We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



3

Atrio-Ventricular Block-Induced Torsades de Pointes: An Update

Chevalier Philippe[1] and Scridon Alina[2]
[1]*Hôpital Louis Pradel, Lyon*
[2]*University of Medicine and Pharmacy, Targu Mures*
[1]*France*
[2]*Romania*

1. Introduction

Torsades de pointes is a potentially life threatening form of rapid, polymorphic ventricular tachycardia. Literally meaning "twisting of the points", torsades de pointes is electrocardiographically characterized by QRS axis undulations over runs of several beats, with a specific twist of the QRS complex around the isoelectric baseline. The definition also requires that an abnormal QT-prolongation be present (usually to 600 msec or greater) and / or abnormal TU complexes. The arrhythmia usually terminates spontaneously, with the exception of rare degeneration into ventricular fibrillation. The episodes are often repetitive and frequency dependent.

In 1966, Dessertenne first described torsades de pointes in a patient with atrio-ventricular block (Dessertenne, 1966). Ever since, several reports have associated torsades de pointes with bradycardia, especially with atrio-ventricular block (Viskin, 1999). From 5% to 30% of patients with atrio-ventricular block have been reported to develop torsades de pointes (Motté, 1970, Jensen, 1975, Guize, 1993) - an observation that suggests the participation of yet other intrinsic or extrinsic sensitising factors.

Most episodes of torsades de pointes are paroxystic, not longer than 5-20 beats, with a very elevated heart rate (160-300 bpm). The typical morphology of torsades de pointes includes a complete twist at 180° of QRS complexes and a progressive change of the surface ECG. A QT interval prolongation to 600 ms or longer is always evident. These episodes are often preceded by ventricular bigeminism with fixed and long coupling interval.

2. Risk factors

Several studies have proposed different risk factors for torsades de pointes. Among them, the most commonly encountered are female gender, advanced age, bradycardia, different metabolic disorders, and a number of therapeutic agents (Haverkamp, 2000). The gender-specific preponderance in females to develop drug-induced torsades de pointes when treated with antiarrhythmic drugs or during spontaneous bradyarrhythmias is also well documented. In the general population, women have a longer corrected QT interval than men.

Several endocrine disorders as well as a number of electrolytic imbalances have been incriminated as torsades de pointes facilitators (hypothyroidism, mental anorexia, hypokalaemia, hypomagnesaemia, hypocalcaemia, acidosis).
A great number of drugs are currently considered "torsadogenic". Almost all of these drugs have an IKr channel blocking effect, which explains QT interval prolongation. These agents belong to both "cardiotropic" and "non-cardiotropic" drugs (an exhaustive list is available on Internet at http://www.qtdrugs.org).

2.1 Atrio-ventricular block – a piece in the puzzle

The common element between atrio-ventricular block and torsades de pointes seems to be the presence of QT interval prolongation. Still, the association between atrio-ventricular block and QT interval prolongation is infrequent. Several studies have shown that this exact category of patients who present atrio-ventricular block induced – QT prolongation has the most elevated risk of developing torsades de pointes.

