УФИМСКИЙ УНИВЕРСИТЕТ

Recognition of Potentially Dangerous Physiological Conditions

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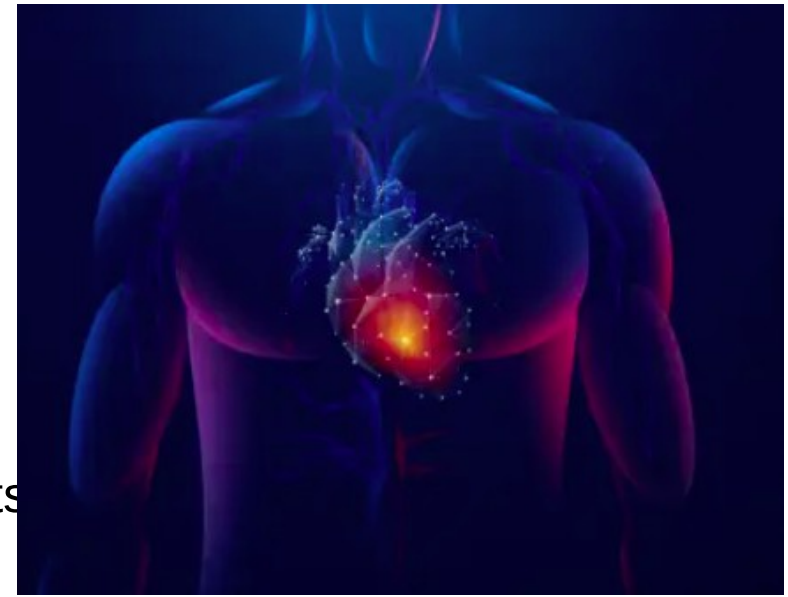
Significance of Study

Cardiovascular diseases are one of the leading causes of death worldwide.

In Russia, between 200,000 and 250,000 people die from cardiovascular diseases every year.



Half of these deaths are caused by the progression of chronic heart failure.

The other half of these deaths are caused by sudden cardiac death (SCD).

In case of timely diagnosis and treatment, these patients could have been saved.

In half of these cases, doctors only discover that the cause of death was SCD after an autopsy.

Often, SCD is caused by genetic factors

Often the SCD diseases are asymptomatic

The main causes of sudden cardiac death (Ruskin, 1994)

1. Coronary Artery Disease
2. Dilated cardiomyopathy
3. Left ventricular hypertrophy
4. Hypertrophic cardiomyopathy
5. Acquired heart defects
6. Congenital heart defects
7. Risk stratification for sudden cardiac death
8. Acute myocarditis
9. Arrhythmogenic right ventricular dysplasia
10. Developmental anomalies of the coronary arteries
11. Sarcoidosis
12. Amyloidosis
13. Cardiac tumors
14. Left ventricular diverticula
15. Wolff-Parkinson-White syndrome
16. Long QT syndrome
17. Brugada syndrome
18. Catecholaminergic polymorphic ventricular tachycardia
19. Ventricular tachycardia
20. Short QT syndrome
21. Drug-induced proarrhythmia
22. Cocaine intoxication
23. Severe electrolyte imbalance
24. Idiopathic ventricular tachycardia

Long QT syndrome (LQTS)

- LQTS is a cardiovascular disease characterized by impaired cardiac repolarization, resulting in an extended QT interval. There is a risk of fainting, seizures, a predisposition to torsade de pointes, and sudden death.
- There are 17 known subtypes of congenital LQTS, each associated with a specific gene.
- Even within the same gene, mutations can affect different mechanisms and manifest themselves in varying degrees of severity, and the same mutation can vary in different patients.
- LQTS has two clinically recognizable forms: autosomal dominant Romano-Ward syndrome and autosomal recessive Jervell and Lange-Nielsen syndrome (which is accompanied by deafness).
- Beta-blockers are commonly used for treatment.
- New approaches in research: the use of human-induced cardiomyocytes derived from pluripotent stem cells, next-generation sequencing, high-throughput patch-clamp, and deep-scan

