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Medicines and QT Prolongation

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1. Introduction

Significant QT interval prolongation may induce severe polymorphic ventricular tachycardia called Torsade de Pointes (TdP). TdP is a type of ventricular tachycardia (VT) characterized by a twist of the QRS wave around the baseline. In some cases this leads to fatal ventricular fibrillation (VF), which is why it is of particular importance among cases of arrhythmia.

QT prolongation causes TdP which may then induce fatal VF. Common causes of QT prolongation include idiosyncratic causes such as gene deficiency, drugs, and drug-drug interactions. There are many cases of QT prolongation caused by drugs used to treat non-cardiac related conditions; these cases involve unintended, adverse 'collateral' effects. Consequently, most of the drug-related cases fall outside the scope of the doctor's area of speciality and/or expectations, which makes it difficult to take preventive and therapeutic measures. It is for this reason that it is important to identify drugs that are likely to cause QT prolongation. Here, we outline drug that may cause QT prolongation and drug-drug interaction induced QT prolongation that could cause serious arrhythmia.

2. What is QT prolongation?

QT interval defines the start of the Q wave and the end of the T wave in an electrocardiogram, representing the time between depolarization and repolarization of the ventricles. Its value is a measurement from phase 0 (upstroke), through phase 1 (spike) and phase 2 (plateau) to phase 3 (rapid repolarization) (Fig. 1). Phase 4 is a phase between action potentials. QRS represents the depolarization of the ventricle, reflecting the membrane potential range as the ventricular depolarization wave propagates from subendocardial to subepicardial. The T wave represents the potential differences of ventricular repolarization. Factors that cause QT interval prolongation include the prolongation of cardiac ventricular action potential duration (APD), and an increase in nonuniformity of repolarization.

The QT interval shortens in tachycardia but prolongs in bradycardia. There is no significant difference based on gender, while there is a weak tendency for the QT interval to prolong in females as they age. It is necessary to distinguish between two types of bradycardia: the PP interval prolongation on the one hand, and the QT interval prolongation on the other. When comparing QT intervals under different pulse rates, it is standard practice to use the corrected QT interval using Bazett's formula ($QT_c = QT / \sqrt{RR}$). Other formulae include Fredericia's ($QT_c = QT / \sqrt[3]{RR}$) and Van de Water's ($QT_c = QT - 0.087 \times (RR - 1000)$) (Kato et al., 2009). The Bazett QT_c values are smaller than actual QT measurements as the RR