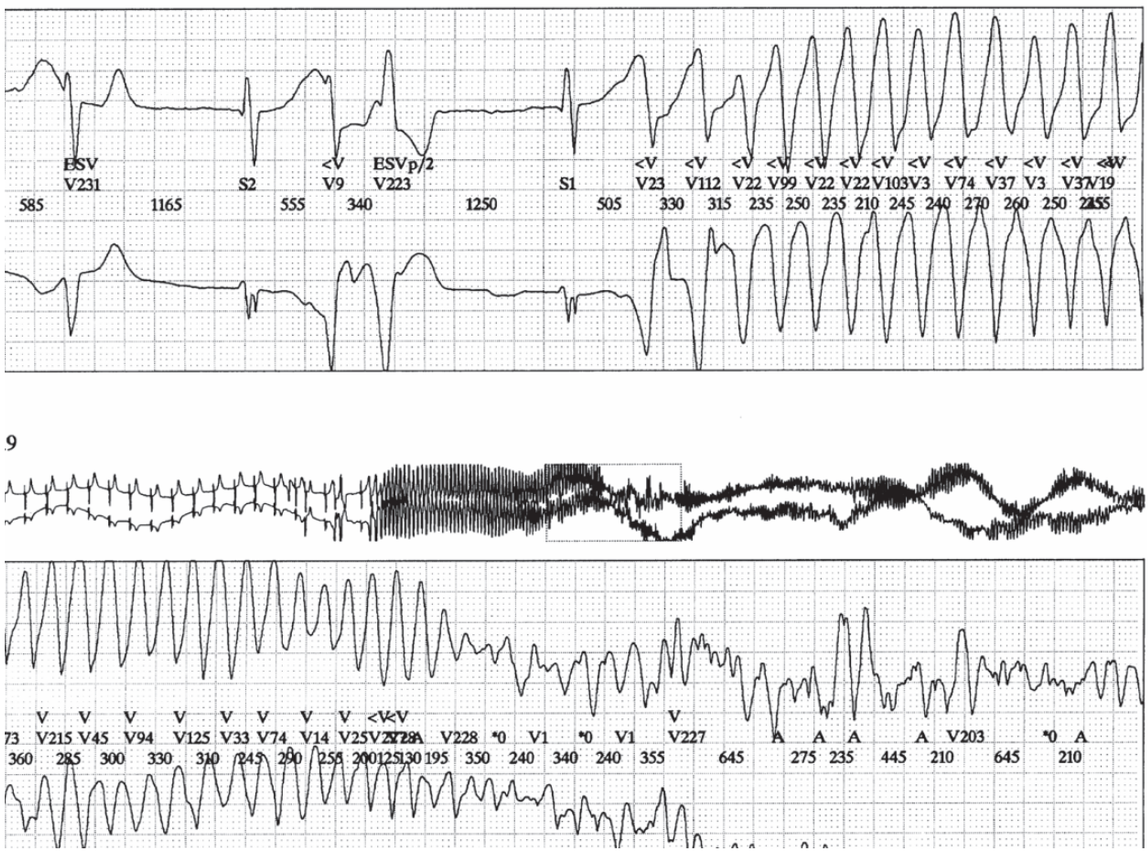


Fig. 1. Holter recording in a patient with post-operative atrio-ventricular block and typical torsades de pointes. Note the association of long QT interval, ventricular bigeminism, bradycardia, and bradycardia-dependant polymorphic ventricular tachycardia degenerating in ventricular fibrillation.

Kurita et al. have reported that patients with bradycardia-induced torsades de pointes have abnormally long QT intervals at slow heart rates, compared with patients with bradycardia

but no tachyarrhythmia (Kurita, 1992). Strasberg et al. compared patients with atrio-ventricular block with torsades de pointes to those without torsades de pointes, and mentioned that the QT interval in patients with torsades de pointes was longer than in those without torsades de pointes, whereas heart rate and QRS interval during the escape rhythm were not significantly different (Strasberg, 1986). Moreover, they reported that QT interval above 600 ms and premature ventricular beats on electrocardiogram appear to indicate an increased risk for the development of polymorphic ventricular tachycardia in a patient with atrio-ventricular block.

In a retrospective review of 43 young patients with congenital atrio-ventricular block, Sholler et al. found QT interval prolongation to be an independent predictor of symptoms, including cardiac arrest and syncope. Overall, the outcome was poor with 21% of the atrio-ventricular block patients in their symptomatic group with rate-corrected QT intervals >0.45 seconds, in contrast with none in the asymptomatic group (Sholler, 1989). Marked QT interval prolongation complicated by torsades de pointes, as a sequela of acquired atrio-ventricular block, has been convincingly demonstrated in paediatric and adult patients. In each of these patients, who ranged in age from 18 months to 80 years on initial presentation with torsades de pointes, there was QT interval normalization and complete suppression of torsades de pointes after institution of ventricular pacing at age-appropriate rates.

Experimental data confirm these observations. In a dog model with chronic atrio-ventricular block, the QT interval was prolonged by 20%.

3. Genetic bases

3.1 Genetic bases of acquired long QT syndrome

In contrast to congenital long QT syndrome, the acquired form has been considered a non-familial disease, which is not transmitted in specific genetic patterns of inheritance. This does not automatically exclude genetic components from the pathogenesis of acquired long QT syndrome, but it implies that these are only cofactors in the pathogenesis.

The unpredictability of acquired long QT syndrome, its similarity to the congenital form and identification of manifest congenital long QT syndrome in patients with the drug-induced form, all suggest a genetic contribution to risk.

With the identification of mutations in ion channel genes underlying congenital long QT syndrome and the investigation of large families, a variable clinical expressivity and especially incomplete penetrance have become apparent (Raviña, 2000). In a given family, some individuals with a certain mutation have frank long QT intervals, while others with the same mutation have normal QT intervals at baseline. In some cases, the latter, who represent less than 10% of the patients with acquired long QT syndrome, experience torsades de pointes only after intervention of a QT-prolonging stressor. In autosomal dominant long QT syndrome (Romano-Ward syndrome), the aspect of incomplete penetrance was reported to be approximately 25% in a specific group of families. This raises the question of the frequency and importance of silent ion channel gene mutations that may become functionally significant in presence of coexisting factors.

