States of Jersey

The States of Jersey Department for
Health & Social Services

Adrenaline (Epinephrine) Drug Challenge for the detection of Long QT Syndrome

December 2017

DOCUMENT PROFILE

Document Registration	HSS-PP-CG-0456-02
Document Purpose	Policy
Short Title	Adrenaline Drug Challenge for the detection of Long QT
Author	Sister Angela Moss
Publication Date	February 2015, reviewed December 2017
Target Audience	Cardiology, Jersey General Hospital, HDU, ICU
Circulation List	Health
Description	Policy and protocol
Linked Policies	
Approval Route	Cardiology Governance
Review Date	3 years from approval
Contact Details	Sister Angela Moss, 442002, Cardiology

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1. INTRODUCTION

1.1 Rationale

The adrenaline (epinephrine) drug challenge is carried out to help diagnose Long QT syndrome type 1. In normal subjects the Q-T interval shortens with Adrenaline (epinephrine). In people with Long QT type 1 syndrome the QT interval increases with low-dose Adrenaline (epinephrine). [1]

Long QT syndrome (LTQS) is usually diagnosed after a person has a cardiac event (e.g. syncope, cardiac arrest). In some situations, this condition is diagnosed after a family member suddenly dies. In some individuals, the diagnosis is made when an electrocardiogram shows QT prolongation.

Triggering events are somewhat different by genotype. Patients with LQT1 usually have cardiac events preceded by exercise or swimming. Sudden exposure of the patient's face to cold water is thought to elicit a vagotonic reflex. Patients with LQT2 may have arrhythmic events after an emotional event, exercise, or exposure to auditory stimuli (e.g. door bells, telephone ring). Patients with LQT3 usually have events during night sleep. [2]

LQTS is the prototypic cardiac channelopathy underscored by profound genetic and phenotypic heterogeneity. In 1991, the first LQTS chromosome was identified and subsequently more than 400 mutations in nine cardiac channel/channel associated-encoding genes have been identified (LQT 1-9). [3]

1.2 Scope

If a person survives a cardiac arrest or experiences ventricular arrhythmias with syncope, the QT interval should be analysed. Even if this yields a normal interval, the patient should be considered for LQTS and undergo adrenaline (epinephrine) provocation.

Surviving family members of a relative who died from sudden cardiac death should also be considered for screening, as should those who have a living family member with diagnosed LQTS.

Adrenaline (epinephrine) testing locally can be performed on those over the age of 18 years. Children would be referred to a specialist centre for monitoring.

The drug challenge will take place in the High Dependency Unit (HDU) or Intensive Care Unit (ICU) where cardiac monitoring is available. Staffing present will include the Arrhythmia Nurse and either the Cardiology Consultant, Cardiac Associate Specialist or Cardiac Clinical Fellow. In addition a staff nurse in HDU / ICU would be allocated to the patients care. A current advanced 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 (an information leaflet can be found in **Appendix 1**). 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

LQTS was originally thought to be extraordinarily rare – 1 in 20,000. Then the estimate became 1 in 10,000, 1 in 5,000, and the latest data suggests it may be as high as 1 in 2,000 or 1 in 3,000 persons.[4, 5] It is one of the most common causes of autopsy negative, sudden unexplained death. Contributing to its lack of identification is the fact that as many as half of individuals may not show QT prolongation at rest.

The most common presentation of LQTS in a child or young adult is without warning. It is usually an unexplained episode of fainting that may be triggered by exertion or auditory startle or an episode that gets wrongly diagnosed as an epileptic event. If LQTS is considered in the differential diagnosis, then the work-up includes an electrocardiogram to look at the QT interval. Since only half of all patients will have QT prolongation, Holter monitoring or stress testing with exercise or adrenaline may be necessary to try to provoke or unmask LQTS.[6]

Adrenaline (epinephrine) QT stress test involves giving the patient adrenaline (epinephrine) to detect an abnormal QT response. Genetic testing, looking for genetic evidence of the LQT substrate may also then be required.

1.4 Adrenaline (epinephrine)

Adrenaline (epinephrine) is a sympathomimetic catecholamine, produced in the adrenal glands. It is a hormone and neurotransmitter. It acts by binding to a variety of adrenergic receptors. Adrenaline (epinephrine) is a nonselective agonist of all adrenergic (epinephrine) receptors, including the major subtypes α_1, α_2, β_1, β_2, and β_3.[7]

As a drug it has a more pronounced effect on beta than adrenergic receptors. At higher doses, alpha effects prevail.

Licensed indications:

In resuscitation during cardiac arrest
Emergency treatment during anaphylaxis
To provide rapid relief of severe hypersensitivity reaction to drugs / allergens
Bronchospasm
Refractory hypotension

Unlicensed indications:

Adrenaline is used as a provocative test for detection of cases of catecholamine polymorphic ventricular tachycardia and hidden long QT syndrome as causes of sudden unexpected death

Possible side effects:

Cardiovascular: Hypertension, tachycardia, arrhythmias, pounding heartbeats and chest pain

Central nervous system: Headache, dizziness, anxiety, insomnia
Gastro-intestinal: Nausea, vomiting
Others: Flushing, pallor, diaphoresis, dry throat, peripheral vasoconstriction, tremor
Large doses may cause cerebral haemorrhage or pulmonary oedema
Extravasation causes local vasoconstriction and severe tissue damage
Because adrenaline (epinephrine) may cause hyperglycaemia, diabetic patients receiving adrenaline may require increased dosage of insulin or oral hyperglycaemia agents.

