VIA MEDICA

REVIEWS

The influence of regional anaesthesia and local anaesthetics on cardiac repolarization

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Abstract

The normal function of the heart muscle is the result of electro-mechanic and hemodynamic coupling. Modification of the structure and activity of ion channels within the cardiomyocytes may induce cardiac arrhythmias. Electrophysiological mechanisms of arrhythmia, generated by a prolonged period of repolarization, result either from conduction disturbances (reentry mechanism) and/or the induction of beats (early after-depolarizations). Local anaesthetic drug deposition does not affect the repolarization period, as long as the concentration of the free drug in the plasma does not reach the critical value to cause toxic effects in the cardiomyocytes.

When analyzing the effect of regional anaesthesia on the repolarization period it is essential to acknowledge the activity or blockade of adrenergic fibres. Blocking the sympathetic fibres', including level T1 to T4, leads to a shortening of the QT interval and a reduction of QT dispersion. Adrenergic blockade as a result of spinal anaesthesia causes severe adrenergic activity above the level of the block and therefore prolongs repolarization. Stellate ganglion block on the right side causes a significant prolongation of the QT interval and QT dispersion.

Regardless of the reasons for prolongation of the repolarization period (congenital or acquired), vigilance is required within the perioperative anaesthetic management of a patient, so as not to lead to the occurrence of ventricular arrhythmias. Regional anaesthesia techniques and properly used local anaesthetic drugs are regarded as being safe in these patients.

Key words: long QT syndromes, cardiac repolarization, regional anaesthesia, local anaesthetics

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CARDIAC ELECTROPHYSIOLOGY

Normal function of the heart muscle is the result of electro-mechanic and haemodynamic coupling. When considering cardiac electrical activity from the point of view of a working myocardial cell, the following must be acknowledged: the relaxed state (polarization of the cell membrane) and active state (depolarization-repolarization) occurring after activation by the conduction system. Changes in the phases of action potential and the resting potential are the result of a synchronized movement of ionic currents through the ion channels, pumps and cardiomyocyte cell membrane carriers. The period of depolarization is initiated by an inward sodium current (I_{Na}), supported by an inward calcium current (I_{Ca-L}). During repolarization the flow of current occurs through the channels conducting the potassium current (I_{Kr}, I_{Ks}, I_{to}, $I_{K(ATP)}$) and to a lesser extent by the sodium current (I_{Na}), calcium current (I_{Ca-L}) and non-selective cation channel (I_{NS}). This is depicted in Figure 1.

The intracellular influx of calcium ions during the plateau phase enables a calcium dependent calcium release from the sarcoplasmic reticulum, leading to a contraction of the working myocardial cell. Under such physiological conditions during repolarization, potassium I_{Kr} and I_{Ks} currents play a key role in deciding the proper course of this phase of the action potential. In contrast, prolonged sodium and calcium currents slow down the cardiac repolarization process, therefore creating an environment for the occurrence of ventricular arrhythmias [1]. The concept of "repolarization reserve" has been described by Roden [2]. The loss of one component (one of the potassium currents) ordinarily
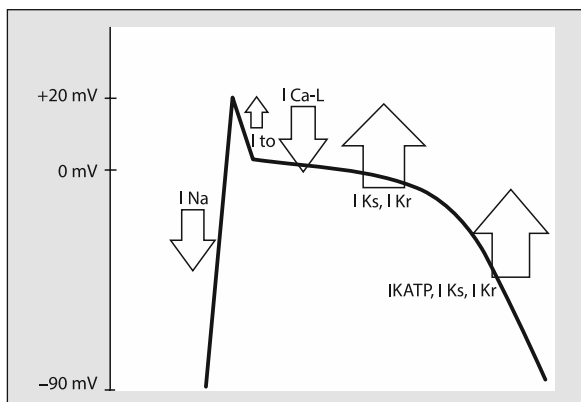
Figure 1. Ion currents and action potential in cardiomyocyte (arrow ↓ inward current, arrow ↑ outward current)

will not lead to failure of repolarization (i.e., marked QT prolongation), because of amplification of the remaining ion currents.

ELECTROCARDIOGRAPHIC ASSESSMENT OF THE REPOLARIZATION PERIOD

The normal sequence of the action potential phases can be determined indirectly on a electrocardiogram (ECG). The clinically most useful indicators of the electrophysiological assessment of the repolarization phase are as follows: QT interval, the length of the QT interval corrected to the frequency of the rhythm (QTc), QT interval dispersion, T wave morphology changes and the transmural dispersion of repolarization (TDR), which is expressed in the precordial ECG leads as the interval measured from the peak of the T wave to its end (Tpeak-Tend, Tp-e) [3, 4]. The QT interval typically is measured by lead II of a 12 lead ECG from the onset of the QRS complex to the point at which the T wave ends. There is an American Heart Association recommendation regarding how to correct the QT interval in the case of a QT interval prolongation in ventricular conduction defects. This can be best accomplished by incorporating QRS duration and RR interval as covariates into the QT-adjustment formula or by using the JT interval (QT duration–QRS duration). If the JT interval is chosen, normal standards established specifically for the JT interval should be used [5]. Under physiological conditions, the QT interval depends mainly on the age, gender and heart rate. The normal range for the rate-corrected QT interval is similar in females and males from birth until late adolescence. In adults, men have slightly shorter QT intervals than females. Corrected QT intervals of more than 0.46 s in females, and more than 0.45 s in men are considered prolonged. This difference decreases with age, as the plasma level of testosterone is correlated with age, so the influence testosterone on the calcium current is decreased [5]. As the QT interval also depends on the heart rate, a correction for

the heart rate must be made. A useful method in order to correct the current value of the QT interval is to use one of the available formulas (i.e., Bazett's, Fridericia's, Ashman's, Hodges' and the Framingham formula,). However, there is no general consensus on the best formula to be useful in clinical practice. . Physiological QT dispersion indicates the variable values of the QT interval length in different ECG leads (QT max – QT min). The correct value is less than 50 ms. QT dispersion values greater than 100ms can be considered as potentially arrhythmogenic [6, 7]. The transmural dispersion of repolarization (TDR) has a recognized prognostic value in relation to the arrhythmogenic potential of polymorphic ventricular tachycardia (namely *torsade de pointes*, TdP) and sudden cardiac death (SCD). Under physiological conditions the fastest repolarization occurs in the cells of the epicardium, while the slowest repolarization takes place in the middle of the myocardial cells. The T peak corresponds to the total repolarization of the epicardial cells and "T end" point – determines the return of excitability of the entire myocardium. The normal value for Tp-e is 40–110 ms and its prolongation above 117 ms is a recognized marker of susceptibility to TdP [8–10]. Repolarization period disorders are defined as arrhythmogenic diseases caused by the disturbed function of ion channel subunits or the proteins that regulate them. The repolarization period can be longer, shorter or the beginning of repolarization can be earlier than normal. Primary electrical disturbances include congenital or acquired long QT syndrome, Brugada syndrome (pseudo RBBB and persistent ST segment elevation in leads V1–V3), catecholaminergic polymorphic ventricular tachycardia, congenital or acquired short QT syndrome (QTc < 0,3 s) and early repolarization syndrome.

THE MECHANISM OF ARRHYTHMIA FORMATION IN DISORDERS OF REPOLARIZATION

Any modification of the structure and activity of the described channels and channel-related proteins (A kinase anchoring protein, AKAP) can induce arrhythmias. Electrophysiological mechanisms of arrhythmia result from conduction disturbances and/or the formation of beats. Conduction abnormalities occur in the type of reentry in which unidirectional conduction block coexists with the heterogeneous duration of refraction. They are usually initiated by an additional ventricular beat (premature ectopic depolarization) which occurs during repolarization (the incomplete return of sodium channel activity after previous excitation). The ECG picture shows that the additional stimulation occurs during the T wave (the so-called "R on T" phenomenon).