Mutations in KCNE1 and KCNE2, KCNH2, HERG itself, and SCN5A have been identified in acquired forms of long QT syndrome (Abbott, 1999). However, the gene in which mutations are seen most commonly is KCNQ1, encoding for potassium channel IKs (Donger, 1997, Napolitano, 2000, Kubota, 2000).

Several frequently occurring polymorphisms have also been described in the long QT syndrome population, distributed in nearly all the genes associated with this condition. Although these changes are apparently not pathogenic, some can generate individual susceptibility to the development of arrhythmia. This is the case of the K897T polymorphism in KCNH2 (Crotti, 2005), which is present in up to 15% of the population and is linked with susceptibility to certain drugs. Another example is the R1047L polymorphism, the second most frequent polymorphism encountered in KCNH2, which has been associated with the development of torsades de pointes while using the drug dofetilide (Sun, 2004).

Polymorphisms that confer susceptibility to the development of ventricular arrhythmia have also been documented in sodium channel Na1.5. This is the case of the H558R polymorphism (Viswanathan, 2003), which is present in up to 30% of the population, or S1103Y, found mainly in blacks, with an incidence of nearly 13%, and associated with an increased risk of sudden death in childhood (Splawski, 2002, Paulussen, 2004). Most of these DNA polymorphisms do not occur in coding regions and may either have no functional significance, or modulate expression levels of functionally normal proteins. Other rare polymorphisms with minor allele frequencies (1-2%) that have been implicated in drug-induced torsades de pointes include D85N (KCNE1) (Paulussen, 2004) and T8A (KCNE2) (Sesti, 2000). I447 polymorphism in KCR1 was also proposed as potential modulator of the risk of drug-induced torsades de pointes (Roden, 2005). The valine variant was seen in 1.1% of patients, compared with 7% in controls, suggesting that the presence of valine in this position protects against drug-induced torsades de pointes.

It is not yet clear if all patients with acquired long QT syndrome have a genetic predisposition. Systematic evaluation of genes known to be involved in congenital long QT syndrome has therefore been recommended in patients with acquired long QT syndrome.

3.2 Genetic bases of atrio-ventricular block-induced torsades de pointes

A general observation is that only a minority of patients with atrio-ventricular block develop torsades de pointes. Moreover, in the early nineties, in patients with atrio-ventricular block and torsades de pointes compared with those without torsades de pointes, it was reported that the QT interval was longer than the bradycardia could account for. These observations suggested a genetic predisposition of the affected subjects. Furthermore, common clinical features and the presence of long QT intervals in patients with congenital long QT syndrome and in those with atrio-ventricular block–induced torsades de pointes suggested that patients with atrio-ventricular block-mediated QT-related arrhythmia could have latent congenital long QT syndrome or a vulnerable genetic polymorphism.

Moreover, several similarities have been found between experimental models of atrio-ventricular block–induced torsades de pointes and specific forms of human congenital long QT syndrome. Frequent episodes of spontaneous torsades de pointes during day and night, abnormal QTU complex, and reduction of both IKr and IKs in a rabbit atrio-ventricular block model (Tsuji , 2002) closely resemble the clinical characteristics of the malignant form of human congenital long QT syndrome caused by double mutation of HERG and KCNQ1. An enhanced susceptibility to acquired torsades de pointes, the adrenergic dependence of torsades de pointes, the typical T-wave patterns during prolonged QT intervals and the reduction of IKs in dog with chronic atrio-ventricular

block closely resemble the clinical characteristics of the LQT1 or LQT5 form of human congenital long QT syndrome.
Using recently introduced molecular biology techniques, these bradycardia-related repolarisation abnormalities appear to be allelic variants in the coding region of congenital long QT syndrome genes, variants that can be identified in 10–15% of affected subjects. A recent retrospective study showed that 14% to 18% of subjects with atrio-ventricular block-related QT-interval prolongation were carriers of a genetic mutation in genes coding for potassium channels. Another study showed that 36% of patients with complete atrio-ventricular block and torsades de pointes had a genetic mutation involving HERG and SCN5A (Yoshida, 2001). In fact, the most commonly encountered mutation in this setting is in HERG genes, coding for potassium channel IKr.
The scarcity of this association in the general population is directly responsible for the limited amount of information that we dispose of regarding this issue. Still, much is expected from future molecular testing in these patients.

