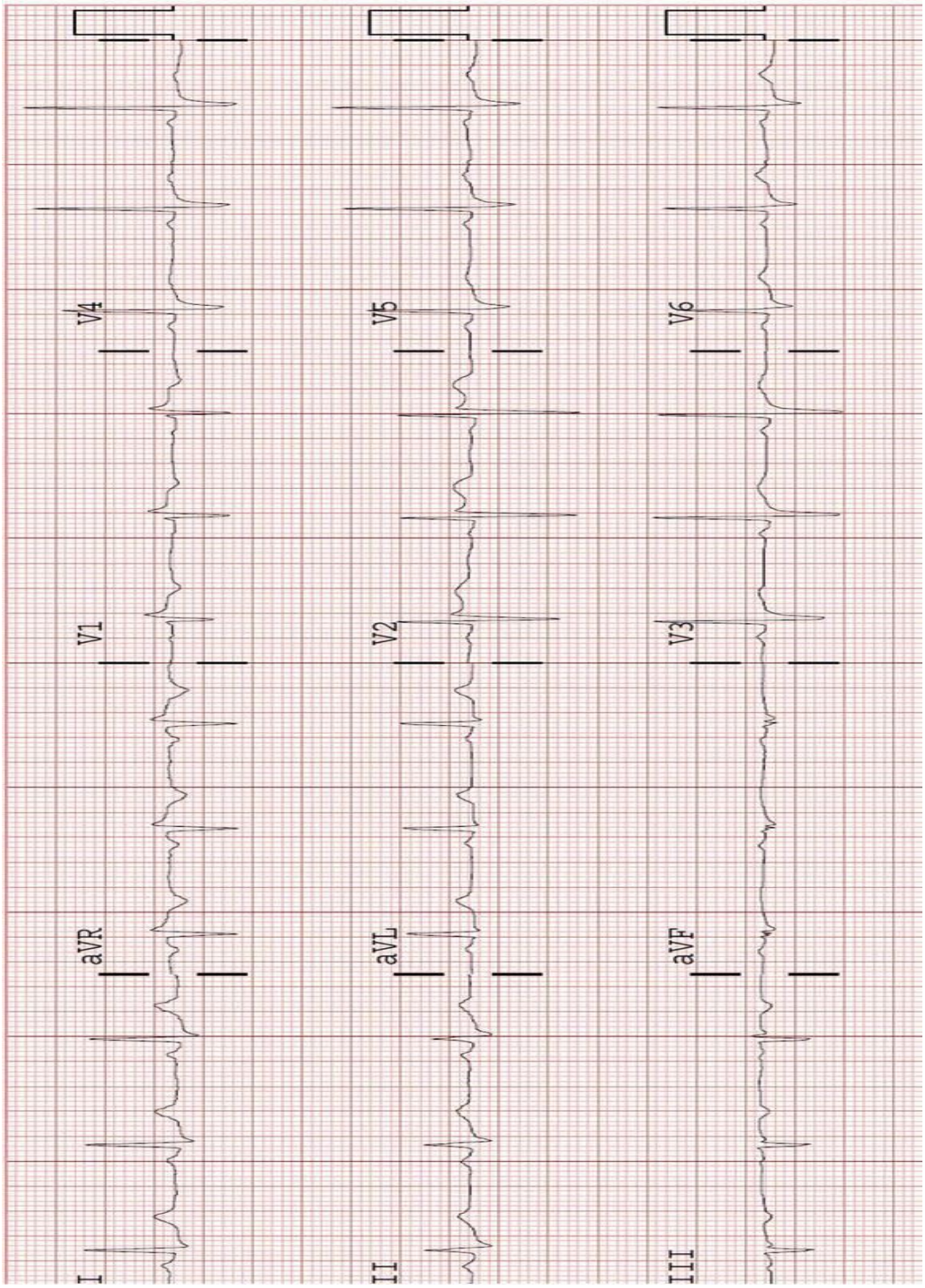
Brugada Type 1



Brugada Type 2

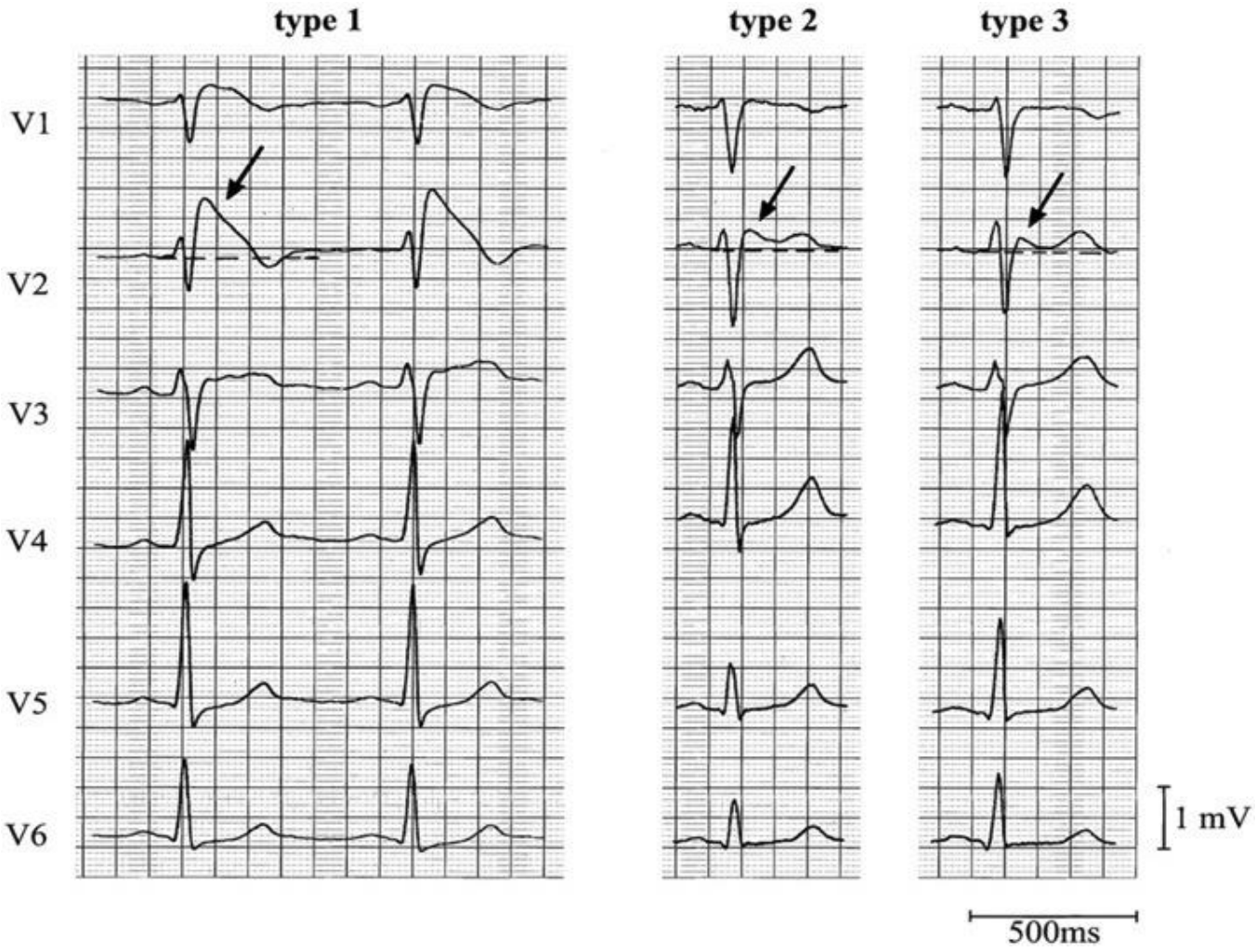


Brugada Type 3



Brugada presentations

Alternative view



Appendix 7:

Patient Information Sheet for Ajmaline Challenge

The Ajmaline Challenge for Brugada Syndrome

Your doctor has recommended that you have an Ajmaline challenge. The purpose of this test is to see if you are likely to have Brugada syndrome, a disorder that affects the heart. Some people with Brugada syndrome may be at risk of developing fast heart rhythms (arrhythmia). If the heart starts beating at an abnormally fast rate then it does not work as efficiently. This can cause symptoms such as weakness, dizziness, chest pain, shortness of breath, collapse, or even death in very rare cases. If you have a close family member who has either been diagnosed with the condition or who has died young from a suspected heart condition, it is very important that all remaining relatives are screened for Brugada syndrome.

It is important to remember that the majority of patients who have the Brugada appearance on an electrocardiogram (ECG) do not experience arrhythmia and feel perfectly well. If your doctor suspects that you may have Brugada syndrome he or she will have advised you to have this well-established, simple clinical test known as an Ajmaline challenge to confirm the diagnosis.
Ajmaline is a drug used in this test to show up ECG changes in patients with Brugada syndrome. In patients with normal cardiac cells, Ajmaline has little or no effect on the ECG.

What happens during the Ajmaline challenge?

When you arrive on the ward you will be introduced to your nurse who will explain what will happen and answer any questions you may have. Before the procedure you will have blood taken and an ECG recorded. The arrhythmia nurse will be present and again explain the procedure. A cardiac doctor will also see you and ask you to sign a consent form; this is to confirm that you understand the procedure and its associated risks. If you have any worries or questions, please do not be afraid to ask. It is important to tell your nurse or doctor if you have any allergies or have had a previous reaction to any drugs or other test.

Just before the procedure a nurse will help you to get ready. The doctor or nurse will insert a small needle (cannula) into a vein in your hand or arm to allow the drug to be given. You will then be given a hospital gown to wear, making it easier to record the ECG. A member of your family may stay with you during the test to help you relax.