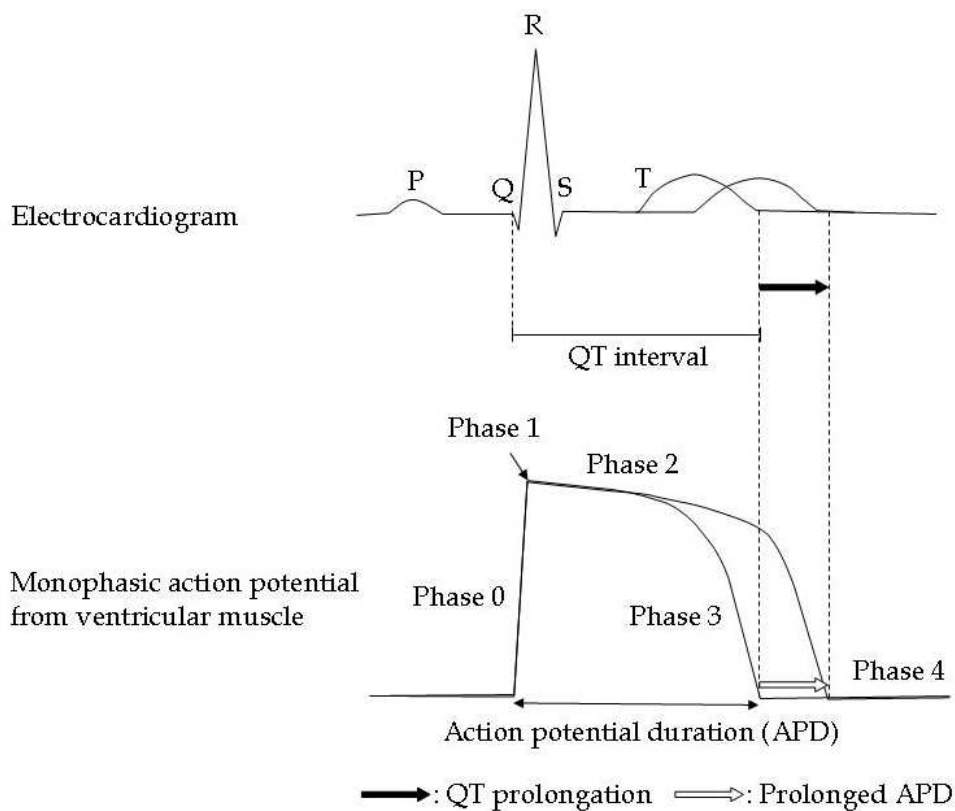


Fig. 1. The relation between electrocardiogram and monophasic action potential from ventricular muscle.

interval prolongs in bradycardia, while in tachycardia they are larger. Here, we adopt the formula among those mentioned above that shows the lowest correlation between the QTc and the RR interval. Normally, QTc values remain constant during both rest and exercise. QT prolongation occurs when QTc values fluctuate to greater than 0.44 sec. When the QTc values are normal (constant), the QT interval should be shortened under exercise compared with resting. QT prolongation occurs when this balance was disrupted. Significant QT interval prolongation may induce a severe polymorphic ventricular tachycardia called Torsade de Pointes (TdP). TdP is a type of ventricular tachycardia (VT) characterized by a twist of the QRS wave around the baseline. The pulse rate can reach 150-300 beats per minute, leading to severe symptoms such as fainting. In some cases this leads to fatal ventricular fibrillation (VF), which is why it is of particular importance amongst cases of arrhythmia. QT prolongation causes TdP that may induce fatal VF, which is why it is important to distinguish PP interval prolongation from QT interval prolongation.

3. What causes QT prolongation?

Long QT syndrome (LQTS) is roughly classified into two types, namely hereditary and acquired LQTS. The former is known to be caused by a disparity between the left and right sympathetic nerve systems stemming from some genetic defect, or by defect in *SCN5A* (the Na^+ channel encoding gene) (Lehnart et al., 2007) or *hERG* (the K^+ channel encoding gene) (Lehnart et al., 2007). Risk factors for the latter include: 1. An electrolyte abnormality such as hypokalemia (outward K^+ current decreases, with APD prolonging) and magnesium

deficiency (diuretics can also be a significant cause); 2. Bradycardia; 3. Hypothyroidism; 4. Myocardial infarction with abnormality of K^+ channel; 5. Drugs, and interactions between them.

Next, let us turn now to the electrophysiological mechanism of LQTS. There are a number of different kinds of membrane currents on myocardial cells that are involved with resting potential and action potential formation. Extracellular Na^+ and Ca^{2+} concentration levels are higher than intracellular levels, and the Na^+ current that moves inward (from outside to inside of the cell) forms the depolarization phase (fast channel) while the Ca^{2+} current forms the plateau phase (slow channel). On the other hand, K^+ concentration levels outside the cell are lower than levels inside, and the repolarization phase involves the delayed outward rectifying K^+ current as well as the time-independent inward-rectifying K^+ current. When factors such as drugs are introduced and suppress these K^+ currents, the QT interval prolongs as the prolongation of action potential duration. In the case of TdP accompanying the acquired LQTS, the triggered activity by early afterdepolarization (EAD) or delayed afterdepolarization (DAD) is presumed to play an important role with a possible re-entry involvement.

EAD is an oscillatory potential that occurs in the vulnerable period at the end of the plateau phase when APD prolonged. Triggered activity is generated when EAD reaches the threshold potential and triggers a new action potential. Proposed causes of EAD include: 1. K^+ conductance reduction (K^+ channel blocking); 2. Na^+ conductance increases (aconite poisoning, familial LQTS); 3. Ca^{2+} conductance increases (sympathetic nervous system excitation, catecholamine administered). DAD, on the other hand, is an oscillation in the membrane potential immediately after the myocardial action potential, or oscillatory after potential. The DAD oscillation can get big enough to constitute triggered activity. One way to grasp the effects on EAD and DAD is to measure the monophasic action potential (MAP) of the myocardium. The MAP measurement makes it possible to examine the Na^+ , Ca^{2+} and K^+ currents. MAP_{30} (MAP duration at 30% of repolarization) indicates the Ca^{2+} -ion inward current. MAP_{90} (MAP duration at 90% of repolarization) indicates the K^+ -ion outward current. MAP triangulation (MAP_{90-30}) indicates if Ca^{2+} channels or IKr channels are involved (Kato et al., 2009).