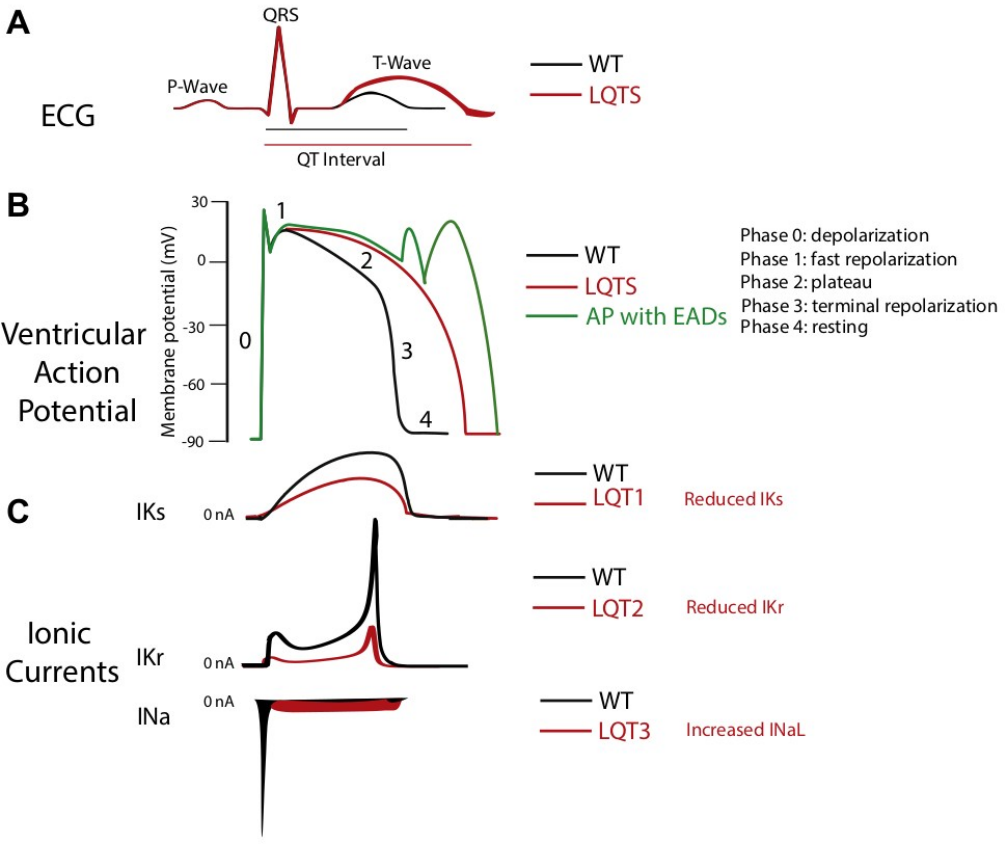
The genetic basis of LQTS

Table 1 Subtypes of congenital long QT syndrome and their associated genes, proteins and effects on cardiac currents

LQTS type	Gene	Protein	Function	Mechanism	Reference
LQT1	*KCNQ1*	Kv7.1	α-subunit I_{Ks}	Loss of function	Wang et al 1996
LQT2	*KCNH2*	Kv11.1	α-subunit I_{Kr}	Loss of function	Sanguinetti et al 1995; Curran et al 1995
LQT3	*SCN5A*	$Na_V1.5$	α-subunit I_{Na}	Gain of function	Wang et al 1995
LQT4	*ANK2*	Ankyrin B	Adaptor	Loss of function	Mohler et al 2003; Schott et al 1995
LQT5	*KCNE1*	minK	β-subunit I_{Ks}	Loss of function	Splawski et al 1997; Schulze-Bahr et al 1997
LQT6	*KCNE2*	MiRP1	β-subunit I_{Kr}	Loss of function	Abbott et al 1999
LQT7 (Andersen syndrome)	*KCNJ2*	Kir2.1	α-subunit I_{K1}	Loss of function	Plaster et al 2001
LQT8 (Timothy syndrome)	*CACNA1C*	$Ca_V1.2$	α-subunit I_{Ca}	Gain of function	Splawski et al 2004
LQT9	*CAV3*	Caveolin	Adaptor	Loss of function	Vatta et al 2006
LQT10	*SCN4B*	$Na_V\beta4$	β-subunit I_{Na}	Loss of function	Medeiros-Domingo et al 2007
LQT11	*AKAP9*	Yotiao, (A- anchor protein 9)	Adaptor	Loss of function	Chen et al 2007; Bottigliero et al 2019
LQT12	*SNTA1*	α1-syntrophin	scaffolding	Loss of function	Ueda et al 2008
LQT13	*KCNJ5*	Kir3.4	α-subunit $I_{K\text{-}Ach}$	Loss of function	Yang et al 2010
LQT14	*CALM1*	Calmodulin 1	Signaling protein	Dysfuntional Ca^{2+} Signaling	Pipilas et al 2016; Boczek et al 2016
LQT15	*CALM2*	Calmodulin 2	Signaling protein	Dysfunctional Ca^{2+} Signaling	Boczek et al 2016
LQT16	*CALM3*	Calmodulin 3	Signaling protein	Dysfuntional Ca^{2+} Signaling	Reed et al 2015; Chaix et al 2016; Boczek et al 2016
LQT17	*TRDN*	Triadin	Ca^{2+} homeostasis regulation	Loss of function	Altmann et al 2015

LQTS = Long QT syndrome.
Adapted from reference Bohnen et al 2017[28] and Adler et al 2020.[8]

The molecular basis of LQTS



- Voltage-activated Na+ and K+ currents determine the ventricular action potential and the QT interval on the ECG.

