

# A&I

## ANÄSTHESIOLOGIE & INTENSIVMEDIZIN

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**Timothy syndrome**

**Tracheal agenesis**

orphan**a**nesthesia

a project of the German Society  
of Anaesthesiology and Intensive Care Medicine

**SUPPLEMENT NR. 2 | 2019**

## OrphanAnesthesia –

### ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter [www.ai-online.info](http://www.ai-online.info) veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

## OrphanAnesthesia –

### a common project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommendations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via [www.ai-online.info](http://www.ai-online.info). As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

**Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:**

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# orphan**a**nesthesia

## Anaesthesia recommendations for patients suffering from **Timothy Syndrome**

**Disease name:** Timothy Syndrome

**ICD 10:** I45.8

**Synonyms:** LQT8, Long QT syndrome type 8, Long QT syndrome-syndactyly syndrome

Timothy Syndrome is one of the many syndromes causing long QT and is referred to as 'Long QT Syndrome Type 8'. It was first described by Timothy et al in 2004 and is a rare genetic disorder.

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Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

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**Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)**

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### Disease summary

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It has a broad spectrum of characteristics which include:

- cardiac arrhythmias (prolonged QT/QTc interval, bradycardia, 2:1 AV block, T-wave alternans)
- congenital cardiac defects (PDA, PFO, VSD, Tetralogy of Fallot, HOCM)
- syndactyly (variably involving the index, middle, ring and little fingers)
- bilateral cutaneous syndactyly of the second and third toes

The following features have also been described:

- craniofacial characteristics
- immunodeficiency
- neurodevelopment delay
- a tendency to hypoglycaemia
- autistic spectrum disorders

Two forms of Timothy Syndrome exist. Type 1 includes all of the characteristic features. Type 2 causes a more severe form of long QT syndrome (LQTS) but does not appear to cause the fusion of interdigital skin.

All cases of Timothy Syndrome arise from a mutation of the CACNA1C gene which is located on the short arm of Chromosome 12. This gene encodes the L-type Ca(v)1.2 calcium channel protein. The gene mutation causes a reduction in the inactivation of the calcium channels during the plateau phase of the cardiac action potential. The result is that the calcium channels never close properly allowing excess calcium to influx into the cell. This in turn leads to prolongation of the plateau phase and thus the QT/QTc interval. The clinical implications of this are: an increased risk of spontaneous ventricular tachyarrhythmia, especially Tornadoes de points (TdP), and sudden death.

A recent study identified five variants in the CACNA1C gene associated with long QT syndrome, however not all were associated with the phenotypical manifestations of Timothy Syndrome. Timothy Syndrome is inherited in an autosomal dominant manner, however most cases arise as spontaneous mutations rather than from direct parental inheritance.

Tachyarrhythmia is the leading cause of death, followed by infection and complications of intractable hypoglycaemia. The life expectancy of a patient with Timothy Syndrome is 2.5 years, however as many patients live for much longer, anaesthetists may need to provide anaesthesia to patients of a variety of ages with Timothy Syndrome.

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### Typical surgery

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Typical surgeries performed on patients with Timothy Syndrome are: corrective cardiac surgery, insertion of implantable automated defibrillator or pacemaker, plastic surgery for the correction of syndactyly.

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### Type of anaesthesia

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Given the patient cohort and likely nature of the surgeries, anaesthesia would involve a general anaesthetic with the possible addition of central or regional neuroblockade.

### **Necessary additional diagnostic procedures (preoperative)**

Pre-operative planning is of paramount importance and should involve a multidisciplinary team comprising the relevant paediatric surgeon, anaesthesiologist and paediatric cardiologist.

Pre-operative evaluation must include an ECG. Whilst the calculation of the resting heart rate, QTc interval and recognition of other electrical abnormalities is essential, no recommendations are published regarding the specific cut-offs which may contraindicate surgery. Ambulatory ECG monitoring can be considered to identify the presence, frequency and duration of paroxysmal arrhythmic episodes.

Patients with Timothy Syndrome may exhibit a variety of ECG changes as described above. As the QT interval varies with heart rate the QTc is calculated using Bazette's equation:

$$QTc = QT / \sqrt{RR}$$

The QT interval is usually measured in lead II as the T-wave end is usually discrete and the QT interval itself has good correlation with the maximal QT measurement across the entire 12 lead ECG.

T-wave alternans is a pathognomonic feature of LQTS. However, this beat to beat variation in T-wave amplitude has high specificity but very low sensitivity for LQTS.

Echocardiography should be performed to identify previously undiagnosed congenital structural cardiac defects and to assess cardiac function.

Serum electrolytes, especially potassium, magnesium and calcium, should be measured and corrected. Low levels of these electrolytes predispose to delayed ventricular depolarisation and therefore prolongation of the QT interval.

Patients with proven LQTS require pre-operative treatment, beta blockade is the usual form of pharmacological intervention. Beta blockers maintain QT interval stability and suppress cardiac sympathetic stimulation. Beta blockers should be continued up to and including the morning of surgery. The acute use and effectiveness of beta blocker therapy during and acute arrhythmic crisis during surgery is currently unknown.

Any pacemaker or implanted internal defibrillator must be checked preoperatively and surgical teams must consider the effect diathermy may have on the device.

As with any anaesthetic candidate, a thorough respiratory history and examination should be performed. In addition to assessing for respiratory sequelae of cardiac function abnormalities, signs of intercurrent infection must be looked for as this may influence the preoperative course.

### **Particular preparation for airway management**

There are no specific prerequisites for the airway management other than to ensure that the patient is adequately anaesthetized and analgesed prior to airway manipulation to prevent sympathetic surges precipitating tachyarrhythmias.

Given the likely age group of patients with Timothy syndrome, the anaesthetist should be familiar with the management of the paediatric airway.

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### **Particular preparation for transfusion or administration of blood products**

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There are no specific recommendations regarding the administration of blood products. The maintenance of tissue oxygen delivery should be considered especially with co-existing congenital cardiac co-morbidities.

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### **Particular preparation for anticoagulation**

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There is no prerequisite for anticoagulation for Timothy Syndrome itself. No coagulopathies have been described. However, there may be indications for anticoagulation specific to congenital cardiac abnormalities and their subsequent correction.

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### **Particular precautions for positioning, transport or mobilisation**

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There are no specific precautions for the mobilisation and positioning of patients with Timothy syndrome.

The transportation of the anaesthetized patient with Timothy Syndrome should be performed with the same care as with any anaesthetized patient with full, continuous, invasive monitoring and easy access to emergency resuscitation drugs and equipment. Particular attention must be paid to ensuring an adequate depth of anaesthesia, gentle handling and maintaining a temperature controlled environment.

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### **Probable interaction between anaesthetic agents and patient's long term medication**

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During surgery, drugs known to increase the QTc and induce TdP should be avoided. The list potential drugs is long a resource providing an up to date list of medications should be regularly consulted, e.g. [www.qtdrugs.org](http://www.qtdrugs.org)

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### **Anaesthesiologic procedure**

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Precautions should begin during the immediate pre-operative period and should focus on minimizing the stress associated with the impending surgery. The patient should be kept in a warm, quiet and supportive environment. The application of topical local anaesthetic creams to potential venipuncture sites is advised. There is also a suggestion that sedation prior to venepuncture and cannulation should be considered as the act of venipuncture has been documented to induce arrhythmias.

Adequate sedation and analgesia reduces catecholamine release. Midazolam is considered an appropriate drug for providing sedation as it has no effect on the QTc in healthy adults. Midazolam reduces sympathetic activity in unstimulated patients; however, it does not blunt the haemodynamic response to oral or nasal intubation. Fentanyl and morphine are commonly used analgesics and, whilst the effects of fentanyl on the QTc are conflicting, fentanyl and morphine have been used in patients with congenital LQTS without any adverse effects.

Some literature has advocated the administration of magnesium sulphate prophylactically, even in the presence of normal serum magnesium levels.

Positive pressure ventilation strategies should ensure that sustained high intra thoracic pressures are avoided as this mimics a vasalva manoeuvre, which can lengthen QT intervals in patients who are not fully beta blocked.

Induction agents:

Induction of anaesthesia can be performed using either halogenated volatile anaesthetics or with intravenous agents. Many anaesthetic drugs are known to prolong the QTc, nevertheless all anaesthetic agents have been successfully used. Halothane, enflurane, isoflurane, desflurane and sevoflurane all prolong the QTc, even if the data available for some of these agents is controversial. Propofol infusion is an alternative to inhaled anaesthetic gases for the maintenance of anaesthesia and is a drug with which most anaesthesiologists are very familiar.

Ketamine should be avoided in patients with LQTS as its sympathomimetic properties may precipitate the onset of TdP.

Paralytics:

Succinylcholine is known to prolong the QTc. Rocuronium, vecuronium, atracurium and cisatracurium do not prolong the QTc and are considered safe for use in patients with Timothy Syndrome.

Intraoperative analgesia:

Case reports describing the use of remifentanyl infusions have suggested that it is an excellent sympatholytic intra-operatively, and also during the induction of anaesthesia.

Vasopressors and chronotropes:

The use of vasopressors in the management of hypotension is a balance of risk. Epinephrine, norepinephrine, ephedrine and phenylephrine are known to increase QTc, however case reports of their successful use are published. The authors would recommend optimisation of fluid balance together with the use of metaraminol as this is not known to prolong the QTc.

Atropine and glycopyrolate are thought to be safe.

Antiemetics:

Droperidrol, domperidone and the 5-HT<sub>3</sub> antagonists (e.g. ondansetron) prolong the QTc and should be avoided. Metoclopramide is not contraindicated. However, dexamethasone is considered to represent the safest, most effective option.

Central and regional neuroblockade:

The use of central and regional neuroblockade has been described and, if successful, provides excellent analgesia and sympatholysis. However, should any block fail, additional analgesia would be required. Epidural anaesthesia with the gradual establishment of the sympathetic block is preferred to single dose spinal anaesthesia due to the associated lower risk of hypotension with the need for vasopressors. Due to the young age of patients, epidural catheters are placed following the induction of general anaesthesia.

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### Particular or additional monitoring

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The need for invasive monitoring of this group of patients is determined by the type of surgery being performed. Every patient undergoing general anaesthesia should have continuous ECG monitoring, non-invasive blood pressure monitoring at regular intervals, pulse oximetry and capnography as standard throughout induction, maintenance and emergence.

Anaesthetists should have a low threshold for invasive monitoring, especially an arterial line, considering the risk of tachyarrhythmia with associated cardiac instability. Arterial access would also allow regular glucose and electrolyte monitoring. Volume status must be carefully monitored as beta-blocked patients tolerate hypovolaemia poorly.

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### Possible complications

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The anaesthetist must be prepared to deal with malignant arrhythmias particularly TdP. The evidence for the specific treatment of arrhythmias associated with Timothy syndrome is based on isolated case reports and empiric treatments of specific arrhythmias.

Electrolyte abnormalities, particularly hypokalaemia, should be corrected. Magnesium is the drug therapy of choice both for the prevention of repeated and treatment of established TdP. An initial bolus of 30mg/kg should be administered over 2-3 minutes followed by an infusion of 2-4mg/min. For resistant TdP a further bolus may be given after 15 minutes. Plasma magnesium levels should be monitored to avoid toxicity. Magnesium acts as a calcium channel blocker and also promotes membrane stability by the activation of sodium-potassium ATPase.

Intravenous lidocaine is also advocated at a dose of 1-2mg/kg. This may be administered either before or with magnesium and may prevent degeneration of the arrhythmia. Should magnesium prove ineffective temporary overdrive pacing may be necessary. Calcium channel blockers and ranolazine has been found effective in one case report. The most serious sequelae of TdP is the progression to ventricular fibrillation. The anaesthetist must be familiar with advanced paediatric life support algorithms and prepared to deliver asynchronous defibrillation and chest compressions.

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### Postoperative care

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In the post-operative period, continuous ECG monitoring in a high dependency environment is advised. The environment should be kept quiet, calm and warm in order to reduce sympathetic stimulation. Senior recovery staff are recommended to care for this cohort of patients. There should be easy access to emergency resuscitation equipment and drugs. The duration of ECG monitoring may be required for up to 24 hours post-surgery.

It is important to rapidly recognize and treat post-operative pain, nausea and vomiting, thus reducing the associated sympathetic stimulation. Serum glucose levels would be monitored, as hypoglycaemia is common and poorly tolerated.

Hypothermia prolongs the QTc, so core temperature should be checked regularly and normothermia maintained. Hypothermia can increase the risk of postoperative infection.



In the longer term, patients required a complete bundle of care including a ventilation strategy if not immediately extubated, plus physiotherapy in order to reduce the risk of chest sepsis.

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#### **Information about emergency-like situations/ Differential diagnostics**

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*caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the diseases, e.g.:*

Not reported.

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#### **Ambulatory anaesthesia**

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Cases of ambulatory anaesthesia are not reported most likely due to the nature of the syndrome and the likely surgical procedures. However, the advantages of early mobilisation of patients post operatively should not be overlooked.

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#### **Obstetrical anaesthesia**

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There are currently no case reports or descriptions of obstetric anaesthetic procedures for patients with Timothy Syndrome. This is most likely attributable to the high infant mortality rate due to significant cardiac comorbidities. However, multiple case reports do exist for obstetric anaesthesia in patients with congenital LQTS.

### **Literature and internet links**

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