4. Pathophysiology

4.1 Pathophysiology of torsades de pointes

The association between torsades de pointes and a prolonged QT interval has long been known, but the underlying mechanisms of torsades de pointes have yet to be satisfactorily elucidated. In general, alterations in cardiac ion currents which dictate the normal action potential play a major role in arrhythmogenesis. Both early afterdepolarisation - induced triggered activity (Cosio, 1991, Shimizu,1995, Burashnikov, 2002) and increased dispersion of repolarisation have been suggested as playing a role in the genesis of torsades de pointes. Significantly increased transmural dispersion of repolarisation favours re-entrant substrates that initiate and maintain torsades de pointes.
QT intervals in humans are very variable, being strongly influenced by age, sex, heart rate or heart diseases. It would appear that subjects with a propensity to develop the syndrome have a subclinical abnormality in some of the ion channels dictating repolarisation, and / or a reduced repolarisation reserve.
The latter hypothesis has been suggested by Roden et al (Roden, 1998). They hypothesized that the extent of QT lengthening in response to specific environmental triggers depends on the ventricular "repolarisation reserve". This concept proposes that loss of one component (e.g. IKs) ordinarily will not lead to failure of repolarisation since multiple other currents flow across the myocyte membrane (e.g. IKr) also act to maintain repolarisation in normal ranges. However, when a reduction or down regulation in any of the currents involved in the repolarisation phase is overlapped by a destabilizing factor, this "reserve" is overcome and acquired long QT syndrome may become clinically obvious (Roden, 1998). This issue may occur in the female gender, when a factor such as bradycardia or hypokalaemia is present, in conditions that predispose to electrical remodelling such as heart failure, myocardial ischemia, or ventricular hypertrophy.
It is well known that local action potential duration of myocardial cells displays considerable variability depending on many factors, including, in normal conditions, location in the ventricular wall (epicardium, mid-myocardium or endocardium) and rate of stimulation. These differences in action potential duration across the ventricular wall determine the transmural dispersion of repolarisation. When this transmural dispersion is exaggerated, opposite voltage gradients may occur and trigger oscillatory potentials,

namely phase 2 early afterdepolarisations and sustained abnormal electrical activity (Dangman, 1981, Brachmann, 1983, Levine, 1985, Roden, 1985, Davidenko, 1989).
Rarely, a single severe abnormality in a major repolarizing current can elicit an abnormal phenotype, as in congenital long QT syndrome (Roden, 1996). More commonly, one or more pre-existing minor abnormalities of repolarisation result in a subclinical phenotype. Following recent advances in molecular biology and genetics, it has become clear that in some clinical instances (e.g. congestive heart failure or cardiac hypertrophy) ion channel genes become down-regulated and the consequent reduced ion currents are likely to cause prolonged myocardial repolarisation. If, within this framework, an environmental stressor able to further destabilize the "repolarisation reserve" interferes, a long QT syndrome may be unburied and the arrhythmic consequences may appear.
Thus, a potentially dangerous stressor may appear completely safe when present in a large number of subjects. The risk may only be evident when the factor is present in a certain individual under certain circumstances.

4.2 Pathophysiology of atrio-ventricular block-induced torsades de pointes

Although a slow ventricular rate may be a major factor for inducing abnormal QT prolongation, the mechanism of QT prolongation in patients with bradycardia-related torsades de pointes is poorly understood.
Farkas et al. showed for the first time that bilateral vagotomy can prevent drug-induced torsades de pointes in an in vivo rabbit model, demonstrating that vagally-mediated reductions in heart rate are necessary for the development of torsades de pointes (Farkas, 2008). Torsades de pointes has been described in many conditions associated with bradycardia, such as atrio-ventricular block, drugs, vagotonia or hypothyroidism. Moreover, the occurrence of torsades de pointes in the presence of bradycardia is influenced by other factors such as gender, degree of QT prolongation or duration of bradycardia.
An interesting observation shows that arrhythmogenic bradycardias are most commonly chronic, with a slow ventricular escape rhythm – a profile corresponding to atrio-ventricular block. Studies have reported that patients with atrio-ventricular block have significantly longer QT intervals than those with sinus bradycardia, even at comparable heart rates. This relative QT prolongation may be one of the major reasons that torsades de pointes is more commonly observed in chronic atrio-ventricular block than in sinus bradycardia.
Clinical and experimental data show that the duration of atrio-ventricular block is an important determinant of the susceptibility to acquired torsades de pointes. Experimental studies show that torsades de pointes is rarely inducible at 0 weeks of atrio-ventricular block (acute atrio-ventricular block) but is inducible at 5 weeks (chronic atrio-ventricular block) in most animals (Vos, 1998). In a series of 64 patients with chronic atrio-ventricular block, Yiginer et al. reported a longer duration of bradycardia in the three patients who developed torsades de pointes (Yiginer, 2010). Concomitant to the duration of atrio-ventricular block, the likelihood of structural and electrical alterations in myocardial cells may increase.