Contraindications:

There are no absolute contraindications, but extreme caution should be shown whenever it is used owing to its profound effect on the cardiovascular system. Particular care must be taken when using it in patients suffering from arrhythmias, hypertension or ischaemic heart disease since these conditions may be acutely exacerbated.

Additionally, known hypersensitivity.

Caution with:

Elderly, diabetic patients, cardiovascular disorders including angina and myocardial infarction, hyperthyroidism, closed angle glaucoma [7]

Interactions:

Concurrent use of Tricyclic antidepressants, Digoxin, parenterally administered diuretics, Guanethidine, Methyldopa or other similar agents may potentiate the effects of Adrenaline. Beta blockers especially non-selective, increase the pressor effect and decrease the bronchodilator effects of Adrenaline. Caution should also be shown in patients taking monoamine oxidase inhibitors.

1.5 Diagnosing

Findings on physical examination usually do not indicate a diagnosis of LQTS, although some patients may present with excessive bradycardia for their age, and some patients may have hearing loss (congenital deafness), indicating the possibility of Jervell and Lange-Nielsen syndrome. Skeletal abnormalities, such as short stature and scoliosis are seen in the LQT7 type (Andersen syndrome), and congenital heart diseases, cognitive and behavioural problems, musculoskeletal diseases, and immune dysfunction may be seen in those with LQT8 type (Timothy syndrome). [8]

Diagnostic studies in patients with suspected LQTS include the following:

- Serum potassium and magnesium levels
- Thyroid function tests
- Electrocardiography of the patient and family members
- Pharmacologic provocation with epinephrine or isoprenaline in patients with a borderline presentation
- Genetic testing of the patient and family members
- Exercise stress testing for the evaluation of LQTS (recovery phase analysis)

The LQTS diagnostic score may be useful and can be found in **Appendix 2**. This requires assigning points to different criteria. A score of four or more indicates a higher probability for LQTS whilst one or zero suggests a lower risk. A score of two or three means an intermediate probability.

Bradycardia and tachycardia

Bradycardia and tachycardia each need special attention. Bradycardia is included in the diagnostic criteria and adds 0.5 point to the score. Tachycardia needs special attention, too, because the QTc may be overcorrected in a tachycardic situation (e.g. in infants).

T-wave alternans

Visible T-wave alternans in patients with LQTS indicates an increased risk of cardiac arrhythmias (i.e. torsade de pointes and ventricular fibrillation).

Detection of microvolt T-wave alternans has low sensitivity and high specificity in diagnosing LQTS.

Pharmacologic provocation

Pharmacologic provocation with Adrenaline helps in diagnosing LQTS in patients with a borderline presentation. It may also provide information regarding the type of mutation present.

Exercise treadmil test

Treadmil stress testing can unmask patients with concealed LQTS, particularly LQTS1 with good diagnostic accuracy (17, 18). Provocative adrenaline QT stress testing is unavailable in many centres but exercise testing alone can offer valuable clues towards aiding diagnosis. An increase in QTc during the recovery phase of treadmil stress testing distinguishes LQTS (particularly LQTS1) from controls even when the resting QTc is normal. A QTc of ≥30ms at 3 minutes of recovery may provide a 75% pre-genetic test probability for LQT1 status (17).

Testing family members

It is important to review the ECG's of family members of a patient with LQTS, to obtain detailed histories, and to perform physical examinations. However, an absence of ECG findings of LQTS in family members does not exclude LQTS. In the ideal setting, all family members should be tested for mutations to help limit the small, but definite, risk of arrhythmia and sudden cardiac death. Testing is especially relevant if the patient was exposed to a drug that prolongs the QT interval.

Measuring QTc

QTc must be accurately analysed and a calculation used to determine length is offered by Bazett's formula (see **Appendix 3** for examples and ECG's).

Isolating the end of the T wave if unclear, should be defined by isolating the intersection of the maximum downslope of the ST segment with the isoelectric line of the T-P segment.

The normal parameters for QTc in females is <470ms and in males, <450ms. QTc of >500ms requires referral to a specialist for monitoring and management. This may simply require the discontinuation of medications known to prolong the QT interval.

QT prolonging drugs

www.qtdrugs.org provides up to date information of QT prolonging drugs.

All patients with long QT syndrome (LQTS) should avoid drugs that prolong the QT interval or that reduce their serum potassium or magnesium level. Potassium and magnesium deficiency should be corrected.

1.6 Management

Routinely check serum levels of potassium (and sometimes magnesium) and thyroid function in patients who present with QT prolongation after arrhythmic events, to eliminate secondary reasons for repolarisation abnormalities.

Analysis of repolarisation duration (QTc) and morphology on a patient's ECG and on ECGs of the patient's relatives frequently leads to an accurate diagnosis.

Imaging studies

Imaging studies (e.g. echocardiography, MRI may help only in excluding other potential reasons for arrhythmic events (e.g. hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) or associated congenital heart diseases in a small subset of patients with LQTS, such as persons with LQT8.

Diagnostic criteria

A presentation with syncope or sudden cardiac death, in combination with a long QT on an ECG, typically suggests long QT syndrome (LQTS) and leads to genetic testing to diagnose the disease. In many patients, however, the presentation may not be typical. Therefore, other tests may be indicated. [4]

1.7 LQTS variations

The most helpful ECG findings are prolongation of the QT interval, torsade de pointes, T-wave alternans, and certain morphology of the T waves.