Mechanisms interfering with the formation of beats arise from pathological automaticity or triggered activity

Table 1. Congenital long QT syndromes

LQTS	Gene	Phenotype effect
LQTS 1	KCNQ1 (KVLQT1)	alfa subunit of the delayed rectifier potassium channel I_{Ks} – slowly activating
LQTS 2	KCNH2 (HERG) *	alfa subunit of the delayed potassium rectifier channel I_{Kr} – rapidly activating
LQTS 3	SCN5A	Sodium channel I_{Na}
LQTS 4	Ankyrin-B	Ankyrin B protein responsible for normal function of the Na^+/Ca^{++} exchanger, Na^+/K^+ ATP-ase pump
LQTS 5	KCNE1 (minK)	beta subunit of the delayed potassium rectifier channel I_{Ks}
LQTS 6	KCNE2 (MiRP1)	beta subunit of the delayed potassium rectifier channel I_{Kr}
LQTS 7	KCNJ2	inward rectifier potassium channel KIR2.1
LQTS 8	CACNA1C	Calcium channel (I_{Ca-L})
LQTS 9	CAV3	caveolin 3, sodium channel I_{Na}
LQTS 10	SCN4B	Sodium channel I_{Na} beta 4 subunit
LQTS 11	AKAP9	A-kinase anchoring protein 9
LQTS 12	SNTA1	alfa-1 syntrophin
LQTS 13	KCNJ5	alfa subunit of the delayed potassium rectifier channel I_{Kr}

* HERG (human ether-a-go-go-related gene) is a widely accepted equivalent of a cloned gene encoding the alpha subunit of the I_{Kr} potassium channel

in the form of after-depolarizations. After-depolarizations are the result of the oscillation of the membrane potential, following the previous accumulation phase of the action potential (early - during repolarization, late - after repolarization). The ionic basis for early after-depolarizations (EADs), which begins at the plateau phase of the action potential, is the reactivation of the calcium current through L-type channels. On the other hand, within the EADs, which begin in phase 3 of the action potential, the inducing mechanism is a sodium-calcium exchanger current and the sodium current [11]. Variable expressions of sodium channels in different parts of the myocardium and the potassium current flow modification coexist with the inhomogeneous return of excitability (dispersion of repolarization), which is a substrate for the development of arrhythmias. The basic phenomenon that favours the induction of EAD is prolongation of the ventricular action potential. Electrocardiograms show a prolongation of the QT interval [12, 13]. In contrast, the same EAD may underlie the occurrence of polymorphic ventricular tachycardia (TdP) and SCD, with the image being mainly due to a significant transmural dispersion of repolarization. There is also a dispersion of repolarization as a result of electrical remodelling, which results from hypertrophy or ventricular myocardial ischemia, or during adrenergic stimulation.

LONG QT SYNDROME

Prolongation of the QT interval may be congenital or acquired. Although the precise incidence of congenital QT prolongation is not known, it is estimated to be 1:2000–3000 live births. Modifications of the structure of ion channels leading to the prolongation of repolarization results from single nucleotide polymorphism (SNP) or the mutations of

single genes. The genetic background is complex, and the list of candidate genes is still open [11]. Table 1 shows the congenital long QT syndromes identified thus far [14]. The most common genetic mutations that cause QT prolongation have been repeatedly discussed in the literature. The first type of congenital long QT syndrome results from KCNQ1 mutation, which is the gene encoding the proteins of the slow component of the delayed rectifier potassium current channel (I_{Ks}). The second type, resulting from KCNH2 mutation which disrupts the flow of the rapid component of the delayed rectifier potassium current channel (I_{Kr}), occurs most frequently.

Hundreds of mutations have been identified in the 13 genes associated with the susceptibility to QT prolongation. While more than 75% of them are related to the LQTS 1–3, about 1–2% correspond to LQTS 4. Most commonly, the effect of the above-mentioned mutations is the lengthening of repolarization as a result of the inactivation of potassium channels (extended potassium current flow) or excessive activation of sodium channels ("late" sodium current). Normally, after a brief opening at the beginning of the action potential, the sodium channel is inactivated, carrying only a trace sodium current during the repolarization plateau. Mutations in genes encoding structural proteins of the sodium channel, as well as medicines, toxins, inflammatory agents, ischemia and oxidative stress can cause the destabilization of the period of inactivation. This leads to an increase in the flow of sodium ions (the so-called "late" sodium current), resulting in the disruption of sodium-calcium homeostasis (Na^+/Ca^{++} exchanger), which is reflected by an increase in intracellular calcium during diastole. The flow of "late" sodium current is not uniform in all cells, so the dispersion of the action potential is observed, along with the increased,

pathological excitability of the working cardiomyocytes, triggered activity (EADs) and the substrate for reentry. The presence of the pathological "late" sodium current also contributes to the prolongation of the action potential resulting from the blocking of the I_{Kr} channel, which results in bradycardia-dependent ventricular arrhythmias [15]. Moreover, the arrhythmogenic potential of the LQTS3 is aggravated during bradycardia [16]. However some experimental data indicate that beta-blockade effectively prevents ventricular arrhythmias in a validated LQTS3 model [17].

The mechanisms, reentry and activity triggered by afterdepolarizations are the underlying cause of acquired long QT syndrome and are related to adrenergic activation. Specific disorders of the ionic currents similar to those resulting from genetic disorders can occur as a result of the action of different medications. The I_{Ks} current can be blocked as a result of such anaesthetic agents, i.e. thiopentone, isoflurane or sevoflurane, resulting in an image similar to congenital LQTS1. The I_{Kr} current can be blocked by the administration of haloperidol or erythromycin, giving an image similar to the innate LQTS2 [18]. Hypokalemia, hypomagnesemia, hypocalcemia, bradycardia and drugs (e.g. anti-arrhythmic agents from groups IA and III, certain antidepressants, neuroleptics, some antibiotics, some prokinetic agents), heart conditions (ischemia, heart failure, cardiomyopathy, myocarditis), endocrine disorders (diabetes, hypothyroidism or hyperthyroidism), predispose one to the occurrence of arrhythmias by extending the duration of the action potential and the QT interval. Table 2 shows the main causes of acquired LQTS.

The list of drugs that can induce a prolongation of ventricular repolarization, therefore presenting pro-arrythmogenic activity is constantly updated and available on the following website: www.crediblemeds.org. It is extremely rare that the mere fact of the prolongation of repolarization leads to an induction of arrhythmia. The initiation and persistence of arrhythmias has a multifactorial etiology [10].

The treatment of patients with congenital and acquired LQTS differs. The therapeutic approach to congenital LQTS begins with medical termination of the sympathetic input to the myocardium with beta blockers. Rare methods include surgical left cervicothoracic sympathectomy, permanent cardiac pacing or implantation of a cardioverter-defibrillator. Acquired LQTS is commonly associated with pauses or bradycardia, in contrast to some forms of congenital LQTS in which arrhythmias often follow a sudden adrenergic stimulation. The management of acquired LQTS involves acute therapy of arrhythmia, discontinuation of any precipitating drug, as well as the correction of metabolic disorders (e.g. hypokalemia, hypomagnesemia).

THE MODIFICATION OF CARDIAC REPOLARIZATION AFTER THE USE OF LOCAL ANAESTHETICS

Local anaesthetics reversibly inhibit the formation, the propagation and oscillation of electrical impulses in all excitable tissues by blocking the depolarization process of the cell membrane by combining with sodium channel proteins. The deposition of the drug in the desired site of action results in blocking the nerve fibres, as the effect of a high concentration of local anaesthetic. If the drug, at a certain concentration, enters the systemic circulation, its effect becomes generalized. From the clinical point of view, the key impact of toxicity is on the heart and brain. Toxic activity within the cardiomyocytes reduces electrical excitability, conduction velocity and force of contraction, while the intensity of the effect is parallel to the potency of the local anaesthetic drug. The main factors affecting the occurrence of toxic symptoms, in addition to the differences between individual local anaesthetics, are associated with the concentration of the free fraction of the drug in the plasma. This depends on the chemical properties, the applied dose of the drug, the rate of absorption resulting from local perfusion, the method for distribution to other tissues, the degree of protein binding and the rate of metabolism. Methods for depositing local anaesthetics are very diverse, from the application to the skin surface or mucous membranes, as well as through different blocks, namely: infiltration blocks, plexus blocks and single peripheral nerve blocks, spinal nerve root blocks, nerves and sympathetic ganglia blocks until segmental intravenous anaesthesia. Not without significance is also the choice of the drug delivery technique: a single bolus or continuous application.

Table 2. The main causes of acquired LQTS

Drug-induced acquired LQTS
• Anti-arrhythmic drugs
• Certain non-sedating antihistamines
• Macrolide antibiotics
• Certain psychotropic medications
• Certain gastric motility agents
Metabolic factors:
• Electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia)
• Impaired hepatic and/or renal function
Structural heart disease
Bradyarrhythmias (especially complete heart block)
Cerebrovascular diseases (stroke, increased intracranial pressure, subarachnoid haemorrhage)
Hypothermia
Hypothyroidism

When analyzing the available literature, it is apparent that the impact of some local anaesthetic drugs and techniques of regional anaesthesia on the repolarization process of the cardiomyocytes has not been studied sufficiently.

BUPIVACAINE

In the case of accidental inadvertent intravenous injection, the toxic effect of bupivacaine on cardiac myocyte function refers to the rapid inhibition of both the sodium current (I_{Na}) and calcium current (I_{Ca-L}). In addition, in the induction of arrhythmia, the blocking effect on the transient outward potassium current (I_{to}) and the rapid component of the delayed potassium current (I_{Kr}) is considered. With regard to patients with baseline repolarization disorders (e.g. in congenital LQTS syndrome), either a shortening or a prolongation of the QT interval can be expected, depending on which of the above mechanism prevails. In the case of congenital LQTS type 1 syndrome, the blocking of the potassium current of the I_{Ks} leads to prolonged repolarization, which is then dependent on the rapid component. Therefore, the blockade of the rapid component occurring after exposure to bupivacaine also significantly prolongs repolarization [19]. On the other hand, if the underlying cause of repolarization disorders is the inhibition of the rapid potassium current component, as observed in LQTS 2, then additional prolongation of the repolarization period as a result of bupivacaine will not occur. Thereafter, the blocking effect on the fast sodium channels (I_{Na}) and slow calcium channels (I_{Ca-L}) predominates, which gives one the picture of the shortening of the duration of the activation potential. Moreover, it has been shown that the ability to block potassium currents relates rather to the Ito and I_{Kr} channels. In contrast, the I_{Ks} and I_{K1} channels tend to be insensitive to the action of bupivacaine. Therefore, the final effect is the sum of the above-described varying degrees of influence on the ionic currents and depends on the concentration of bupivacaine in the blood. According to some reports, an intravenous administration of bupivacaine does not extend the period of repolarization (no changes in the QT interval, Tp-e) [20]. The difference in pathophysiology between bupivacaine (mainly arrhythmogenic) and lidocaine (which, in therapeutic doses, has minimal negative inotropic effects) should be taken into account.

LIDOCAINE

Class Ib drugs, according to the Vaughan-Williams classification of anti-arrhythmic drugs, which includes, among others, lidocaine, selectively bind themselves to sodium channels in the inactivated state, causing a reduction of the repolarization duration. In cases of congenital (especially LQTS 3) or acquired prolongation of repolarization, lidocaine

is considered to possess a preventive action in relation to the occurrence of ventricular tachycardia (TdP), although its sole effect on repolarization is small [21, 22].