4.2.1 Bradycardia-induced cardiac remodelling

Atrio-ventricular block-induced volume overload initiates a number of adaptative processes that are aimed to compensate the decreased cardiac output and the increased end-diastolic

pressure. These remodelling processes offer both the "trigger" and "substrate" for the occurrence of torsades de pointes.
Bradycardia-induced volume overload causes the development of a biventricular eccentric hypertrophy and consequently a non-homogenous lengthening of the ventricular action potential duration. Exact information concerning the sequence and nature of the time-related electrophysiological process in hypertrophy are lacking, but there seems to be a parallelism between the evolutions of the two processes. These adaptations, alone or synergistically, increase the risk of early afterdepolarisations and / or delayed afterdepolarisation and therefore the risk of torsades de pointes.

4.2.2 Structural remodelling during atrio-ventricular block

Ventricular hypertrophy in this setting is a response of the heart to compensate the altered hemodynamic load induced by atrio-ventricular block (Vos, 1998). The process is initiated by mechanical factors and thereafter amplified by neurohumoral factors, such as adrenergic stimuli, the renin-angiotensin system, endothelin, or insulin-like growth factor.
Autopsy studies have demonstrated increased heart weight to body weight ratios, with significant contributions of both the right and left ventricular mass. Morphologically, biventricular hypertrophy is characterized by an eccentric expansion with increased right and left ventricular diameters, as seen during volume overload (Verduyn, 2001). Photo- and electron-micrograph analyses have shown myocardial cell hypertrophy together with the parallel increases of collagen fibbers and extracellular space.
Morphopathological studies have shown larger growth responses in the right than left ventricular myocytes, supporting the autopsy finding of a larger relative increase of the right than the left ventricular weight, as well as a more significant hypertrophy of right ventricular free wall and septal wall than of the left ventricular free wall (Verduyn, 2001, Sugiyama, 2002). The preponderance of right ventricular cell growth in atrio-ventricular block may reflect a greater impact on this chamber after the transition from sinus rhythm to idioventricular rhythm.
This structural adaptation process is accompanied by electrophysiological remodelling. Prolongation of the left ventricular action potential is a consistent observation in myocardial hypertrophy of different causes in several species. Many of the sarcolemmal ion channels, exchangers, and pumps, as well as intracellular ion transporters, can show functional defects leading to delayed repolarisation.

4.2.3 Electrical remodelling during atrio-ventricular block

While electrical and structural changes in chronic atrio-ventricular block are aimed to maintain cardiac function, they also predispose to QT prolongation, leading to the onset of torsades de pointes. This association has been extensively evaluated in animal studies.
Tsuji et al. reported the results obtained in a rabbit model with atrio-ventricular block induced by injection of formaldehyde into the atrio-ventricular node (Tsuji, 2002). These rabbits received ventricular pacing support after atrio-ventricular block induction. The authors demonstrated significant QT interval prolongation in the same day that they discontinued pacing, with further prolongation later on. Seventy % of the animals developed spontaneous torsades de pointes, with most episodes occurring during the first week of uncompensated bradycardia. Even more information has been offered by a rabbit model with atrio-ventricular block induced by transcatheter radiofrequency ablation of

atrio-ventricular node. Chronic endocardial ventricular pacing at near-physiologic rate was installed immediately after the ablation procedure. The authors showed identical amplitudes of all repolarizing currents in atrio-ventricular block group and sham-operated group. Moreover, they showed a similar down-regulation in the affected currents regardless of ventricular cavity stimulation (left or right ventricle) and they concluded that secondary electrical remodelling is unrelated to the loss of atrio-ventricular synchrony, suggesting that bradycardia alone suffices to turn on the electrical remodelling process.

In vivo experiments in dogs indicate the importance of bradycardia-dependent early afterdepolarisations, increased regional dispersion of repolarisation and multiple ectopic beats for the initiation of torsades de pointes. Fast heart rates tend to oppose these actions, preventing torsades de pointes.

Several mechanisms have been proposed for early afterdepolarisations occurrence in this setting (Emori, 2001, Yan, 2001). These abnormalities appear to be secondary to both bradycardia-dependent depression of electrogenic Na^+ pumping and more complete inactivation of K^+ currents. Vos et al. showed a high incidence of early afterdepolarisations in dogs with chronic atrio-ventricular block after d-sotalol administration and proposed significant down-regulation of the slow component of the delayed rectifier K^+ current (IKs) and that of the rapid component (IKr) as potential mechanism (Vos, 1995, 1998).