Correlation between the type of mutation and T-wave morphology has been suggested. Wide-based T waves are most frequently seen in LQT1, and notched T waves are most commonly seen in LQT2. In LQT3, T waves may appear normal, with a long, isoelectric ST segment (see **Appendix 4**).

Follow-up

Asymptomatic individuals with LQTS should be carefully monitored and followed-up in an ambulatory setting by a Cardiologist or member of the cardiology specialist team.

1.8 Treatment

Beta-blockers are drugs of choice for patients with LQTS. The protective effect of beta-blockers is related to their adrenergic blockade, which diminishes the risk of cardiac arrhythmias. They may also reduce the QT interval in some patients. [9]

Beta-blockers are effective in preventing cardiac events in approximately 70% of patients, whereas cardiac events continue to occur despite beta-blocker therapy in the remaining 30%.

Propranolol and nadolol (latter not stocked locally) are the most frequently used beta-blockers, though atenolol and metoprolol are also prescribed in patients with LQTS.

Response to beta-blocker therapy may vary depending on the triggering event. In patients with LQT1, beta-blocker therapy is effective when exercise triggers the event but is ineffective if the event happens during sleep or arousal. [9]

The ICD has been shown to be highly effective in preventing sudden cardiac death in high-risk patients. In a study of 125 patients with long QT syndrome (LQTS) who received an ICD, there was a 1.3% death rate in high-risk ICD patients, compared with 16% in non-ICD patients, during a mean 8-year follow-up.[14] High-risk patients are defined as those with aborted cardiac arrest or recurrent cardiac events (e.g. syncope or torsade de pointes) despite conventional therapy (i.e. beta-blocker alone) and those with very prolonged QT interval (>500 ms). [10]

2. POLICY PURPOSE

The standard follows that of similar protocols used routinely in cardiac units nationally. Specific policies have been used to inform local practice along with relevant research. Close links with the John Radcliffe Cardiac Unit in Oxford have been maintained and used to guide local practice. Guidelines from St Georges Hospital have also been referred to throughout the preparation of this document.

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 Adrenaline 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 European Society of Cardiology, and the National Institute of Clinical Excellence, along with evidenced contemporary literature, referenced throughout this document.

In normal subjects Adrenaline shortens the QT interval. In people with LQTS type 1, low dose Adrenaline will result in a prolonged QT interval (see **Appendix 6**).

2.1 Service design – Medical and Nursing Responsibility

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

Clinical / Operational Lead

The clinical lead is the Consultant Cardiologist. The operational lead responsibility lies with the Consultant Cardiologist and Arrhythmia Nurse Specialist with overall nursing management from the Ambulatory Care Manager. Studies will not take place in the event of the aforementioned cardiology staff absence.

All policies, procedures 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.

2.2 Assessment

2.3 Pre-assessment

Patients will be seen by the Arrhythmia Nurse following the arrangement of an appointment to attend pre-assessment. Clinic slots to be fully utilised. Document ‘did not attend’ if relevant. 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 (Trak) will be updated accordingly.

2.4 Patient assessment

Patient assessment includes:

History taking and checking cardiology notes for patient screening for inclusion
Checking risk factors including blood results
Perform baseline ECG, check echocardiogram and other relevant investigations

Calculate QTc
Determine the need for further / repeat investigations
Provide the patient with detailed information and a patient information sheet
Reassure patient / family and answer any questions

3. PROCEDURE

3.1 Preparation

Preparation of Adrenaline to be used to diagnose Long Q-T syndrome Type 1

I Add 2mls of 1:1000 (2mg) adrenaline to 48ml sodium chloride 0.9% (making 50ml in total). This gives a strength of 40 microgram/ml
2 The adrenaline infusion needs to be drawn up into a 50 ml luer lock syringe and the IV giving set primed with the preparation
3 An independent check by a second qualified member of staff is required
4 Apply a yellow drug label to the syringe and place in the syringe pump
5 Set the rate of the syringe pump according to the table below
6 Using ANTT technique, flush the cannula with sodium chloride 0.9% and then attach the infusion to the patient
7 Start the test and the stopwatch. The test should be stopped after a total infusion time of 25 minutes.

NB: Infusion protocol follows the Mayo Protocol, adopted by The John Radcliffe Hospital, Oxford and St Georges Hospital, London.

3.2 Infusion Table

Time	Infusion Rate	ECG
Baseline	No infusion	Take a 12 lead ECG
Start of test	0.025microgram/kg/min = 0.0375 ml/kg/hour = patient's weight divided by 26.7 to get the rate in ml/hr	Take a 12 lead ECG after 10 minutes Note the QT and QTc in Lead II and/or V5
After 10 minutes, double the dose i.e. double the rate of the syringe pump. The new rate should be independently checked by a second person.	0.05 microgram/kg/min = 0.075 ml/kg/hour = double the initial rate = patient's weight divided by 13.3 to get the rate in ml/hr	Take a 12 lead ECG after 5 minutes Note the QT and QTc in Lead II and/or V5
After 5 more minutes (total of 15 minutes infusion), double the dose again i.e. the rate of the syringe pump. The new rate should be independently checked by a second person.	0.1 microgram/kg/min = 0.15 ml/kg/hour = 4 x the initial rate = patient's weight divided by 6.7 to get the rate in ml/hr	Take a 12 lead ECG after 5 minutes Note the QT and QTc in Lead II and/or V5
After 5 more minutes (total of 20 minutes infusion), double the dose again i.e. the rate of the syringe pump. The new rate should be	0.2 microgram/kg/min = 0.3 ml/kg/hour = 8 x the initial rate = patient's weight divided by 3.3 to get the rate in ml/hr	Take a 12 lead ECG after 5 minutes Note the QT and QTc in Lead II and/or V5

independently checked by a second person.		
After 5 more minutes (total infusion time 25 minutes), stop infusion	Stop infusion	Take 2 more ECG's, one 5 minutes after, the next 10 minutes after the infusion stops. Note the QT and QTc in Lead II and/or V5