The Ajmaline will be injected through the cannula by a special pump to make sure it is given at the correct speed. During the infusion, and once the injection is complete, your ECG will be recorded frequently until discharge. By this time the Ajmaline should be out of your system and even if you have been shown to have the changes associated with Brugada syndrome, your ECG will have returned to normal. You will then be given a drink and something to eat and the cannula will be removed before you go home.

Benefits

Making a diagnosis of Brugada syndrome is important as it may mean that you need other tests and treatment to prevent the problems associated with it. Also, because there is a hereditary factor, other family members may need to be tested. However, if the test is negative then this will provide re-assurance that it is unlikely that you have Brugada syndrome.

Side effects and risks

The Ajmaline challenge is safe. However, as with any procedure, there are potential risks that may occur either during or after the procedure. Complications associated with this procedure are very rare, can be treated, and are rarely life threatening.
It is common (and harmless) to experience a metallic taste in your mouth while you are being given the Ajmaline. You may also experience visual disturbance such as double vision. Such side effects usually resolve quickly once the infusion is completed.
Very rarely, the Ajmaline may cause your heart to go into a very fast heart rhythm. When this happens it often needs no treatment other than monitoring you while the drug wears off. Rarely this heart rhythm can require urgent treatment with cardioversion (a controlled electrical shock to restore normal heart rhythm). Cardioversion is a well-established and effective treatment for fast heart rhythms. Before the cardioversion you may be given a sedative to make you sleepy. Once you are asleep a machine called a defibrillator is used to send electrical energy to the heart muscle to restore its normal rhythm and rate. In very rare cases the heart may stop briefly and need cardioversion and other treatment to restart it as the drug wears off. No cases of death have ever been reported as a result of an Ajmaline challenge worldwide.

Your doctor will only recommend that you have an Ajmaline challenge if he/she feels that the benefits clearly outweigh the risks.

Alternatives

Other drugs can be used to test for Brugada syndrome but these take a lot longer to get out of your system so they require patients to be monitored for a longer period of time and any side effects may last longer. For these reasons many hospitals worldwide use Ajmaline for this test.

After the Ajmaline challenge

You should be able to go home 2-3 hours after the test. You are allowed to drive yourself to and from the hospital.

In the rare cases where you have had a cardioversion, you will need to be monitored for a longer period of time but if you remain stable you should be able to go home later that day (but you would not be able to drive in this case).

The ECGs will often need to be reviewed after the test by a specialist doctor (Consultant Cardiologist) to determine the result, so it may be that the doctor / nurse giving you the drug will not be able to tell you the result of the test immediately. However, you will normally be told the result of the test the same day, before you leave the hospital.

If you require any further information please contact either:

Arrhythmia Nurse, Sister Angela Hall Telephone 01534 442002 / 442000 bleep 121
Dr Mitchell's secretary Telephone 01534 442490
In an event of immediate assistance call 999 / attend the Emergency Department

Further information

More information can be found at the following websites:
SADS UK at www.sadsuk.org
Cardiac Risk in the Young (CRY) at www.c-r-y.org.uk
Heart Rhythm UK at www.heartrhythmuk.org
Heart for Life www.heartforlife.co.uk

Appendix 8: Isoprenaline treatment of ventricular arrhythmias during Ajmaline testing.

Only under direct guidance of Consultant Cardiologist or Cardiology Registrar

Isoprenaline (Isoproterenol) attenuates and acetylcholine accentuates ECG changes in affected patients (Miyazaki et al, 1996). It is a non-selective beta-adrenergic agonist and structurally similar to adrenaline.

Jongman et al (2007) researched electrical storms (≥ sequential shocks from the ICD for termination of VF) in Brugada which were successfully treated with Isoproterenol infusion (and Quinidine orally).

Sympathetic agonists, especially Isoproterenol, is effective in suppressing ST elevation in leads V1-3 and in restoring the action potential dome because it increases the Ica secondary to an elevation in the intracellular level of cyclic AMP.

The therapeutic effect of Beta-adrenergic stimulation is probably due to the direct effect on myocytes instead of the elevation in heart rate.

In Brugada, the loss of the action potential dome (phase 2) is in turn responsible for the development of a vulnerable window during which a premature impulse / extrasystole can induce re-entrant arrhythmia.

Dose: IV bolus injection, initially 0.02-0.06mg (1-3ml of a 1:50,000 dilution).
Subsequent dose range 0.01-0.2mg
Infusion 5mcg/minute. Adjust according to patient's response; usual range 2-20mcg/minute
Infusion with normal saline 0.9% or glucose 5%

Magnesium Sulphate Treatment of arrhythmias

Treatment of serious arrhythmias (refractory VF, VT with possible hypomagnesium, torsade de pointes VT, digoxin toxicity)

Dose: 8mmol (2g) of 50% solution magnesium sulphate over 10-15 minutes, repeat x 1 if needed
Suggested concentration up to 200mg/ml (20%)
Infusion with normal saline 0.9% or glucose 5%
Maximum rate 150mg/minute