In the case of arrhythmia from digitalis, Na^+ / K^+ -ATPase inhibition increases intracellular Na^+ which activates the Na^+ / Ca^{2+} exchange mechanism. This in turn increases the intracellular Ca^{2+} concentration level, generating an inward current which makes the sarcoplasmic reticulum unstable. Ca^{2+} may then be released from the sarcoplasmic reticulum during phase 4 in the action potential, again causing depolarization leading to DAD. However, DAD from digitalis should follow a relatively mild development, as it is caused by the pumping function of Na^+ / K^+ -ATPase; it is unlikely to induce TdP that leads to VF.

4. TdP's clinical manifestations, outcome and treatment

While a number of TdP cases go unnoticed with no recognizable clinical symptoms, there are also cases with clear manifestations. Initial symptoms include increased dizziness, palpitation, pain in the chest, and discomfort in the epigastric region and in the chest. These are attributable to the elimination of the P wave by VT; blood ejection from the heart is suspended and no palpable pulse is detected, although the heart is still beating. At this stage, it is possible to manage the situation by discontinuing or reducing medication if there

is any suspected drugs. Symptoms may worsen to include anacatesthesia, fainting, and convulsion before proceeding to VF that causes sudden death. It is necessary at this stage to discontinue medication immediately (if any) and arrange for an AED as well as for an ambulance. The patient needs to be admitted to an ICU or CCU for treatments such as electrolyte correction, defibrillation, lidocaine administration, and temporary pacing.

5. Drugs that may cause QT prolongation

Drugs that may cause QT prolongation include anti-arrhythmics, psychotropics, and antibiotics among others (Table 1).

5.1 Anti-arrhythmic drugs

The drugs that fall under Ia in the Vaughan Williams classification reduce action potential slew rate ($dP/dt \max$), and prolong APD by Na^+ channel inhibition (depolarization phase). It follows then that reducing $dP/dt \max$ prolongs APD, but there is a limitation on the overloading of Ca^{2+} from sustained depolarization. Abnormal Na^+ channel activities are unlikely to cause TdP unless there is a deficiency of *SCN5A*. TdP tends to occur in K^+ currents where the K^+ channel is inhibited, which delays repolarization time, with the result that APD is prolonged; K^+ channel inhibition can prolong ADP indefinitely. Under Ic, propafenone is also thought to be a factor because of its β -blockade function that causes bradycardia.

Under III, amiodarone, sotalol and bretyrium can prolong APD mainly by inhibiting outward K^+ current (depolarization phase). They also share β -blocking properties that lead to bradycardia and hence to TdP.

Under IV, bepridil, which is classified as Ca antagonist, is thought to inhibit Na^+ channel and outward K^+ current, which causes APD prolongation and TdP.

5.2 Psychotropic drugs

QT prolongation and TdP can be caused by antipsychotic drugs (chlorpromazine, phenothiazine; haloperidol, butyrophenone), tricyclic antidepressants (amitriptyline) and tetracyclic antidepressants (maprotiline). The mechanism appears to involve a quinidine-like effect, while a range of factors are also cited such as electrolyte imbalance, myocardial membrane enzyme disorder, myocardial tissue degeneration, and effects on autonomic nervous system, among others (Hunt et al., 1995).

5.3 Peripheral anti-histamine drugs

Antiallergic drugs with antihistaminic properties such as terfenadine and astemizole fall under this group. Terfenadine and astemizole are prodrugs whose metabolites have antihistaminic properties. Their parent compounds significantly inhibit K^+ currents. There have been fatal cases involving astemizole overdose as well as terfenadine administration where ventricular arrhythmia accompanied QT prolongation. In the five years after going on sale, seven severe side-effect cases of arrhythmia involving terfenadine were recognized. In 1995, a 'warning' section was added and the instructions for use were revised. However, in the two years following that, ten potentially fatal side-effect cases surfaced that involved QT prolongation and ventricular arrhythmia. In 1997, 'Urgent Safety Information' was submitted to call for extra care for the use of the drug before its sale was suspended in 2001.