OTHER LOCAL ANAESTHETICS

There are few studies that have examined the effect of the newer local anaesthetics (levobupivacaine, ropivacaine) on cardiac repolarization [23–25]. Comparative analysis of the effects of bupivacaine and ropivacaine in relation to their impact on the myocardial repolarization in humans has demonstrated that ropivacaine is a safe alternative for the current intraventricular conduction disorder [26, 27]. However, the results of research conducted using levobupivacaine and bupivacaine for spinal anaesthesia in patients undergoing caesarean section were inconclusive. There are reports of non-inferiority and of the advantages of a particular drug, even in cases of long QT syndrome, as well as an important extension of the QT interval after the application of levobupivacaine when compared to bupivacaine. Moreover, in these cases it must be emphasized that QT interval is prolonged during normal pregnancy: regarding certain pathologies (pre-eclampsia), and after the application of oxytocin [28–34].

THE EFFECT OF REGIONAL ANAESTHESIA TECHNIQUES ON THE PERIOD OF REPOLARIZATION

It is important to determine the range of blocking adrenergic fibres. Stimulation of adrenergic activity through thoracic fibres (T1-4) prolongs repolarization and increases its dispersion [35, 36]. Blocking the sympathetic fibres with epidural anaesthesia and T1-T4 covering the chronotropic effect, leads to a shortening of the QT interval and a reduction in dispersion. What also remains important is the impact of baroreceptor stimulation and the effect of hypotension resulting from extensive sympathetic blockade. The adrenergic blockade as a result of spinal or epidural, not including T1-4 fibres, causes severe adrenergic activity above the level of the block and consequently prolongs repolarization [37, 38].

Left-sided stellate ganglion blockade may even lead to a shortening of the QT interval [39, 40]. Left cardiac sympathetic denervation — LCSD's antifibrillatory effect — has been well described. Indeed, it is both, a safe and effective treatment option to reduce life-threatening ventricular arrhythmias in patients with heritable channelopathies such as LQTS. A prophylactic LCSD, rather than a prophylactic ICD, may represent a good treatment option for patients with unacceptable β-blocker–related side effects [41]. In contrast, a stellate ganglion blockade on the right side significantly prolongs the QT interval while the QT dispersion increases.

With respect to the brachial plexus, blocked access between the oblique muscles, regardless of the drug, did not interfere with the duration of repolarization [42].

No results have been found regarding the impact of intravenous anaesthesia techniques on cardiac repolarization in humans. In animal studies, after the intravenous administration of bupivacaine, mepivacaine and etidocaine, QT prolongation, QT dispersion and T wave morphology changes were observed [43].

RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH CONGENITAL OR ACQUIRED LQT SYNDROME FOR PLANNED REGIONAL ANAESTHESIA

There are no guidelines for the perioperative management of a patient with confirmed long QT syndrome [44]. Therefore, spinal or epidural anaesthesia, peripheral nerve block and intravenous regional anaesthesia may be used. However, the concomitant drugs which can prolong repolarization should be avoided. The following opinion may only be used for guidance in these situations. A patient with documented LQT syndrome requires special vigilance by the therapeutic team. The significant prevention of arrhythmias is optimal perioperative management (avoiding acid-base balance disturbances, avoiding ion deficiency — namely potassium, magnesium and calcium — avoiding hypothermia). The therapeutic principles for acquired or congenital LQTS are different. Please note that for 25% to 40% of patients with congenital LQT, the 12-lead ECG reading is not diagnostic. Therefore, the anaesthetist should focus on the past medical history of sudden unexplained episodes of loss of consciousness or sudden death in the family.

During perioperative care, adrenergic stimulation resulting from stress and pain should be prevented (appropriate premedication, adequate analgesia). Secure direct access to the resuscitation equipment is obligatory in case of a high risk of TdP. The predisposing factors for TdP include: female sex, bradycardia, electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), heart failure, left ventricular hypertrophy, subclinical LQTS, some polymorphisms of genes encoding ion channel proteins or proteins associated with the channels relevant to myocardial ventricular repolarization. In the case of arrhythmia induction in the perioperative period, the therapeutic management should be implemented according to the mandatory guidelines of the local heart society.

SUMMARY

Regardless of the reasons for the prolongation of the repolarization period (congenital, acquired), vigilance is required in perioperative anaesthetic management so as not to lead to the occurrence of ventricular arrhythmias.

Regional anaesthesia techniques and properly applied local anaesthetic drugs are regarded as safe in these patients.

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