Enhanced regional dispersion of repolarisation is considered to be the consequence of inhomogeneous prolongation of ventricular action potential (more in the left than the right ventricle), probably reflecting the existence of significant repolarisation gradients in closely adjacent areas, possibly the septum. Interventricular differences of the action potential are known to exist in the normal myocardium of dogs with sinus rhythm. In chronic atrio-ventricular block, larger action potential durations have been documented in left mid-myocardial compared with right ventricular myocytes, in contrast to the larger degree of hypertrophy in the latter. The observation that a down-regulation of IKs is present in both ventricles while IKr down-regulation is mainly expressed in the right ventricle could explain these abnormalities.

Other currents such as It0, ICaL or IK1 have been reported as unchanged in a number of studies.

However, the observations are contradictory. While some suggest that the role of It0 is unlikely given the fact that the spike-and-dome configuration of the action potential is preserved, others suggest that low ventricular rates are associated with submaximal activation of It0, which would shift the plateau phase of the action potential to voltage levels in which Ca^{2+} window current availability is increased, predisposing to torsades de pointes.

The fact that the action potential duration to 95% of complete repolarisation and action potential duration to 50% of complete repolarisation have been found to be increased to a similar extent indicates that the delay of repolarisation is most likely due to a disturbance at the plateau level, sustaining the central role of IKr and IKs in this setting.

Additional insights into the ionic mechanisms of action potential prolongation in chronic atrio-ventricular block come from experiments with almokalant. After block of IKr during almokalant treatment, the action potential duration was found much larger in chronic atrio-ventricular block myocytes than in sinus rhythm controls. This suggests that ionic currents other than IKr contribute to the abnormal repolarisation in chronic atrio-ventricular block, even though the role of IKr can not be excluded. These results have been confirmed by other similar studies, which show uniformly distributed IKs down-regulation by 50% in both

ventricles, while a similar degree of IKr inhibition was apparent only in the right but not in the left ventricle.
In vivo recordings in dog with chronic atrio-ventricular block demonstrate that another important factor involved in the occurrence of torsades de pointes is represented by ventricular ectopic beats. However, their origin and mechanisms remain obscure for the moment.

5. Conclusions

Investigations of the clinical aspects and molecular mechanisms of long QT syndrome have provided novel and important insights into the basis of ventricular arrhythmias and shown how small perturbations in ion flow can have important consequences in human health.
Even if molecular diagnosis appears to be an appealing way of integrating contemporary genomics with arrhythmia science, several obstacles limit its wide availability. Molecular diagnosis is restricted by the very large number of candidate genes and the correspondingly huge number of described polymorphisms. Moreover, most association studies have not proven to be reproducible, raising the problem of false positives. There is also the issue that, owing to its restrictive costs, mutation screening will be limited to a limited number of specialized centres for some time.
Though great progress has been made, many important issues require further clarification. A major challenge in the future will be to understand the complex mechanisms of repolarisation and to assess the individual risk of malignant arrhythmia more precisely. Moreover, mutations in other ion channel genes, still unrecognized, could be responsible for different variants of long QT syndrome.
We recommend systematically genotyping patients with acquired long QT syndrome and torsades de pointes. The next step could be represented by case-control studies of gene polymorphisms in pace-maker patients to find the possible markers of susceptibility to malignant arrhythmias during bradycardia.

6. References

Abbott GW, Sesti F, Splawski I, et al. (1999) MiRP1 Forms IKr Potassium Channels with HERG and Is Associated with Cardiac Arrhythmia. *Cell*. 97(2): 175-187.

Brachmann J, Scherlag BJ, Rosenshtraukb LV, et al. (1983) Bradycardia-dependent triggered activity: relevance to drug-induced multiform ventricular tachycardia. *Circulation*. 68: 846-85.

Burashnikov A, Antzelevitch C. (2002) Prominent IKs in epicardium and endocardium contributes to development of transmural dispersion of repolarization but protects against development of early afterdepolarizations. *J Cardiovasc Electrophysiol*. 13: 172–177.

Cosio FG, Goicolea A, López-Gil L, et al. (1991) Suppression of Torsades de Pointes with verapamil in patients with atrio-ventricular block. *Eur Heart J*. 12: 635–63 8.

Crotti L, Lundquist AL, Insolia R et al. (2005) Common KCNH2 polymorphism (K897T) as a genetic modifier of congenital long QT syndrome. *Circulation*. 112: 1251–1258.