See also **Appendix 6**

3.3 Monitoring - Care of the patient

1 The patient will be monitored in the HDU / ICU environment
2 One relative or significant other may accompany the patient during the test
3 The patient will be attached to the monitoring equipment (blood pressure, ECG and SpO_2). The defibrillator must be present in the room but not attached to the patient
4 The patient's baseline observations will be recorded before the infusion is started
5 The patient will be continuously monitored during the test but the observations (HR, BP & SpO_2) will be recorded at the same time as the ECG is recorded
6 An ECG must be recorded at the time intervals specified in the table above. The QT interval and heart rate are to be measured at the end of each 5 minute period and QTc calculated according to Bazett's formula (the end of the T wave is defined as the intersection of the maximum down slope of the ST segment with the isoelectric line of the T-P segment).
7 If the patient develops symptoms that are of concern, whether associated with ECG changes or not, then the infusion/test should be stopped and, if necessary, assistance sought

<u>ECG changes</u>?

8 Stop the infusion if ventricular arrhythmias occur (see 5.4)
9 Monitor the patient until the ECG has returned to baseline
10 If ventricular arrhythmias are observed and the patient is haemodynamically compromised, call for senior cardiology support
11 Treatment is with IV beta blockers (*Metoprolol 2.5-5mg IV over one minute*). Metoprolol can also be given if symptoms persist after discontinuation.
<u>DO NOT give an Adrenaline bolus if the patient is in cardiac arrest</u>
12 If the patient suffers a full cardiac arrest, pull the crash bell, put out the Crash Call: 2222 and commence cardiopulmonary resuscitation

<u>When the infusion is complete</u>

13 Monitoring to continue for up to 2 hours post procedure
14 Blood pressure to be documented at least every 30 minutes

15 The patient may eat and drink
16 The cannula must be removed prior to discharge
17 Prior to discharge the patient will be reviewed by the Cardiologist / Associate Specialist / Clinical Fellow

See **Appendix 5** for a simplified flow chart.

3.4 End points

The study will complete when:

The infusion is complete (target dose is reached)
If ventricular arrhythmias occur (Ventricular tachycardia or polymorphic ventricular Tachycardia – sustained or non-sustained - or Ventricular Fibrillation)
Frequent ventricular ectopics (>10 premature ventricular contractions in <1 minute)
If there is an increase of 40msec in QT interval (a QTc prolongation of ≥65msec is considered above the mean control response to Adrenaline). [11, 12, 13] (**Appendix 2)**
T-wave alternans (a periodic beat to beat variation in the amplitude or shape of the wave)
Marked hypertension i.e. systolic BP ≥200mmHg
Hypotension i.e. when systolic BP falls <80mmHg
Patient intolerance (e.g. headache and / or nausea)

3.5 Audit

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

Waiting time form referral to admission
Hours of bed occupancy
Positive test for LQTS Type 1
Prolongation of QT interval at baseline and five minute ECG intervals
Arrhythmias during infusion / haemodynamic compromise
Patient satisfaction
Other complications requiring medical assistance

4. DEVELOPMENT AND CONSULTATION PROCESS

4.1 Consultation Schedule

Name and Title of Individual	Date Consulted
Dr Andrew Mitchell, Cardiologist	5.9.14
Dr Ranji Thomas, Associate Specialist	19.1.15
Sebastian McNeilly, Pharmacist	19.1.15, feedback 12.2.15
Andrew Norman, Manager, CID	19.1.15
Geoff Benning, ICU Manager	19.1.15

5. REFERENCE DOCUMENTS

1. Vyas, H., Hejlik, J and Ackerman, M (2006) Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation*. (11) 113. p1385-1392.

2. Moss, A (2003) Long QT syndrome. *Journal of the American Medical Association*. 289. p2041-2044.

3. Ackerman, M (2005) Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Current Opinion in Cardiology*. p175-81.

4. Schwartz, P et al (2009) Prevalence of the congenital long QT syndrome. *Circulation*. (18) 120. p1761-1767.

5. Goldman and Lee (2011) *Goldman's Cecil Medicine* (24th ed.) Philadelphia: Elsevier Saunders. p1196.

6. Sudden arrhythmia death syndromes. 2014. www.sads.org. [Online]. [Accessed November 2014]. Available from: http://www.sads.org

7. International Medications Systems (UK) Ltd. Summary of Product Characteristics for Epinephrine (Adrenaline) Injection 1:10,000. Last updated on eMC 15-Jul-2014. www.medicines.org.uk/emc. [Online]. [Accessed November 2014]. Available from: http://www.medicines.org.uk

8. Sovari, A (2014) Long QT syndrome. *Medscape*. [Online]. [Accessed September 2014]. Available from: http://emedicine.medscape.com.