The sale of astemizole was suspended in 1999. The mechanism of QT prolongation by terfenadine is thought to involve prolongation of myocardial repolarization time via delayed outward K^+ current inhibition; it appears that antihistaminic metabolites do not significantly inhibit the K^+ channel (Valenzuela et al., 1997). QT prolongation or TdP caused by these drugs is due not to antihistaminic properties but to K^+ current inhibition. At present, there have been no reports of QT prolongation involving ebastine though it has been known to block delayed rectifier K^+ current, albeit to a significantly lesser degree when compared to terfenadine (Valenzuela et al., 1997; Ko et al., 1997). It is in this context that fexofenadine, a metabolite of terfenadine, was developed. Fexofenadine is presumed to be safe, but its structural similarity to terfenadine suggests a possible parallel effect. Ebastine and fexofenadine need further careful study.

5.4 Gastrointestinal prokinetic agents

Cisapride was withdrawn from the market after the claim was made that it caused diabetic QT prolongation. Cisapride causes APD prolongation in extracted myocardial cells of laboratory animals, and dose-dependent prolongation of monophasic action potential duration (MAPD) in anesthetized animals, leading to QT prolongation and TdP (Carlsson et al., 2007). Mosapride is another gastrointestinal prokinetic agent with a similar chemical structure to that of cisapride. Animal testing has shown that it does not affect APD or MAPD, and it does not induce abnormal ECG such as QT prolongation or TdP (Carlsson et al., 2007).

It appears then that QT prolongation caused by this group of drugs is based not on the serotonin agonist property, which is the drug's main effect, but rather on its inhibition of the K^+ channel.

5.5 Macrolide anti-biotics

Erythromycin causes QT prolongation by inhibiting the delayed rectifier K^+ current (Rubart et al., 1993; Daleau et al., 1995). When combined with terfenadine or cisapride (discussed above), erythromycin enhances QT prolongation by blocking drug-metabolizing enzymes.

5.6 Anthracycline anti-cancer drugs

Among anthracycline anti-cancer drugs, doxorubicin is known to cause myocardial damage. It appears to enhance the sensitivity of depolarization in phase 4 (Mitrius et al., 1990).

5.7 Azole anti-fungal drugs

Azole anti-fungal drugs such as fluconazole and voriconazole are also known to cause QT prolongation. They are metabolized by the drug-metabolizing enzyme CYP3A4 while simultaneously inhibiting it. QT prolongation is caused either by the increasing serum concentration of the drug itself, or by increasing the serum concentration of some other drug that would otherwise be metabolized by CYP3A4; the latter case may involve a drug such as erythromycin. This calls for extra care for combinatory use of these drugs.

5.8 Sulfonylureas (SUs) and Glinides as Oral Anti-diabetic Drugs

SU and glinide agents are known to inhibit ATP-dependent K^+ channels. The similarity in mechanism is also increasingly evident between Class Ia anti-arrhythmic drugs and the hypoglycemic function of SUs and glinides (Kakei et al., 1993; Hayashi et al., 2004). SUs and

glinides can potentially induce QT prolongation when they affect the heart's ATP-dependent K⁺ channels.

5.9 Sulfa drugs

Like SUs, a pentamidine and ST mixture may cause QT prolongation and hypoglycemia. Considering that SUs are modified sulfa drugs, they belong to the same strain that may affect ATP-dependent K⁺ channels.

5.10 New quinolones

There have been cases of TdP from QT prolongation caused by sparfloxacin and moxifloxacin, both new quinolones. The mechanism appears to involve K⁺ channel inhibition.

5.11 Molecular targeted cancer drugs

There have been cases of QT prolongation or myocardial damage from sunitinib, bortezomib, sorafenib, lapatinib, and nilotinib, among others.