Dangman KH, Hoffman BF. (1981) In vivo and in vitro antiarrhythmic and arrhythmogenic effects of N-acetyl procainamide. *J Pharmacol Exp Ther*. 217: 851-862.

Davidenko JM, Cohen L, Goodrow R, et al. (1989) Quinidine-induced action potential prolongation, early afterdepolarizations, and triggered activity in canine purkinje tibsrs: effects of stimulation rate, potassium, and magnesium. *Circulation.* 79: 674-686.

Dessertenne F. (1966) La tachycardie ventriculaire a deux foyers opposes variables. *Arch Mal Coeur Vaiss.* 59 (2): 263–272.

Donger C, Denjoy I, Berthet M, et al. (1997) KVLQT1 c-terminal missense mutation causes a forme fruste long-QT syndrome. *Circulation.* 96: 2778–2781.

Emori T, Antzelevitch C. (2001) Cellular basis for complex T wave and arrhythmic activity following combined IKr and IKs block. *J Cardiovasc Electrophysiol.* 12: 1369 –1378.

Farkas A, Dempster J, Coker SJ. (2008) Importance of vagally mediated bradycardia for the induction of torsade de pointes in an in vivo model. *British Journal of Pharmacology.* 154: 958–970.

Guize L, Iliou MC, Bayet G, et al. (1993) Les torsades de pointes. *Arch Mal Coeur Vaiss.* 86: 769 –776.

Haverkamp W, Breithard G, Camm AJ et al. (2000) The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Reports on a policy conference of the European Society of Cardiology. *Cardiovasc Res.* 47: 219-233.

Jensen G, Sigurd B, Sandoe E. (1975) Adams-Stokes seizures due to ventricular tachydysarrhythmias in patients with heart block: prevalence and problems of management. *Chest.* 67: 43-48.

Kubota T, Shimizu W, Kamakura S, et al. (2000) Hypokalemia-induced long QT syndrome with underlying novel missense mutation in S4-S5 linker of KCNQ1. *J Cardiovasc Electrophysiol.* 11: 1048 –1054.

Kurita T, Ohe T, Marui Aihara N, et al. (1992) Bradycardia-induced abnormal QT prolongation in patients with complete atrioventricular block with torsades de pointes. *Am J Cardiol.* 69: 628–633.

Levine JH, Spear JF, Guamieri T, et al. (1985) Cesium chlorideinduced long QT syndrome: demonstration of afterdepolarizations and triggered activity in vivo. *Circulation.* 72: 1092-110.

Motté G, Coumel P, Abitbol G, et al. (1970) Le syndrome du QT long et syncopes par torsades de pointes. *Arch Mal Coeur Vaiss.* 63: 831-853.

Napolitano C, Schwartz PJ, Brown AM, et al. (2000) Evidence for a cardiac ion channel mutation underlying drug-induced QT prolongation and life-threatening arrhythmias. *J Cardiovasc Electrophysiol.* 11: 691–696.

Paulussen AD, Gilissen RA, Armstrong M, et al. (2004) Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med.* 82(3): 182-188.

Raviña T, Gutierrez J. (2000) Amiodarone-induced AV block an ventricular standstill. A forme fruste of an idiopathic long QT syndrome. *Int J Cardiol.* 75: 105-108.

Roden DM. (1998) Taking the "idio" out of "idiosyncratic": predicting Torsades de Pointes. *PACE.* 21: 1029–1034.

Roden DM, Hoffman BF. (1985) Action potential prolongation and induction of abnormal automaticity by low quinidine concentrations in canine purkinje fibers:relationship to potassium and cycle length. *Circ Res.* 56: 857-86.

Roden DM, Lazzara R, Rosen M, et al. (1996) Multiple mechanisms in the long-QT syndrome: current knowledge, gaps, and future directions. *Circulation.* 94: 1996–2012.

Roden DM, Viswanathan PC. (2005) Genetics of acquired long QT syndrome. *J Clin Invest.* 115: 2025–2032.

Sesti F, Abbott GW, Wei J, et al. (2000) A common polymorphism associated with antibiotic-induced cardiac arrhythmia. *Proc Natl Acad Sci U S A.* 97(19): 10613-10618.

Shimizu W, Ohe T, Kurita T, et al. (1995) Effects of verapamil and propranolol on early afterdepolarizations and ventricular arrhythmias induced by epinephrine in congenital long QT syndrome. *J Am Coll Cardiol.* 26: 1299 –1309.

Sholler GF, Walsh EP. (1989) Congenital complete heart block in patients without anatomic cardiac defects. *Am Heart J.* 118: 1193-1198.

Splawski I, Timothy KW, Tateyama M, et al. (2002) Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science.* 297: 1333–1336.