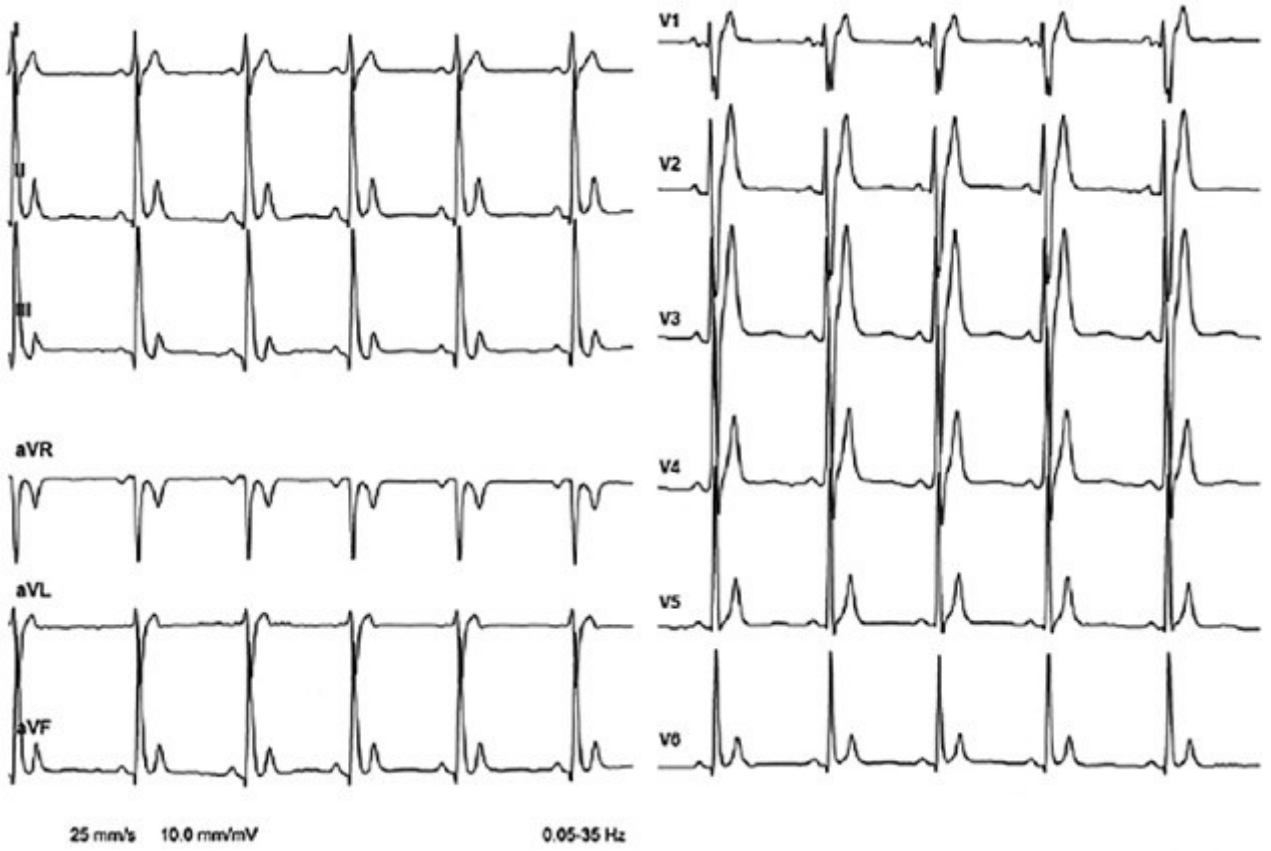
  A: ECG under normal conditions (black curve) and LQTS (red curve). The duration of the QT interval is determined by the repolarization time of the ventricles.

  B: Normal ventricular action potential (black graph), where the rapidly activating and inactivating INa peak causes membrane depolarization; there is a very small sustained or late INaL. Two K+ currents, IKs and IKr, contribute mainly to the plateau phase and repolarization phase of the action potential, which restores the resting membrane potential. The functional effect of loss of IKs or IKr function or enhancement of INaL function on the ventricular action potential leads to prolongation of the ventricular action potential associated with LQT1, LQT2, and LQT3, respectively (red graph). Action potential with early post-depolarization events (green line).

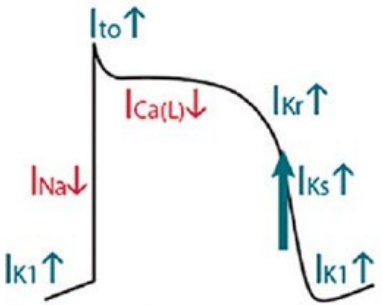
- C: Simulation of the normal time course and amplitude of the currents IKs, IKr, and INa (black lines). Simulate

Short QT syndrome (SQTS)

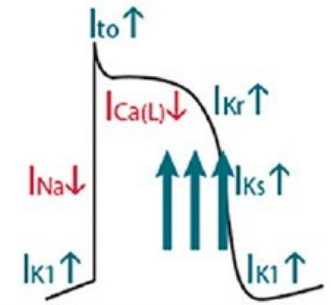
- SQTS is a hereditary cardiac channelopathy characterized by an abnormally short QT interval (QTc <330 ms) and an increased risk of atrial and ventricular arrhythmias and sudden death.
- These patients experience cardiac arrest, unexplained fainting, or atrial fibrillation (AF) at a young age.
- Diagnosis is based on the assessment of symptoms (fainting or cardiac arrest), family history, and electrocardiogram (ECG) findings.



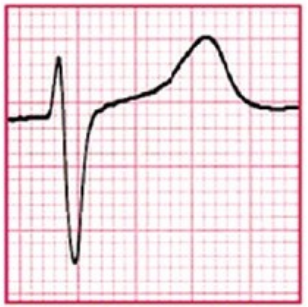
The proposed molecular mechanism of short QT syndrome



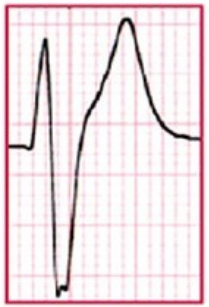
Normal action potential duration



Shortened action potential duration



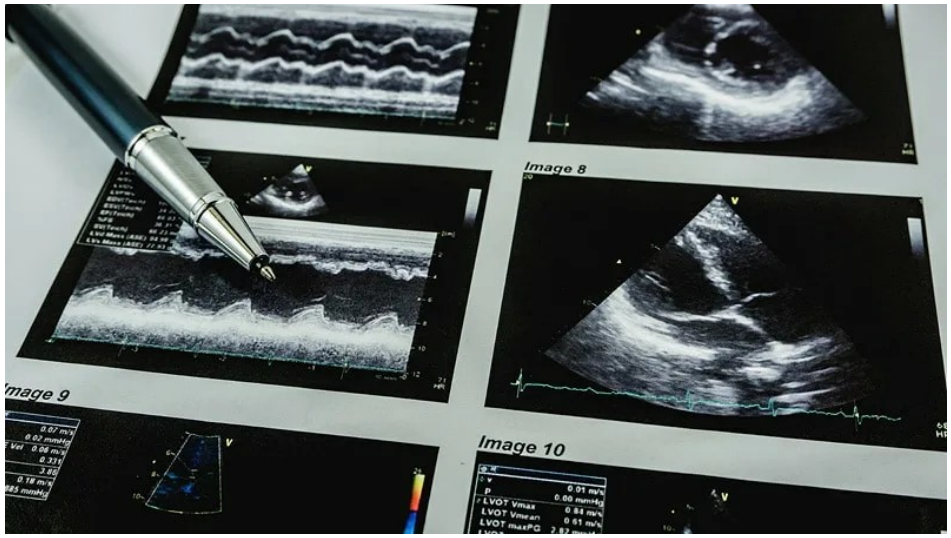
Normal QT interval

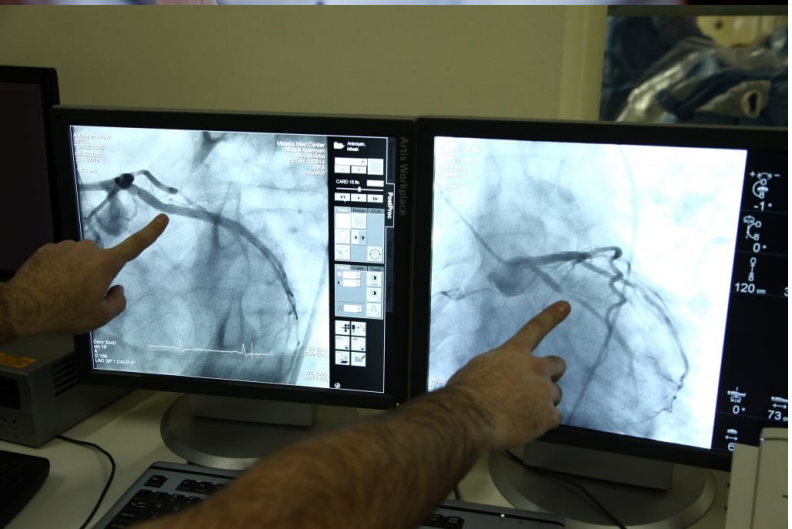


Short QT interval

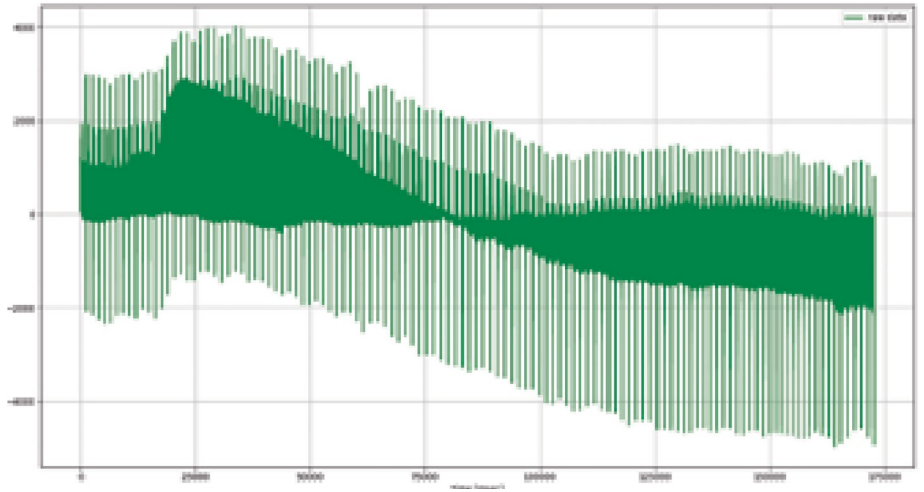
- SQTS describes three main genetic variants involving potassium channel genes. Mutations that enhance potassium function and mutations that impair calcium channel function result in shorter repolarization phases during the action potential and shorter QT intervals.

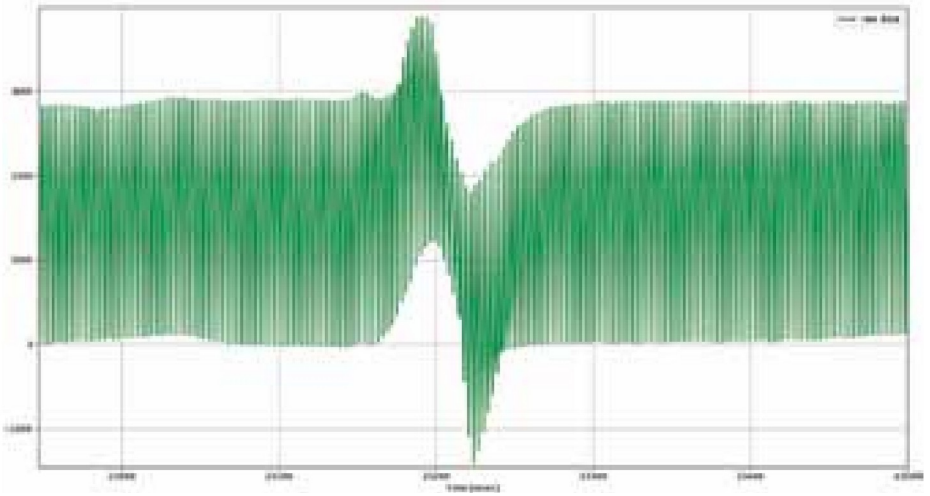
Diagnosing of SCD

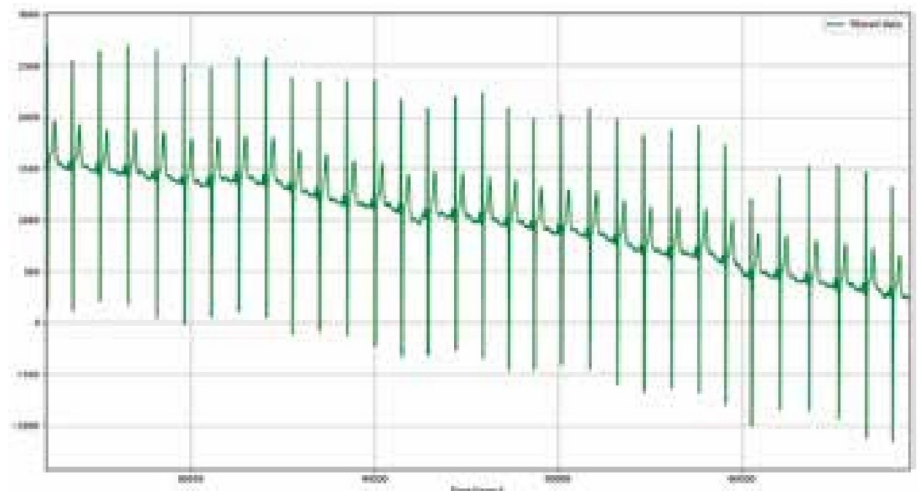


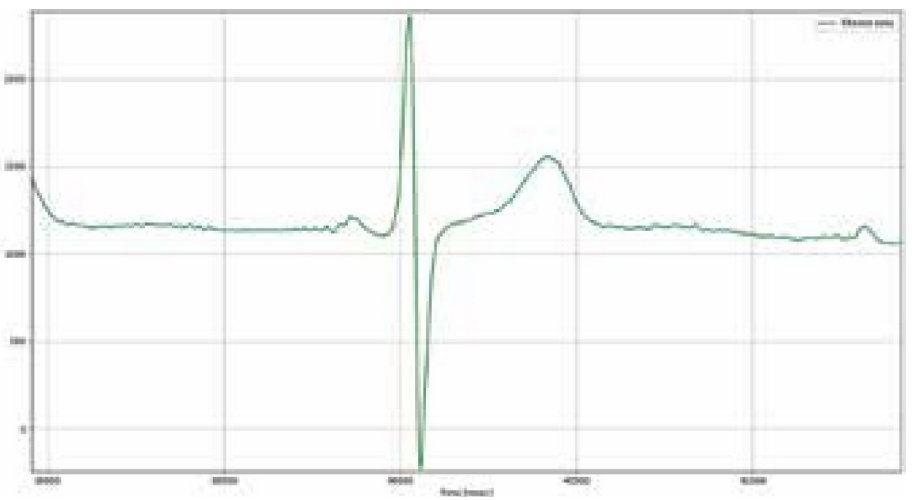


ECG Preprocessing

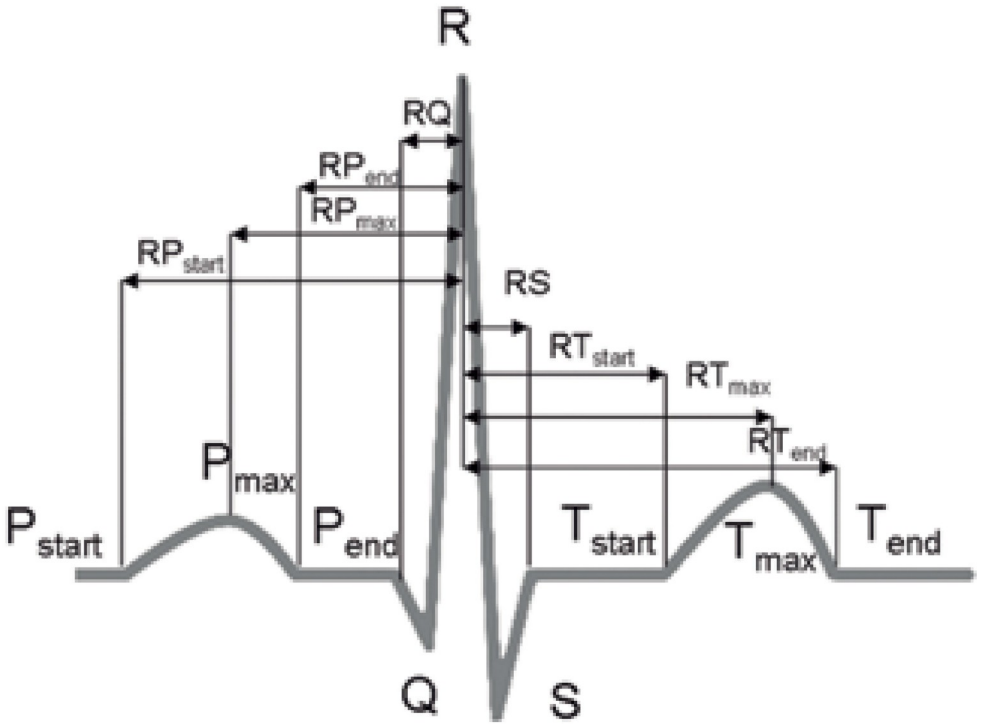


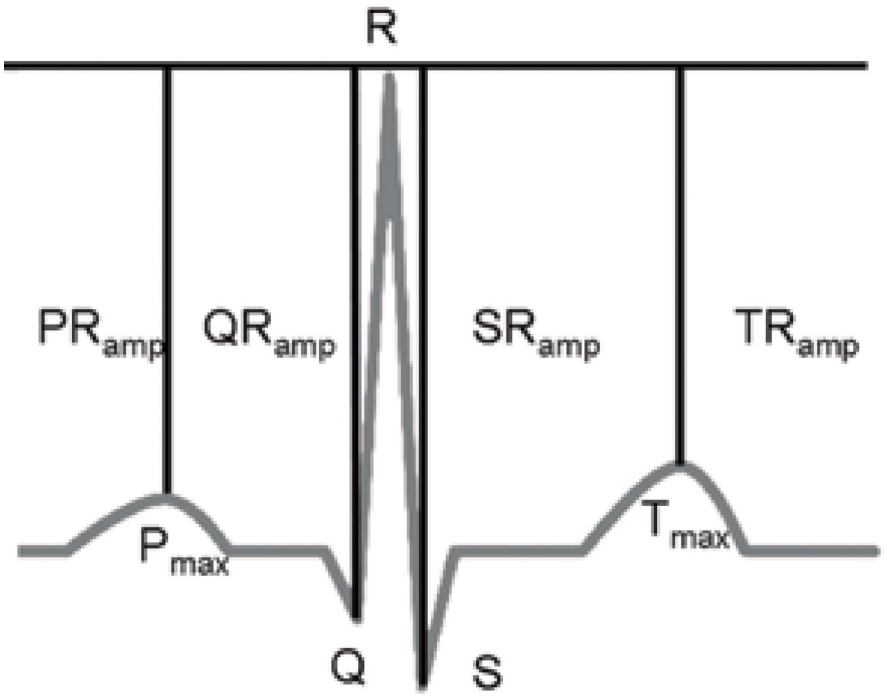




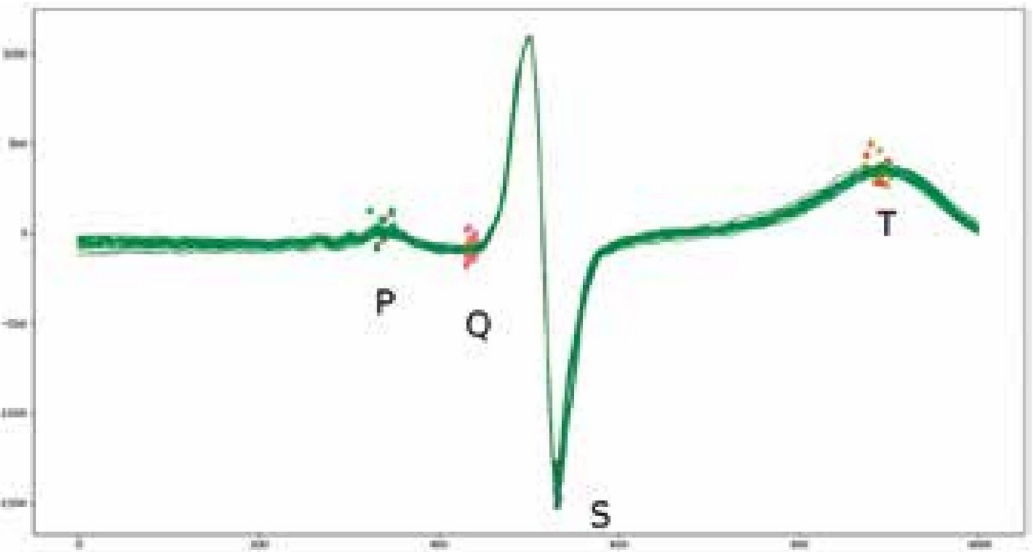