9. Goldenberg, I and Moss, A (2008) Long QT syndrome. *Journal of the American College of Cardiology*. (24) 51. p2291-2300.

10. Wojciech, Z., Moss, A., Daubert, J., Hall, W., Robinson, J., Andrews, M (2003) Implantable Cardioverter Defibrillator in High-Risk Long QT Syndrome Patients. *Journal of Cardiovascular Electrophysiology.* 14 (4). p337-341.

11. Ackerman, M., Khositseth, A., Tester, D., Hejlik, J., Shen, W., Porter, C (2002) Epinephrine-induced QT prolongation: A gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clinical Procedures*. (77). p413-421.

12. Shimize, W., Noda, T., Takaki, H., Kurita, T., Nagaya, N., Satomi, K., Suyama, K., Aihara, N., Kamakura, S., Sunagawa, K., Echigo, S., Nakamura, K., Ohe, T., Towbin, J., Napolitano, C., Priori, S (2003) Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome. *Journal of American College of Cardiology*. (41). p633-642.

13. Shimizu, W., Noda, T., Takaki, H., Nagaya, N., Satomi, K., Kurita, T., Suyama, K., Aihara, N., Sungawa, K., Echigo, S., Miyamoto, Y., Yoshimasa, Y., Nakamura, K., Ohe,

T., Towbin, J., Priori, S., Kamakura, S (2004) Diagnostic value of epinephrine test for genotyping LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Heart Rhythm*. (3). p273-286.

14.Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox J, Giuli LC, Shen J, Splawski I, Priori SG, Compton SJ, Yanowitz F, Benhorin J, Moss AJ, Schwartz PJ, Robinson JL, Wang Q, Zareba W, Keating MT, Towbin JA, Napolitano C, Medina A (2001) Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes*. Circulation*. 102. p2849–285

15.Modi, S and Krahn, A (2011) Sudden Cardiac Arrest without Overt Heart Disease. *Circulation*. **(**123). p2994-3008

16. Krahn, A., Healey, J., Chauhan, V., Birnie, D., Champagne, J., Sanatani, S., Ahmad, K., Ballantyne, E., Gerull, B., Yee, R., Skanes, A., Gula, L., Leong-Sit, P., Klein, G., Gollob, M., Simpson, C., Talajic, M., Gardner, M (2012) Epinephrine Infusion in the Evaluation of Unexplained Cardiac Arrest and Familial Sudden Death. *Circulation, Arrhythmias and Electrophysiology*. p933-940.

17. Horner, J., Horner, M and Ackerman, M (2011) The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome. *Heart Rhythm*. 8 (11). p1698-1704.

18. Schwartz, P and Crotti, L (2011) QTc behaviour during exercise and genetic testing for the long-QT Syndrome. *Circulation*. 124. p2181-2184.

6. BIBLIOGRAPHY

Vyas, H., Hejlik, J and Ackerman, M (2006) Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation*. (11) 113. p1385-92.

Viskin, S (2005) Drug Challenge with Epinephrine or Isoproterenol for Diagnosing a Long QT Syndrome. *Journal of Cardiovascular Electrophysiology*. 16. p285-287.

(2012) *Cardiac Drug Challenge: Ajmaline and Adrenaline*. Department of Cardiology. John Radcliffe Hospital, Oxford.

Varnava, A (2013) *Protocol for Adrenaline Challenge*. Imperial College, London.

Behr, E (2009) *Protocol for the use of Epinephrine (Adrenaline) in diagnosis of Adult catecholaminergic polymorphic ventricular tachycardia (CPTV) and hidden long QT syndrome*. St Georges Hospital, London.

7. IMPLEMENTATION PLAN

Action	Responsible Officer	Timeframe
Review by Dr Mitchell	Sr A Moss	By mid September 2014
Send to Dr R Thomas	Sr A Moss	End September

Send to Adam North	Sr A Moss	End September
Send to Andrew Norman	Sr A Moss	End September
Meet with and send to Geoff Benning, ICU Manager	Sr A Moss	End September
Present to next Cardiology Governance meeting	Sr A Moss	October 2014
Complete any amendments and send to Ann Kelly for publication	Sr A Moss	October 2014

Reviewed 19.1.15

Action	**Responsible Officer**	**Timeframe**
Review by Dr Mitchell	Sr A Moss	Feedback 19.1.15
Send to Dr R Thomas – Amend where necessary	Sr A Moss	End January 2015
Send to Adam North – amend where necessary	Sr A Moss	End January 2015
Send to Andrew Norman – amend where necessary	Sr A Moss	End January 2015
Meet with and send to Geoff Benning, ICU Manager	Sr A Moss	End January 2015
Present to next Cardiology Governance meeting	Sr A Moss	28.1.15
Complete any amendments and send to Ann Kelly for publication	Sr A Moss	13.2.15

8. APPENDICES

Appendix 1: Patient Information Sheet for Adrenaline Challenge

The adrenaline challenge for Long QT Syndrome (LQTS)

Your doctor has recommended that you have an adrenaline challenge. The purpose of this test is to see if you are likely to have long QT syndrome (LQTS), particularly type 1. This is a disorder that affects the heart. Some people with LQTS 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 LQTS.
It is important to remember that the majority of patients who have a long QT appearance on an electrocardiogram (ECG) do not experience arrhythmia and feel perfectly well. If your doctor suspects that you may have LQTS he or she will have advised you to have this well-established, simple clinical test known as an adrenaline challenge to confirm the diagnosis.
Adrenaline is a natural substance in our bodies, but is also used as a drug for a number of reasons, one of which is to test for ECG changes in patients with LQTS. In patients with normal cardiac cells, adrenaline will not have any abnormal effect on the ECG.

What happens during the adrenaline 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. If you haven't already, you will sign your 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 doctor to give you the adrenaline during the procedure. You will then be given a hospital gown to wear, making it easier to record the ECG. A member of your family can stay with you during the test to help you relax if you wish.

The adrenaline will be injected through the cannula by a special pump to make sure it is given at the correct speed. During the infusion your ECG will be recorded every 3-5 minutes for up to 30 minutes. By this time the adrenaline should be out of your system and even if you have been shown to have the changes associated with LQTS, your ECG will rapidly return 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 LQTS 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 LQTS.

Side effects and risks
The adrenaline 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 some or all of the sensations of a rush of adrenaline. These include feeling your heart racing and beating more forcefully, and sometimes feeling a bit sweaty. Such side effects usually resolve quickly once the infusion is completed. Very rarely, the adrenaline 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 adrenaline challenge worldwide.

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

Alternatives
Some people use an exercise treadmill test as well but the adrenaline challenge has been shown to be most accurate for specific types of LQTS.

After the adrenaline 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 to be cardioverted, 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 drive in this case).
The ECGs will often need to be reviewed after the test by a specialist doctor known as an Electrophysiologist to determine the result, so it may be that the doctor 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.

How to contact us
If you require any further information please contact either:

Cardiology: 01534 442490
Arrhythmia Nurse Specialist, Angela Moss: 01534 442002

Appendix 2 LQTS diagnostic score

The diagnosis of LQTS is not easy since 2.5% of the healthy population have prolonged QT interval, and 10–15% of LQTS patients have a normal QT interval.[8] A commonly used criterion to diagnose LQTS is the LQTS "diagnostic score".[9] The score is calculated by assigning different points to various criteria (listed below). With four or more points, the probability is high for LQTS; with one point or less, the probability is low. A score of two or three points indicates intermediate probability.

- QTc (Defined as QT interval / square root of RR interval)
  - ≥ 480 ms - 3 points
  - 460-470 ms - 2 points
  - 450 ms and male gender - 1 point
- Torsades de pointes ventricular tachycardia - 2 points
- T wave alternans - 1 point
- Notched T wave in at least 3 leads - 1 point
- Low heart rate for age (children) - 0.5 points
- Syncope (one cannot receive points both for syncope and torsades de pointes)
  - With stress - 2 points
  - Without stress - 1 point
- Congenital deafness - 0.5 points
- Family history (the same family member cannot be counted for LQTS and sudden death)
  - Other family members with definite LQTS - 1 point
  - Sudden death in immediate family members (before age 30) - 0.5 points

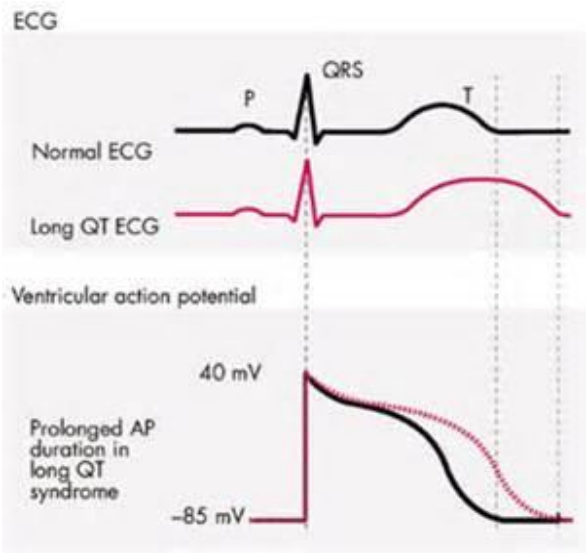
In relation to the Adrenaline challenge :

An absolute QT prolongation of equal / >60ms at low dose adrenaline (0.05 - 0.10mcg/kg/min) is considered positive for LQTS1.

Bidirectional VT / frequent VE's (>10/minute) or non-sustained VT or T wave alternans are considered positive for diagnosis of catecholaminergic polymorphic VT (CPTV).

Appendix 3 LQTS calculation and ECG example

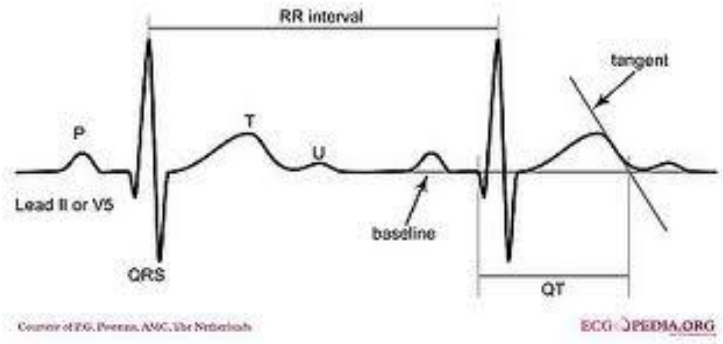
Use lead II or lead V5 if lead II cannot be read
Draw a line through the baseline (preferably the PR segment)
Draw a tangent against the steepest part of the end of the T wave
The QT interval starts at the beginning of the QRS interval and ends where the tangent and baseline cross

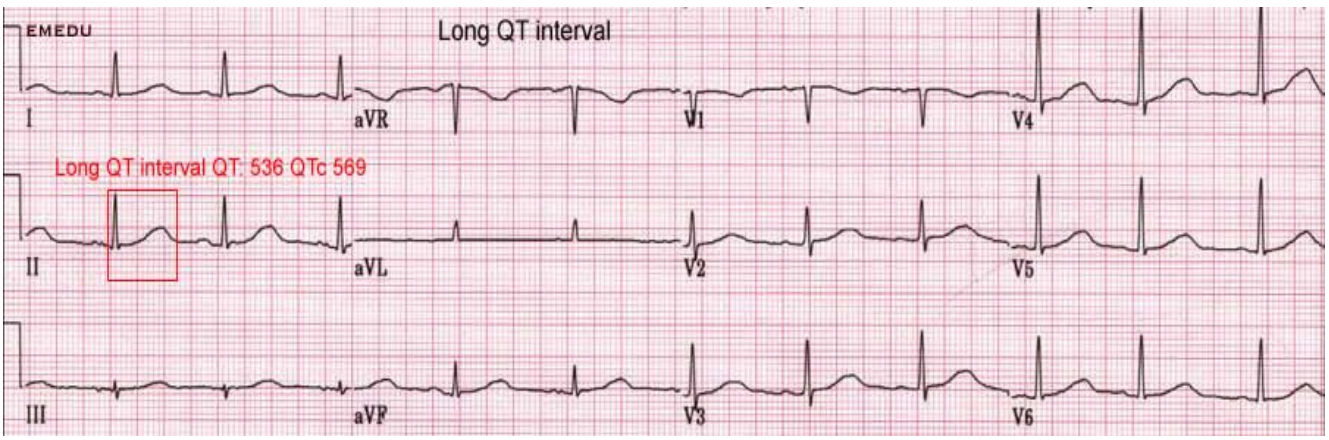


Bazetts formula

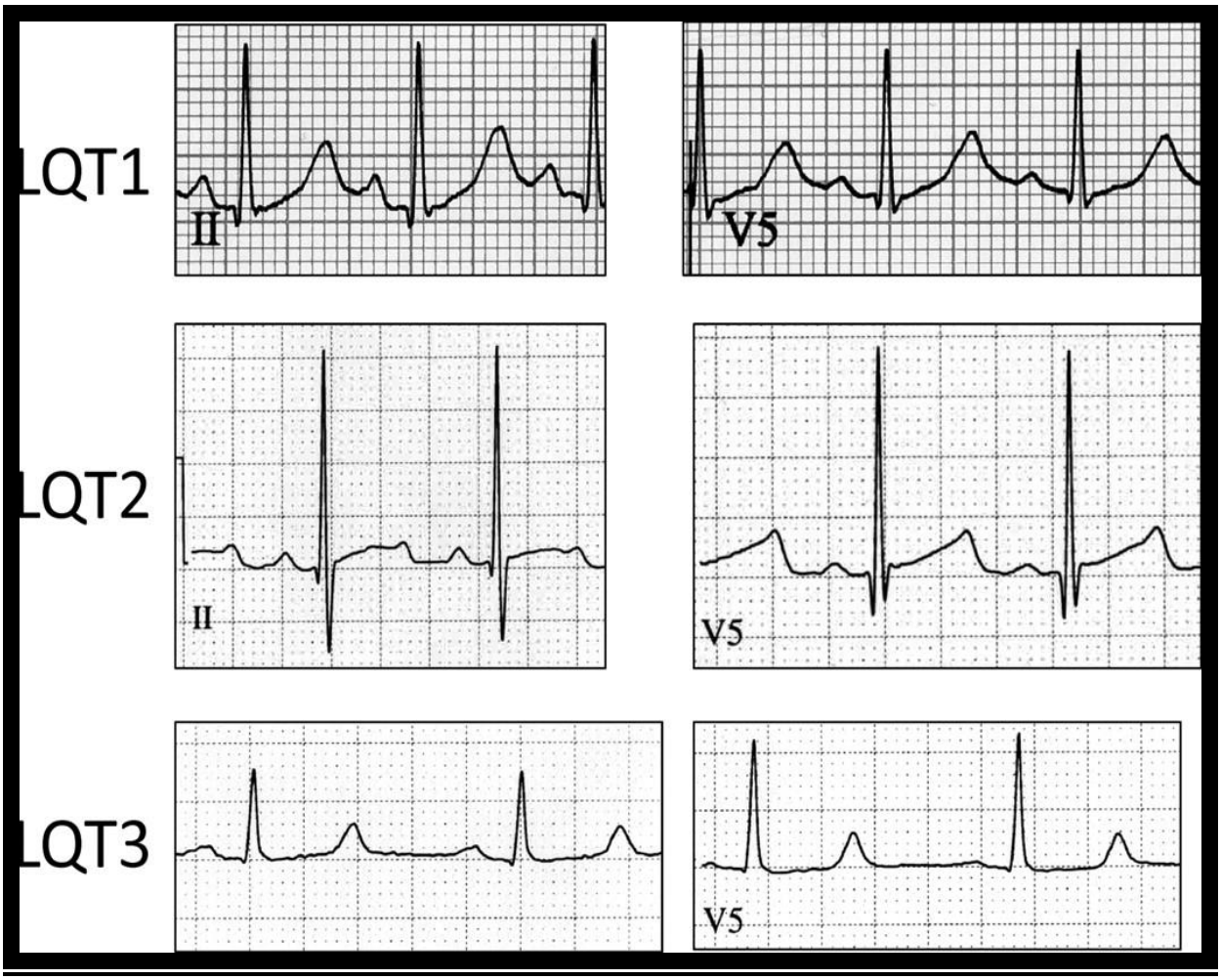
$$QTc = \frac{QT\ interval}{\sqrt{RR}}$$

QTc – corrected QT interval
QT interval – Q wave to end of T wave
RR – time from 2 consecutive R waves





Appendix 4 LQTS 1, 2 and 3 on the ECG



LQT 1 has a broad T wave
LQT 2 has a notched T wave with an asymmetrical appearance
LQT 3 has a long isoelectric segment with a normal symmetrical T wave

Absolute QT intervals seen here are unimpressive until correction for heart rate is performed. The upper 2 ECGs were obtained after standing, known to unmask QTc prolongation. As a general principle, a T wave terminating within the latter half of the same R-R interval is highly suspicious for long-QT syndrome.

Zhang (et al) (2001) [14]

Modi and Krahn (2011) [15]

Appendix 5 Simplified Flow Chart for Adrenaline Challenge

- Patient consent obtained
- Patient weighed (kg) and cannula inserted
- Baseline observations and 12 lead ECG
- Ensure resuscitation equipment present including a defibrillator
- Continuous observation equipment connected including BP cuff, heart monitoring and saturation probe

↓

- Add 2mls of 1:1000 (2mg) adrenaline (epinephrine) to 48mls sodium chloride 0.9% (making 50ml in total). This gives a strength of 40mcg/ml
- The drug dose needs to be drawn up into 50ml luer lock syringe and the IV giving set primed with the drug
- A double check by the 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 according to the table below

Time from start	Dose	Infusion Rate	Times of ECG (from start)
Start infusion (time 0)	0.025mcg/kg/min = patient's weight divided by 26.7 to get rate in ml/hr	= 0.0375 ml/kg/hour	After 9 minutes
10 minutes	0.05mcg/kg/min = 2 x initial rate = patient's weight divided by 13.3 = mls/hr	= 0.075 ml/kg/hour	After 14 minutes
15 minutes	0.1mcg/kg/min = 4 x initial rate = patient's weight divided by 6.7 = mls/hr	= 0.15 ml/kg/hour	After 19 minutes
20 minutes	0.2mcg/kg/min = 8 x initial rate = patient's weight divided by 3.3 = mls/hr	= 0.3 ml/kg/hour	After 24 minutes
25 minutes	Stop infusion		After 30 and 40 minutes

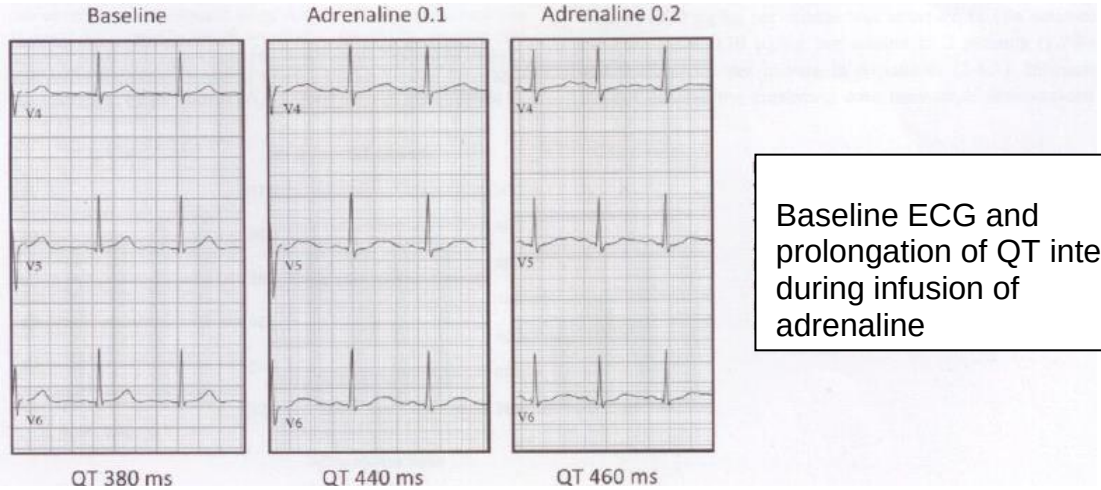
↓

At the end of the test discuss with the Consultant Cardiologist for interpretation

Stop the infusion before the end of the test when:

If ventricular arrhythmias occur (VT or polymorphic VT – sustained or non-sustained - or VF)
Frequent ventricular ectopics (>10 premature ventricular contractions in <1 minute)
An increase of 40msec in QT interval (a QTc prolongation of ≥65msec is considered above the mean control response to Adrenaline). [11, 12, 13] **(Appendix 2)**
T-wave alternans (a periodic beat to beat variation in the amplitude or shape of the wave)
Marked hypertension i.e. systolic BP ≥200mmHg
Hypotension i.e. when systolic BP falls <80mmHg
Patient intolerance (e.g. headache and / or nausea)

Appendix 6 ECG before and with Adrenaline provocation



Baseline ECG and prolongation of QT interval during infusion of adrenaline

From Krahn, A et al (2012) [16]