Strasberg B, Kusniec J, Erdman S, et al. (1986) Polymorphous ventricular tachycardia and atrioventricular block. *Pacing Clin Electrophysiol.* 9: 522-526.

Sugiyama A, Ishida Y, Satoh Y, et al. (2002) Electrophysiological, Anatomical and Histological Remodeling of the Heart to AV Block Enhances Susceptibility to Arrhythmogenic Effects of QT-Prolonging Drugs. *Jpn J Pharmacol.* 88: 341 – 350.

Sun Z, Milos PM, Thompson JF, et al. (2004) Role of a KCNH2 polymorphism (R1047 L) in dofetilide-induced torsades de pointes. *J Mol Cell Cardiol.* 37: 1031-1039.

Tsuji Y, Opthof T, Yasui K, et al. (2002) Ionic mechanisms of acquired QT prolongation and torsades de pointes in rabbits with chronic complete atrioventricular block. *Circulation.* 106: 2012–2018.

Verduyn SC, Ramakers C, Snoep G, et al. (2001) Time course of structural adaptations in chronic AV block dogs: evidence for differential ventricular remodeling. *Am J Physiol Heart Circ Physiol.* 280: H2882-H2890.

Viskin S. (1999) Long QT syndromes and torsades de pointes. *Lancet.* 354: 1625-1633.

Viswanathan PC, Benson DW, Balser JR. (2003) A common SCN5A polymorphism modulates the biophysical effects of an SCN5A mutation. *J Clin Invest.* 111: 341–346.

Vos MA, Groot SHM, Verduyn SC, et al. (1998) Enhanced susceptibility for acquired Torsade de Pointes arrhythmias in the dog with chronic, complete AV block is related to cardiac hypertrophy and electrical remodeling. *Circulation.* 98: 1125–1135.

Vos MA, Verduyn SC, Gorgels APM, et al. (1995) Reproducible induction of early afterdepolarizations and Torsade de Pointes arrhythmias by d-sotalol and pacing in dogs with chronic atrioventricular block. *Circulation.* 91: 864 –872.

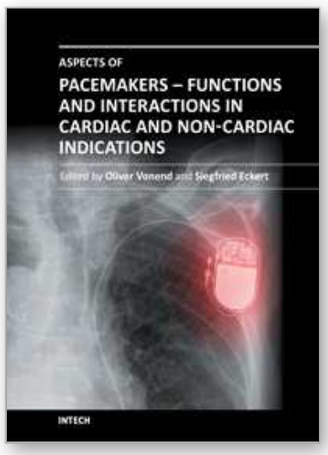
Yan GX, Wu Y, Liu T, et al. (2001) Phase 2 early afterdepolarization as a trigger of polymorphic ventricular tachycardia in acquired long-QT syndrome, direct evidence from intracellular recordings in the intact syndrome, direct evidence from intracellular recordings in the intact. *Circulation.* 103: 2851– 2856.

Yiginer O, Kilicaslan F, Aparci M, et al. (2010) Bradycardia-induced Torsade de Pointes – An arrhythmia Less Understood." *Indian Pacing Electrophysiol J.* 10(10): 435-438.

Yoshida H, Horie M, Otani H, et al. (2001) Bradycardia-induced long QT syndrome caused by a de novo missense mutation in the S2-S3 inner loop of HERG. *Am J Med Genet*. 98: 348 –352.

IntechOpen

IntechOpen



Aspects of Pacemakers - Functions and Interactions in Cardiac and Non-Cardiac Indications

Edited by Dr. Oliver Vonend

ISBN 978-953-307-616-4
Hard cover, 194 pages
Publisher InTech
Published online 15, September, 2011
Published in print edition September, 2011

Outstanding steps forward were made in the last decades in terms of identification of endogenous pacemakers and the exploration of their controllability. New â€œartificialâ€ devices were developed and are now able to do much more than solely pacemaking of the heart. In this book different aspects of pacemaker â€“ functions and interactions, in various organ systems were examined. In addition, various areas of application and the potential side effects and complications of the devices were discussed.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Chevalier Philippe and Scridon Alina (2011). Atrio-Ventricular Block-Induced Torsades de Pointes: An Update, Aspects of Pacemakers - Functions and Interactions in Cardiac and Non-Cardiac Indications, Dr. Oliver Vonend (Ed.), ISBN: 978-953-307-616-4, InTech, Available from: http://www.intechopen.com/books/aspects-of-pacemakers-functions-and-interactions-in-cardiac-and-non-cardiac-indications/atrio-ventricular-block-induced-torsades-de-pointes-an-update

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License, which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen