3rd Paris NASH Symposium

French-US Meetings

July 6 & 7, 2017

Institut Pasteur - Paris

Organized by

Arun Sanyal & Lawrence Serfaty

Virginia Commonwealth University School of Medicine, Richmond, Virginia, US
Hôpital Saint-Antoine, APHP, Inserm, Université Pierre & Marie Curie, Paris, France

With the partnership of

AFEF Société Française d'Hépatologie

Société Francophone du Diabète

FORUM for Collaborative Research

QTc and NASH
from molecular biology to clinical significance

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Conflict of interest

- None with this presentation

- Consulting : Amgen
- Lectures fees: AstraZeneca, MSD, ViiV healthcare, Gilead, NovoNordisk
- Travel fees: AstraZeneca, ViiV healthcare, MSD

Summary

- Why DO we have to detect QTc prolongation?
- How to detect QTc prolongation? How to manage QTc prolongation?
- NASH/NAFLD and QTc prolongation

Why DO we have to detect QTc prolongation?

- QT interval represents the duration of electrical depolarization and repolarization of the ventricle.

- A prolonged QT interval reflects a lengthening of this vulnerable period and increases the risk of malignant arrhythmias.

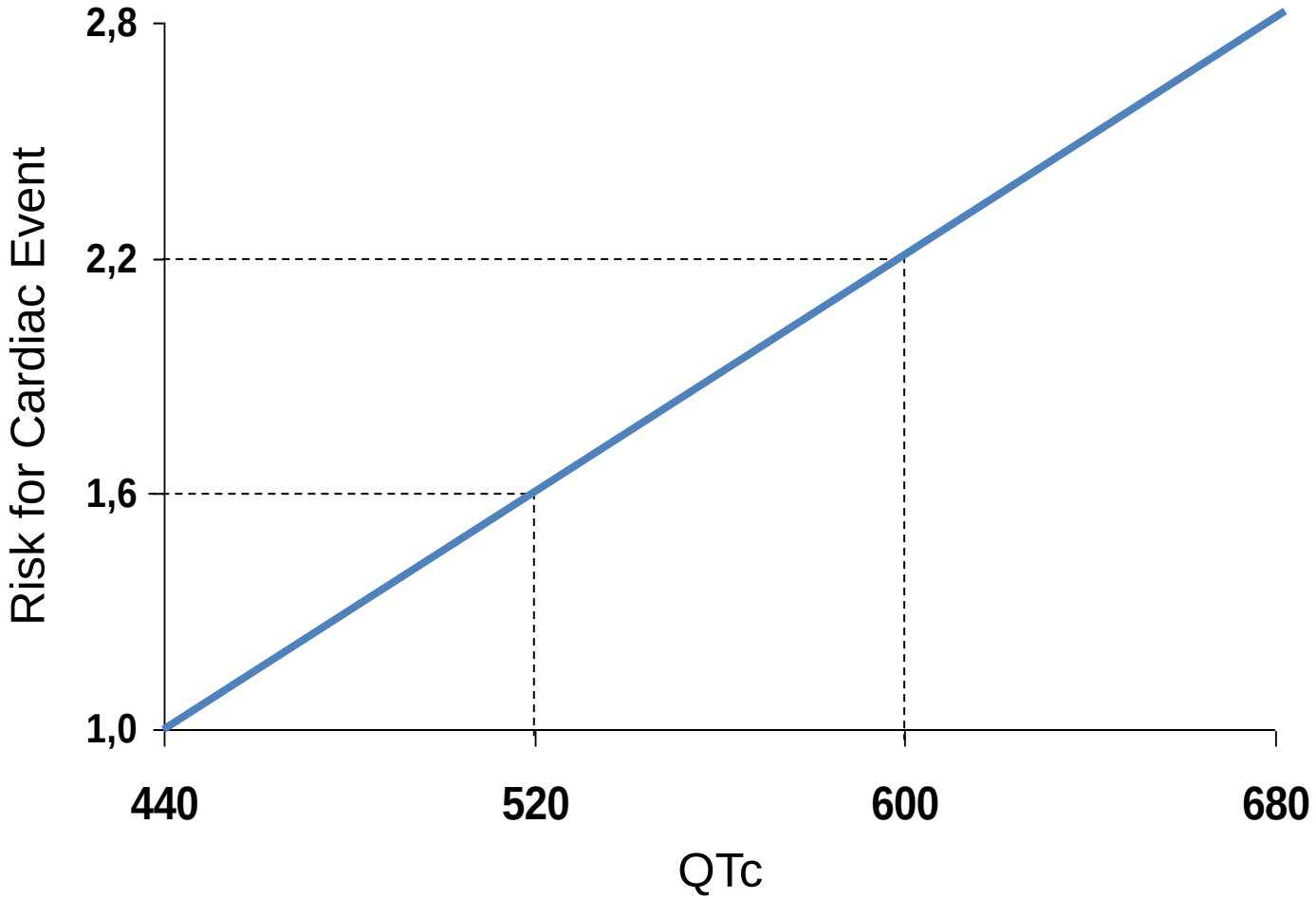
- Extreme prolongation of the QT interval is also associated with sudden cardiac death. Moreover, the duration of the QT interval, even within a reference range, is a predictor for cardiovascular death in the general population. [Cardiovascular Health Study, the Strong Heart study, the Rotterdam study, the NHAMES study]

- QT prolongation among patients with diabetes has also been associated with all-cause and cardiovascular mortality. QT prolongation is common in patients with liver cirrhosis and is associated with a lower survival rate.

- NAFLD is associated with higher rates of cardiovascular complications, atrial fibrillation, and mortality.

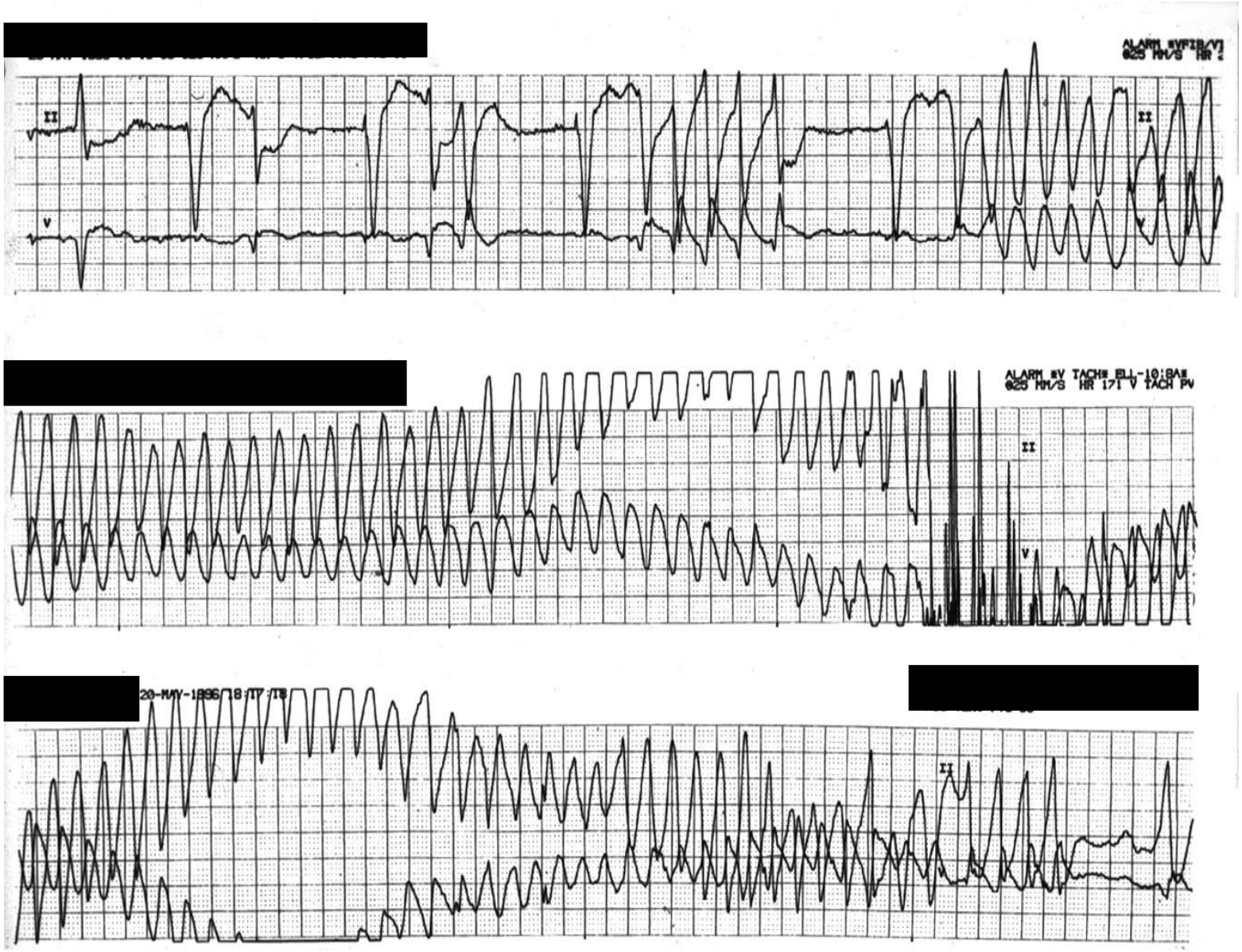
Targher G, et al. N Engl J Med. 2010;363:1341–1350.
Ballestri S, et al. World J Gastroenterol. 2014;20:1724–1745

QTc Interval and Risk

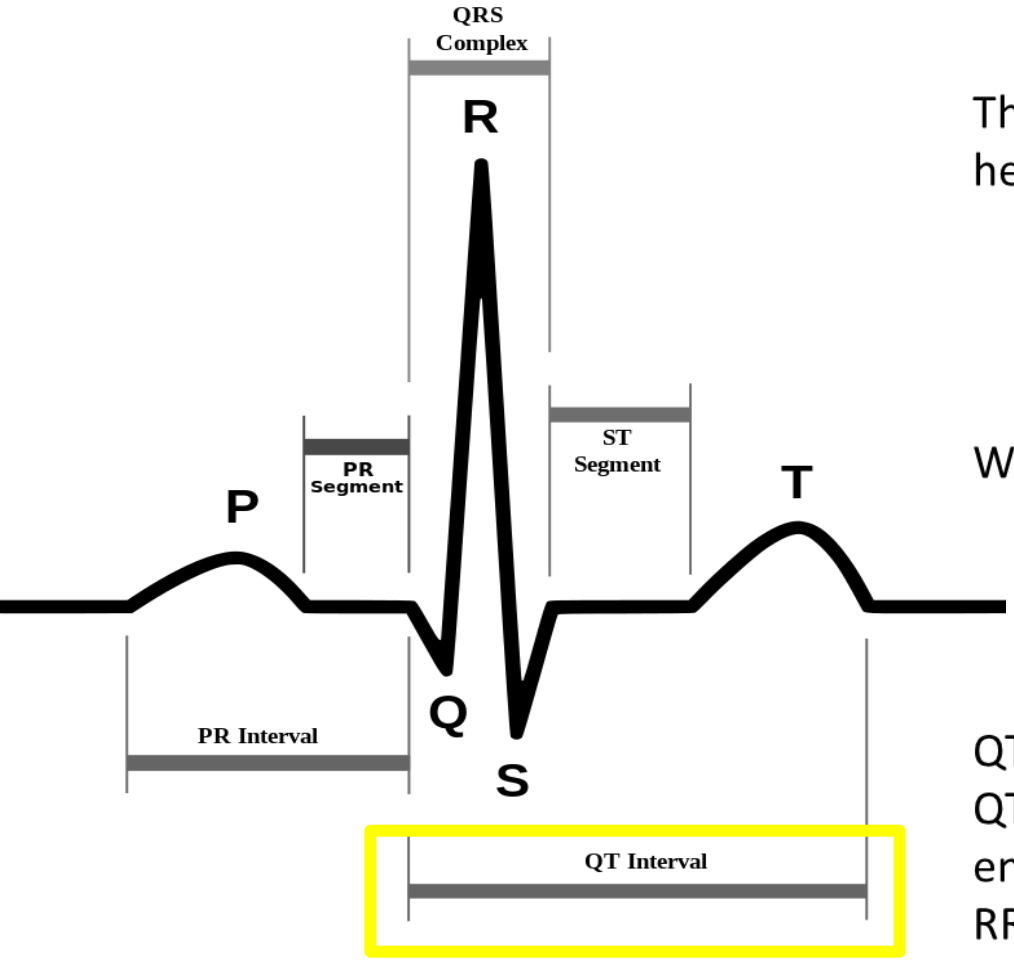


AJC 1993;72:21B

Torsades de Pointe. Life threatening arrythmias



How to detect QT prolongation?



Bazett Formula: $$QT_c = \frac{QT}{\sqrt{RR}}$$

The QTc Fridericia's formula corrects for the heart rate :

$$\mathrm{QTcF} = \frac{QT}{\sqrt[3]{RR}}$$

Where:

QTcF = corrected QT interval
QT = time between start of QRS complex and end of T wave
RR = time between start of one QRS complex and start of the next QRS complex

Automated QT and QTc Analysis

- Reliable with normal T waves at physiologic heart rates
- Unreliable:
  - High heart rates
  - Abnormal T waves
  - Prominent U waves
  - T-U wave complex morphology

Normal QTc Interval - Criteria

QTc (msec)	Male	Female
Normal	<430	<450
Borderline	431-450	451-470
Prolonged	>450	>470

How to manage QTc prolongation?

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Prolongation of QTcF	QTcF 450 – 480 ms	QTcF interval 481 – 500 ms	QTcF ≥ 501 ms on at least two separate ECGs.	QTcF ≥ 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
Action	Monitor more closely; at least weekly ECG until QTcF has returned to grade 1 or less.	Monitor more closely; at least weekly ECG until QTcF has returned to grade 1 or less.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

ICH Expert Working Group

Causes of prolonged QT interval

- **Congenital [Long QT syndrome]**

- **Drug-induced**

  www.qtdrugs.org

  https://www.crediblemeds.org/ → QT drugs list

- Acquired: obesity, diabetes, NASH

Risk Factors for drug-induced Torsade de Pointes

- Female sex
- Older age
- Hypokalemia
- Bradycardia
- Severe hypomagnesemia
- Severe Hypocalcemia
- Atrial fibrillation
- Congestive heart failure

- **High serum drug concentrations**
- **Exposure to other drugs with either "QT liability" or "metabolic liability"**
- **Baseline QT prolongation**
- **Ion channel mutations/ polymorphisms**
- **Anorexia nervosa, starvation**

Roden DM. N Engl J Med 2004;350:1013-22
Fitzgerald PT, Ackerman MJ. Heart Rhythm 2005;2:S30–7

Drugs Which Prolong the QTc

Anticonvulsants	Fosphenytoin; Felbamate
Antihistamines	Azelastine; Clemastine
Anti-Infectives	Amantadine; Clarithromycin; Chloroquine; Foscarnet; Erythromycin; Halofantrine; Mefloquine; Moxifloxacin; Pentamidine; Sparfloxacin; Quinine; Trimethoprim-Sulfamethoxazole, Ketoconazole
Antineoplastics	Tamoxifen
Cardiovascular: Antiarrhythmics	Amiodarone; Bretylium; Disopyramide; Flecainide; Ibutilide; Procainamide; Quinidine; Sotalol; Dofetilide
Calcium Channel Blockers	Bepridil; Israpidine; Nicardipine
Diuretics	Indapamide; Moexipril/HCTZ
Hormones	Octreotide; Vasopressin
Immunosuppressives	Tacrolimus
Migraine: S erotonin Receptor Agonists	Zolmitriptan; Naratriptan; Sumatriptan
Muscle Relaxant	Tizanidine
Narcotic Detoxification	Levomethadyl
Psychotherapeutics: Antidepressants	Amitriptyline; Desipramine; Fluoxetine; Imipramine; Venlafaxine
Antipsychotic	Chlorpromazine; Haloperidol; Pimozide; Quetiapine; Risperidone; Thioridazine
Antianxiety	Doxepin
Antimanic	Lithium
Respiratory: Sympathomimetics	Salmeterol

Causes of prolonged QT interval

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- Drug-induced

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  https://www.crediblemeds.org/ → QT drugs list

- **Acquired: obesity, diabetes, NASH**

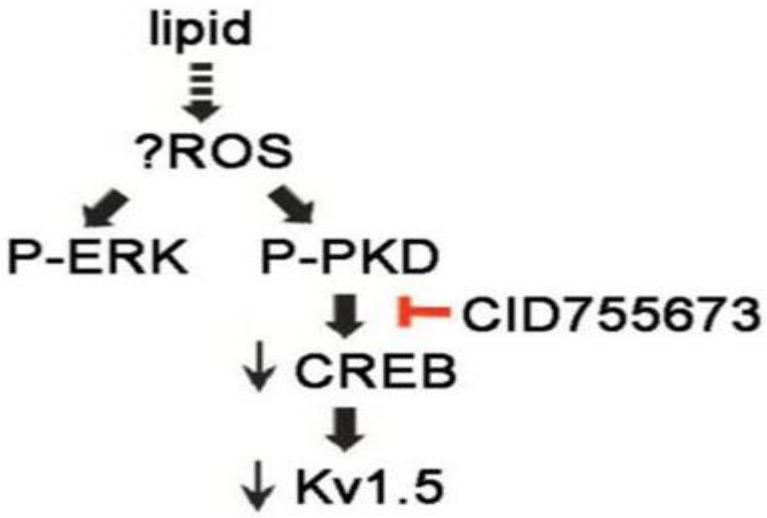
Obesity and QT in humans and mice

Obesity is associated with long QT, increased frequency of premature ventricular complexes, and sudden cardiac death.

- Diet-induced obese mice have long QT, similar to obese H

- Transcription of potassium channels is reduced because of lower cAMP response element binding protein (CREB) levels.

- Reduced cardiac CREB is a novel mechanism causing electrophysiologic remodeling in obesity.

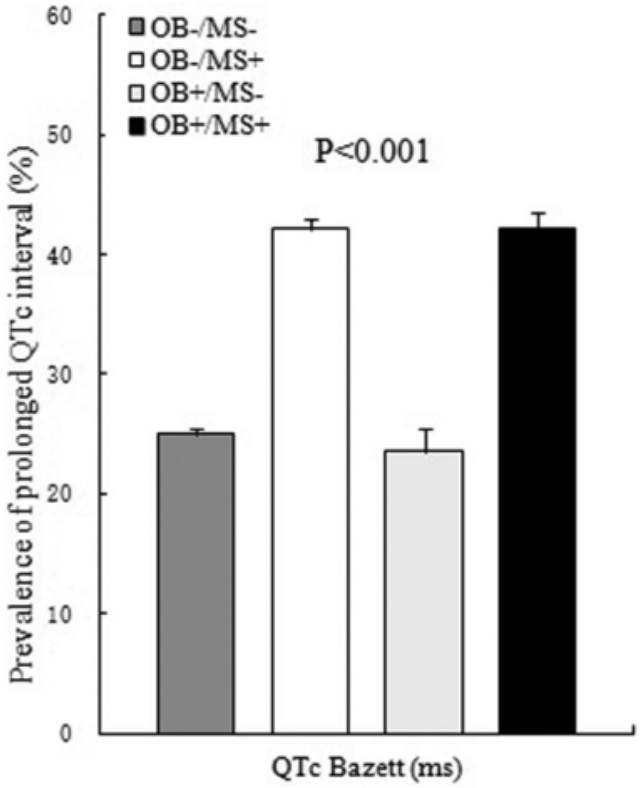


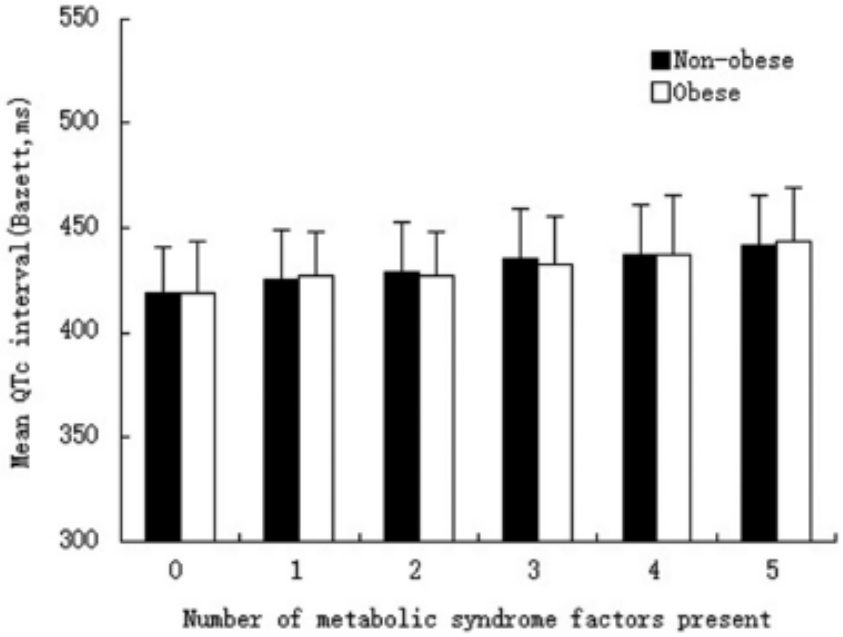
Haiyan Huang et al. J of Mol and Cell Cardiol 2013;59:151-158

Obesity and QT in relation with the metabolic syndrome

China, n= 11 956

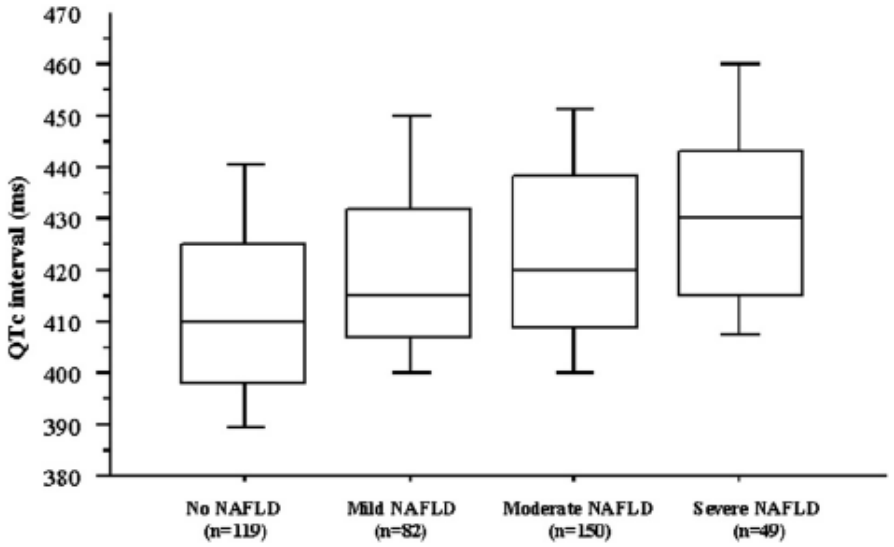
Prevalence increased with each MS component (aOR 1.27, 95% CI 1.22 to 1.32) but not with body mass index (aOR 1.01, 95% CI 0.99 to 1.02).





Guo X, et al. Am J Cardiol 2017;119:1199-1204

Diabetes, NASH and QTc prolongation



Italy, n= 400
Ultrasonographic NAFLD
Bazett computerized EKG

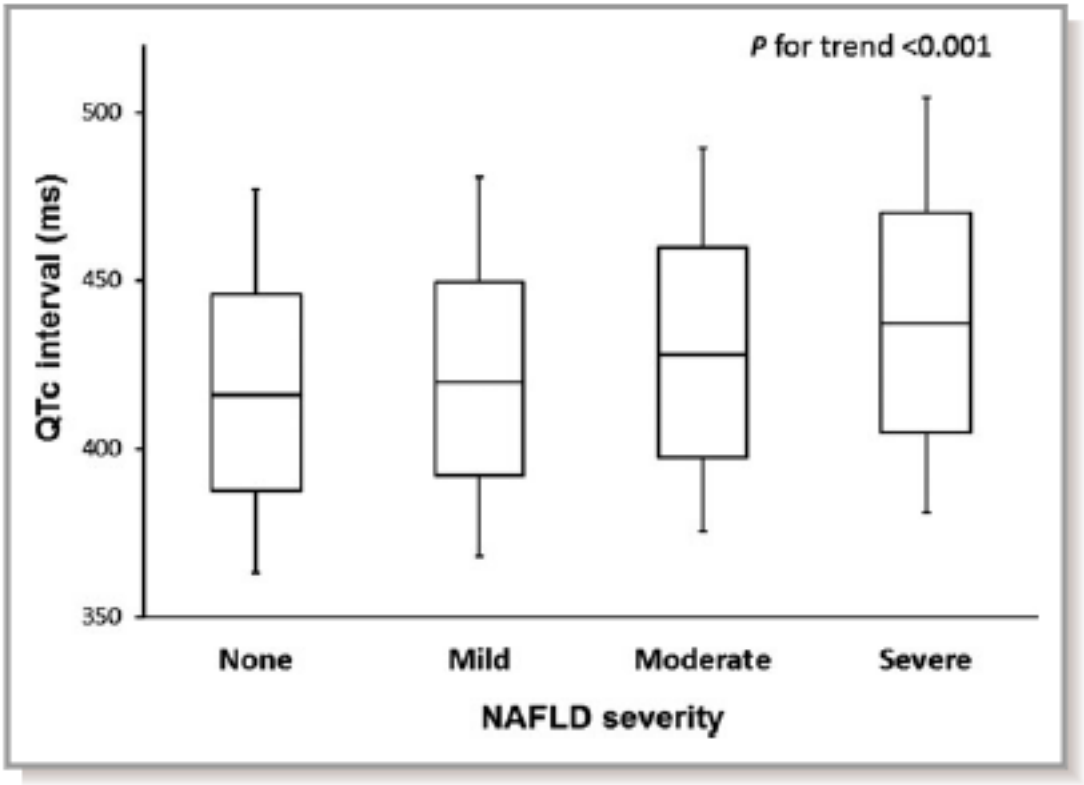
Logistic regression models for NAFLD as a predictor for increased QTc interval duration.

Logistic regression models	OR (95% CI)	*p* Value
NAFLD (yes *vs.* no)		
Unadjusted model	2.16 (1.4–3.4)	<0.001
Adjusted model 1	2.28 (1.5–3.6)	<0.001
Adjusted model 2	2.20 (1.4–3.5)	<0.001
Adjusted model 3	2.26 (1.4–3.7)	<0.001
Other independent predictors of increased QTc interval in model 3		
Sex (female)	1.88 (1.2–2.9)	<0.01
Hypertension (yes *vs.* no)	2.01 (1.2–3.3)	<0.01
Peripheral artery disease (yes *vs.* no)	1.76 (1.1–3.0)	<0.05
Lower-limb sensory neuropathy (yes *vs.* no)	1.90 (1.1–3.5)	<0.05

Targher G, et al. Nutr Metab Cardiovasc Dis. 2014;24:663–669.

NAFLD and QTc. Large cohort

Taiwan cohort
Cross sectional study D+/-
N= 31 116



Significant association of blood pressure, hemoglobin A1c, and high-density lipoprotein concentration with QTc interval.

NAFLD : Abdominal ultrasonography and classified as none, mild, moderate, or severe

Chi-Sheng Hung et al. J Am Heart Assoc. 2015

Characteristics. NAFLD and QTc

Baseline Characteristics N=31 116	No NAFLD n=18 225	NAFLD Mild n=9152	NAFLD Moderate n=2976	NAFLD Severe n=796	*P* Value for Heterogeneity	*P* Value for Trend
Age, y	48.8 (12.8)	52.2 (11.0)	51.4 (11.0)	48.9 (11.0)	<0.001	<0.001
Sex, male, n (%)	7843 (42.6)	5660 (61.5)	2139 (71.5)	568 (73.9)	<0.001	<0.001
Comorbidities						
Diabetes, n (%)	1133 (6.2)	1210 (13.2)	697 (23.4)	221 (29.0)	<0.001	<0.001
Hypertension, n (%)	2970 (16.3)	2800 (30.6)	1237 (41.6)	424 (55.6)	<0.001	<0.001
Metabolic syndrome, n (%)	1096 (6.0)	1931 (21.1)	1170 (39.3)	440 (57.7)	<0.001	<0.001
Coronary artery disease, n (%)	170 (1.0)	106 (1.2)	55 (1.9)	20 (2.7)	<0.001	<0.001
Stroke, n (%)	69 (0.4)	60 (0.7)	13 (0.5)	1 (0.1)	0.008	0.325
Chronic obstructive pulmonary disease, n (%)	570 (3.3)	307 (3.5)	105 (3.7)	35 (4.8)	0.123	0.037
Smoking, n (%)	1976 (10.9)	1396 (15.3)	557 (18.7)	146 (19.2)	<0.001	<0.001
Anthropometric measures						
Body mass index, kg/m^2	22.4 (2.8)	25.2 (2.8)	27.2 (3.2)	29.6 (4.2)	<0.001	<0.001
Waist circumference, cm	81.3 (8.1)	88.7 (7.4)	93.5 (8.2)	99.1 (10.2)	<0.001	<0.001
Systolic blood pressure, mm Hg	119.5 (15.4)	127.6 (15.2)	132.8 (14.8)	137.2 (16.5)	<0.001	<0.001
Diastolic blood pressure, mm Hg	71.6 (10.1)	76.7 (10.4)	80.2 (10.3)	82.9 (11.2)	<0.001	<0.001
QTc interval, ms (by Bazett's formula)	418.9 (60.4)	422.5 (44.8)	430.9 (49.2)	439.9 (48.2)	<0.001	<0.001
QTc interval, ms (by Hodges' formula)	411.6 (32.9)	413.4 (32.6)	418.6 (33.3)	424.6 (34.4)	<0.001	<0.001
QTc >440 ms, n (%) (by Bazett's formula)	5302 (29.1)	2923 (31.9)	1190 (40.0)	366 (48.0)	<0.001	<0.001
QTc >440 ms, n (%) (by Hodges' formula)	3412 (18.7)	1823 (19.9)	755 (25.4)	239 (31.3)	<0.001	<0.001
Left ventricular hypertrophy, n (%)	703 (3.8)	527 (5.7)	186 (6.2)	46 (6.0)	<0.001	<0.001

Chi-Sheng Hung et al. J Am Heart Assoc. 2015

NAFLD is associated with Ventricular Arrhythmias in Diabetics

SVT or AF

	Without NAFLD (n = 92)	With NAFLD (n = 238)	P value
Paroxysmal SVT	33.6	47.4	0.023
Paroxysmal atrial fibrillation	2.2	7.6	0.044

nVT or PVC

Logistic regression models	ORs	95% CIs	P value
NAFLD (yes vs. no)			
Unadjusted model	3.47	1.65–7.30	<0.001
Adjusted model 1	3.39	1.60–7.20	0.001
Adjusted model 2	3.26	1.44–7.37	0.005
Adjusted model 3	3.01	1.26–7.17	0.013
Other independent predictors of ventricular arrhythmias in model 3			
Male sex	3.03	1.31–7.01	0.008
Serum GGT (units/L)	1.02	1.01–1.03	0.009
LV ejection fraction (%)	0.96	0.93–0.99	0.028

Italy, N= 330 diabetics
Retrospective, Cross-sectional
without AF, ESRD, LD
24-h Holter monitoring for clinical reasons (2013-2015)
Ventricular arrhythmias= nonsustained VT, or >30 premature ventricular complexes (PVCs) per hour
Ultrasonography NAFLD

Mantovani A. et al. Diabetes Care 2016;39:1416–1423

Atrial fibrillation and NAFLD

Persistent or permanent AF

Italy
N= 702 patients with Type 2 diabetes
NAFLD on ultrasonography

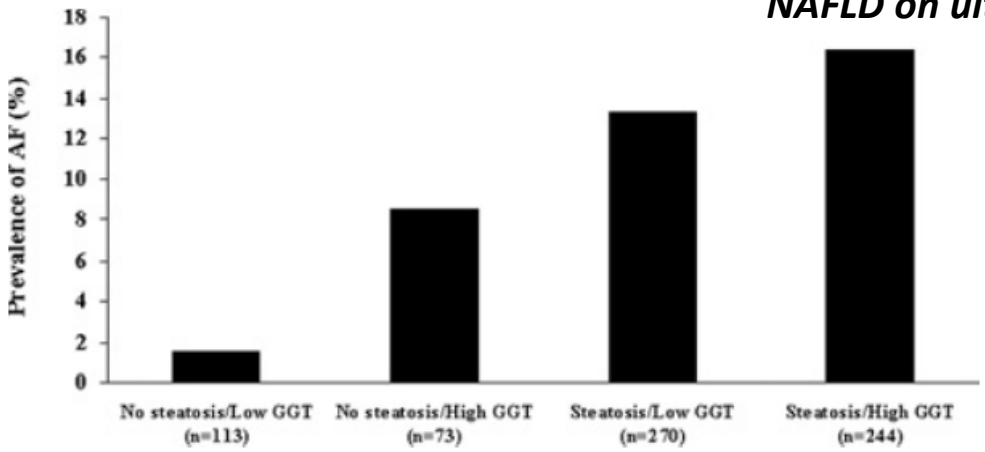


Figure 1 Prevalence of AF in hospitalized Type 2 diabetic patients stratified by NAFLD status on ultrasound and the median serum GGT concentration

P value <0.001 for trend by the χ^2 test.

Logistic regression model	OR (95% CI)	P value
NAFLD (yes comapred with no)		
Unadjusted model	3.04 (1.54–6.02)	<0.001
Adjusted model 1	4.45 (2.17–9.11)	<0.001
Adjusted model 2	5.88 (2.72–12.7)	<0.001
Adjusted model 3	5.17 (2.05–13.0)	<0.001
Other independent predictors of AF in model 2		
Age (years)	1.06 (1.03–1.09)	<0.001
Estimated GFR (ml/min per 1.73 m^2)	0.98 (0.97–0.99)	= 0.013
History of HF (yes against no)	3.29 (1.60–6.79)	<0.005
History of hyperthyroidism (yes against no)	5.01 (1.42–17.7)	= 0.012

Targher G, et al. Clinical Science 2013;125, 301–309.

Epicardial fat and NAFLD

Italy, 147 consecutive biopsy-proven NAFLD cases (Kleiner score). Epicardial fat thickness was measured by echocardiography.

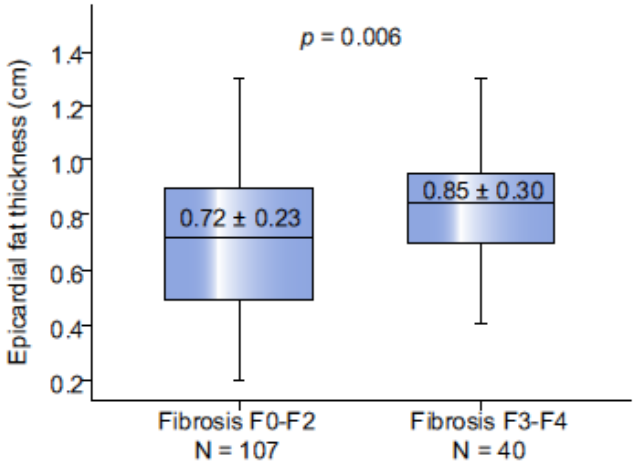


Table 2. Multivariate analysis of risk factors associated with severe liver fibrosis (F3–F4) in 147 patients with non-alcoholic fatty liver disease.

Variable	Multivariate analysis	
	OR (95% CI)	*p* value
Female gender	0.59 (0.25-1.37)	0.22
Age >50 yr	7.38 (2.51-21.6)	<0.001
Visceral obesity	6.77 (0.80-57.0)	0.07
IFG/diabetes	2.97 (1.29-6.80)	0.01
Epicardial fat, mm	1.22 (1.04-1.44)	0.01
Steatosis grade 3	1.90 (0.80-4.49)	0.14

IFG, impaired fasting glucose.

South Korea, 772 subjects underwent abdominal ultrasonography, treadmill test (Heart rate recovery (HRR) is an easy method for measuring Autonomic Nervous System dysfunction), and cardiac echocardiography.

Severe liver steatosis (LS) → higher EFT than those with moderate LS (14.2 ± 2.0 vs. 7.5 ± 3.1 mm, P < 0.001),

EFT was positively correlated with severity of LS (r = 0.431, P < 0.001).

HRR was significantly correlated with EFT (r = -0.386, P < 0.001) and severity of LS (r = -0.324, P < 0.001). EFT and NAFLD were significantly correlated with HRR in patients with MetS and they may be highly related to increased cardiovascular risk. These results suggest a cross-link among EFT, NAFLD, and cardiac autonomic dysfunction in patients with MetS.

Petta S, et al. J Hepatol 2015;62: 928–933.
Cho K. et al. Metab Syndr Relat Disord 2017;15:226-232

What is the relation between NAFLD and the Autonomic nervous System ?

1/ Relation between cardiovascular autonomic functions and time-to-death in patients with terminal hepatocellular carcinoma[1].
2/ NAFLD is associated with autonomic neural modulation of cardiac function in the sympathetic direction[2] independently of conventional cardiovascular risk factors and serum biomarkers (insulin resistance and leptin).

Autonomic Nervous System dysfunction cause or consequence of NAFLD ?

Taiwan, 497 subjects (mean age, 46.2 years), 176 (35.4%) had NAFLD.
5-mn Heart Rate Variability (HRV)

Table 2. Comparison of HRV indices between NAFLD subjects and controls.

HRV indices	NAFLD group (n = 176)	Control group (n = 321)	*P* value
Ln SDNN (ms)	3.50±0.39	3.64±0.38	<0.001
Ln rMSSD (ms)	3.04±0.5	3.23±0.51	<0.001
Ln LF (ms^2)	5.27±0.99	5.49±1.01	0.021
Ln HF (ms^2)	4.84±1.07	5.24±1.07	<0.001

[1] Chiang JK et al. J Pain Sympto Manag 2010
[2] Liu YC, et al. PLoS One 2013

Physiopathology of QTc prolongation in NASH

NASH

Traditional risk factors: obesity, diabetes, HTN, HDL

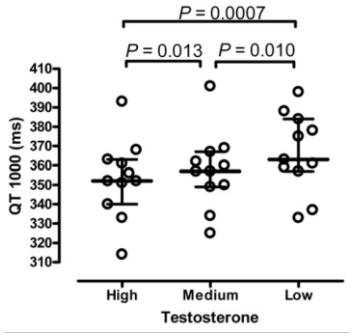
Nervous autonomic dysfunction

Inflammation : elevated CRP, Il6, TNFαR1

Cardiomyocytes

Hormones- Hypogonadism Testosterone?

Prolongation of QTc interval



Conclusions

- NAFLD is a marker of ectopic fat accumulation in other organs, including the myocardium and pericardium→ left atrial remodeling

- Adipocytes from epicardial, retrosternal or abdominal adipose tissues may modulate the electrophysiological properties and ion currents, causing higher arrhythmogenesis (ANS dysfunction)

- NAFLD may release a variety of pro-inflammatory and pro-coagulant mediators and other inflammatory cytokines possibly inducing structural and/or electrical remodelling of the atria

Clinical implications

- Further confirmation using large cohorts studies to assess whether QTc prolongation among patients with NAFLD independently contributes to future cardiovascular events or all-cause mortality is warranted.

- Given the fact that NAFLD is probably a risk factor for cardiovascular morbidity and mortality, a search for every possible link between NAFLD and cardiovascular disease is key to improving outcomes among these patients.

- The pathophysiological pathways through which NAFLD contributes to chronic inflammation, hypogonadism, hypercoagulation, and insulin resistance might represent potential therapeutic targets for the prevention and treatment of myocardial remodeling and the electrophysiological abnormalities of the myocardium in patients with NAFLD.

Thank you

Autonomic Nervous System & Obesity

- ANS regulates cardiovascular system and energy expenditure
- 10% increase in body weight = decline in parasympathetic tone = increase in resting heart rate
- Increase of resting HR is associated with high mortality rates
- 10% reduction in body weight in severely obese subject resulted improvement in cardiac function, decrease of QTc interval

3rd Paris NASH Symposium

French-US Meetings

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