5.12 Others

A study has been done on probucol induced QT prolongation as a result of a change in catecholamine sensitivity, as well as K⁺ current inhibition (Hayashi et al., 2004). Further study and consideration is needed. Meanwhile, QT prolongation is also known to be caused by diuretics that cause hypokalemia and magnesium deficiency, by cimetidine the histamine H₂ receptor antagonist, or even by contrast media.

Anti-arrhythmic Drugs	Class Ia : quinidine, procainamide, disopyramide, cibenzoline Class Ic : propafenone Class III: amiodarone, sotalol Class IV: bepridil
Psychotropic Drugs	phenothiazine: chlorpromazine butyrophenone: haloperidol tricyclic: amitriptyline, imipramine, nortriptyline tetracyclic: maprotiline
Peripheral Anti-histamine Drug	terfenadine*, astemizole*, ebastine
Gastrointestinal prokinetic Agents	cisapride*
Macrolide Anti-biotics	erythromycin, clarithromycin
Anthracycline Anti-cancer Drugs	doxorubicin
Azole Anti-fungal Drugs	fluconazole, voriconazole
Sulfonylureas (SUs) and Glinides	SUs: glimepiride, glibenclamide glinides: mitiglinide**, nateglinide
Sulfa Drugs	pentamidine, ST mixture
New Quinolones	sparfloxacin, moxifloxacin
Molecular Targeted Cancer Drugs	sunitinib, bortezomib, sorafenib, lapatinib, nilotinib
Others	probucol

*The drugs were withdrawn from the market in Japan.

**Mitiglinide is marketed only in Japan and China.

Table 1. Drugs that may cause QT prolongation.

6. Drug-drug interaction induced QT prolongation

Drug interaction is an important factor for QT prolongation. Drug-drug interaction is divided into pharmacodynamic interaction and pharmacokinetic interaction.

6.1 Pharmacodynamic Interaction

Drugs that are likely to cause QT prolongation are shown in Table 1. Combining two or more reinforces medicinal action additively; doses should be reduced or avoided altogether.

6.2 Pharmacokinetic Interaction

This involves cases where drug metabolism inhibition increases serum concentration, resulting in QT prolongation. Erythromycin, azole anti-fungal drugs, and molecular targeted cancer drugs are metabolized by CYP3A4, a microsomal drug metabolizing enzyme (that does exist outside the liver). When the above mentioned drugs were combined with a drug metabolized by enzymes of the same molecular kind or with a CYP3A4 blocking drug, the serum concentration to increase compared with a single dose of the drug (Table 2). The former is known as competitive antagonism, the latter as non-competitive antagonism; it is the latter that causes a sharper increase in serum concentration.

An abnormal terfenadine-induced ECG is thought to be the result of increasing serum concentrations of a parent compound, produced by the combined use of terfenadine and a CYP3A4-blocking drug from Table 2. Drug-drug interactions like that just described are why the drugs shown under Table 2 were contraindicated for combined use. An active carboxylic acid metabolite of terfenadine called fexofenadine went on the market. It is claimed that fexofenadine does not have the same cardiac related side effects that terfenadine has, however the structural similarity between the two is enough to warrant some caution. Ebastine metabolism is thought to involve CYP3A4, a microsomal enzyme, as well as another metabolizing enzyme. In theory, ebastine should be less likely to lead to TdP than terfenadine, though extra care must be taken when extrapolating data from clinical and non-clinical testing.

Grapefruit juice is known to inhibit CYP3A4, which means it can cause QT prolongation by increasing the serum concentration of erythromycin, azole anti-fungal drugs, and molecular targeted cancer drugs.

1. CYP3A4-blocking drug (competitive inhibition)

HIV protease inhibitor: indinavir, saquinavir, ritonavir, nelfinavir

2. CYP3A4-blocking drug (noncompetitive inhibition)

Azole Anti-fungal Drugs: itraconazole, ketoconazole, miconazole, fluconazole,
voriconazole

Macrolide Anti-biotics: erythromycin, clarithromycin

Table 2. Drugs that are likely to cause QT prolongation by CYP3A4-blocking.

7. QT prolongation - what measures to take

In the case of drug-induced QT prolongation, the crucial clinical concern is not the QT prolongation itself, but TdP or VF that may follow. It is important then to determine whether QT prolongation is just a simple case of bradycardia (PP interval prolongation), or bradycardia caused by the QT prolongation. The main and intended effect of anti-arrhythmic drugs classified under Ia is QT prolongation. However, drugs intended for other parts of the body can also cause the same QT prolongation in the heart; this is their collateral effect. Under these circumstances it has been extremely difficult for doctors to recognize early symptoms, largely because it falls outside the physician's area of specialty when the case involves drugs other than those described under section 5-1 ('Anti-arrhythmic Drugs'). There was a case of antipruritic (anti-histamine agent) that caused a totally unexpected fatal arrhythmia. Cisapride disappeared from the market, leaving the new term 'Diabetic QT Prolongation'. Furthermore, it is intriguing to note the similarity in mechanism between SUs and cibenzoline, an anti-arrhythmic drug classified under Ia of the Vaughan-Williams classification. Far too many QT prolongation cases that could have been predicted have gone unnoticed. The intended effect of the drug was the focus of attention, while the obvious 'collateral effect' was unobserved.

In order to detect early symptoms of the collateral effect, attention must be paid to: 1. What drugs can cause a collateral effect; 2. Factors on the part of the patient (e.g. certain conditions obtained when sick); 3. Drug-drug interaction. When encountered with early symptoms of TdP such as increased dizziness, palpitation, pain in the chest, and discomfort in the epigastric region and in the chest, medication should be discontinued and immediate medical attention should be sought.

8. Conclusion

Side effects are classified into toxic (dose-dependent) and allergic. The former is a simple extension of the main effect: serum concentration increases dose-dependently in a predictable fashion. The latter is hard to predict because it increases dose-independently in an idiosyncratic fashion. The QT prolongation under discussion belongs to the former and is indeed predictable. When QT prolongation is an extension of the main drug effect (anti-arrhythmic effect) and is confirmed by a specialist as such, preventive or therapeutic measures can be taken before it is too late. However, when QT prolongation is caused by the drugs discussed under sections 5-2 through 5-12 (psychotropics, anti-histamines, gastrointestinal prokinetic agents, anti-biotics, anti-cancer agents, etc.), it is difficult to take preventive or therapeutic measures against these 'collateral' effects because most of these cases are simply beyond the scope of the doctor in charge. This has indeed resulted in a number of cases where QT prolongation was not diagnosed, with unfortunate results. It is essential to learn from these past experiences and develop proactive treatments.

A new guideline (ICH S7B) providing provisions for a QT prolongation screening test for new drug development was issued by ICH, the International conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (<http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html>). Aside from the provided guidelines, it is important to look for substances that do not block K⁺ channels when developing drugs; one can make use of *hERG* or a screening method using MAP (Kato et al., 2009).

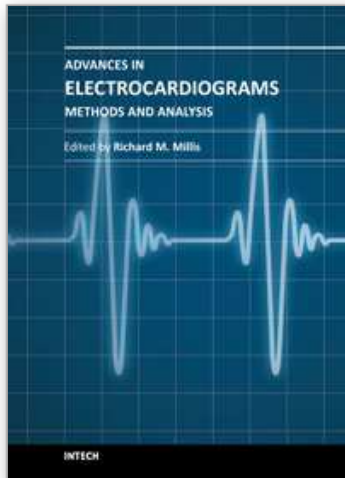
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Electrocardiograms are one of the most widely used methods for evaluating the structure-function relationships of the heart in health and disease. This book is the first of two volumes which reviews recent advancements in electrocardiography. This volume lays the groundwork for understanding the technical aspects of these advancements. The five sections of this volume, Cardiac Anatomy, ECG Technique, ECG Features, Heart Rate Variability and ECG Data Management, provide comprehensive reviews of advancements in the technical and analytical methods for interpreting and evaluating electrocardiograms. This volume is complemented with anatomical diagrams, electrocardiogram recordings, flow diagrams and algorithms which demonstrate the most modern principles of electrocardiography. The chapters which form this volume describe how the technical impediments inherent to instrument-patient interfacing, recording and interpreting variations in electrocardiogram time intervals and morphologies, as well as electrocardiogram data sharing have been effectively overcome. The advent of novel detection, filtering and testing devices are described. Foremost, among these devices are innovative algorithms for automating the evaluation of electrocardiograms.

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