# SINDROME DE QT ADQUIRIDO COVID 19

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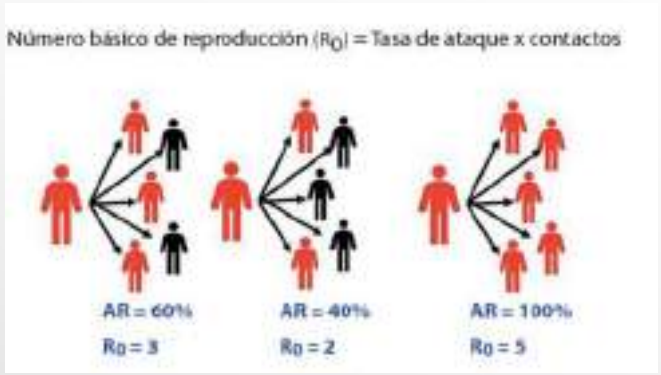
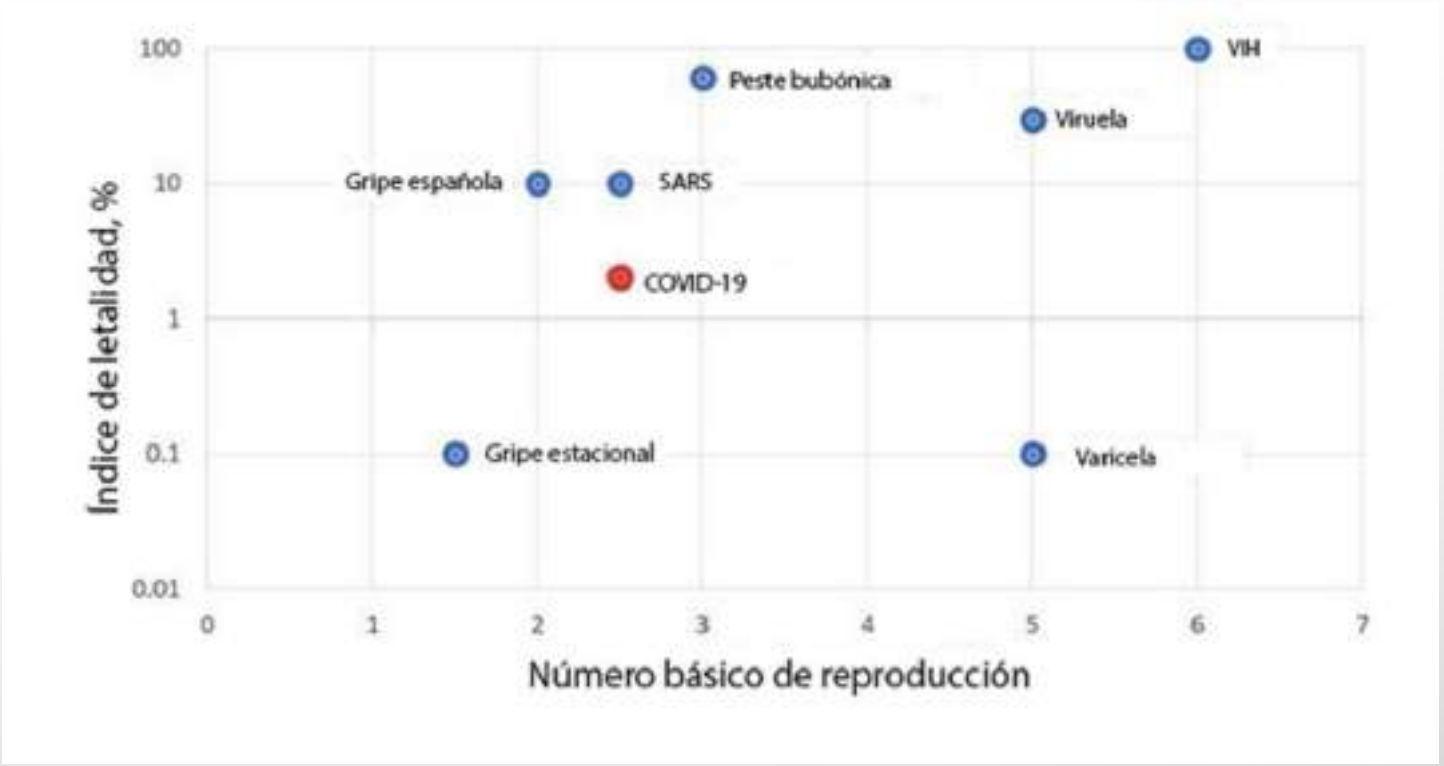

Número básico de reproducción ($R_0$) = Tasa de ataque x contactos
AR = 60%
$R_0$ = 3
AR = 40%
$R_0$ = 2
AR = 100%
$R_0$ = 5


Índice de letalidad, %
100
10
1
0.1
0.01
0
1
2
3
4
5
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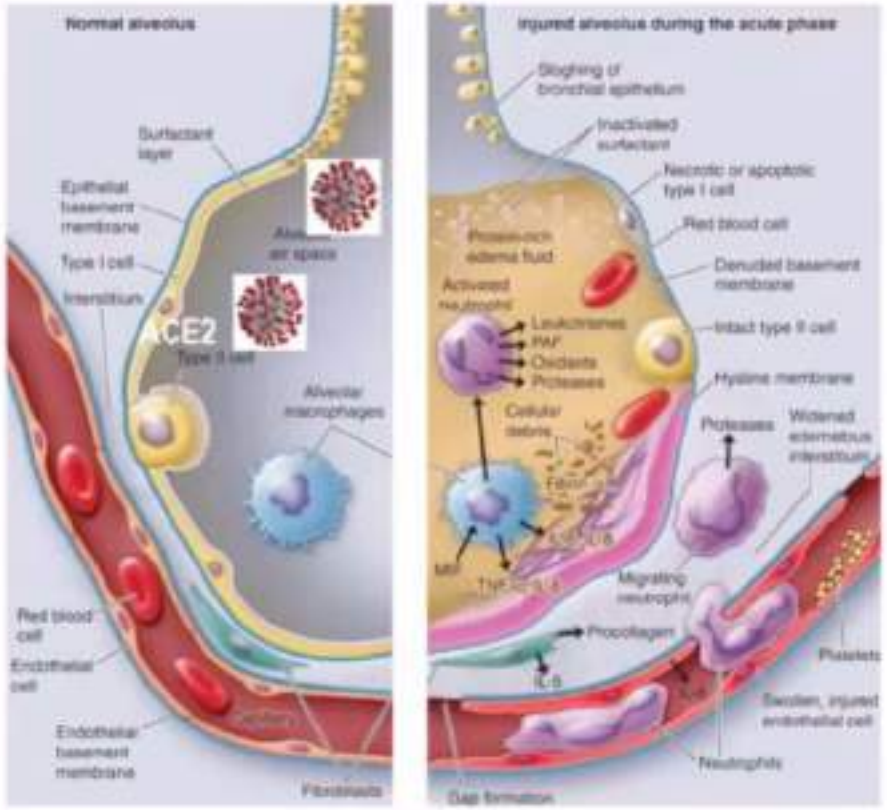
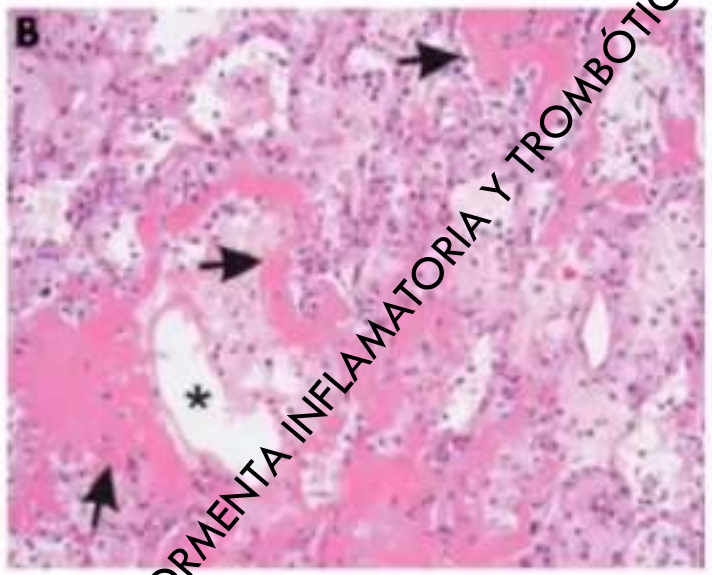
7
Número básico de reproducción
VIH
Peste bubónica
Viruela
Gripe española
SARS
COVID-19
Gripe estacional
Varicela

# SARS-CoV-2 (COVID19) Pathogenesis: ARDS



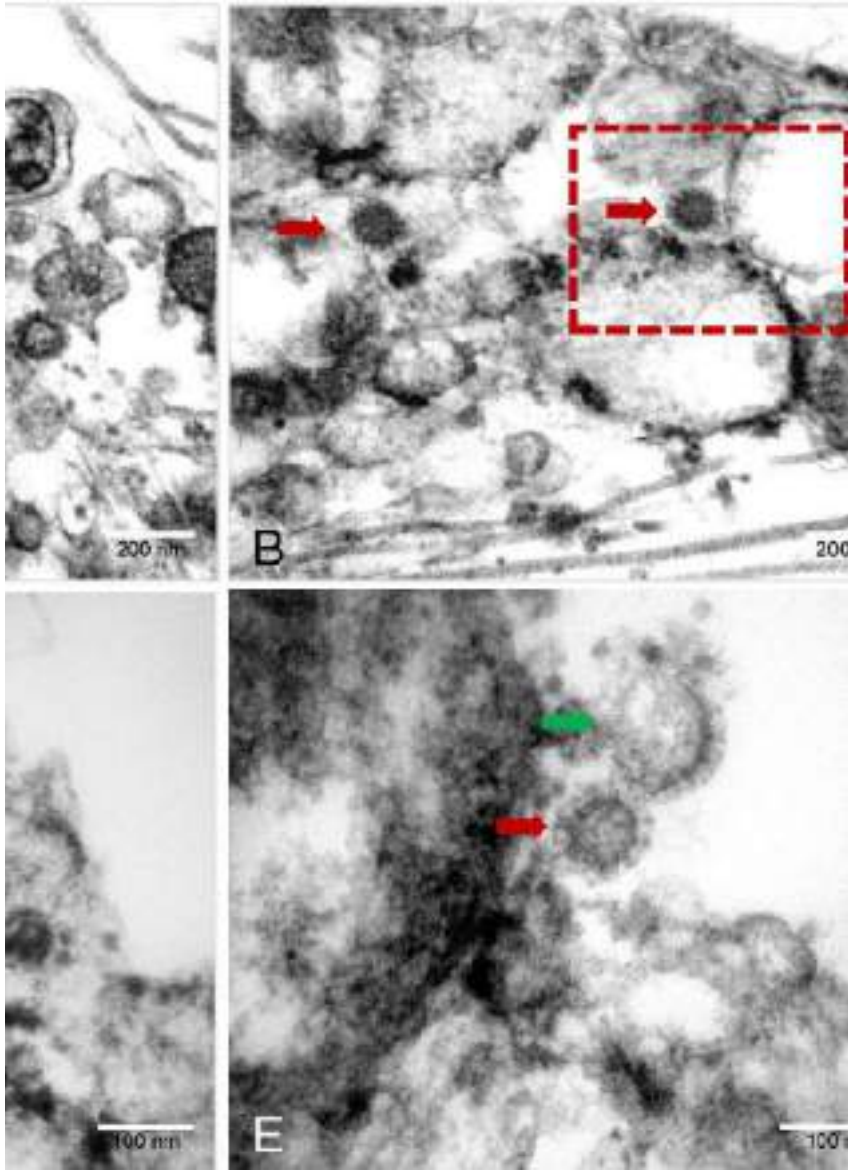

TORMENTA INFLAMATORIA Y TROMBÓTICA

**Acute Respiratory Distress Sydrome (ARDS) pathology**

Acute diffuse alveolar damage, with pulmonary edema and formation of a hyaline membrane in a SARS-CoV patient

The airspaces are indicated by asterisks and some of the hyaline membranes lining the alveolar spaces are highlighted by arrows (hematoxylin and eosin stain, original magnification ×100)

Tse GMK et al. J Clin Pathol 2004;57:260–265


200 nm
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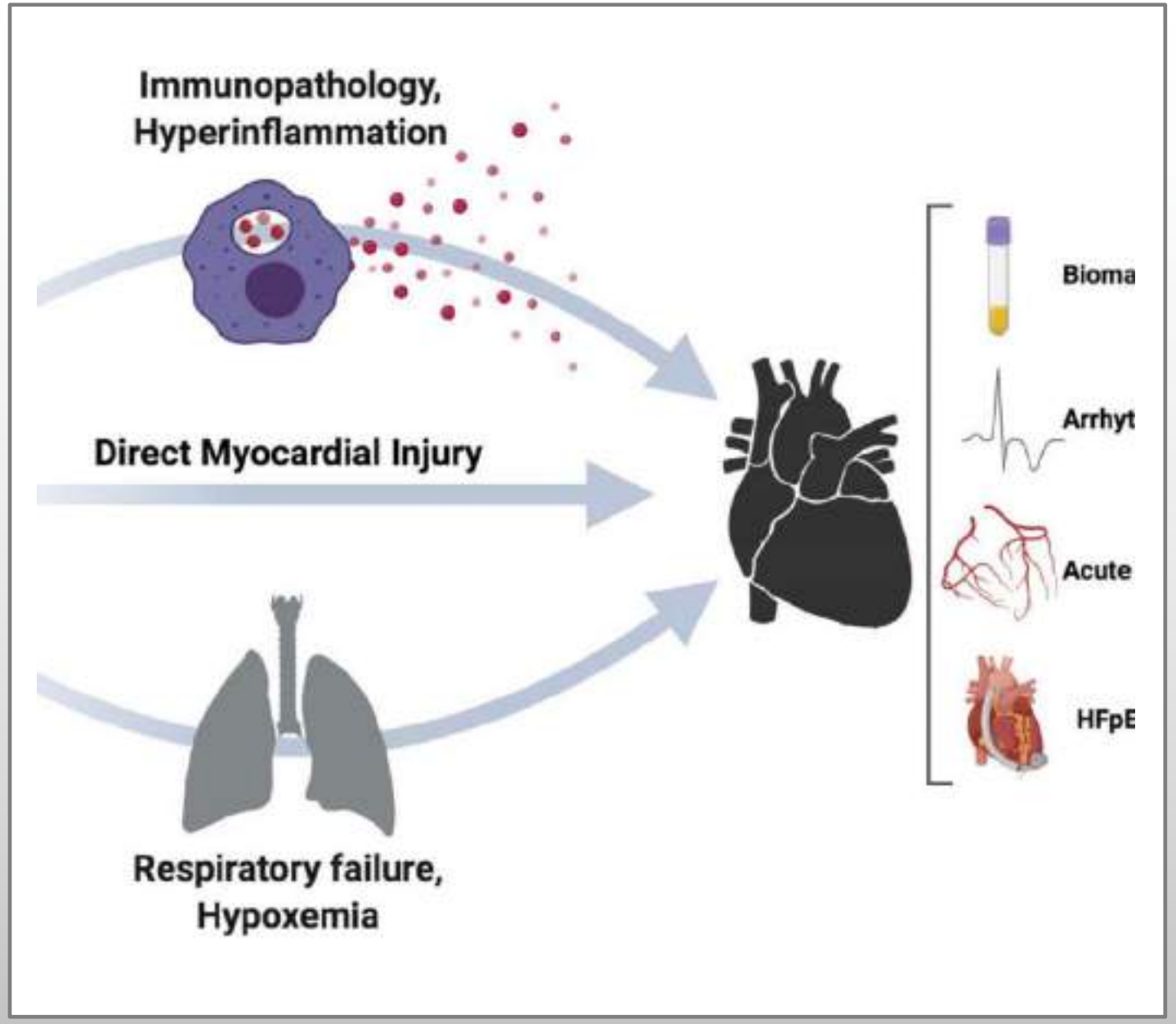
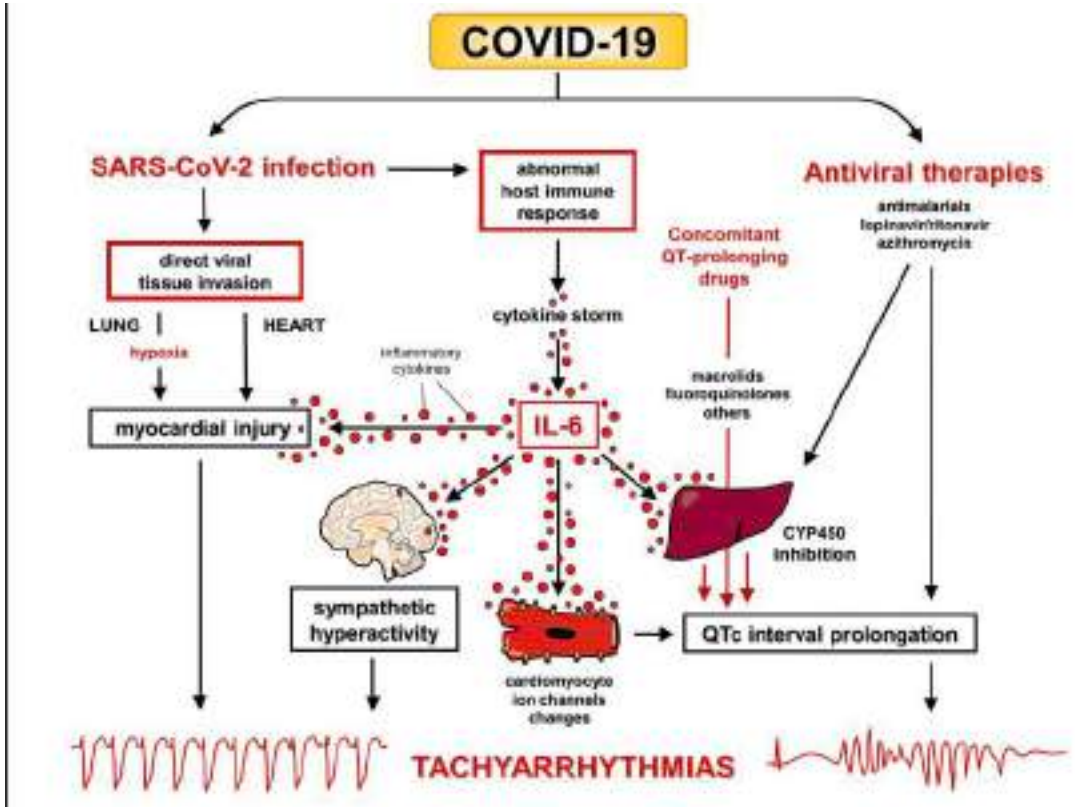
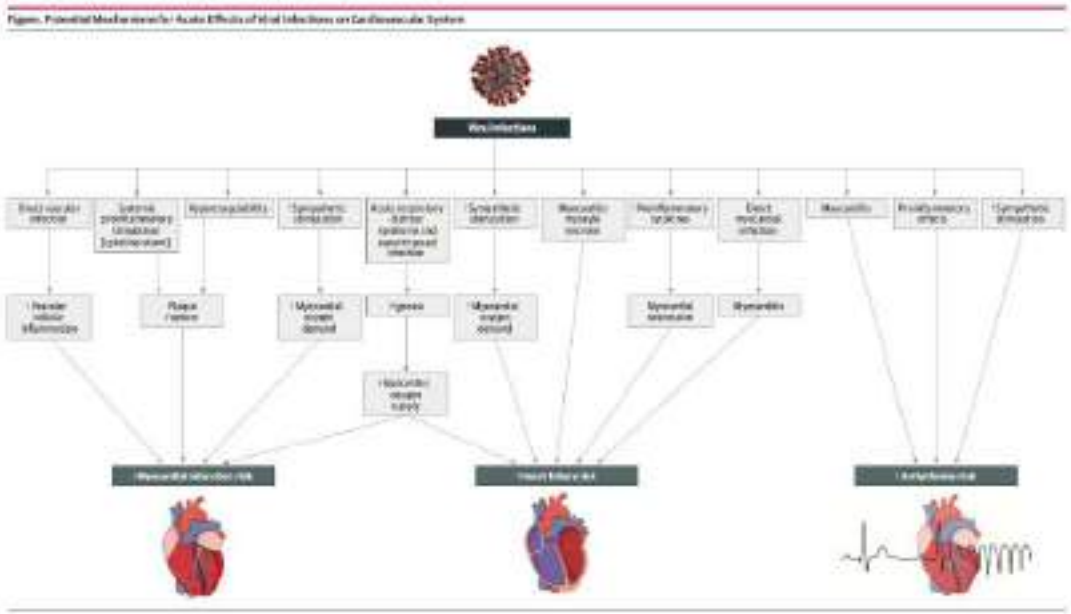
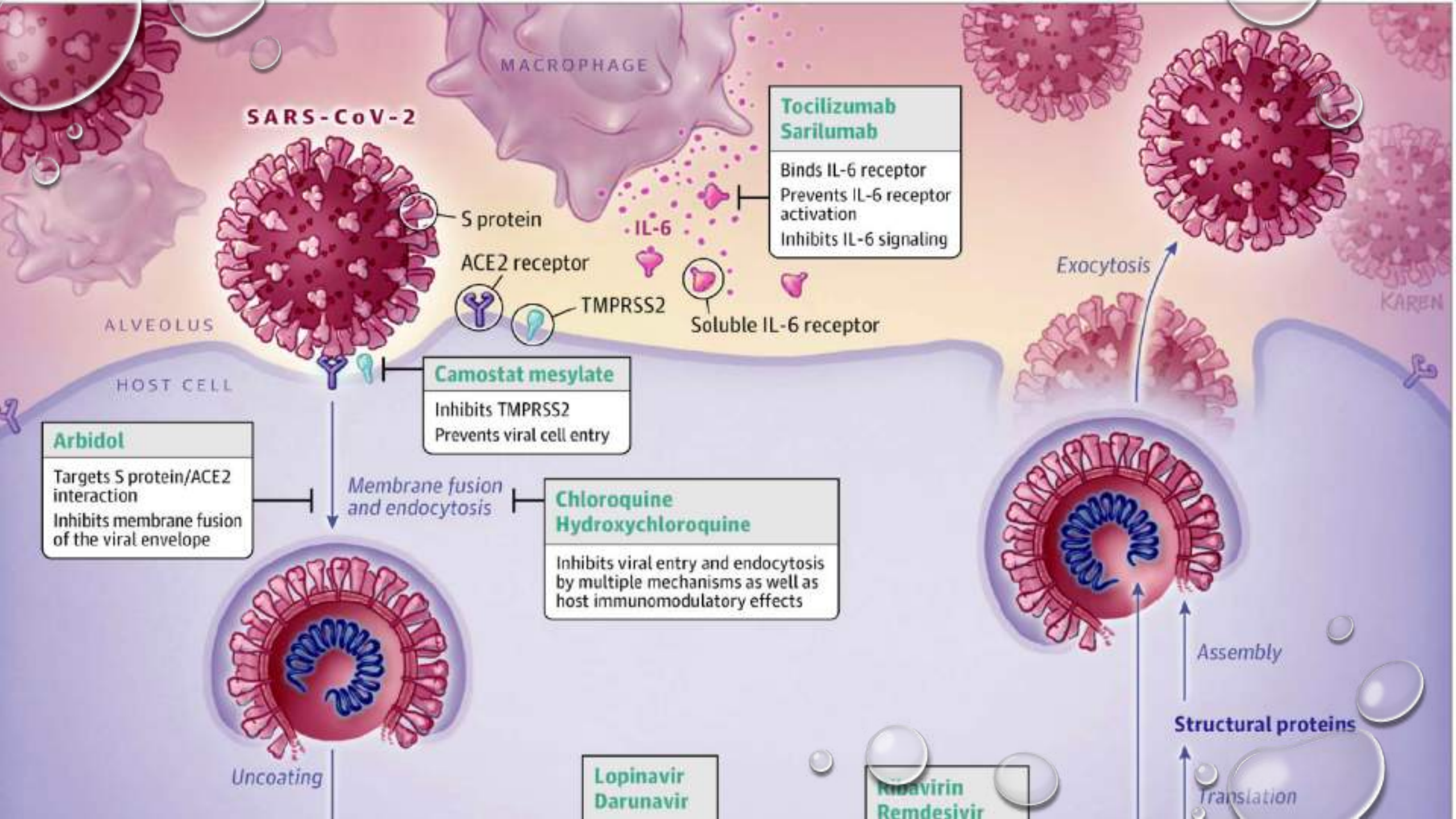
100 nm
E

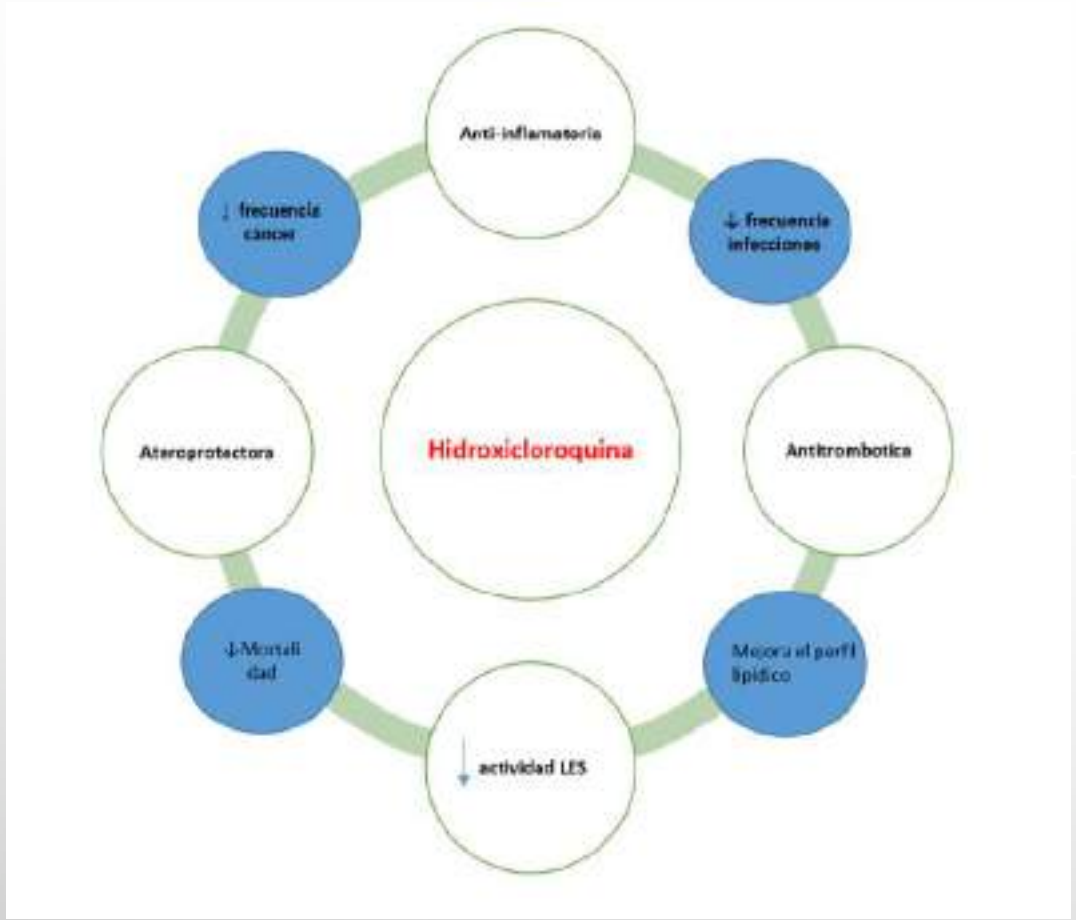

Immunopathology,
Hyperinflammation
Direct Myocardial Injury
Respiratory failure,
Hypoxemia
Bioma
Arrhyt
Acute
HFpE

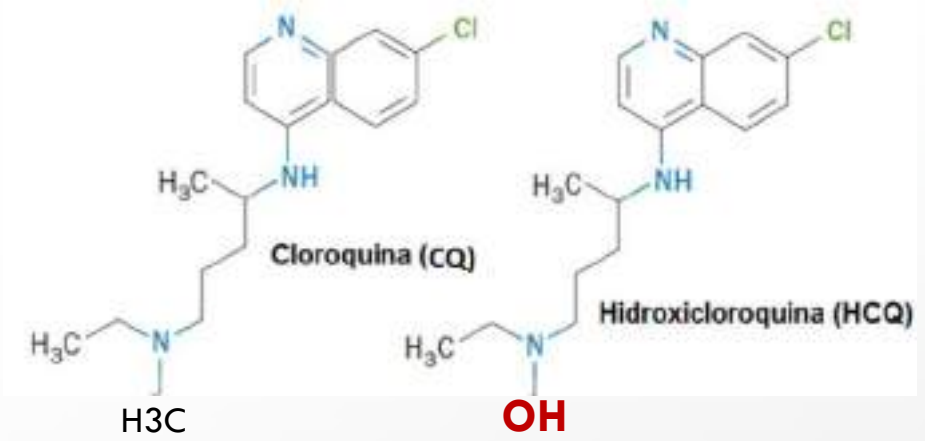

COVID-19
SARS-CoV-2 infection
abnormal host immune response
Antiviral therapies
antimalarials
lopinavir/ritonavir
azithromycin
direct viral tissue invasion
Concomitant QT-prolonging drugs
LUNG
HEART
hypoxia
cytokine storm
inflammatory cytokines
macrolids
fluoroquinolones
others
myocardial injury
IL-6
CYP450 inhibition
sympathetic hyperactivity
QTc interval prolongation
cardiomyocyte ion channels changes
TACHYARRHYTHMIAS

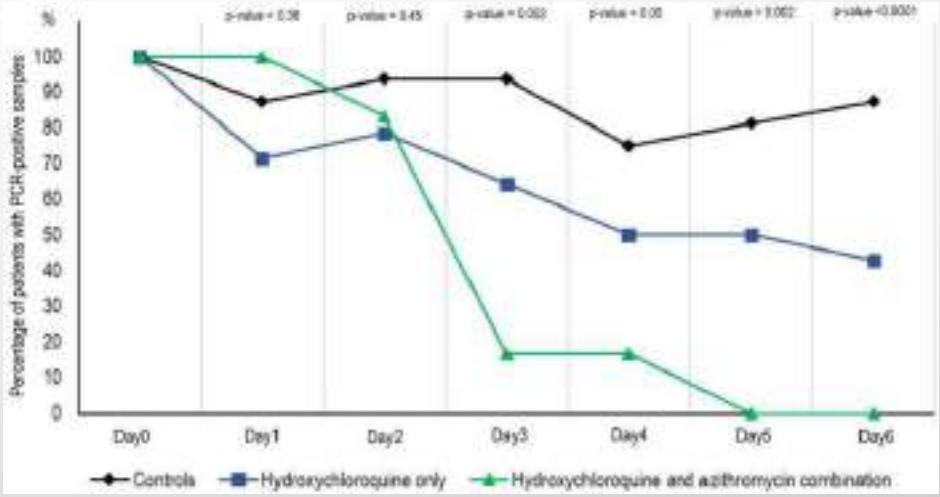



MACROPHAGE
SARS-CoV-2
S protein
ACE2 receptor
TMPRSS2
IL-6
Soluble IL-6 receptor
Tocilizumab
Sarilumab
Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling
Exocytosis
KAREN
ALVEOLUS
HOST CELL
Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry
Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope
Membrane fusion and endocytosis
Chloroquine
Hydroxychloroquine
Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Uncoating
Lopinavir
Darunavir
Ribavirin
Remdesivir
Assembly
Structural proteins
Translation

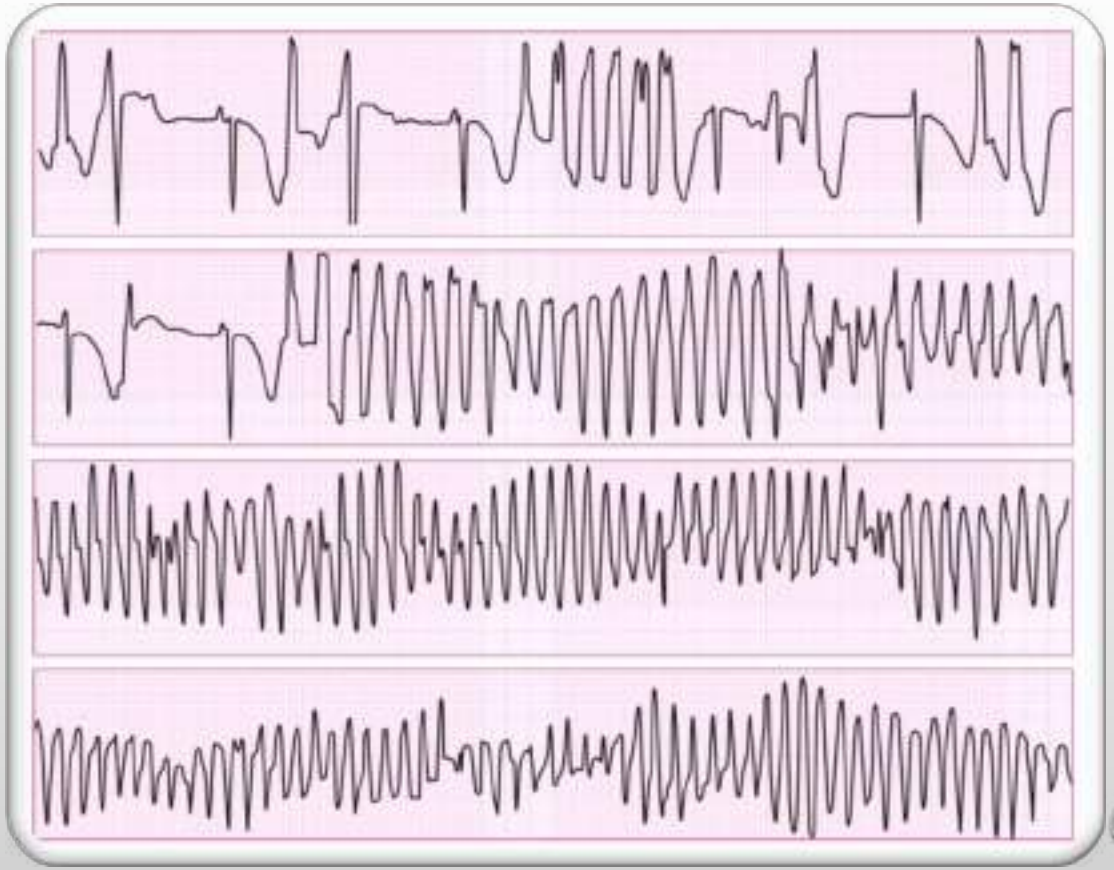
La hidroxicloroquina tiene efecto directo sobre el QT, por alterar los canales iónicos de potasio, y las corrientes de iones de calcio (IcaL).
la azitromicina actuaría sobre la corriente rápida de sodio y sobre la corriente L de calcio



# TAQUICARDIAS VENTRICULARES POLIMÓRFICAS CON QT LARGO ADQUIRIDO



# SINDROME DEL QT LARGO

- GRAVE ALTERACIÓN EN LA REPOLARIZACIÓN VENTRICULAR.
- ELECTROCARDIOGRAMA CON ALARGAMIENTO EN EL INTERVALO QT.
- PREDISPONE A
  - ARRITMIAS VENTRICULARES MALIGNAS --TORSADE DE POINTES-
  - MUERTE SÚBITA

## CONGÉNITOS

- HETEROGENEIDAD GENÉTICA
  - 10 GENES
  - 500 MUTACIONES
- SQTL 1 EJERCICO O ESTÍMULO SIMPÁTICO (30-35%)
- SQTL 2 ESTRÉS EMOCINAL, DESPERTAR, SUEÑO (25-30%)
- SQTL 3 SUEÑO, BRADICARDIA (5-10%)

## ADQUIRIDOS

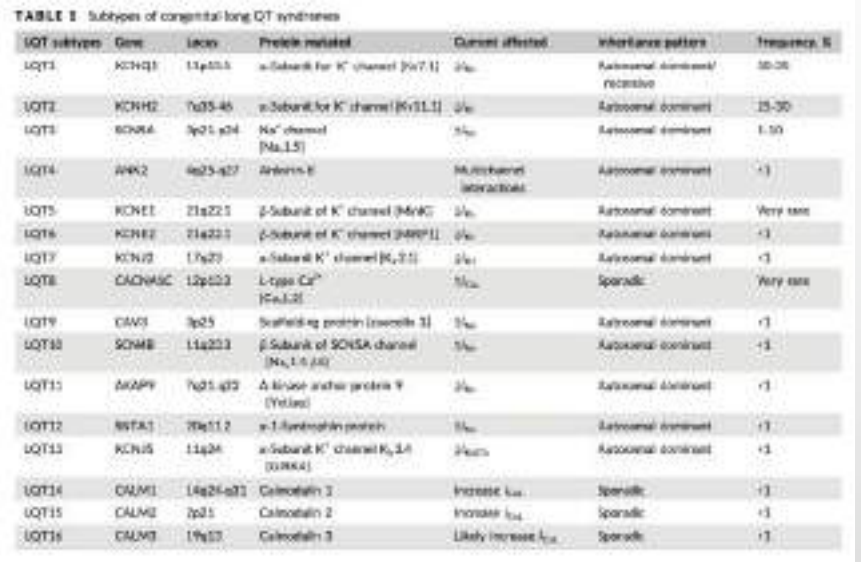


**TABLE 1** Subtypes of congenital long QT syndromes

| LQT subtype | Gene | Locus | Protein mutated | Current affected | Inheritance pattern | Frequency, % |
|---|---|---|---|---|---|---|
| LQT1 | KCNQ1 | 11p15.5 | α-Subunit for K⁺ channel ($K_V7.1$) | $I_{Ks}$ | Autosomal dominant/ recessive | 30-35 |
| LQT2 | KCNH2 | 7q35-46 | α-Subunit for K⁺ channel ($K_V11.1$) | $I_{Kr}$ | Autosomal dominant | 25-30 |
| LQT3 | SCN5A | 3p21-p24 | $Na^+$ channel ($Na_V1.5$) | $I_{Na}$ | Autosomal dominant | 1-10 |
| LQT4 | ANK2 | 4q25-q27 | Ankyrin-B | Multichannel interactions | Autosomal dominant | <1 |
| LQT5 | KCNE1 | 21q22.1 | β-Subunit of K⁺ channel (MinK) | $I_{Ks}$ | Autosomal dominant | Very rare |
| LQT6 | KCNE2 | 21q22.1 | β-Subunit of K⁺ channel (MiRP1) | $I_{Kr}$ | Autosomal dominant | <1 |
| LQT7 | KCNJ2 | 17q23 | α-Subunit $K^+$ channel ($K_{ir}2.1$) | $I_{K1}$ | Autosomal dominant | <1 |
| LQT8 | CACNA1C | 12p13.3 | L-type $Ca^{2+}$ ($Ca_V1.2$) | $I_{Ca,L}$ | Sporadic | Very rare |
| LQT9 | CAV3 | 3p25 | Scaffolding protein (caveolin 3) | $I_{Na}$ | Autosomal dominant | <1 |
| LQT10 | SCN4B | 11q23.3 | β-Subunit of SCN5A channel ($Na_V1.5$ β4) | $I_{Na}$ | Autosomal dominant | <1 |
| LQT11 | AKAP9 | 7q21-q22 | A-kinase anchor protein 9 (Yotiao) | $I_{Ks}$ | Autosomal dominant | <1 |
| LQT12 | SNTA1 | 20q11.2 | α-1-Syntrophin protein | $I_{Na}$ | Autosomal dominant | <1 |
| LQT13 | KCNJ5 | 11q24 | α-Subunit $K^+$ channel $K_{ir}3.4$ (GIRK4) | $I_{K(ACh)}$ | Autosomal dominant | <1 |
| LQT14 | CALM1 | 14q24-q31 | Calmodulin 1 | Increase $I_{Ca,L}$ | Sporadic | <1 |
| LQT15 | CALM2 | 2p21 | Calmodulin 2 | Increase $I_{Ca,L}$ | Sporadic | <1 |
| LQT16 | CALM3 | 19q13 | Calmodulin 3 | Likely increase $I_{Ca,L}$ | Sporadic | <1 |

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Risk Stratification in the Long-QT Syndrome

Silvia G. Priori, M.D., Ph.D., Peter J. Schwartz, M.D., Carlo Napolitano, M.D., Ph.D., Raffaella Bloise, M.D., Elena Ronchetti, Ph.D., Massimiliano Grillo, M.D., Alessandro Vicentini, M.D., Carla Spazzolini, M.V., Janni Nastoli, B.S., Georgia Botteli, B.S., Roberta Folli, B.S., and Renata Cappelletti, B.S.

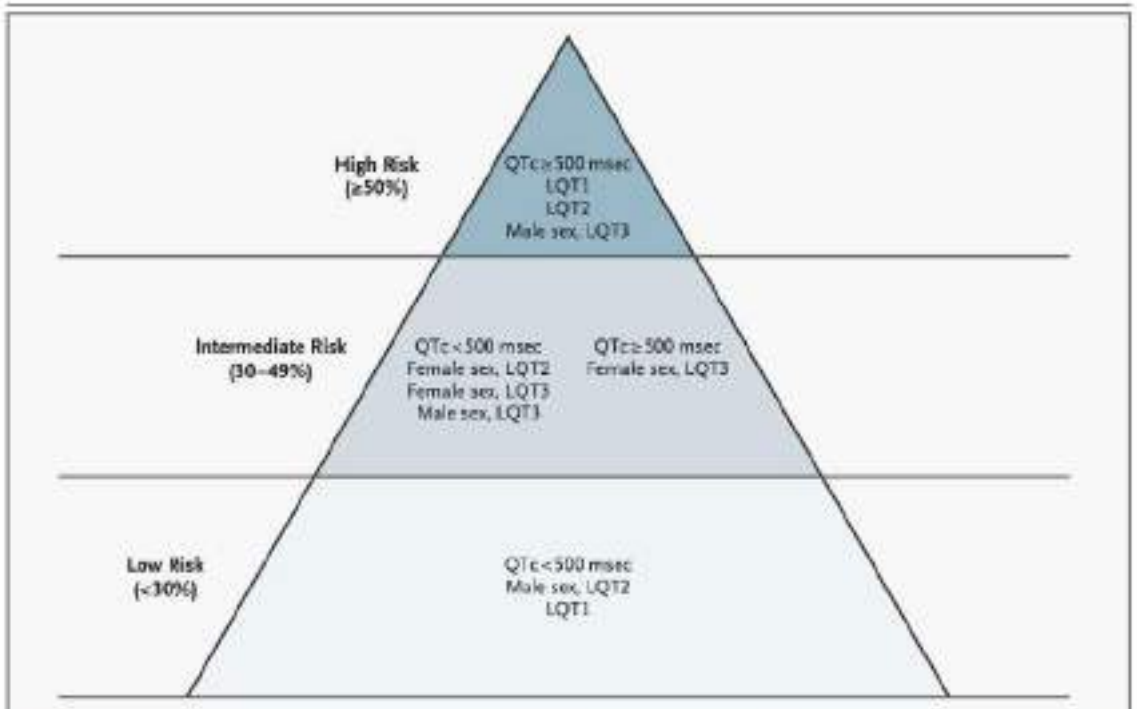



**Figure 4. Proposed Scheme for Risk Stratification among Patients with the Long-QT Syndrome According to Genotype and Sex.**

The risk groups have been defined on the basis of the probability of a first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 years and before therapy. A probability of 50 percent or higher defines the high-risk group, a risk of 30 to 49 percent the intermediate-risk group, and a risk below 30 percent the low-risk group.

| Schwartz Score | | Points | Questionable in Athletes |
|---|---|---|---|
| **Electrocardiographic findings** | | | |
| A | QTc duration (ms) (Bazett formula) | | |
| | ≥480 | 3 | |
| | 460–470 | 2 | x |
| | 450 (in males) | 1 | x |
| B | Torsades de pointes* | 2 | |
| C | T-wave alternans | 1 | |
| D | Notched T wave in three leads | 1 | |
| E | Low heart rate for age | 0.5 | x |
| **Clinical history** | | | |
| A | Syncope* | | |
| | With stress | 2 | |
| | Without stress | 1 | |
| B | Congenital deafness | 0.5 | |
| **Family history** | | | |
| A | Family members with definite LQTS | 1 | |
| B | Unexplained sudden cardiac death below the age of 30 among immediate family members | 0.5 | |

# SINDROME DE QT LARGO ADQUIRIDO

**Factores modificables**

- **Alteraciones electrolíticas:**
  Hipocalcemia (< 4.65 mg/dL)
  Hipokalemia (< 3.4 mmol/L)
  Hipomagnesemia (< 1.7 mg/dL)
- **Medicamentos que prolongan QT**
  Uso simultáneo de ≥ 1 medicamento

**Factores no modificables**

- **Comorbilidades comunes**
  Evento coronario agudo
  Bradiarritmia con FC < 45 lpm
  Falla cardíaca descompensada (FE del VI < 40&)
  Síndrome de QT largo congénito
  Insuficiencia renal en diálisis
  Diabetes Mellitus I-II
  Cardiomiopatía hipertrófica
  Hipoglicemia
  Feocromicitoma
  Estado post-arresto cardiaco (dentro de las 24 horas)
  Estado post-sincopal o convulsivo (dentro de las 24 horas)
  ECV, hemorragia subaracnoidea, TCE (dentro de los 7 días)
- **Antecedentes personales o familiares relacionados:**
  De prolongación previa del QT o muerte súbita inexplicada
- **Factores demográficos**
  Edad > 65 años
  Género femenino

**Table 1.2** Selected (nondrug-related) causes of acquired long QT syndrome.

Heart disease
- Coronary artery disease
- Heart failure
- Ventricular tachyarrhythmias
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Left ventricular hypertrophy
- Hypertension
- Bradycardia (SA nodal dysfunction, AV block)
- Myocarditis

Metabolic abnormalities
- Hypokalemia
- Hypocalcaemia
- Hypomagnesaemia

Liver disease
- Cirrhosis
- Hepatic failure

Renal disease

Endocrine disorder
- Hypothyroidism
- Hyperparathyroidism
- Pheochromocytoma
- Hyperaldosteronism

Intracranial pathology
- Subarachnoid hemorrhage
- Cerebrovascular accident
- Head injury
- Encephalitis

Diabetes mellitus

Anorexia nervosa/starvation

Bulemia

Obesity

Liquid protein diet

Human immunodeficiency virus (HIV) infection

Mechanisms of acquired QT prolongation and TdP **9**

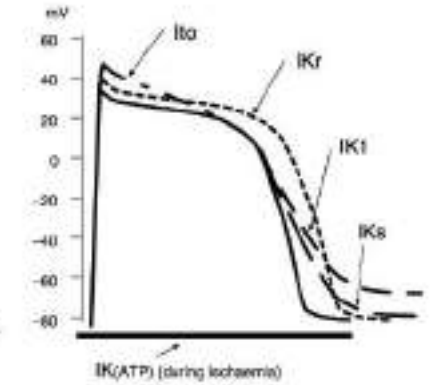



**Fig. 2.2** Alteration in action potential with individual blockade of some potassium channels.

## Endocrine Disorders

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Hypothyroidism | Yes | High | Yes | High |
| Hyperglycemia | Yes | Low | Weak | Very Low |
| Diabetes | Yes | Very Low | Weak | Very Low |
| Obesity (BMI >30, adiponectin) | Yes | Low | None | No evidence |
| Leptin | Yes | Low | None | No evidence |
| Decreased PI3 kinase (inc. INaL) | Yes | Low | None | No evidence |
| Primary Aldosteronism | Yes | Moderate | Yes | Moderate |
| Hypoglycemia | Yes | Low | Yes | Moderate |
| Hyperthyroidism | Yes | Low | Weak | Very Low |
| Panhypopituitarism | Yes | Moderate | Yes | High |
| Hyperparathyroidism | Yes | High | Weak | Very Low |
| Hypogonadism | Yes | Moderate | Yes | Moderate |
| Hypoparathyroidism | Yes | Moderate | Yes | Low |

## Electrolyte Disorders

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Hypokalemia (3.5 mEq/L) | Yes | High | Yes | High |
| Hypomagnesemia ( 1.7 mg/dL) | Yes | High | Yes | High |
| Hypocalcemia ( 8.5 mg/dL) | Yes | High | Yes | High |
| Diarrhea | Yes | Moderate | Weak | Very Low |
| Licorice (Excessive ingestion) | Yes | High | Yes | Moderate |
| Bartter Syndrome | Yes | Moderate | Weak | Very Low |
| Hemodialysis | Yes | Moderate | Weak | Moderate |
| Hypernatremia (extreme) | Yes | Low | Yes | Very Low |
| Apheresis/blood transfusion | Yes | High | Yes | Moderate |
| Gitelman Syndrome | Yes | High | None | No evidence |
| Hypoalbuminemia | Weak | Very Low | None | No evidence |

## Environmental Effects

| | | | | |
|---|---|---|---|---|
| Hypothermia | Yes | High | Yes | Moderate |
| Smoking | Weak | Low | None | No evidence |
| Alcohol (excess) | Yes | Low | None | Very Low |
| Herbals/Dietary Supplements | Yes | Moderate | Yes | Moderate |
| Hypoxia, COPD, sleep apnea | Yes | Moderate | None | Low |
| Lead exposure | Yes | Low | None | No evidence |
| Carbon Monoxide | Yes | High | None | No evidence |
| Electrolytes | Yes | Low | Yes | Low |
| Omega 3 PUFA deficiency | Weak | Very Low | None | No evidence |
| Organic Lead | Yes | High | Yes | Low |
| Synthetic Cannabinoids | Yes | High | None | No evidence |

## Miscellaneous

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Pre-eclampsia | Weak | Low | None | No evidence |
| Genotypic Assoc. | Yes | High | Yes | High |
| Ferritin/Iron overload | Yes | Moderate | Weak | Moderate |
| Propionic acidemia | Yes | High | None | No evidence |
| Epilepsy/Seizures | Yes | Moderate | None | No evidence |
| Uric Acid | Weak | Low | None | No evidence |
| Electrical Shock | Yes | Moderate | None | No evidence |
| Liquid Protein Diet | Yes | High | Yes | Moderate |
| Sickle Cell Disease | Yes | High | Weak | Very Low |
| Congenital Gen. Lipodystrophy (CTRP1) | Yes | Moderate | Weak | Very Low |
| Low density lipoprotein receptor-related protein 8 (LRP8) | None | Very Low | None | No evidence |
| Fatty Acid Binding Protein 4 | Weak | Moderate | None | No evidence |

## General Clinical

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Female Sex | Yes | High | Yes | High |
| Age 65 yr | Yes | High | Yes | Low |
| Renal failure (GFR 30 ml/min) | Yes | Low | Yes | Very Low |
| Liver failure (cirrhosis) | Yes | Moderate | None | No evidence |
| Pulmonary embolism | Yes | Moderate | None | No evidence |
| Thiamine deficiency | Yes | Low | None | No evidence |
| Vitamin D deficiency | Yes | Low | Yes | Moderate |

## Inflammation/Auto-immune

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Sepsis | Yes | Low | Yes | Moderate |
| Systemic Lupus Erythematosus | Yes | Moderate | None | No evidence |
| HIV | Yes | Moderate | None | No evidence |
| C-Reactive protein | Yes | Low | None | No evidence |
| Heat Shock Proteins | Yes | Low | None | No evidence |
| Cytokines (TNF, IL1, IL6) | Yes | Moderate | Weak | Low |
| Fever | Yes | Moderate | Yes | Low |
| Inflammation/Rheum. Arthritis | Yes | High | Yes | Moderate |
| Sarcoidosis | Yes | Low | Weak | Very Low |
| Anti-Ro/SSA Antibody | Yes | Low | Weak | Very Low |
| Multiple sclerosis | Yes | Low | None | No evidence |
| Celiac disase | Yes | High | None | No evidence |
| Psoriasis | Weak | Very Low | None | No evidence |
| Cardiac Allograft Rejection | Yes | Low | None | No evidence |
| Ankylosing Spondylitis | Yes | High | | No evidence |

## Cardiovascular Diseases

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Bradycardia, AV block, Pauses | Yes | High | Yes | High |
| Takotsubo (stress-related) Cardiomyopathy | Yes | High | Yes | High |
| Acute Myocardial Ischemia | Yes | Moderate | Yes | Low |
| Stroke | Yes | High | Yes | Low |
| Hypertension/LVH | Yes | Low | Weak | Very Low |
| Mitral Valve Prolapse | Yes | Moderate | Weak | Very Low |
| Cardiomyopathy/CHF | Yes | Moderate | Weak | Low |
| Atrial Fibrillation Conversion | Weak | Moderate | Yes | Moderate |
| Mitral valve stenosis | Yes | Moderate | None | No evidence |
| Hypertrophic Cardiomyopathy | Weak | Low | Weak | Low |
| Metabolic Syndrome | Yes | Moderate | None | No evidence |
| Aortic Stenosis | Yes | Moderate | Yes | Moderate |

## Autonomic Nervous System

| Clinical Factor | Clinical Association with Increased QT | Quality of Evidence for Assoc. with Increased QT (more info) | Clinical Association with TdP | Quality of Evidence for Assoc. with TdP |
|---|---|---|---|---|
| Pheochromocytoma | Yes | High | Yes | High |
| Alpha adrenergic stimulation | Yes | Moderate | Yes | Low |
| Emotion (Arousal) | Yes | Moderate | Yes | Moderate |
| Head-up tilt | Yes | High | None | No evidence |
| Pure Autonomic Failure | Yes | High | None | No evidence |
| Cold Water Immersion | Yes | Moderate | Yes | Moderate |
| Parkinson's disease | Yes | Moderate | None | No evidence |
| Esophageal ulcer | Weak | Low | None | No evidence |
| Migraine headache | Yes | Moderate | None | No evidence |
| Encephalitis (West Nile virus) | Weak | Moderate | None | No evidence |
| Endotracheal intubation | Yes | Moderate | None | No evidence |
| Sleep Deprivation | Yes | High | None | No evidence |

## EVALUACIÓN DEL RIESGO DE ARRITMIA VENTRICULAR DEBIDO AL USO DE HIDROXICLOROQUINA – AZITROMICINA PARA COVID- 19

| SCORE DE RIESGO TISDALE | |
|---|---|
| Factores de riesgo | Puntos |
| Edad ≥ 68 años | 1 |
| Sexo femenino | 1 |
| Diurético de asa | 1 |
| Potasio sérico ≤ 3.5mEq/L | 2 |
| QTc basal (admisión) ≥ 450ms | 2 |
| Infarto agudo de miocardio | 2 |
| Una droga que prolonga QT | 3 |
| Sepsis | 3 |
| Insuficiencia cardiaca (FEVI) | 3 |
| ≥ 2 drogas prolongan QT | 3 |
| TOTAL | |

| EVALUACION DEL QT | |
|---|---|
| FrC | = _____ lpm |
| QTm (medido) | = _____ ms |
| QTc (Bazett) | = _____ ms |
| QTc (Fridericia) <60 lpm | = _____ ms |
| QTc (Framingham) >100 lpm | = _____ ms |

| ESTRATIFICACION DEL RIESGO | |
|---|---|
| Riesgo bajo | ≤ 7 puntos |
| Riesgo moderado | 7 a 10 puntos |
| Riesgo alto | ≥ 11 puntos |

**RECOMENDACIONES**

a. (  )Evitar o suspender otros agentes no críticos que prolonguan QT.
b. (  )Evaluar la función renal y hepática.
c. (  )Evaluar potasio y magnesio séricos. Corregir y vigilar sus niveles séricos.
d. (  )Uso prudente de Diuréticos de asa y Tiazídicos.
e. (  ) Monitoreo del QTc con EKG seriado: Tomar ECG 2-3 horas después de la segunda dosis de hidroxicloroquina, y diariamente a partir de entonces.

AMERICAN COLLEGE of CARDIOLOGY

# Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19

Table 1. Risk Score For Drug-Associated QTc Prolongation[9]

| Risk Factors | Points |
|---|---|
| Age ≥68 y | 1 |
| Female sex | 1 |
| Loop diuretic | 1 |
| Serum K+ ≤3.5 mEq/L | 2 |
| Admission QTc ≥450 ms | 2 |
| Acute MI | 2 |
| ≥2 QTc-prolonging drugs | 3 |
| sepsis | 3 |
| Heart failure | 3 |
| One QTc-prolonging drug | 3 |
| Maximum Risk Score | 21 |

K+ indicates potassium; and MI, myocardial infarction.

Table 2. Risk Levels For Drug-Associated QT Prolongation[9]

| |
|---|
| Low risk = ≤6 points |
| Moderate risk = 7-10 points |
| High-risk = ≥11 points |

## Fármacos que pueden prolongar el intervalo QT y/o Torsades de Pointes ordenados por grupo terapéuticos

**DIGESTIVO**
Antidiarreicos
-Loperamida (C)

Antieméticos
-Domperidona (D)
-Metoclopramida (C)
-Ondansetrón (D)
-Palonosetrón (*)

Antiulcerosos
-Esomeprazol (C)
-Pantoprazol (C)
-Lansoprazol(C)
-Omeprazol (C)
-Pantoprazol (C)

**SANGRE**
Cilostazol (D)

**CARDIOVASCULAR**
Antiarrítmicos
-Amiodarona (D)
-Disopiramida (D)
-Dronedarona (D)
-Flecainida (D)
-Procainamida (D)
-Sotalol (D)
-Vernakalant (*)

Calcioantagonistas
-Nicardipino (P)

Diuréticos
-Furosemida (C)
-Hidroclorotiazida (C)
-Indapamida (C)
-Torasemida (C)

Otros
-Adenosina (*)
-dantrolfumetacida(C)
-Anfetamina(C)
-Ranolazina(C)

**ANTIINFECCIOSOS**
Macrólidos
-Azitromicina (D)
-Claritromicina (D)
-Eritromicina (D)

Antimicóticos
-Anfotericina B(C)
-Fluconazol (D)
-Itraconazol (C)
-Ketoconazol (C)

Antivirales
-Amantadina (C)
-Atazanavir (C)
-Darunavir (*)
-Efavirenz (P)
-Lopinavir (*)
-Ritonavir (P)
-Ritonavir (C)
-Saquinavir (P)

Quinolonas
-Ciprofloxacina (D)
-Levofloxacina (D)
-Moxifloxacina (D)
-Norfloxacina (P)
-Ofloxacina (P)

Otros
-Metronidazol (C)

**ANTINEOPLÁSICOS INMUNOMODULADORES**
-Anagrelida (D)
-Arsénico, trióxido de (D)
-Bendamustina (P)
-Bortezomib (P)
-Capecitabina (P)
-Crizotinib (P)
-Dabrafenib (P)
-Dasatinib (P)
-Degarelix (P)
-Eribulina, mesilato (P)
-Fingolimod (P)
-Lapatinib (P)
-Lenvatinib (P)
-Lisuride (P)
-Nilotinib (P)
-Oxaliplatino (D)
-Pazopanib (P)
-Sorafenib (P)
-Sunitinib (P)
-Tacrolimus (P)
-Tamoxifeno (P)
-Vandetanib (D)
-Vemurafenib (P)
-Vorinostat (*)

**HORMONAS**
Octreotid (P) Pasireotide (P)
-Terlipresina (D)

**SISTEMA NERVIOSO**
Anestésicos
-Propofol (D)
-Sevoflurano (D)
Antidepresivos, Ansiolíticos
-Domperidona (D)
-Galantamina (C)

Antidepresivos
-Agomelatina (*)
-Amitriptilina (C)
-Citalopram (D)
-Clomipramina (P)
-Doxepina (C)
-Escitalopram (D)
-Fluoxetina (C)
-Imipramina (P)
-Maprotilina (*)
-Mirtazapina (P)
-Nortriptilina (P)
-Paroxetina (C)
-Sertralina (C)
-Trazodona (C)
-Trimipramina (P)
-Venlafaxina (P)

Antipsicóticos
-Amisulprida (C)
-Aripiprazol (P)
-Asenapina (P)
-Clorpromazina (D)
-Clozapina (P)
-Droperidol (D)
-Flufenazina (*)
-Flupentixol (P)
-Haloperidol (D)
-Levomepromazina (D)
-Litio (P)
-Olanzapina (C)
-Paliperidona (P)
-Perfenazina (P)
-Pimozida (D)
-Quetiapina (C)
-Risperidona (P)
-Sertindol (P)
-Sulpirida (D)
-Tioridia (P)
-Ziprasidona (C)

Hipnóticos y sedantes
-Halotano (C)
-Promotazina (P)

Otros
-Apomorfina (P)
-Atomoxetina (P)
-Bupropiona (P)
-Desvenlafaxina (P)
-Metadona (D)
-Tetrabenazina (P)
-Ketigulida (P)

**ANTIPARASITARIOS**
-Pentamidina (D)
-Artemisin piperaquina (P)
-Cloroquina (D)
-Hidroxicloroquina (C)

**RESPIRATORIO**
-Antihistamínicos
-Desloratadina (*)
-Difenhidramina (C)
-Mizolina (*)
-Mizolastina (*)
-Mequitazina (*)
-Acetastina (*)

Broncodilatadores agonistas beta-2 inhalados
-Formoterol (**)
-Indacaterol (**)
-Salbutamol (**)
-Salmeterol (**)
-Terbutalina (**)

Broncodilatadores agonistas beta-2 sistémicos
-Ritodrina (*)

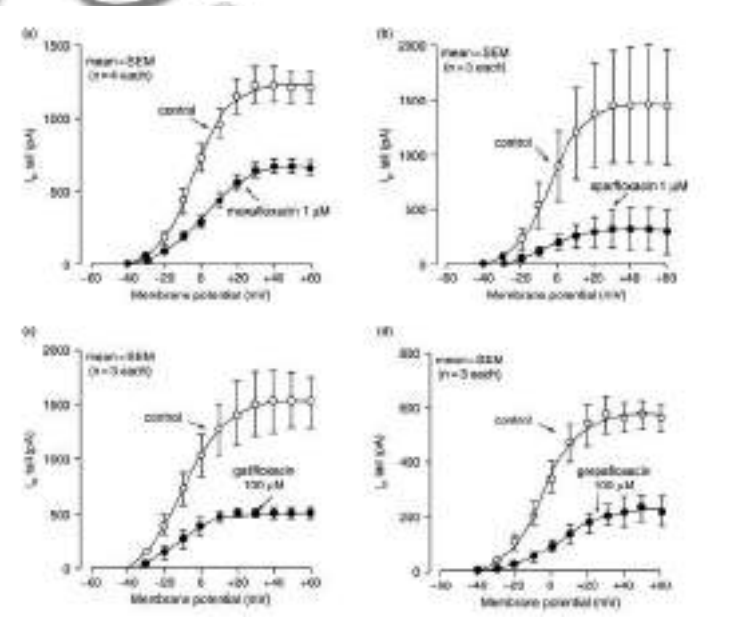
**MEDIOS DE CONTRASTE**
-Gadobutrol (*)
-Lantano (*)

**MUSCULOESQUELÉTICO**
-Tizanidina (P)

**GENITOURINARIO**
-Alfuzosina (P)
-Fesoterodina (*)
-Mifepristona (P)
-Mirabegron (P)
-Solifenacina (C)
-Sildenafilo (*)
-Tadalafilo (*)
-Tolterodina (P)
-Tiospio (*)
-Vardenafilo (P)

| CLASIFICACIÓN | CARACTERÍSTICAS |
|---|---|
| **Clase A**<br>(Potencia torsadogénica alta) | - Potentes bloqueantes de las corrientes de repolarización<br>- Prolongación documentada de **APD** e inducción de **EAD**<br>- Prolongación de intervalo QT documentada y casos de TdP a dosis terapéuticas en ausencia de coadministración de drogas que prolonguen el QT o factores de riesgo<br>- La IC50 para la prolongación de la repolarización está en el mismo rango que la IC50 de la dosis terapéutica |
| **Clase B**<br>(Potencia torsadogénica media) | - Drogas que prolongan la repolarización miocárdica a altas dosis, o a dosis normales con la coadministración de drogas que inhiben la metabolización de la droga<br>- La IC50 para la prolongación de la repolarización está por encima de la IC50 de la dosis terapéutica<br>- Documentación de casos de TdP inducida por la droga sola pero la TdP es generalmente asociada a inhibición metabólica y/o a presencia de factores de riesgo |
| **Clase C**<br>(Potencia torsadogénica baja) | - Drogas que prolongan APD y el intervalo QT a altas dosis/concentraciones por arriba del rango terapéutico<br>- El efecto de la repolarización se manifiesta sólo durante la sobredosis, intoxicación o la presencia de inhibición metabólica severa<br>- Documentación de casos de TdP en presencia de factores de riesgo |
| **Clase D**<br>(Potencia torsadogénica indeterminada) | - Drogas que bloquean la repolarización de las corrientes iónicas in vitro pero que hasta el momento no han evidenciado la prolongación en otros modelos in vitro o la concentración necesaria para este efecto es muy por encima de las concentraciones clínicas.<br>- La prolongación del intervalo QT no ha sido demostrada en estudios sistemáticos randomizados.<br>- Casos de TdP en asociación con tratamientos con la droga pueden haber sido documentados pero la relación causal entre el evento y la droga no es clara. |

Figura 7. Clasificación de la potencia torsadogénica de drogas proarrítmicas




| Antiarrhythmics | Antidepressants | Antipsychotics | Antibiotics | Antihistamines | Others |
|---|---|---|---|---|---|
| Disopyramide | Amitriptyline | Haloperidol | | Loratadine | Methadone |
| Procainamide | Desipramine | Phenothiazines | Pentamidine | Astemizole | Probucol |
| Quinidine | Imipramine | Citalopram | Azithromycin | Diphenhydramine | Droperidol |
| Dofetilide | Doxepin | Tricyclic | Chloroquine | Hidroxyzine | Ondasentron |
| Dronedarone | Fluoxetine | | Ciprofloxacin | | |
| Ibutilide | Sertraline | | | | |
| Sotalol | Venlafaxine | | Levofloxacin | | |
| Amiodarone | | | Moxifloxacin | | |
| | | | Clarithromycin | | |
| | | | Itraconazole | | |
| | | | Ketoconazole | | |

**Table 4.2** Classification of torsadogenic potency of drugs (adapted from [6]).

| *Classification* | *Features* |
|---|---|
| Class A (High torsadogenic potency) | • Potent blockers of repolarization currents<br>• Documented prolongation of APD & induction of EAD<br>• Documented QT prolongation and cases of TdP at therapeutic doses/concentration by the drug alone in the absence of coadministration of QT-prolonging drugs or risk factors<br>• The $IC_{50}$ for the prolongation of repolarization is in the same range as the $IC_{50}$ for the therapeutic action |
| Class B (Medium torsadogenic potency) | • Drugs that prolong myocardial repolarization (i.e., APD and QT interval) at higher doses, or at normal doses with coadministration of drugs that inhibit drug metabolism (e.g., by inhibiting the cytochrome P450 system)<br>• The $IC_{50}$ for the prolongation of repolarization is above the $IC_{50}$ for the therapeutic action<br>• Cases of TdP induced by the drug alone have been documented but TdP is usually associated with metabolic inhibition and/or the presence of other risk factors |
| Class C (Low torsadogenic potency) | • Drugs that prolong APD and QT interval at high doses/concentration clearly above therapeutic range<br>• The effect of repolarization manifests only during overdose, intoxication or in the presence of severe metabolic inhibition<br>• Cases of TdP have been documented but in the presence of risk factors |
| Class D (Torsadogenic potential unclear) | • Drugs that block repolarizing ion currents *in vitro* but which have so far not been shown to prolong repolarization in other *in vitro* models (e.g., papillary muscle fibers or isolated hearts) or the concentrations necessary for this effect were far above the clinical concentrations<br>• Prolongation of the human QT interval has not been demonstrated in systematic randomized studies |

**Table 4.3** (*Continued*)

| *Class of drugs* | *Drugs* | *Torsadogenic risk* |
|---|---|---|
| $5HT_3$ serotonin antagonist | Ketanserin (TdP reported, withdrawn in the US & UK) | A |
| Dopamine-receptor antagonist | Domperidone (intravenous) | A |
| Immunosuppressant | Tacrolimus (TdP reported) | A |
| Antidiuretic hormone | Vasopressin (TdP reported) | B |
| Other agents | Adenosine (TdP reported) | D |
| | Organophosphates (TdP reported) | C |
| | Papaverine (intracoronary) (TdP reported) | A |
| | Probucol (TdP reported) | B |
| | Cocaine | C |
| | Arsenic trioxide (TdP reported) | A |

**Table 4.3** Drugs that can prolong QT interval and/or induce TdP

| *Class of drugs* | *Drugs* | *Torsadogenic risk* |
|---|---|---|
| Antiarrhythmic drugs | Type 1A (TdP reported in all) | |
| | Ajmaline (TdP reported) | A |
| | Disopyramide (TdP reported) | A |
| | Procainamide (TdP reported) | A |
| | Quinidine (TdP reported) | A |
| | Type 1C (increase QT by prolonging QRS interval) | |
| | Encainide | D |
| | Flecainide | D |
| | Moracizine | D |
| | Propafenone | D |
| | Type 3 (TdP reported in all) | |
| | Amiodarone | B |
| | Dronedarone | D |
| | d/l-Sotalol | A |
| | d-Sotalol | A |
| | Bretylium | A |
| | Azimilide | A |
| | Dofetilide | A |
| | Ersentilide | D |
| | Ibutilide | A |
| | Trecetilide | D |
| | Tedisamil | A |
| | Almokalant | A |
| Calcium channel blocker | Prenylamine (TdP reported, withdrawn) | A |
| | Bepridil (TdP reported, withdrawn) | A |
| | Mibefradil | A |
| | Terodiline (TdP reported, withdrawn) | A |

**Table 4.3** (*Continued*)

| *Class of drugs* | *Drugs* | *Torsadogenic risk* |
|---|---|---|
| Psychiatric drugs | Chlorpromazine (TdP reported) | C |
| | Thioridazine (TdP reported) | A |
| | Droperidol (TdP reported) | A |
| | Haloperidol (TdP reported) | A |
| | Amitriptyline | B |
| | Nortriptyline | B |
| | Clomipramine | B |
| | Desipramine (TdP reported) | B |
| | Imipramine (TdP reported) | B |
| | Maprotiline (TdP reported) | A |
| | Chloral hydrate | C |
| | Doxepin (TdP reported) | B |
| | Lithium (TdP reported) | D |
| | Pimozide (TdP reported) | A |
| | Sertindole (TdP reported) | A |
| | Ziprasidone | C/D |
| Antihistamines | Astemizole (TdP reported) | A |
| | Terfenadine (TdP reported) | A |
| | Diphenhydramine | D |
| | Ebastine | C/D |
| | Mizolastine | C |
| Antimicrobial and antimalarial drugs | Clarithromycin (TdP reported) | A |
| | Erythromycin, intravenous (TdP reported) | A |
| | Roxithromycin (TdP reported) | B |
| | Josamycin | D |
| | Erythromycylamine | D |
| | Oleandomycin | D |
| | Fluconazole (TdP reported) | B |
| | Itraconazole (TdP reported when used with other QT prolonging drugs) | B |
| | Ketoconazole | B |
| | Miconazolea | B |
| | Grepafloxacin (TdP reported, withdrawn worldwide) | A |
| | Sparfloxacin (TdP reported) | A |
| | Levofloxacin (TdP reported) | B |
| | Moxifloxacin (TdP reported) | D |
| | Gatifloxacin (TdP reported) | D |
| | [illegible] | D |
| | Chloroquine (TdP reported) | D |
| | [illegible] | A |
| | Quinine (TdP reported) | A |
| | Pentamidine (TdP reported) | A |
| | Pentavalent antimonial meglumine (TdP reported) | A |
| Prokinetics (serotonin agonists) | Cisapride (TdP reported, withdrawn in the US & UK | A |

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**Table 4.3** Drugs that can prolong QT interval and/or induce TdP

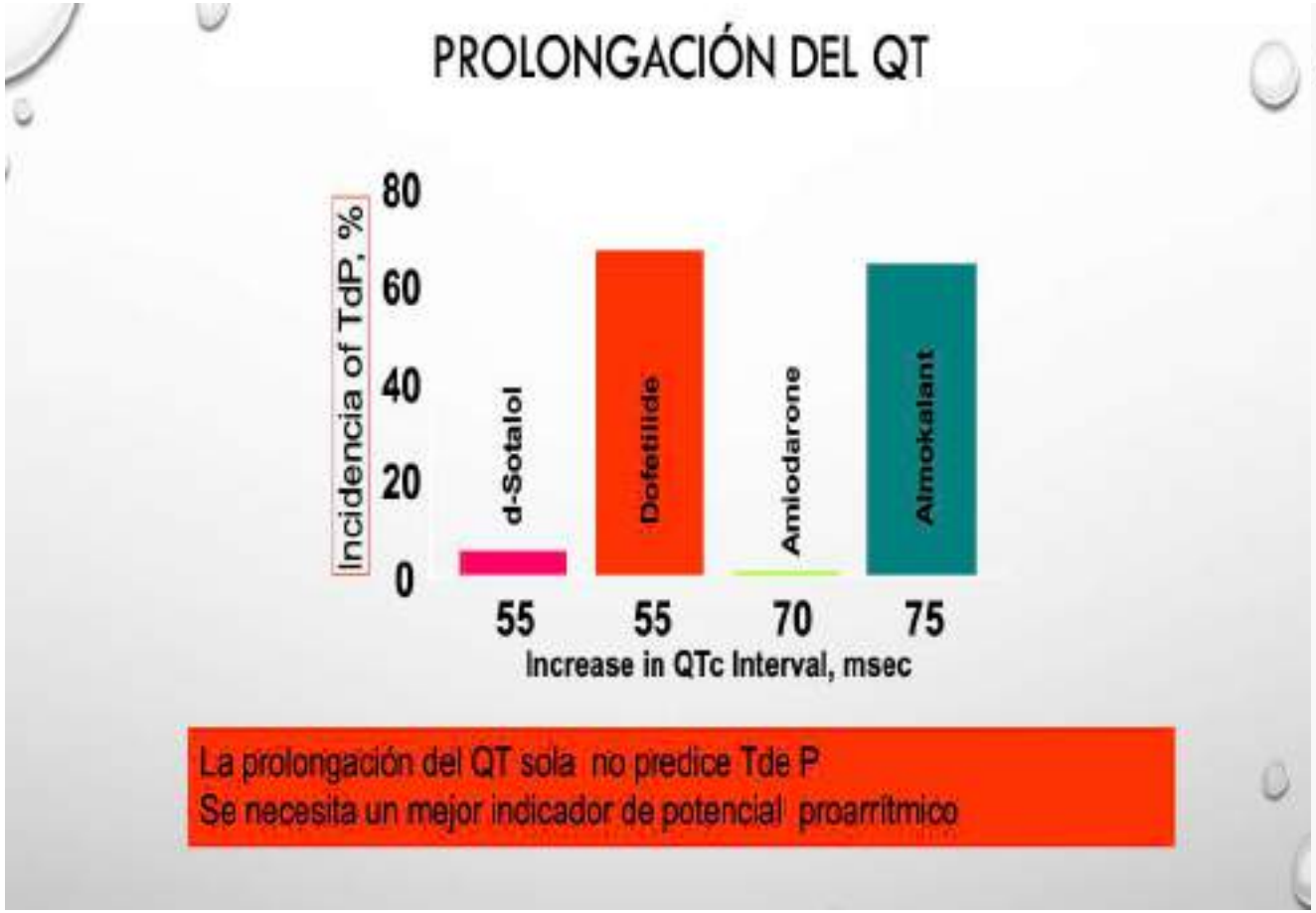
| *Class of drugs* | *Drugs* | *Torsadogenic risk* |
|---|---|---|
| Antiarrhythmic drugs | Type 1A (TdP reported in all) | |
| | Ajmaline (TdP reported) | A |
| | Disopyramide (TdP reported) | A |
| | Procainamide (TdP reported) | A |
| | Quinidine (TdP reported) | A |
| | Type 1C (increase QT by prolonging QRS interval) | |
| | Encainide | D |
| | Flecainide | D |
| | Moracizine | D |
| | Propafenone | D |
| | Type 3 (TdP reported in all) | |
| | Amiodarone | B |
| | Dronedarone | D |
| | d/l-Sotalol | A |
| | d-Sotalol | A |
| | Bretylium | A |
| | Azimilide | A |
| | Dofetilide | A |
| | Ersentilide | D |
| | Ibutilide | A |
| | Trecetilide | D |
| | Tedisamil | A |
| | Almokalant | A |
| Calcium channel blocker | Prenylamine (TdP reported, withdrawn) | A |
| | Bepridil (TdP reported, withdrawn) | A |
| | Mibefradil | A |
| | Terodiline (TdP reported, withdrawn) | A |

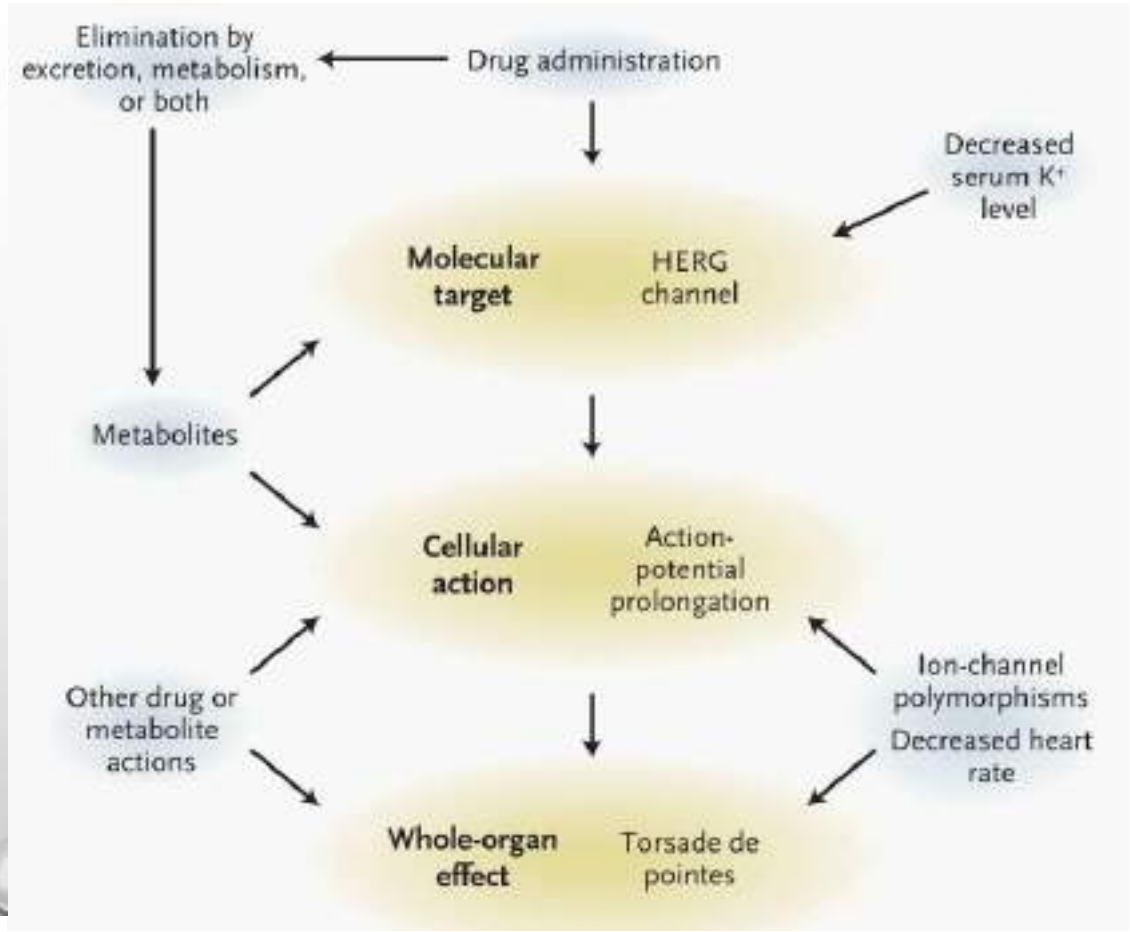
**Table 15** Arrhythmological considerations of novel experimental pharmacological therapies in COVID-19 infection

| | HR | AV CONDUCTION | QRS INTERVAL | QTC INTERVAL | TDP RISK | AAD DRUGS INTERACTIONS[a] | COMMENTS |
|---|---|---|---|---|---|---|---|
| **CHLOROQUINE** | Mild ↑ | Mild ↑ $\Delta_{vs}$: 14.8 ms[116] | Mild ↑ $\Delta_{vs}$: 9.9 ms[116] | Moderate ↑ $\Delta_{QTc}$: 29–50 ms[117,118]<br>↑ $\Delta_{QTc}$ in 14.2% of pts[119] | Very low risk of TdP<br>173 cases of VF/VT/TdP/LQTS in FAERS registry‡ | **SEVERE**[b]<br>Amiodarone, Flecainide, Hexbrenin, Sotalol, Dofetilide<br>**MODERATE**[c]<br>Disopyramide, Propafenone, Quinidine, Digoxin<br>**MILD**[c]<br>Verapamil, Nebivolol, Propranolol, Timolol, Verapamil | - Very low risk of cardiotoxicity during chronic therapy is reported[120,121]<br>- In a study in SLE it was negatively associated with AVB ($P = 0.01$) as was its longer use (6.1 ± 6.9 vs. 1.0 ± 2.5 years, $P = 0.018$)[122,123]<br>- Proarrhythmia occurs mostly with overdosage or in chronic therapy (> years)[124]<br>- Proarrhythmic effect is common<br>- Risk of retinopathy and neuropathy during chronic therapy is reported |
| **HYDROXY-CHLOROQUINE** | Mild ↓ [120,121,125] | Mild ↑ | Mild ↑ | Moderate ↑<br>$\Delta_{QTc}$: 25 ms [120,125] | Very low risk of TdP<br>222 cases of VF/VT/TdP/LQTS in FAERS registry‡ | See Chloroquine | - Very low risk of cardiotoxicity during chronic therapy is reported[120,121]<br>- Proarrhythmia occurs mostly with overdosage or in chronic therapy (> years)[124]<br>- Less cardiotoxicity reported than with Chloroquine[125]<br>- In a study of pregnant women with Ro/La antibodies, AVBs were more frequent in those not using hydroxychloroquine[126] |
| **AZITHROMYCINE** | Mild ↓ [126] | Mild ↑ [126] | Mild ↑ [126] | Moderate-Severe ↑<br>$\Delta_{QTc}$: 5–32 ms[126,127] | Low risk of TdP<br>Considered relative SCD: +643/1 million[128]<br>ROR for TdP: +4.76 compared to other medication: 0.81/1995[129]<br>RR for SCD or VT: 3.40 compared to no exposure to no macrolide use [130,131,132] | **SEVERE**[b]<br>Amiodarone, Dronedarone, Dofetilide, Flecainide, Propafenone, Sotalol<br>**MODERATE**[c]<br>Betaxolol, Digoxin | In a study during treatment days 1 to 5, patients receiving azithromycin had significantly increased risk of serious arrhythmia (HR = 1.77, 95% CI: 1.20–2.62) compared with patients receiving amoxicillin[133,134] |
| **LOPINAVIR/ RITONAVIR** | NR | Moderate ↑<br>$\Delta_{vs}$: 31.5 ms[135] | Mild ↑<br>$\Delta_{vs}$: 7 ms[135] | Moderate ↑<br>$\Delta_{QTc}$: 20 ms[136] | Low risk of TdP<br>27 cases of VF/VT/TdP/LQTS in FAERS registry‡<br>HR for TdP: 1.82 (0.36–9.1)[137] | **SEVERE**[b]<br>Amiodarone, Dronedarone, Disopyramide, Dofetilide, Flecainide, Sotalol<br>**MODERATE**[c]<br>Lidocaine, Mexiletine, Propafenone, Quinidine, Digoxin, All Beta-blockers, $Ca^{2+}$ blockers | Cases of AV blockers reported |
| **TOCILIZUMAB** | No ECG changes described[138] | | | | Unknown | **MILD**[c]<br>Amiodarone, Quinidine | |
| **FINGOLIMOD/ SIPONIMOD** | Moderate-Severe ↓<br>$\Delta_{vs}$: -23 bpm[139] | Mild-moderate ↑ | Unknown | Mild ↑ | Unknown | **MODERATE**[c]<br>Beta-blockers, $Ca2+$ Blockers, Ivabradine, Amiodarone, Flecainide, Propafenone | Reported risk of runs, tachycardia and benign bradycardia and AV conduction abnormalities[140]:<br>- In a study of 769 patients, 89 patients (1.8%) developed bradycardia (<45 bpm), 62 patients (1.4%) had second-degree Mobitz I and/or 2:1 AV block[141]<br>- In study of 5513 patients new-onset first-degree AVB was experienced by 132 (2.4%) on fingolimod and 74 (2.5%) on other patients, and atrioventricular Mobitz type II second-degree AVB by four (0.07%) and nine (0.1%) patients, with no cases of third-degree AVB[142]<br>- In study of 66 patients with MS fingolimod led to an increase of vagal activation which persisted even after 14 months of treatment[143] |
| **REMDESIVIR** | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown | Very limited preclinical data on heart safety[144] |
| **INTERFERON ALFACON-1** | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown | Limited data: cases of hypotension, arrhythmia, and cardiomyopathy reported |
| **RIBAVIRIN** | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown | No cardiac side effect |
| **METILPRED-NISOLONE** | Unknown | Unknown | Unknown | Unknown | Unknown | Unknown | - May cause electrolyte disturbance<br>- High dose intravenous prednisolone might cause acute renal tubulopathy[145] or in MS patients since fingolimod, teriflunomide, and newly AE and VE[146] |

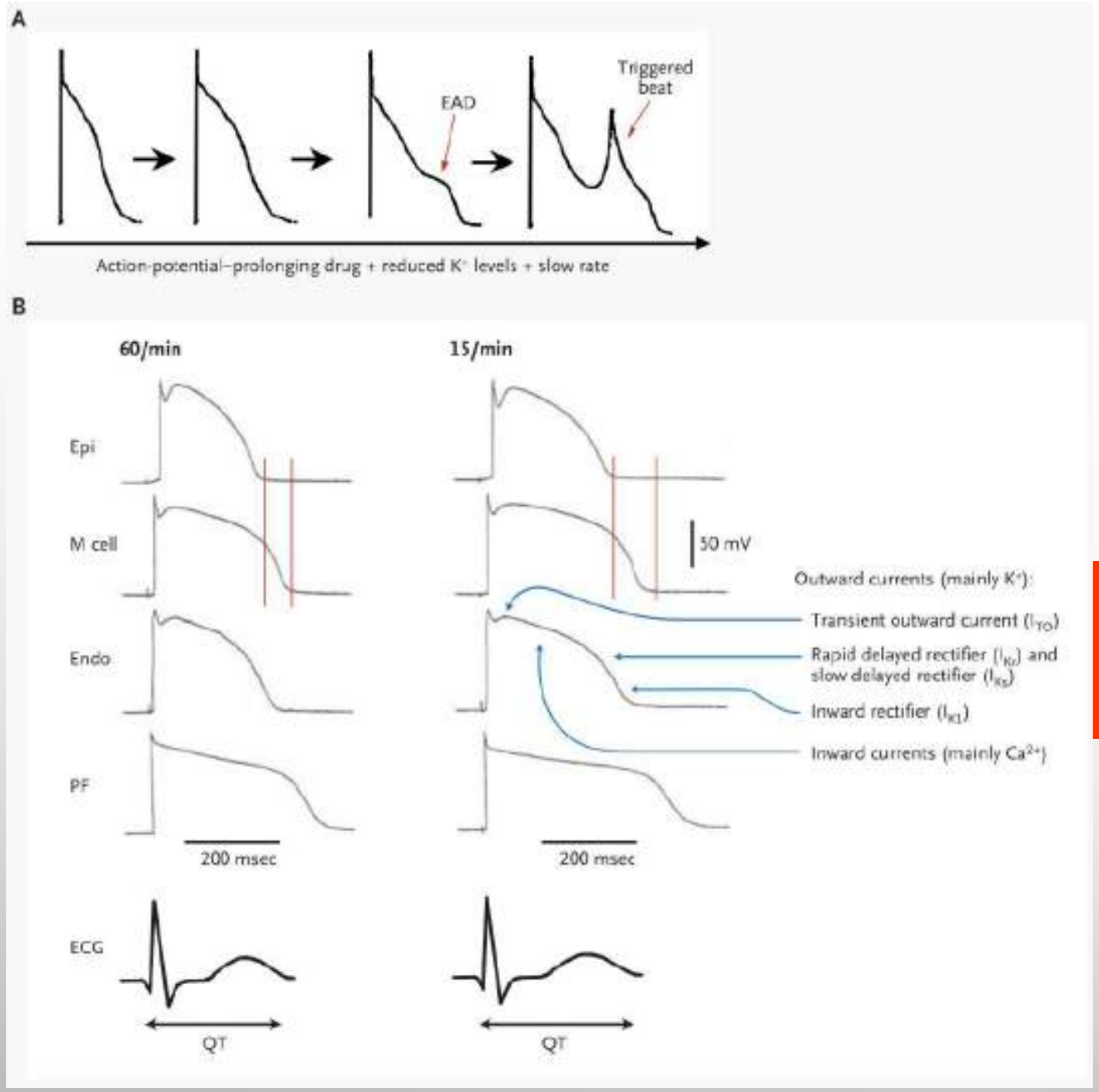
AAD = drug interactions.
[a]These drugs should not be co-administered.
[b]Potential interaction (need dose adjustment/close monitoring).
[c]Weak interaction (need dose adjustment/close monitoring/safety scale required).

AAD = antiarrhythmic drugs; AF = Atrial fibrillation; AVB = atrioventricular; AVB = AV block; CI = Confidence interval; FAERS = FDA Adverse Event Reporting System; HR = Hazard ratio; HR = Hazard ratio; LQTS = Long QT Syndrome; MS = Multiple Sclerosis; NR = Not reported; OR = Odds ratio; ROR = Reporting Odds Ratio; RR = Risk ratio; SCD = Sudden cardiac death; SLE = Systemic Lupus erythematosus; TdP = Torsade de Pointes; VF = Ventricular fibrillation; VT = Ventricular tachycardia.



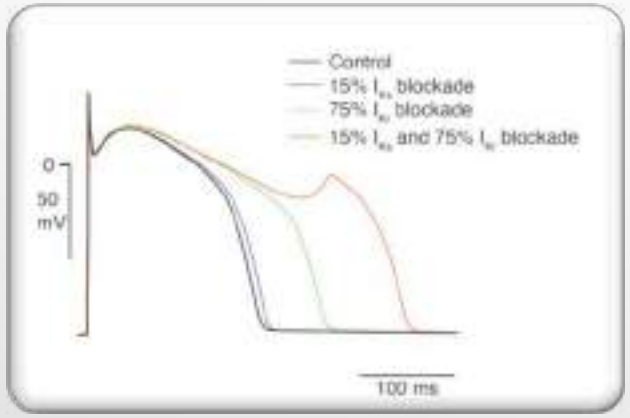



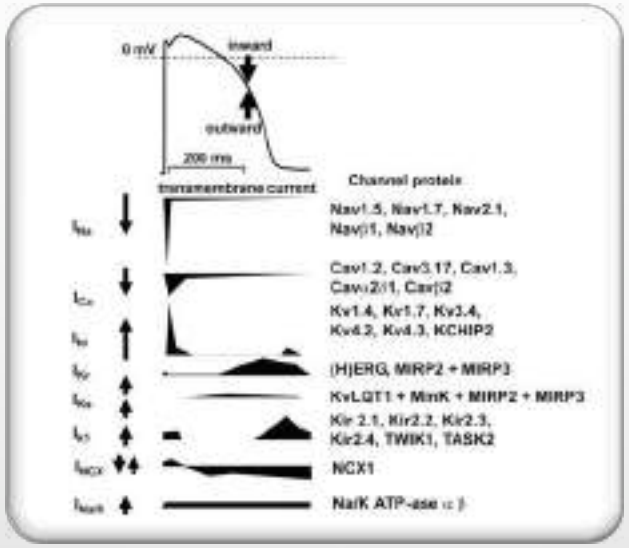

•**Todas las drogas que bloquean el HERG producen prolongación del QT pero no todas producen torsades de pointes**




- **Todas las drogas que bloquean el HERG producen prolongación del QT**
- **pero no todas producen torsades de pointes**

¿Porque pocos pacientes mueren súbitamente cuándo se bloquea el HERG?




# RESERVA DE REPOLARIZACIÓN

Otras corrientes iónicas

REVIEW

# Cardiac ventricular repolarization reserve: a principle for understanding drug-related proarrhythmic risk

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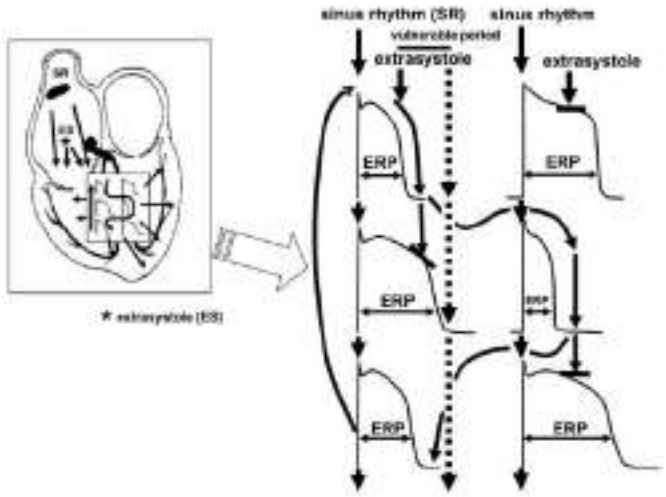
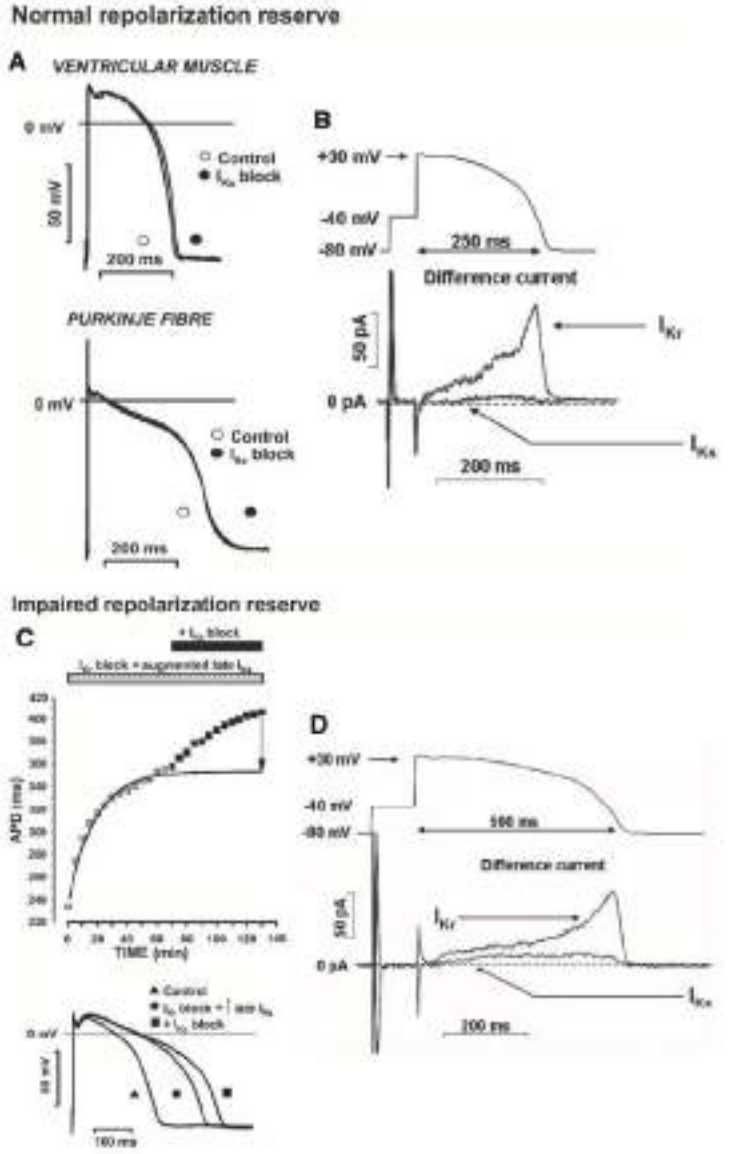
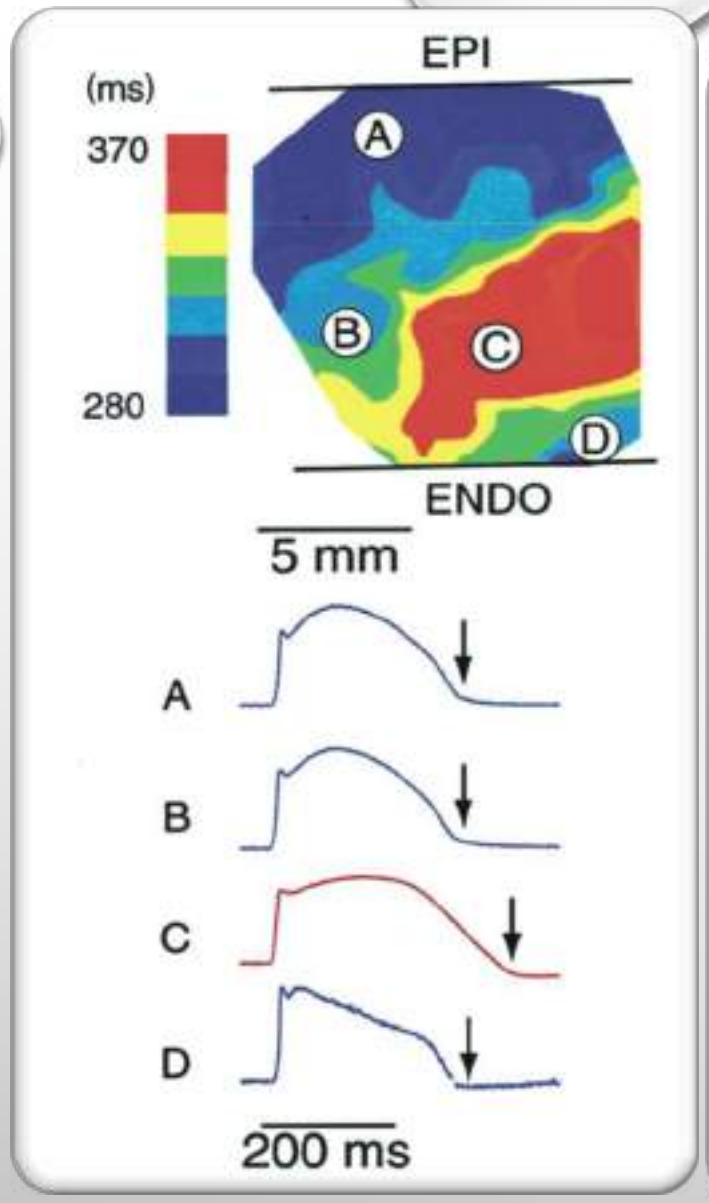
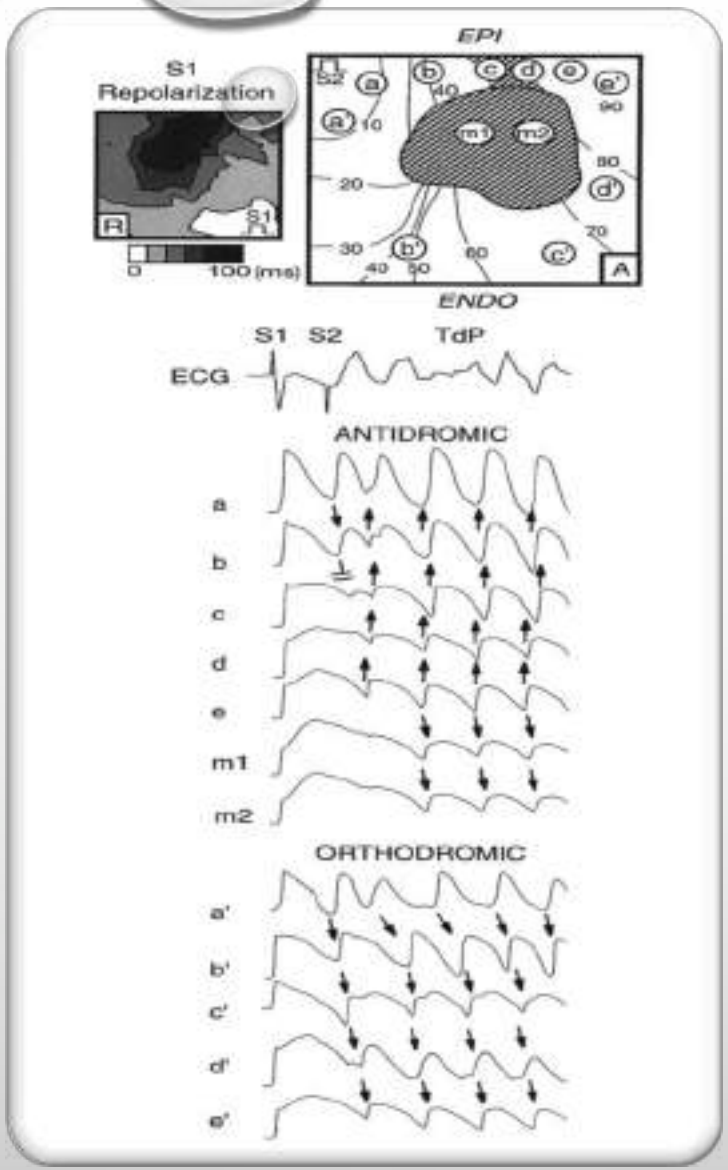





# HETEROGENEIDAD TRANSMURAL DE LA DURACIÓN DEL POTENCIAL DE ACCIÓN

## AMIODARONA??

As mentioned previously, decreasing repolarization reserve by drugs can have detrimental consequences by increasing the risk of proarrhythmia. As such, decreasing repolarization reserve represents an important adverse side effect of drug treatment. In addition, it must be emphasized that drugs which block multiple potassium channels without decreasing inward currents such as $I_{Na}$ or $I_{Ca}$ are expected to have higher proarrhythmic risk than selective potassium channel inhibi- tors because they tend to further depress repolarization reserve (Kodama *et al*., 1999; Biliczki *et al*., 2002). Therapeu- tically, it would be useful to enhance repolarization reserve and thereby attenuate the proarrhythmic risk caused by repo- larization abnormalities.
Inhibition of inward sodium and calcium currents may represent pharmacological interventions that may have indi- rect beneficial effects on repolarization reserve. Amiodarone, a drug that inhibits both $I_{Na}$ and $I_{Ca}$, is one of the best examples illustrating beneficial actions on repolarization. Amiodarone lengthens repolarization substantially but its proarrhythmic effect is much less than that of class III anti-arrhythmics which lengthen APD by inhibiting outward potassium currents only.

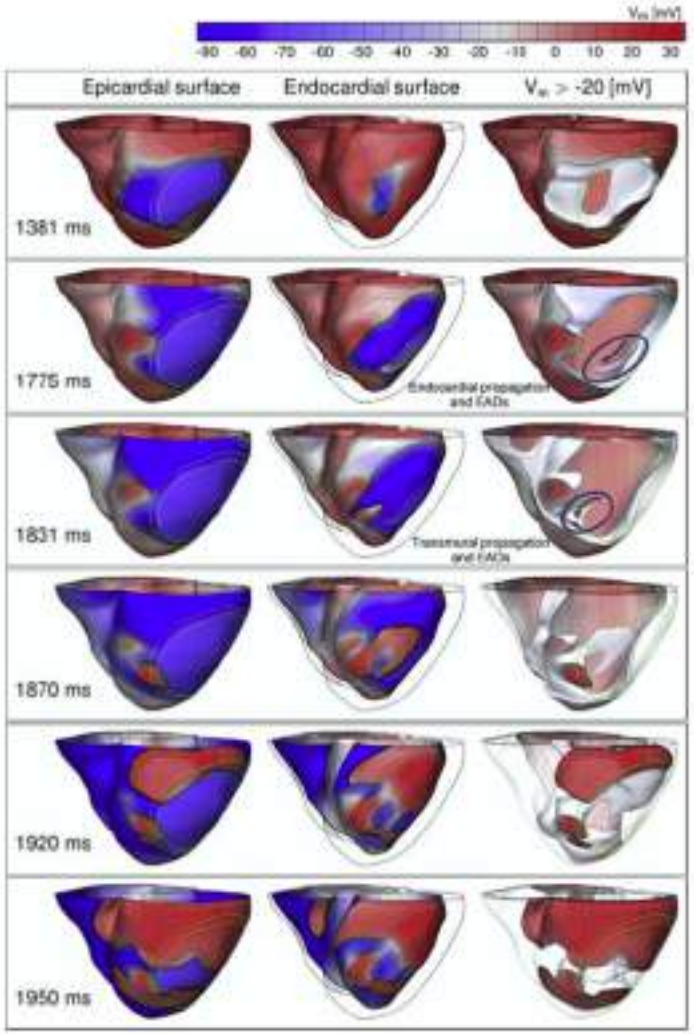
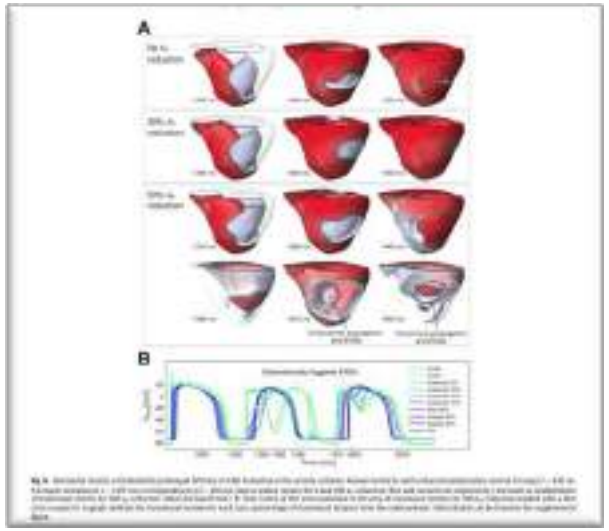
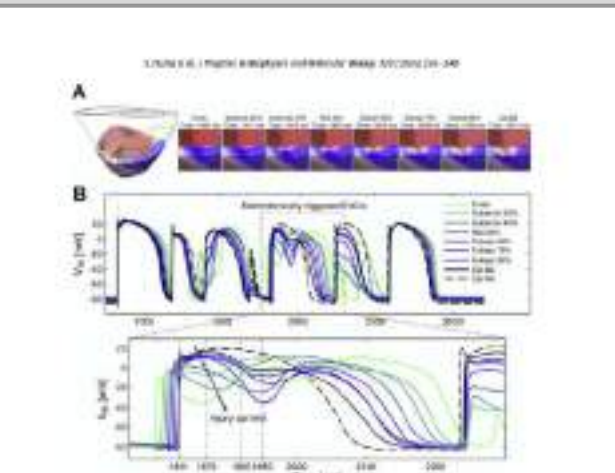
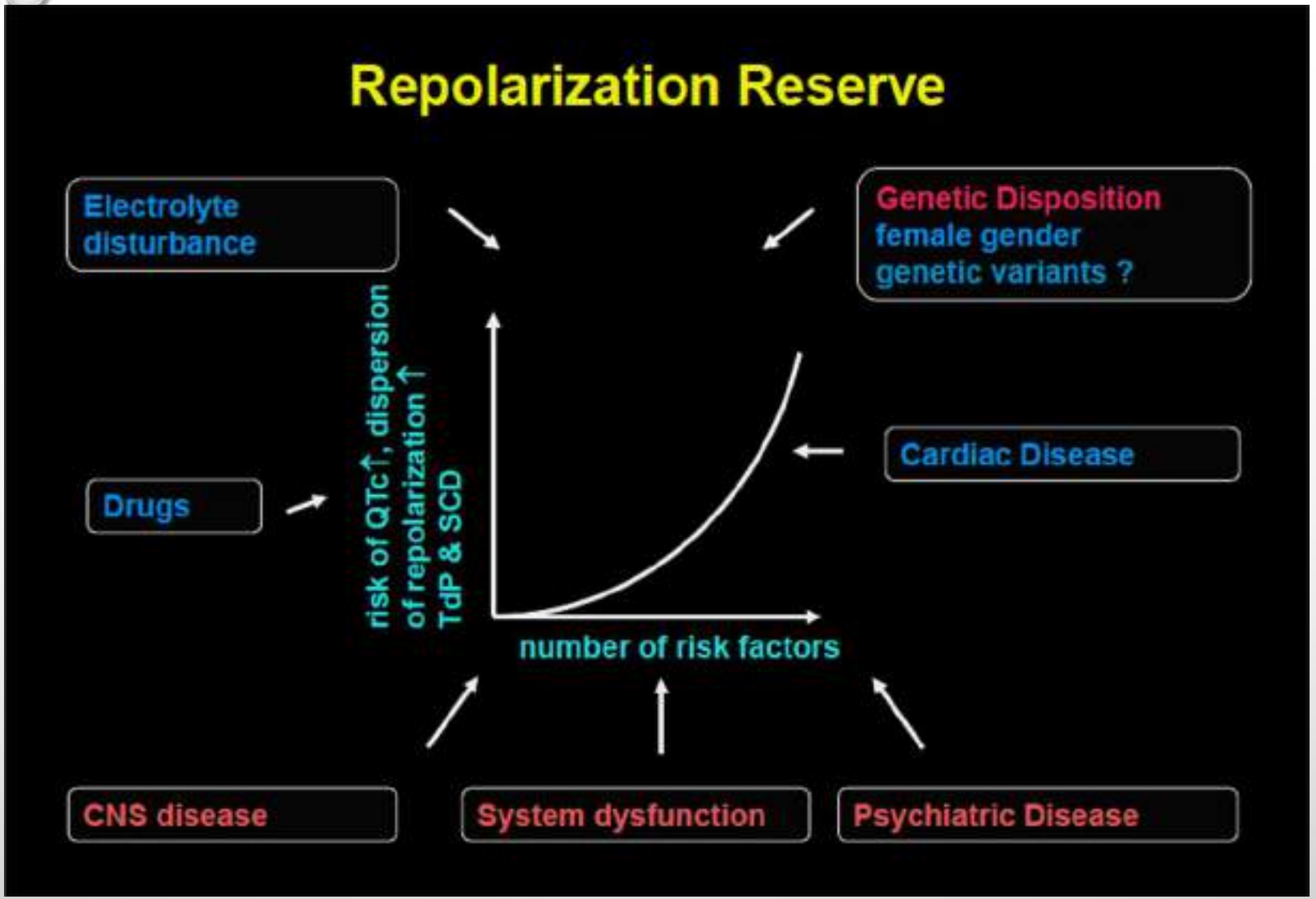



**Fig. 4.** Distribution of transmembrane voltage ($V_m$) throughout the ventricles at different times following ectopic excitation resulting initially in macro-reentry, but failure to support retrograde propagation (1381 ms), followed by propagation through the endocardial BZ (1775 ms) and transmurally (1831 ms), leads to intramural reentry (1831–1950 ms). For each time instant, three different views are shown, from left to right: the epicardium, the endocardium and the depolarized tissue with $V_m$ above −20 mV (cells with $V_m$ < −20 mV are transparent). Isopotential lines are shown in grey linking same potential levels. More details can be found in the supplemental movies.




Repolarization Reserve
Electrolyte disturbance
Genetic Disposition
female gender
genetic variants ?
Drugs
risk of QTc↑, dispersion of repolarization ↑ TdP & SCD
Cardiac Disease
number of risk factors
CNS disease
System dysfunction
Psychiatric Disease

**Bloqueo de los canales Ikr**

De la corriente Intracelular de K

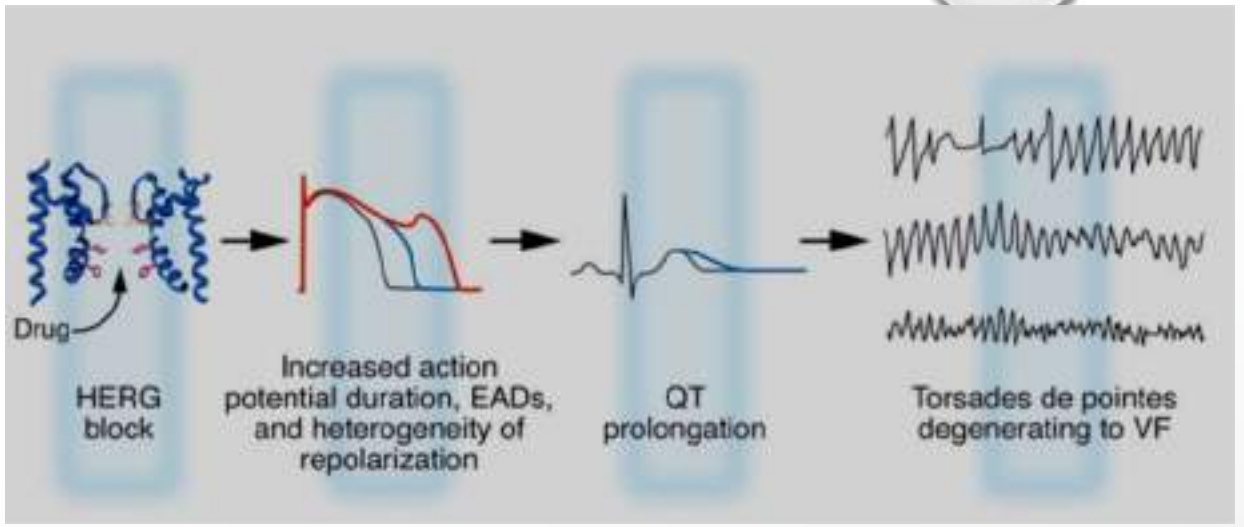
Post despolarizaciones precoces

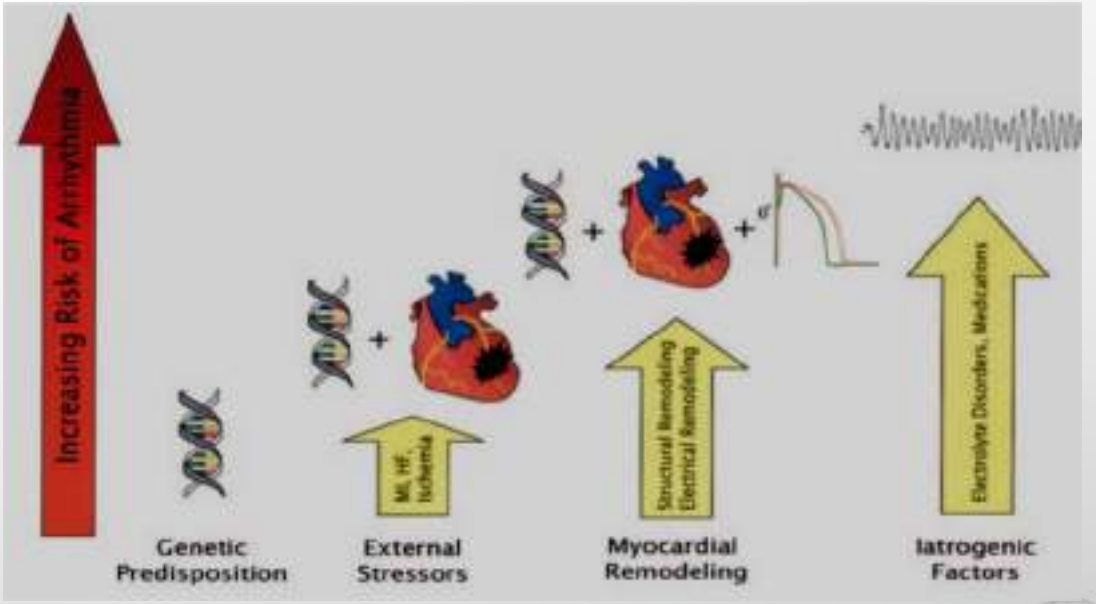
Actividad gatillada

Duración del potencial de acción en pukinje y celulas M

Dispersión de la repolarización

BLOQUEO UNIDIRECCIONAL Y REENTRADA INTRAMURAL



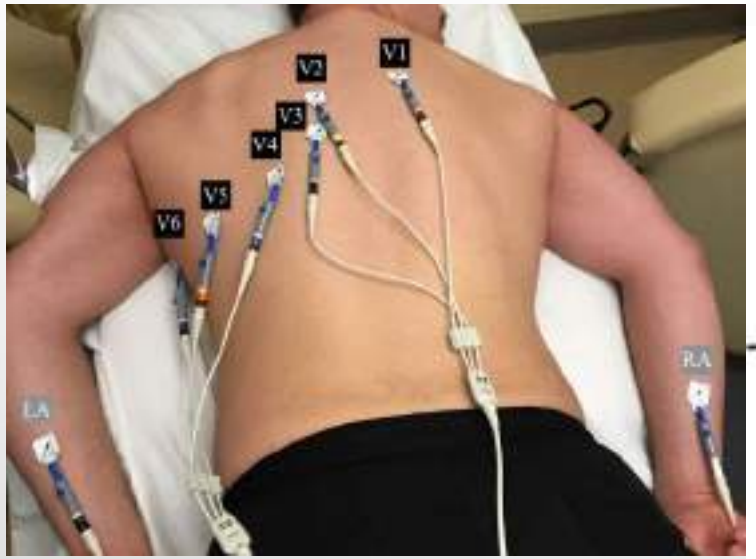
## CUÁNDO Y CÓMO se mide el QT?

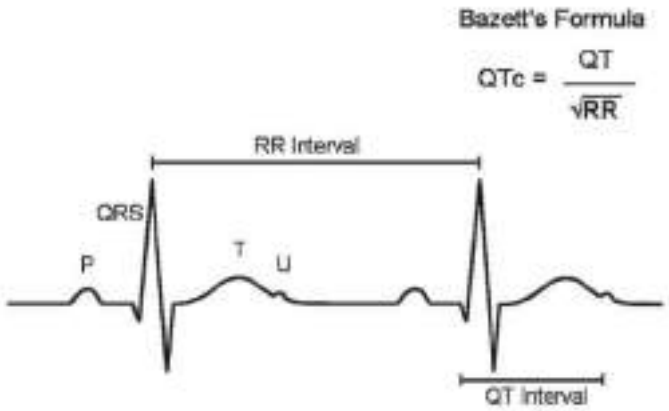
1. SIEMPRE QUE UTILICEMOS ESTAS DROGAS.
2. DII largo a su ingreso y diariamente.
3. con medio interno corregido: potasio (> 4 mEq/L) y magnesio(> 2 mEq/L).
4. En presencia de condiciones generales arritmogénicas como la hipoxia, hipovolemia, isquemia miocárdica, acidosis, hipotermia, hipopotasemia, hipomagnesemia, hipocalcemia o asociación de drogas que prolonguen el QT.

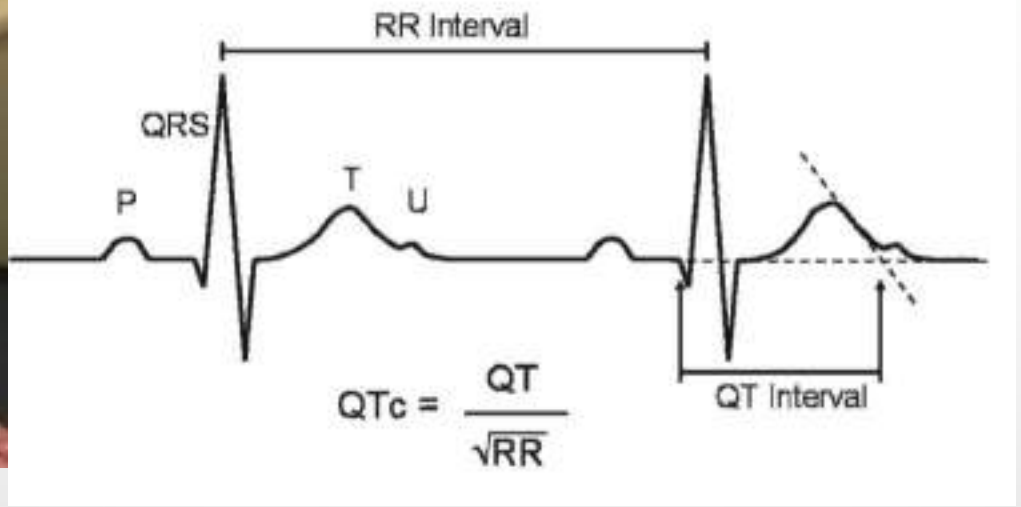
| Formula | Mathematical formula | Comments |
|---|---|---|
| Bazett [28] | $QT/RR^{0.5}$ | Most commonly used but inaccurate at extreme of heart rates |
| Fridericia [29] | $QT/RR^{0.333}$ | |
| Mayerde [30] | $QT/RR^{0.404}$ | Adult cohort without heart disease |
| Karvetski [31] | $QT/RR^{0.354}$ | |
| Yoshinaga [32] | $QT/RR^{0.33}$ | Children |
| Boudoulas [33] | $QT/RR^{0.366}$ | Patients undergoing minimally stressful diagnostic tests |
| Ashman [34] | $QT/\log 10(RR + 0.07)$ | Children (0–14 year) included. A reference RR of 930 ms used |
| Adams [35] | $QT - 0.1464(1-RR)$ (all subject)<br>$QT - 0.1536(1-RR)$ (male)<br>$QT - 0.1259(1-RR)$ (female) | Gender-based formula |
| Ljung [36] | $QT - 0.2(1-RR)$ | Adults with hypocalcaemia |
| Schlamowitz [37] | $QT - 0.225(1-RR)$ | Healthy soldiers at rest and after exercise |
| Simonson [38] | $QT - 0.16(1-RR)$ | Healthy subjects |
| Framingham [39] | $QT - 0.154(1-RR)$ | Population-based study (noncardiac) |
| Akhras & Rickards [40,41] | $QT - 1.87(1-HR/60)$ | Mixture of patients undergoing treadmill exercise to evaluate QT-RR relationship (patients taking beta-blockers, patients with complete heart block exercised with fixed ventricular pacing at 70 bpm & patients with atrial pacing/stress testing) |
| Hodges [42] | $QT - 1.75(1-HR/60)$ | Healthy subjects |
| Kligfield [43] | $QT - 1.32(1-HR/60)$ | |
| Wehrlort [44] | $QT - 1.23(1-HR/60)$ | |
| Karjalainen [45] | values in a published table | Men only, formula intended for heart rate 60–100 bpm |
| Rautaharju [46,47] | $QT/(1 + 1.41 \times 10^{-2}(QT(60-HR)))$ (male)<br>$QT/(1 + 1.54 \times 10^{-2}(QT(60-HR)))$ (female) | Population-based study |
| Kovacs [48] | $QTc = QT/(0.664(1 + 0.01 \times HR) + 0.41$ | |
| Arnsweed [49] | $QTc = QT + 0.504 - 0.492e^{(-0.008 \times HR)}$ | |
| Sarma [50] | $QTc = QT - 0.0148 - 0.864 \times e^{(-0.7 \times HR)}$ | Mixture of healthy subjects undergoing bicycle exercise and patients with VVI pacing |
| Lecocq [51] | $QTc = QT - 0.017 - 0.676 \times e^{(-0.7 \times HR)}$ | |

- **MÉTODO DE BAZETT:** $QTC = QT / (\sqrt{RR})$
- **RANGO NORMAL : QTC 350 A 450 MSG.**

| | QTc interval | | |
|---|---|---|---|
| *Moss [52]* | *Normal* | *Borderline* | *Prolonged (top 1%)* |
| Adult men | <430 ms | 430–450 ms | >450 ms |
| Adult women | <450 ms | 450–470 ms | >470 ms |
| Children (1–15 year) | <440 ms | 440–460 ms | >460 ms |
| *Levels* | | | |
| Adult men | 450 ms (upper limit) | CPMP [58] | |
| Adult women | 470 ms (upper limit) | | |
| Concern of drug-effect | 500 ms | | |



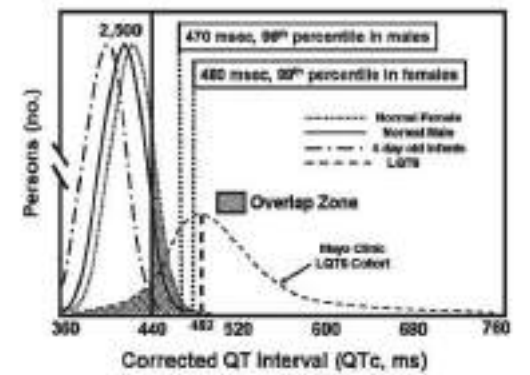




**Figure 1** Distribution of QTc values for patients with and without long QT syndrome (LQTS). The "borderline" QTc level of 440 ms is shown with a solid line. Note the significant overlap between "normal" and QTc values of mutation-positive patients from Mayo's LQTS Clinic. Also note that the average QTc value in normal postpubertal females is on average 10 ms longer than that of normal postpubertal males. Modified from Taggart *et al*[1] with permission from the American Heart Association, copyright 2007.

# PROBLEMAS A LA HORA DE LA MEDICIÓN

## MARCAPASOS

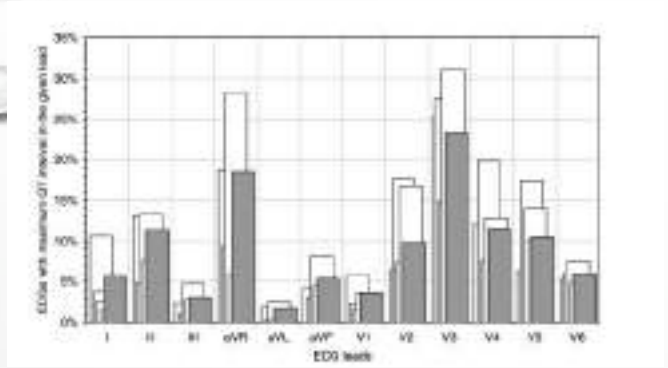
TRASTORNOS DE CONDUCCIÓN

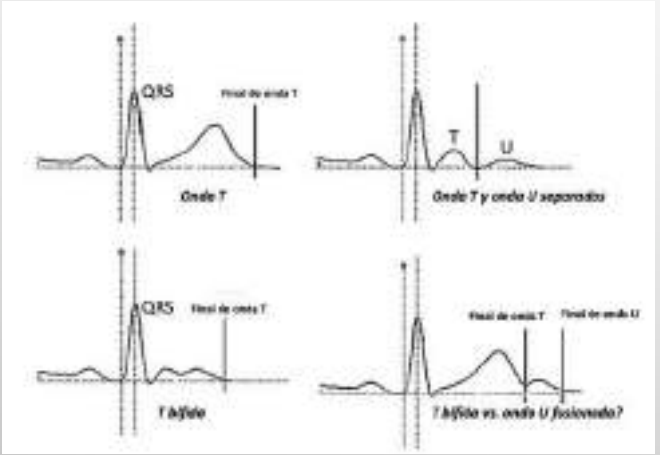
ONDA T APLANADA CON ONDA U

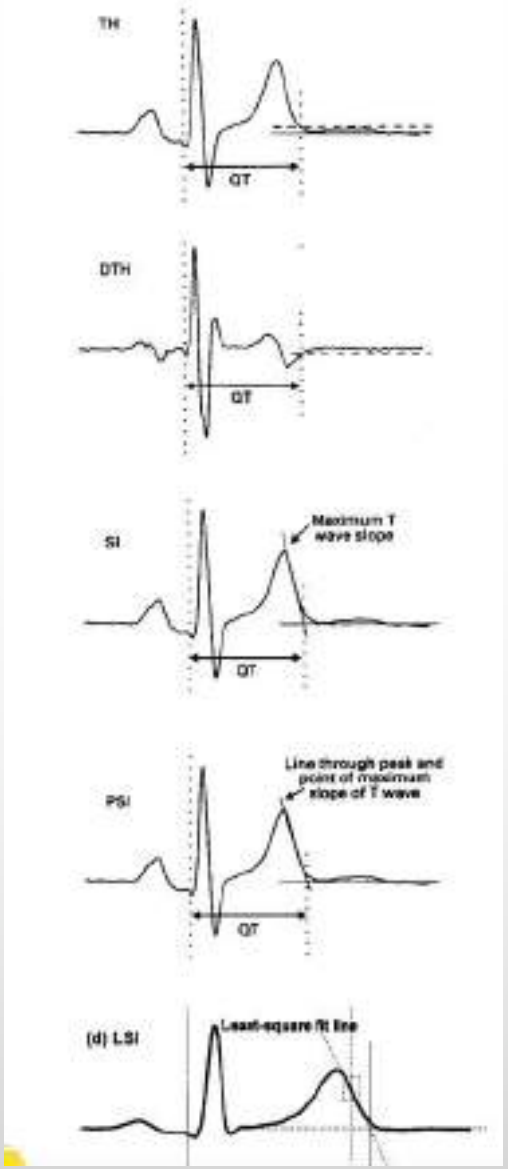
## S. DE PREEXCITACIÓN

FIBRILACION AURICULAR

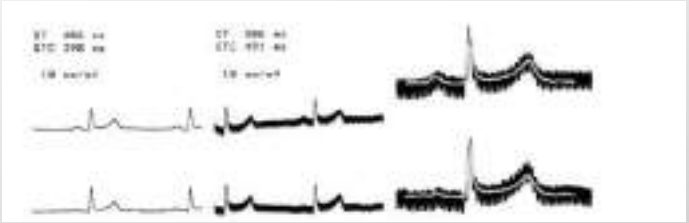
EN PRESENCIA DE FA TOMAR PROMEDIO DE 10 LATIDOS

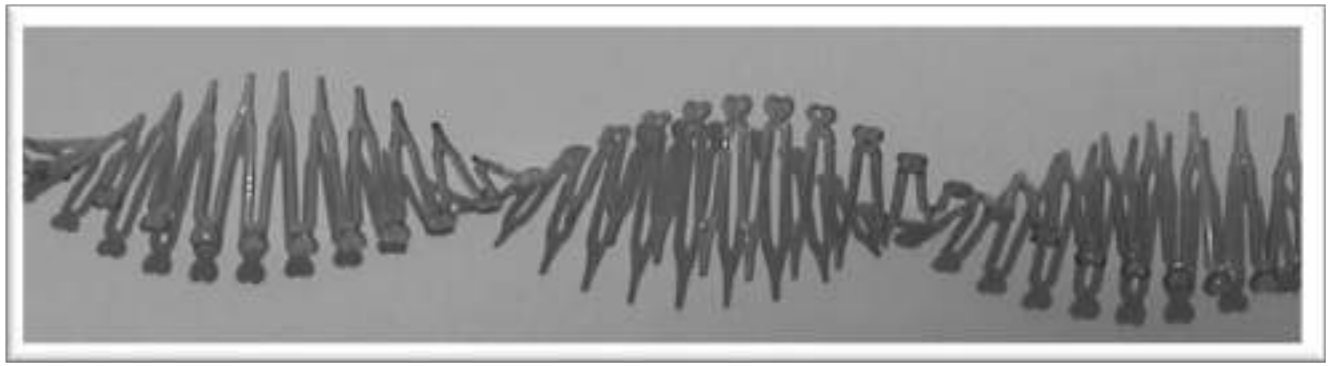


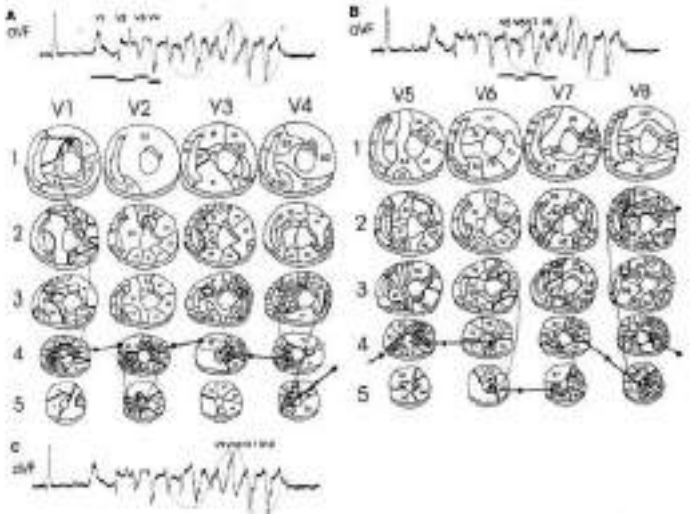



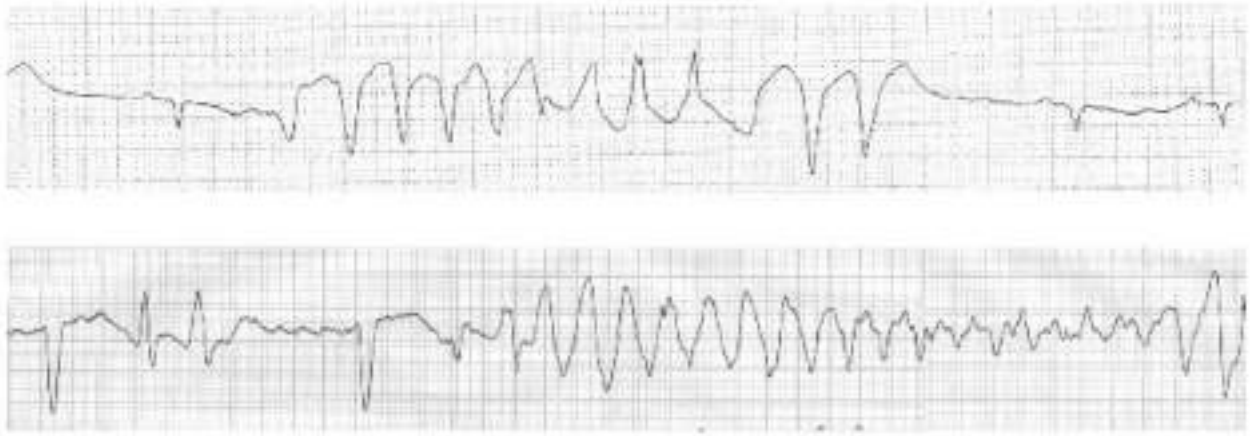

| | QTc interval | | |
|---|---|---|---|
| Males (SI) | Normal | Borderline | Prolonged (top 1%) |
| Adult men | <430 ms | 430–450 ms | >450 ms |
| Adult women | <450 ms | 450–470 ms | >470 ms |
| Children (1–15 years) | <440 ms | 440–460 ms | >460 ms |
| Levels | | | |
| Adult men | 450 ms (upper limit) | CPMP [56] | |
| Adult women | 470 ms (upper limit) | CPMP [56] | |
| Concern of drug-effect | 500 ms | | |

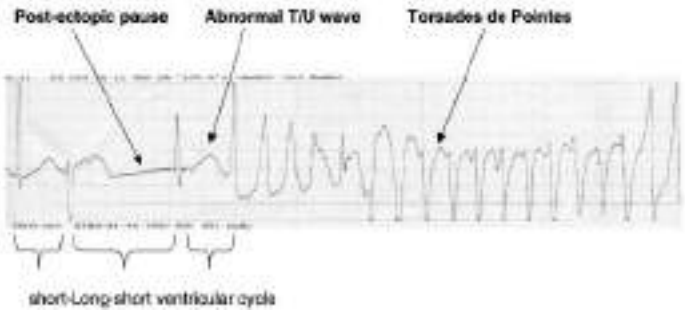


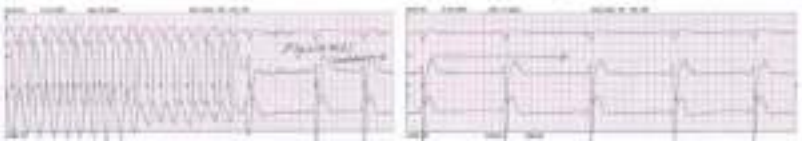


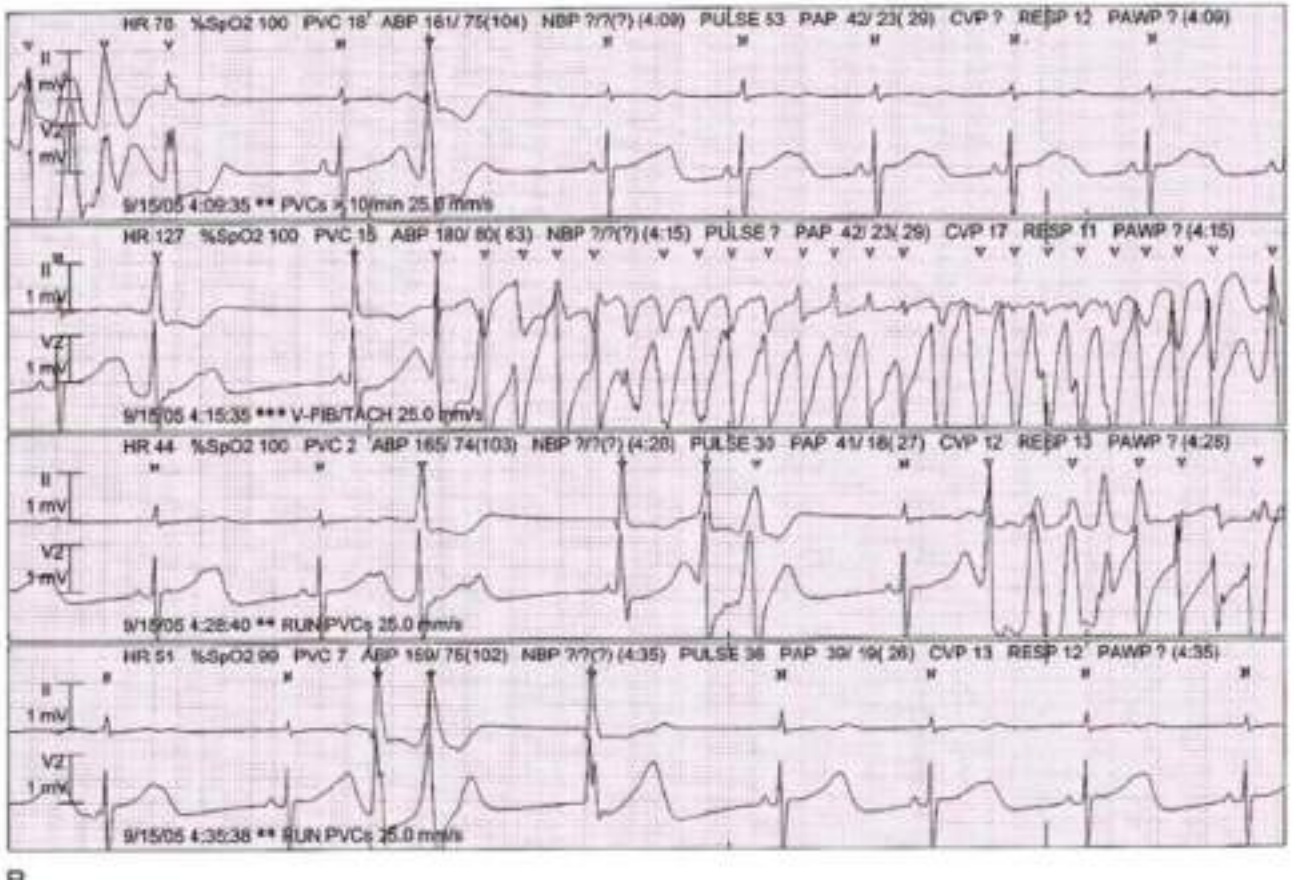
Dessertenne to describe TdP. the authors did find a circular detachable hair band that could be twisted to demonstrate how the points of the teeth and the intermediary gap simulated the pointed side and the broad side, respectively, of the asymmetrical electrocardiographic waves that formed the TdP.

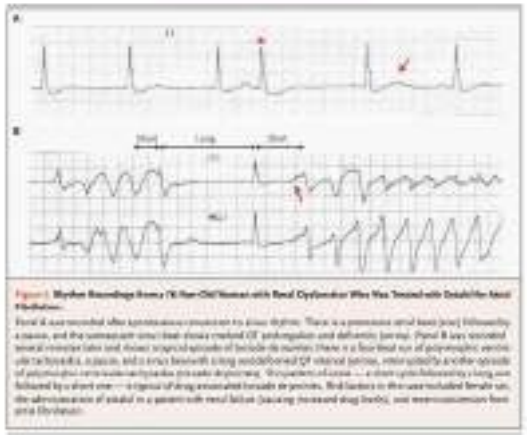







HR 78 %SpO2 100 PVC 18 ABP 161/ 75(104) NBP ?/?(?) (4:09) PULSE 53 PAP 42/ 23( 29) CVP ? RESP 12 PAWP ? (4:09)
II 1 mV
V2 1 mV
9/15/05 4:09:35 ** PVCs > 10/min 25.0 mm/s
HR 127 %SpO2 100 PVC 15 ABP 180/ 80( 63) NBP ?/?(?) (4:15) PULSE ? PAP 42/ 23( 29) CVP 17 RESP 11 PAWP ? (4:15)
II 1 mV
V2 1 mV
9/15/05 4:15:35 *** V-FIB/TACH 25.0 mm/s
HR 44 %SpO2 100 PVC 2 ABP 165/ 74(103) NBP ?/?(?) (4:28) PULSE 39 PAP 41/ 18( 27) CVP 12 RESP 13 PAWP ? (4:28)
II 1 mV
V2 1 mV
9/15/05 4:28:40 ** RUN PVCs 25.0 mm/s
HR 51 %SpO2 99 PVC 7 ABP 159/ 75(102) NBP ?/?(?) (4:35) PULSE 36 PAP 39/ 19( 26) CVP 13 RESP 12 PAWP ? (4:35)
II 1 mV
V2 1 mV
9/15/05 4:35:38 ** RUN PVCs 25.0 mm/s



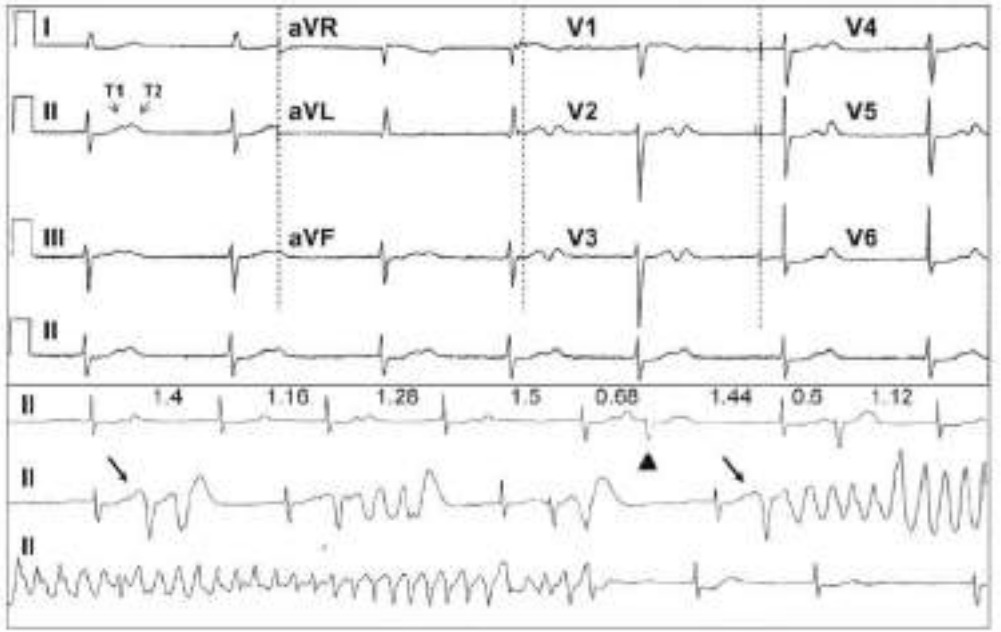
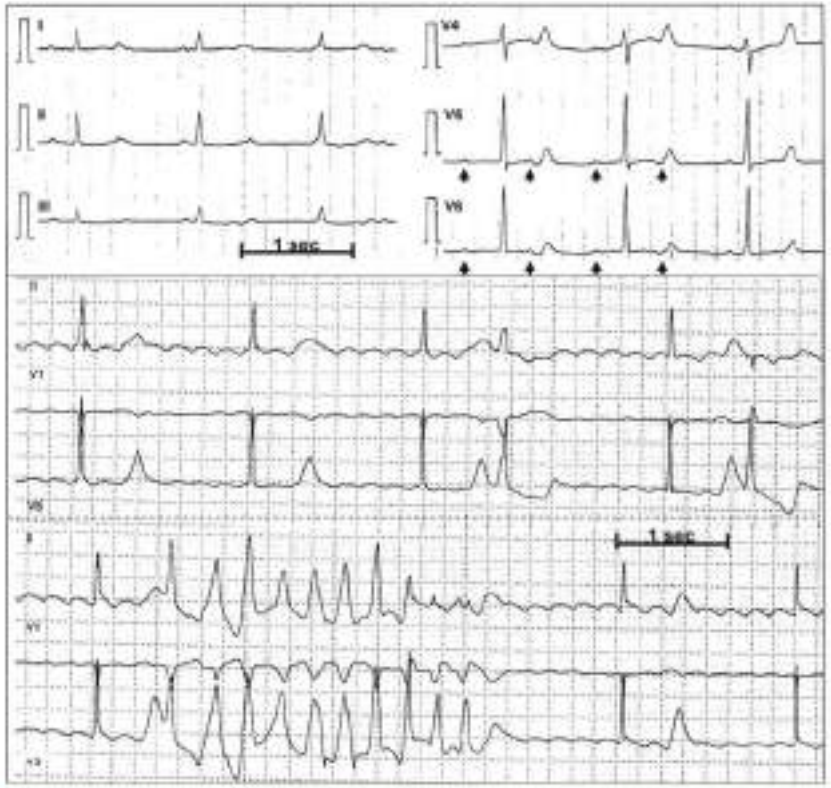


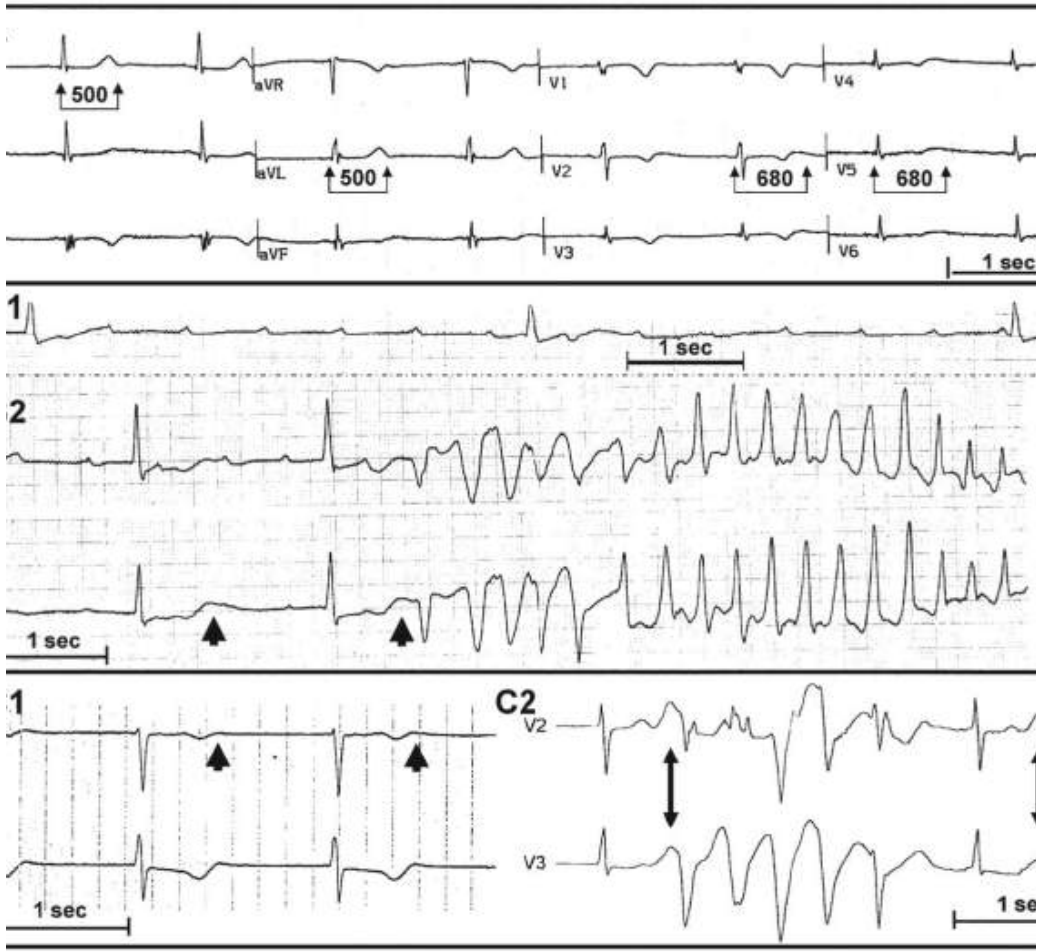

**Figure 2** **Atrial Fibrillation With Slow Ventricular Rate (36 to 40 beats/min) in an 83-Year-Old Woman Presenting With Effort Intolerance**

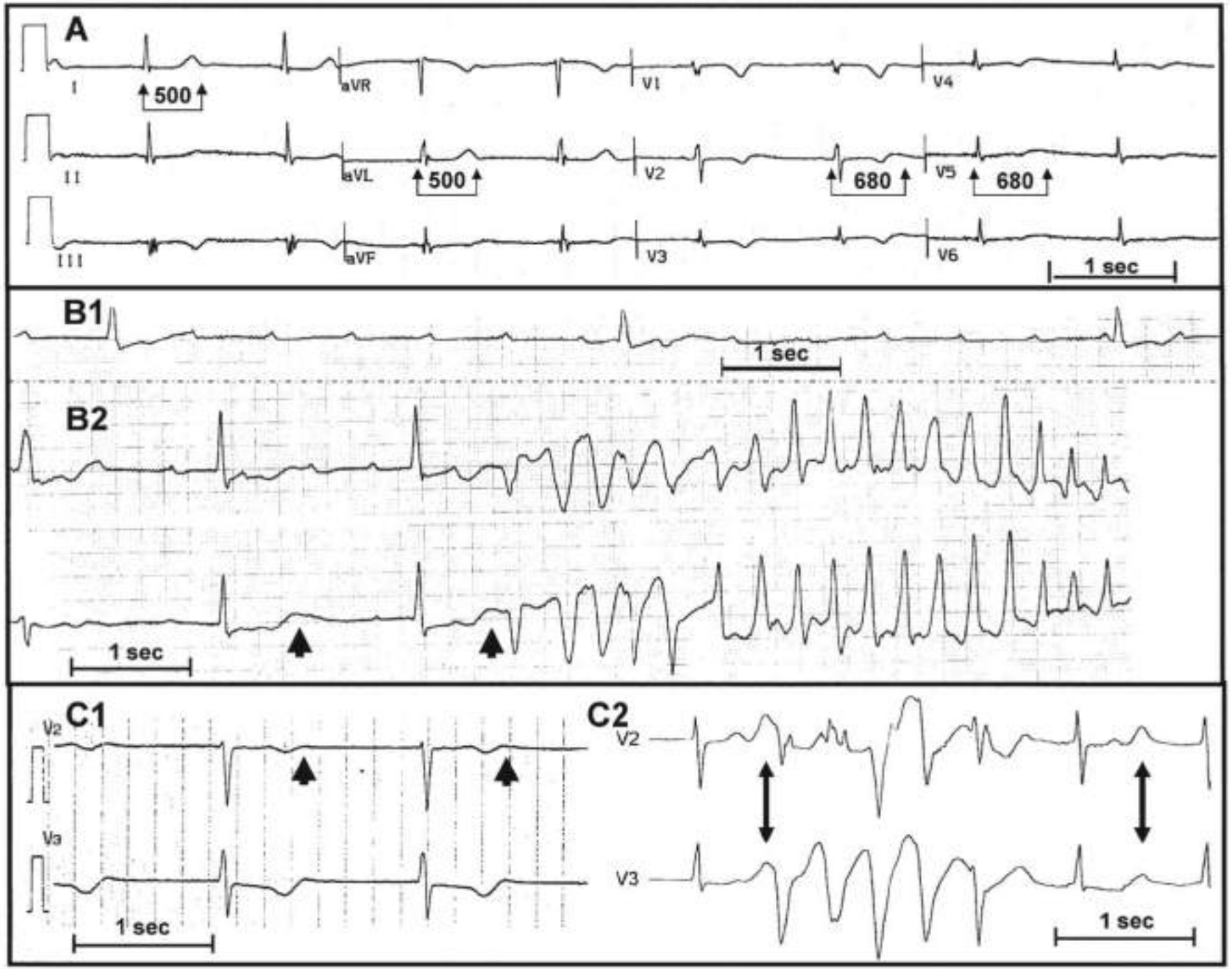
The patient's only medication, verapamil, was stopped 48 h before this electrocardiogram. The potassium level was 4 meq/l. Note the LQT2-like morphology (T1-T2) in the inferior and anterior leads (with T2>>T1 in $V_4$ to $V_6$). **(Lower panel)** Shortly thereafter, this patient had torsade de pointes. Note that the irregularity of ventricular rate during atrial fibrillation creates short and long cycles (time duration between 2 consecutive R waves of the ECG [RR intervals] shown in seconds). The longest cycle (RR interval of 1.5 s) antecedes the complex that is followed by the first extrasystole **(arrowhead)**, which probably represents triggered activity. A series of short-long sequences ensues and culminates in torsade de pointes. As expected, the torsade de pointes complexes originate from T2 **(arrows)**.




Sinus Rhythm With Complete AVB (Post-Surgical AVB After Mitral Valve Replacement) Complicated by Torsade de Pointes

The **top panel** shows sinus rhythm with complete AVB (P waves marked with **arrowheads**). Note the narrow QRS escape with a rate of 42 beats/min, suggesting proximal block. Also, note the LQT3-like (small and very late T waves) morphology of the QT segment. (**Lower panel**) The same patient later developed atrial flutter with very slow ventricular rate (36 beats/min). A series of shortening sequences, due to ventricular bigeminy, culminates in torsade de pointes.




A
I
500
aVR
V1
V4
II
aVL
500
V2
680
V5
680
III
aVF
V3
V6
1 sec
B1
1 sec
B2
1 sec
C1
V2
V3
1 sec
C2
V2
V3
1 sec

Bloqueo de los canales Ikr

De la corriente Intracelular de K

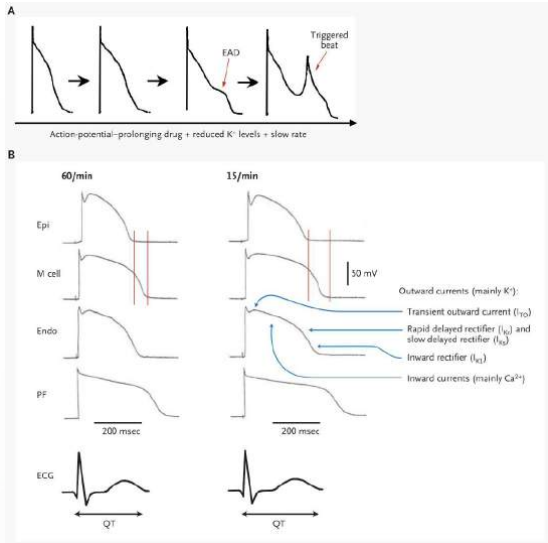
Post despolarizaciones precoces

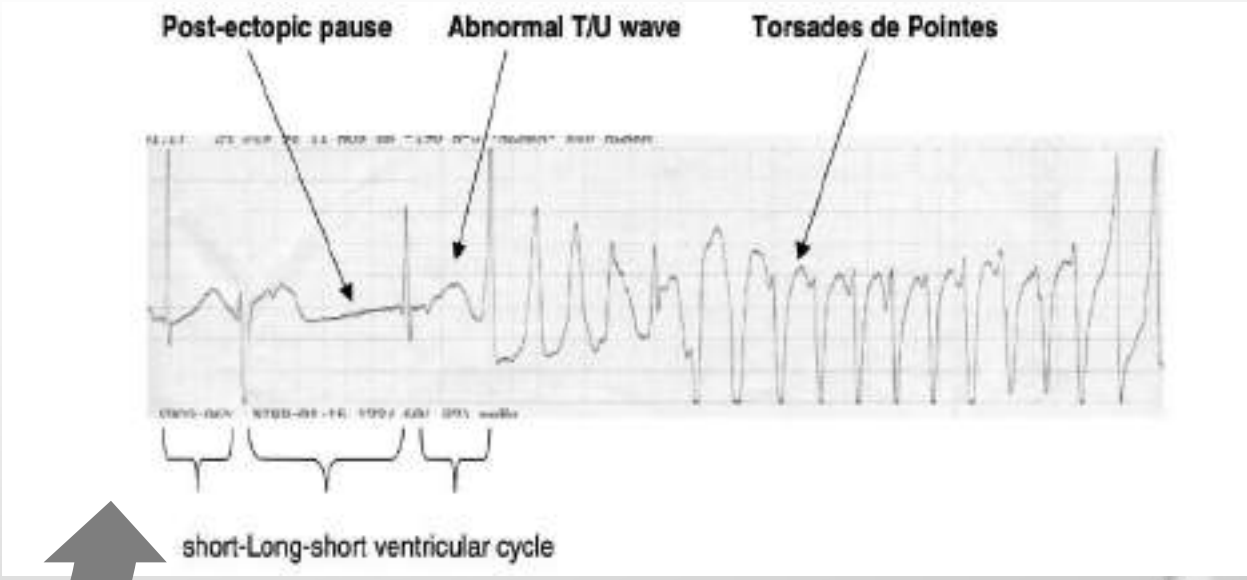
Actividad gatillada

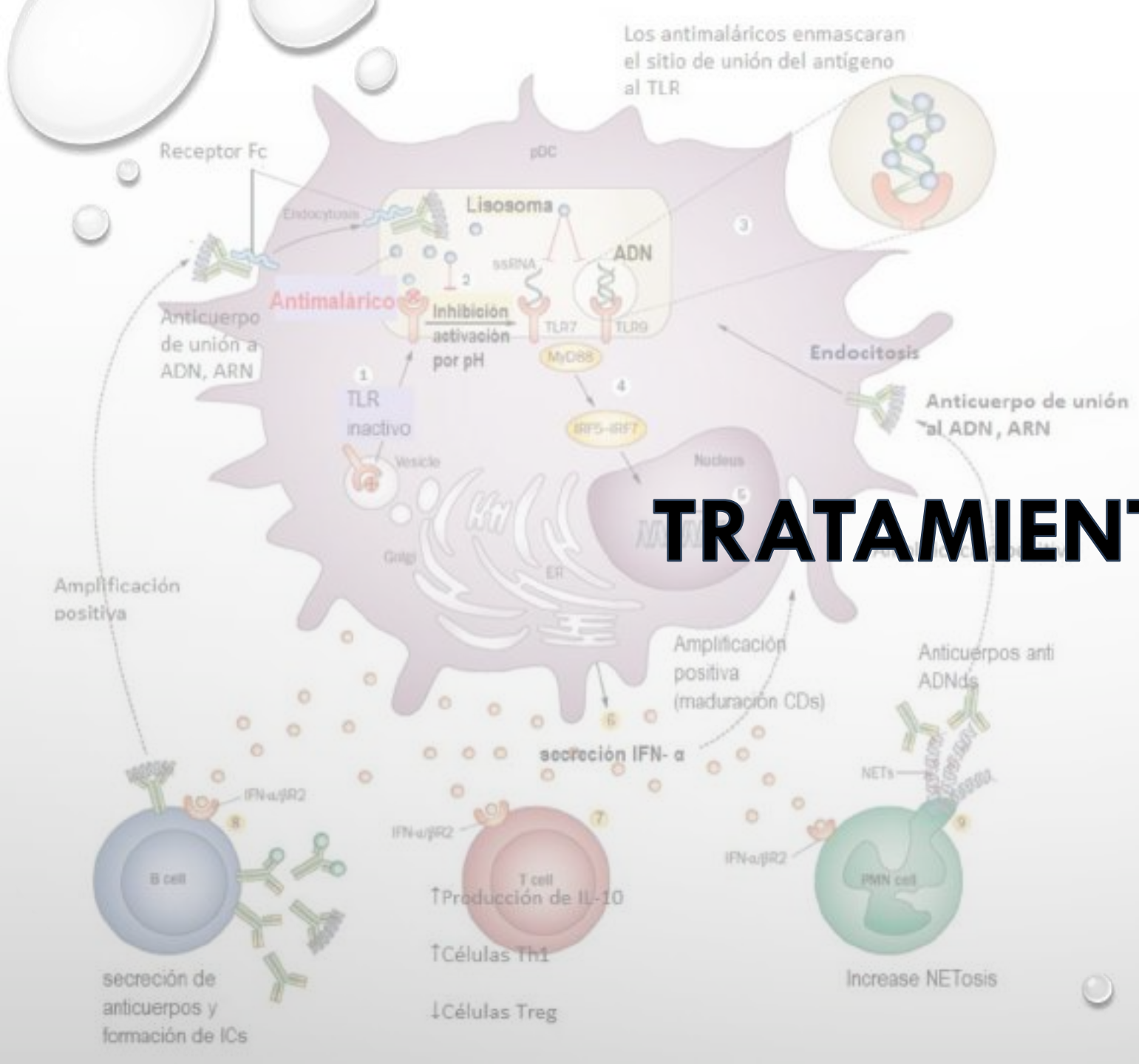
Duración del potencial de acción en pukinje y celulas M

Dispersión de la repolarización

BLOQUEO UNIDIRECCIONAL Y REENTRADA INTRAMURAL

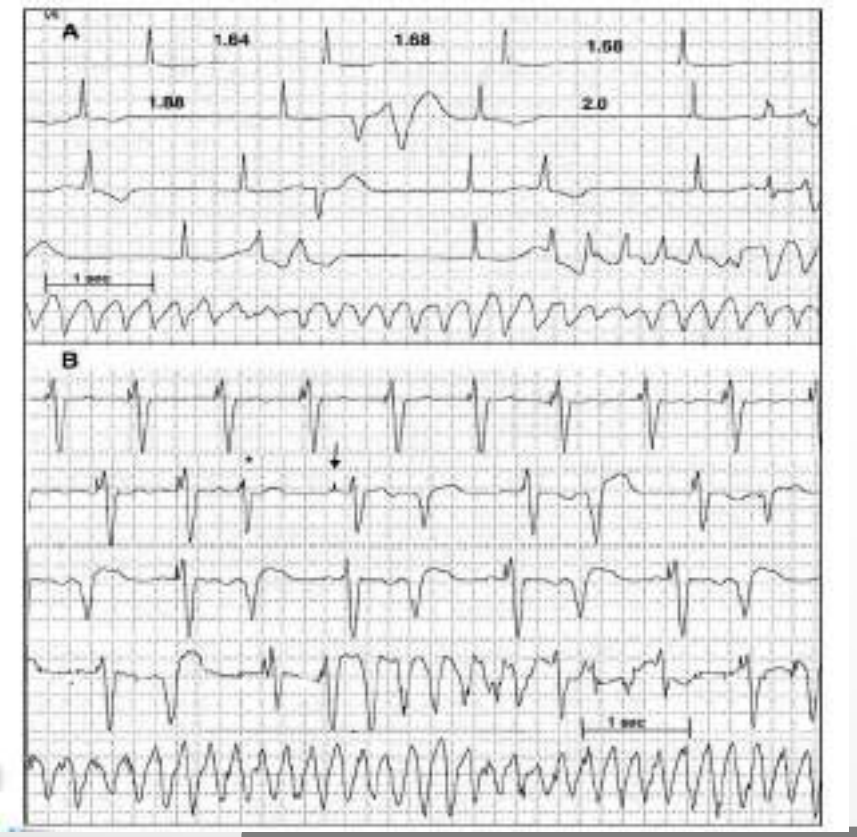






# TRATAMIENTO




# TRATAMIENTO DE LA TDP

Stop Hidroxi

Sukfato de Mg 1-2 grs IV

Reponer K hasta llegar a 4,5 Meq

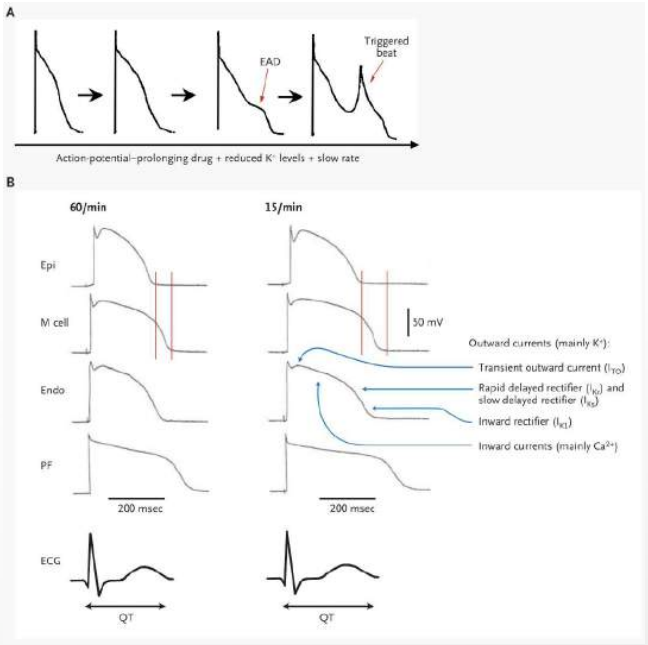
- Si no responde

Isoproterenol

- Si no responde

MCP transitorio 90 LPM

- Si no responde




Mario Fitz Maurice

An algorithm for managing QT prolongation in Coronavirus Disease 2019 (COVID-19) patients treated with either chloroquine or hydroxychloroquine in conjunction with azithromycin: Possible benefits of intravenous lidocaine

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DOI: https://doi.org/10.1016/j.hrcr.2020.03.016

Reference: HRCR 850

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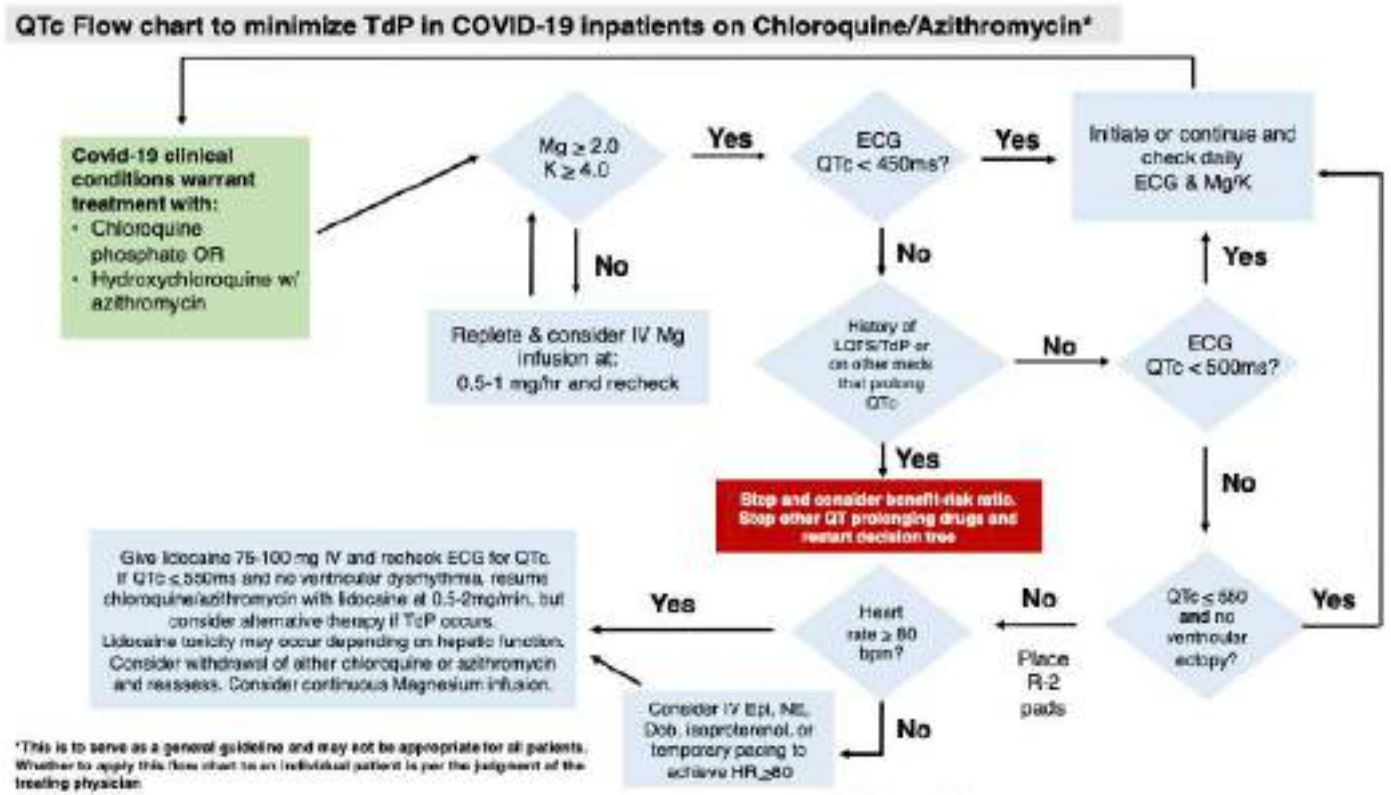


Figure 3. Flow chart to manage effects on QTc with chloroquine, hydroxychloroquine with azithromycin. Abbreviations: Mg-Serum magnesium; K-Serum Potassium; ms: milliseconds; LQTS: long QT syndrome; TdP: Torsades de Pointes; bpm: beats per minute; IV: intravenous; Epi: epinephrine; NE: norepinephrine; Dob: dobutamine

# Prevención arrítmica COVID19

Hospital Universitario La Paz
S. Cardiología
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## Factores Riesgo Arrítmico (FR)

1. Hª de S. de QT Largo (congenito o adquirido), TdP o canalopatía (S. Brugada, TV catecolaminérgica, etc)
2. Bradicardia (<50 lpm) o trastorno de la conducción
3. Alteraciones hidroelectrolíticas (hipoK o Ca o Mg)
4. Insuficiencia renal
5. ICC o inflamación cardiaca (miocarditis/IM)

## Vigilancia

1. Minimizar alteraciones hidroelectrolíticas:
   1. Corregir hipoK (>4) o Ca (>9) o Mg (>2) y seguimiento
   2. Evitar pérdidas urinarias (diuréticos) y digestivas (vomito/diarrea) y reponerlas
2. S. Brugada I sin DAI: evitar fiebre >38ºC y monitorizar ECG
3. En caso de uso de drogas proarrítmicas:
   1. Evitar fármacos potenciadores (crediblemeds.org)
   2. Seguimiento ECG

## Seguimiento ECG

| | FR - | FR + |
|---|---|---|
| Basal | No/Si | Si |
| Impregnación | A las 24-48 hs | A las 4-24 hs |
| Seguimiento | No | Diario |

*Se puede utilizar ECG de solo 1 o 2 derivaciones si previamente se ha comprobado que la diferencia de QTc con el medido en el de 12 derivaciones es <20 ms*

*Cálculo QTc: qtcalculator.org*

NO QTc >500 ms, ΔQTc >60 ms, EV o bradiarritmias:
**CONTINUAR TTO***

QTc >500 ms, ΔQTc >60 ms, EV o Bradiarritmias:
1. **ECG diario**
2. **Isoproterenol si FC <50 lpm**
3. **Suplementos K y Mg** (aun siendo normales y sin toxicidad)
4. **REPLANTEAR TTO:**
   1. Valorar prioridad COVID (< 7dias COVID, severidad respirator.) vs Bradiarritmia/QTc (severidad QT, TdP)
   2. Priorizar HCQ frente AZT y antivirales

*Δ: incremento, AZT: Azitromicina, EV: extrasistolia ventricular, ICC: insuficiencia cardiaca, HCQ: hidroxicloroquina, TdP: torsade de pointes, TV: taquicardia ventricular, TTO:*

## Según la movilización del QT durante su tratamiento

### QRS ancho > 120 msg

QTc < 500msg : evaluar luego de la 2da dosis si aumenta o no > 50msg, si no aumenta seguir.
Si aumenta, reevaluar posterior a la 4ta dosis de hidroxicloroquina. Si el QTc es < 50msg no requiere más monitoreo del QT. Si el QTc > 50msg considerar suspensión.

QTc 500-550 msg: idem anterior, y en la 4ta dosis si queda < 550msg seguir y si aumenta a >550msg suspender.

QTc >550 msg: no adminstrar

### QRS angosto < 120msg

QTc < 460 msg : evaluar a la 2da dosis si aumenta o no > 50msg, si no aumenta seguir.
Si aumenta, reevaluar posterior a la 4ta dosis de hidroxicloroquina. Si el QTc es < 50msg no requiere más monitoreo del QT. Si el QTc > 50msg considerar suspensión.

QTc 460-500 msg: idem anterior, y en la 4ta dosis si queda < 550msg seguir y si aumenta a >550msg suspender.

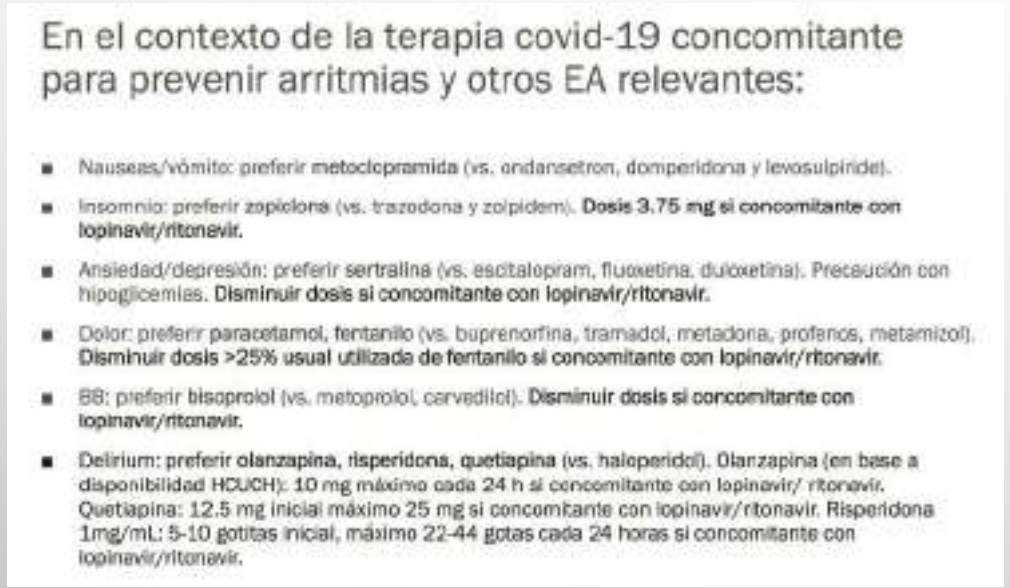
QTc >500 msg: no adminstrar

-Si el QT se prolonga con cualquier dosis un 20 a 25% partiendo de un basal normal, suspender TTO

Christian Hocht, Javier AW Opezzo y Carlos Taira

# SÍNTESIS

-Discontinuar drogas que prolonguen el QT
-Mantener K por arriba de 4.0mEq/L y Mg por arriba de 2.0mEq/L.
-Evitar la bradicardia.
-Evaluar marcapaseo transitorio



En el contexto de la terapia covid-19 concomitante para prevenir arritmias y otros EA relevantes:

- Nauseas/vómito: preferir **metoclopramida** (vs. ondansetron, domperidona y levosulpiride).
- Insomnio: preferir zopiclona (vs. trazodona y zolpidem). **Dosis 3.75 mg si concomitante con lopinavir/ritonavir.**
- Ansiedad/depresión: preferir sertralina (vs. escitalopram, fluoxetina, duloxetina). Precaución con hipoglicemias. **Disminuir dosis si concomitante con lopinavir/ritonavir.**
- Dolor: preferir paracetamol, fentanilo (vs. buprenorfina, tramadol, metadona, profenos, metamizol). **Disminuir dosis >25% usual utilizada de fentanilo si concomitante con lopinavir/ritonavir.**
- BB: preferir **bisoprolol** (vs. metoprolol, carvedilol). **Disminuir dosis si concomitante con lopinavir/ritonavir.**
- Delirium: **preferir olanzapina, risperidona, quetiapina** (vs. haloperidol). Olanzapina (en base a disponibilidad HCUCH): 10 mg máximo cada 24 h si concomitante con lopinavir/ ritonavir. Quetiapina: 12.5 mg inicial máximo 25 mg si concomitante con lopinavir/ritonavir. Risperidona 1mg/mL: 5-10 gotitas inicial, máximo 22-44 gotas cada 24 horas si concomitante con lopinavir/ritonavir.

NO DAR HIDROXICLOROQUINA CON QT INICIO > 550 MSG

SI ES < A 550 REEVALUAR EN 2 Y 4 DOSIS SI >550 SUSPENDER

SI NO PROLONGA QT >550 CONTROL

Si el QT se prolonga con cualquier dosis un 20 a 25% partiendo de un basal normal, se deberá suspender TTO


# COVID 19 VINO PARA CAMBIAR TODO

DR FITZ MAURICE

ARTÍCULO DE REVISIÓN

# Muerte súbita en el ámbito prehospitalario en época de COVID-19

*Sudden death in the prehospital setting in times of COVID-19*

MARIO D. FITZ MAURICE[1], FERNANDO DI TOMMASO[1], NADIA D. FORMICA MAZRAANI[1], PABLO AGÜERO[1], PAULA C. SASTRE[1], ALFREDO HIRSCHON PRADO[1]

**RESUMEN**

Una de cada cinco muertes de adultos en países desarrollados se debe a causas cardiovasculares; la mitad de esas muertes se produce de forma súbita y un gran porcentaje en el ámbito extrahospitalario. Múltiples estudios demostraron que el acceso de la población general al aprendizaje de maniobras de reanimación cardiopulmonar sencillas y pragmáticas y la presencia de desfibrilador externo automático se traducen en un gran aumento de sobrevida sin secuelas en casos de muerte súbita cardíaca extrahospitalaria. Hoy en día existe una situación especial representada por la pandemia por COVID-19, que deja bajo un interrogante todo lo aprendido hasta la fecha y nos enfrenta a dos situaciones sumamente complejas. Por un lado, la afectación cardiovascular y el aumento consecuente de arritmias ventriculares malignas que genera esta infección, tanto en pacientes sanos como en sujetos con patologías preexistentes, han puesto de manifiesto un aumento en la incidencia de episodios de muerte súbita extrahospitalaria. Por otro lado, se vuelve necesario reevaluar todo el accionar puesto en marcha cuando un paciente presenta un episodio de muerte súbita cardíaca extrahospitalaria, ya que ahora se agrega la posibilidad de transmisión de esta enfermedad de alta contagiosidad durante las maniobras de reanimación. Volver a encontrar un equilibrio riesgo-beneficio que permita aumentar la sobrevida del paciente con el mínimo riesgo posible para la persona que realiza la reanimación es el verdadero desafío hoy en día.

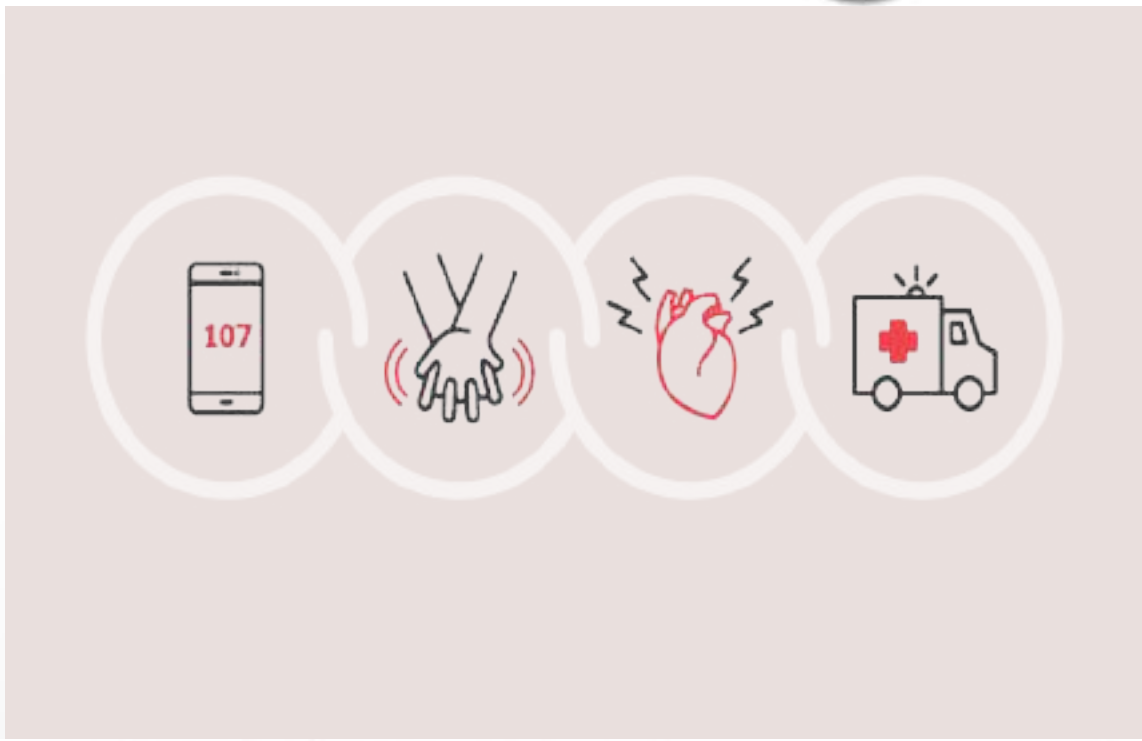
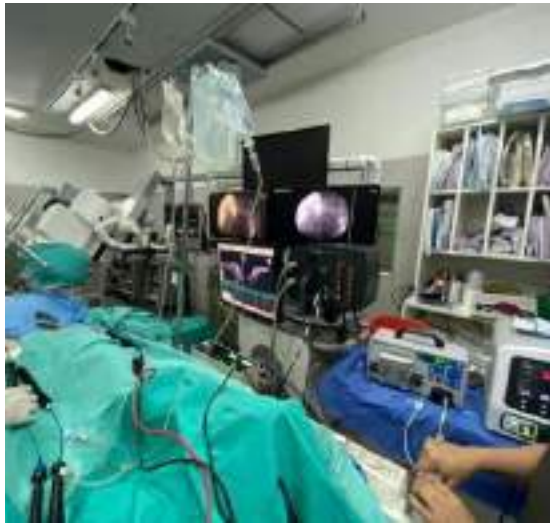
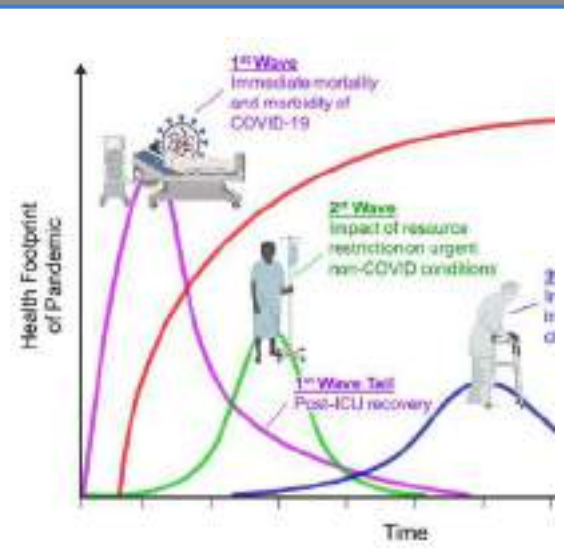





Fig. 4. RCP en adultos y COVID-19.


DR FITZ MAURICE






SADEC

TEMA DE ACTUALIDAD

# Taquicardias ventriculares polimórficas en el escenario de la pandemia por COVID-19. Hidroxicloroquina, Azitromicina y prolongación de QTc

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**Resumen.** Desde que se informó el primer caso a fines de 2019, el virus SARS-CoV-2 se ha propagado internacionalmente desencadenando una pandemia global infectando a más de 5 millones de personas y provocando más de 300.000 muertes en todo el mundo. La alta tasa de transmisión del virus lo ha convertido en una amenaza para la salud pública a nivel mundial. Los pacientes con factores de riesgo cardiovasculares, así como aquellos con enfermedad cardiovascular y cerebrovascular han sido identificados como poblaciones particularmente vulnerables con mayor morbilidad y mortalidad cuando sufren de Coronavirus Infectious Disease 19 (COVID-19). Si bien actualmente no existe tratamiento antiviral específico recomendado para el tratamiento de la enfermedad, a medida que se ha expandido el virus SARS-CoV-2 se han realizado diversos estudios a nivel mundial a fin de determinar la efectividad de los drogas y los posibles efectos adversos de los mismos. Un grupo de drogas que ha estado en boca de todos ha sido la hidroxicloroquina, ligada originalmente a la autoinmunidad. Todas estas drogas, en especial la hidroxicloroquina, comparten un efecto adverso potencialmente arritmogénico, observado cuando se utilizan a altas dosis y en conjunto: la prolongación del intervalo QT. Si bien las primeras publicaciones fueron esperanzadoras, sobre todo con relación a la hidroxicloroquina, otras publicaciones recientes han dado a conocer su alto potencial arritmogénico y mortalidad al favorecer el desarrollo de taquicardias ventriculares polimórficas, particularmente la Torsades de Pointes. Aun así, esta droga continúa utilizándose en distintas instituciones a nivel mundial, por lo que es importante tener en cuenta sus interacciones y desarrollar un estricto control de su uso, así como conocer los factores predisponentes a generar arritmias y estudiar la fisiopatología de la Torsades de Pointes a fin de reducir la mortalidad asociada al uso de estas drogas.

**Palabras** clave. Coronavirus Infectious Disease 2019 (COVID-19), SARS-CoV-2, Hidroxicloroquina, Taquicardias ventriculares polimórficas, Torsades de Pointes, COVID-19.

**Abstract.** Since the first case was reported at the end of 2019, the SARS-CoV-2 virus has spread internationally resulting in a global pandemic, infecting approximately more than 5 million people and produce more than 300.000 deaths. The high transmission rate of this virus has made it a threat to public health worldwide. Patients with cardiovascular risk factors, as well as patients with cardiovascular and cerebrovascular diseases, have been identified as specific vulnerable populations with greater morbidity and mortality when suffering from Coronavirus 19 Infectious Disease (COVID-19). Although there is currently no specific antiviral treatment recommended for the treatment of the disease, ever since SARS-CoV-2 virus has spread, different studies have been initiated worldwide to determine the efficacy of the drugs and their possible side effects. One group of drugs that has been the focus of the studies has been hydroxychloroquine, originally used for autoimmunity. All these drugs, especially hydroxychloroquine, have a potentially arrhythmogenic adverse effect, especially when given together and at high doses: prolongation of the QT interval. Although the initial publications were encouraging, especially in relation to hydroxychloroquine, recent publications have revealed its high arrhythmogenic potential and mortality by the development of polymorphic ventricular tachycardias, especially Torsades de Pointes. Despite the results, these drugs continue to be used in different institutions, so it is important to know their interactions and develop a strict control of their use, as well as to know the predisposing factors and pathophysiology of the Torsades de Pointes in order to reduce the mortality that has been associated with the use of these drugs.

**Keywords:** Coronavirus Infectious Disease 2019 (COVID-19), SARS-CoV-2, Hydroxychloroquine, Polymorphic ventricular tachycardia, Torsades de pointes.

## Introducción

Desde la peste antonina, a lo largo de la historia, los brotes de enfermedades han complicado a la humanidad, muchas veces cambiando el curso de la historia y devastando civilizaciones. Incluso en esta era moderna, los brotes son constantes, aunque no todos alcanzan el nivel de pandemia como lo ha hecho el Nuevo Coronavirus (COVID-19).

Numerosos coronavirus han sido descubiertos desde 1930 como causantes de enfermedades respiratorias, gastrointestinales, hepáticas y neurológicas en animales. Únicamente se conocían siete coronavirus causantes de enfermedad en los seres humanos. La mayoría de las veces son los responsables del resfrío común y en raras ocasiones se pueden producir infecciones graves de las vías respiratorias inferiores. Estos coronavirus que causan infecciones respiratorias graves son patógenos zoonóticos, que comienzan en animales infectados y se transmiten de los animales a las personas.

En el siglo XXI, tres de siete de estos virus han sido responsables de importantes brotes de enfermedad de variada mortalidad. En el 2002 se identificó en el sur de China el SARS-CoV como la causa de un brote de síndrome respiratorio agudo grave (SARS) y se extendió rápidamente a otros 29 países. Más de 8.000 personas se infectaron en julio de 2003, y 774 murieron. En 2012 se identificó el MERS-CoV como la causa del síndrome respiratorio de Oriente Medio (MERS) que comenzó en Arabia Saudita en 2012 y afectó

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# GRACIAS!

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