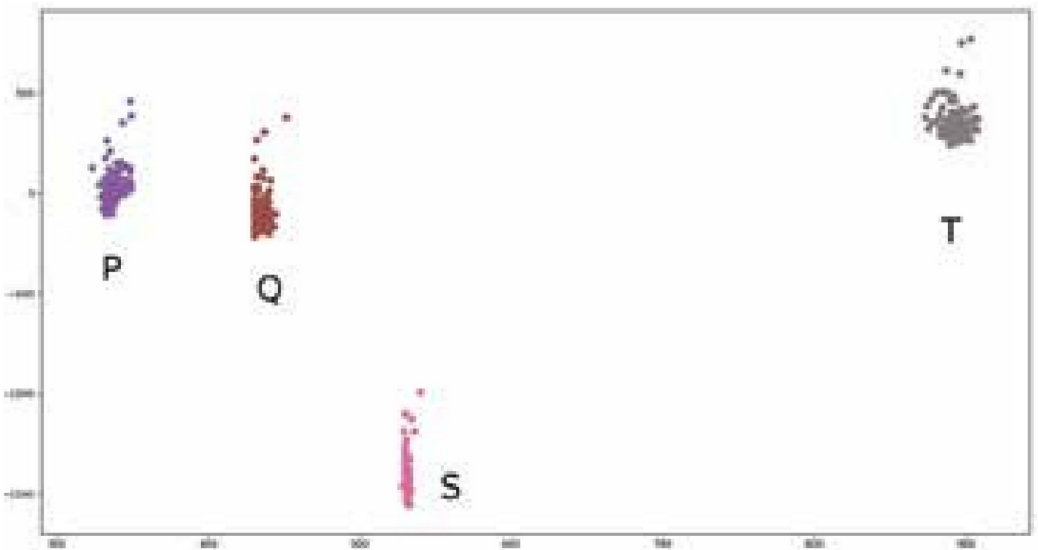
Recognizing of ECG (biomarker extacting)





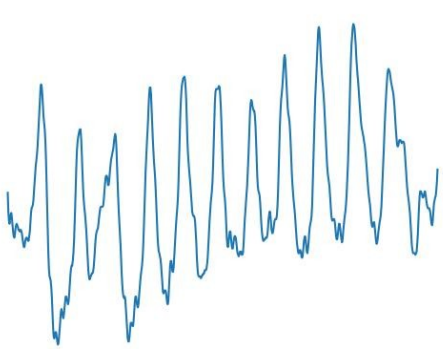
Recognizing of ECG (feature extacting)

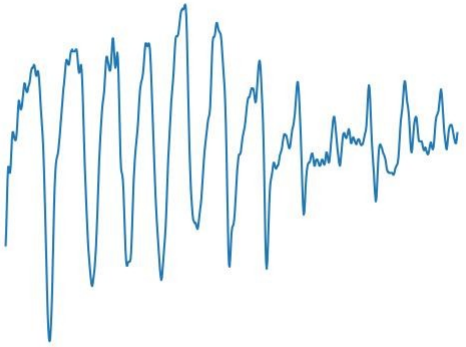


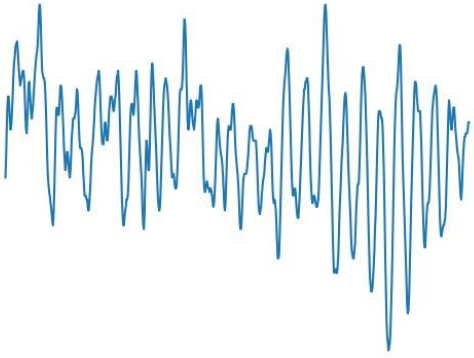


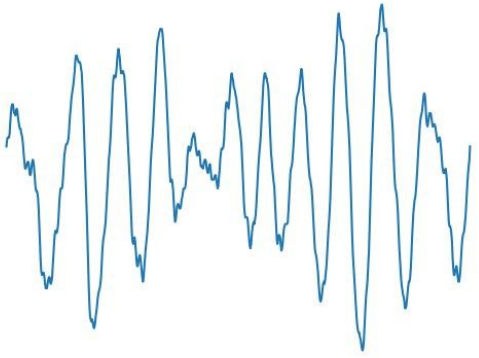
Heart rate variability

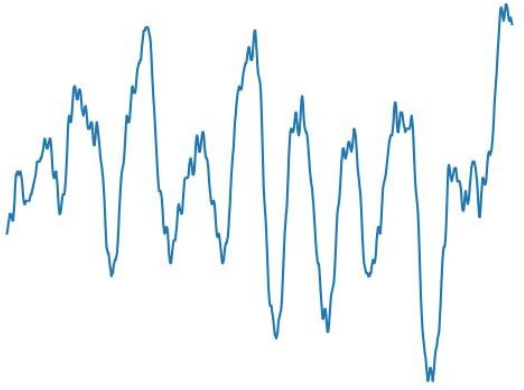
Dangerous Ventricular Fibrillation



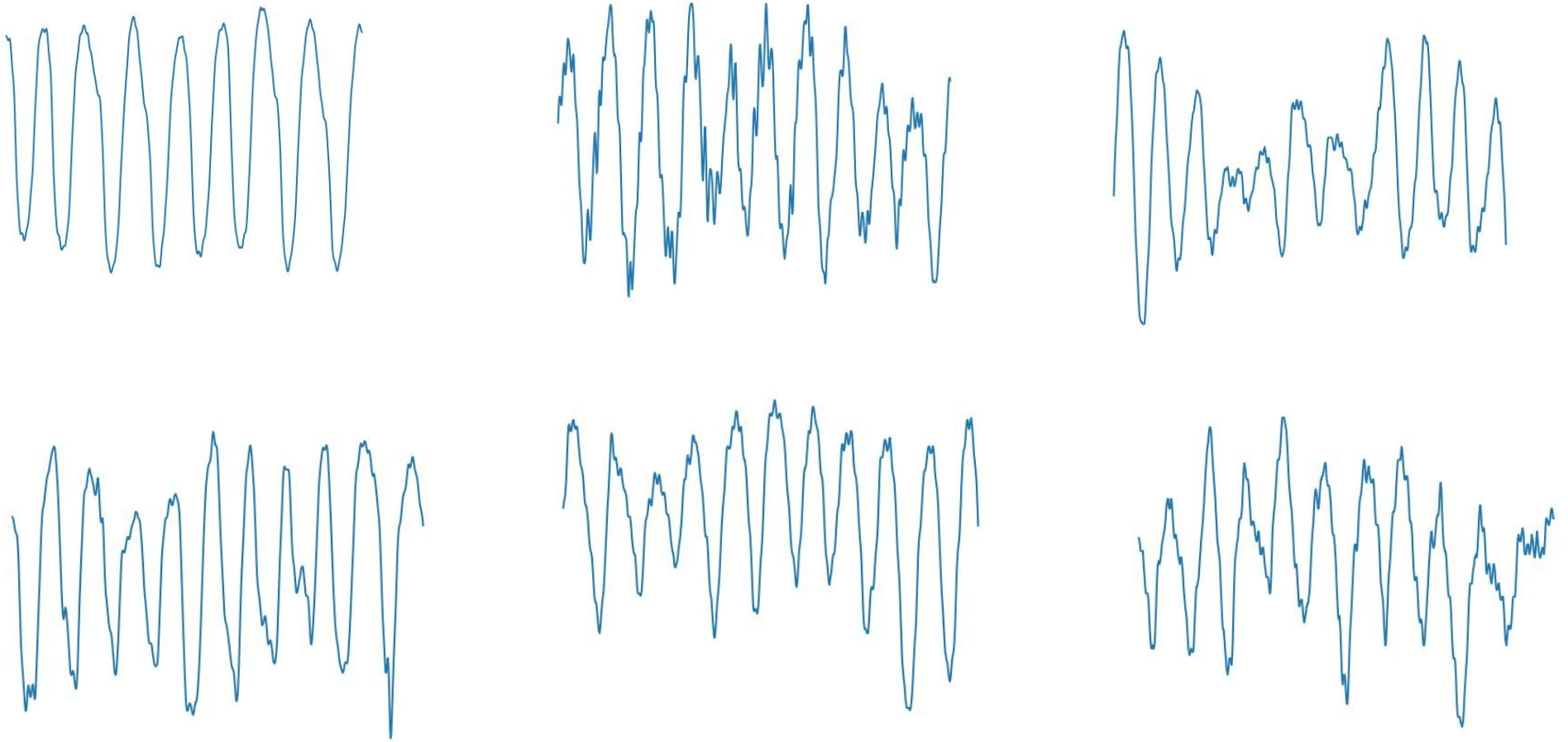




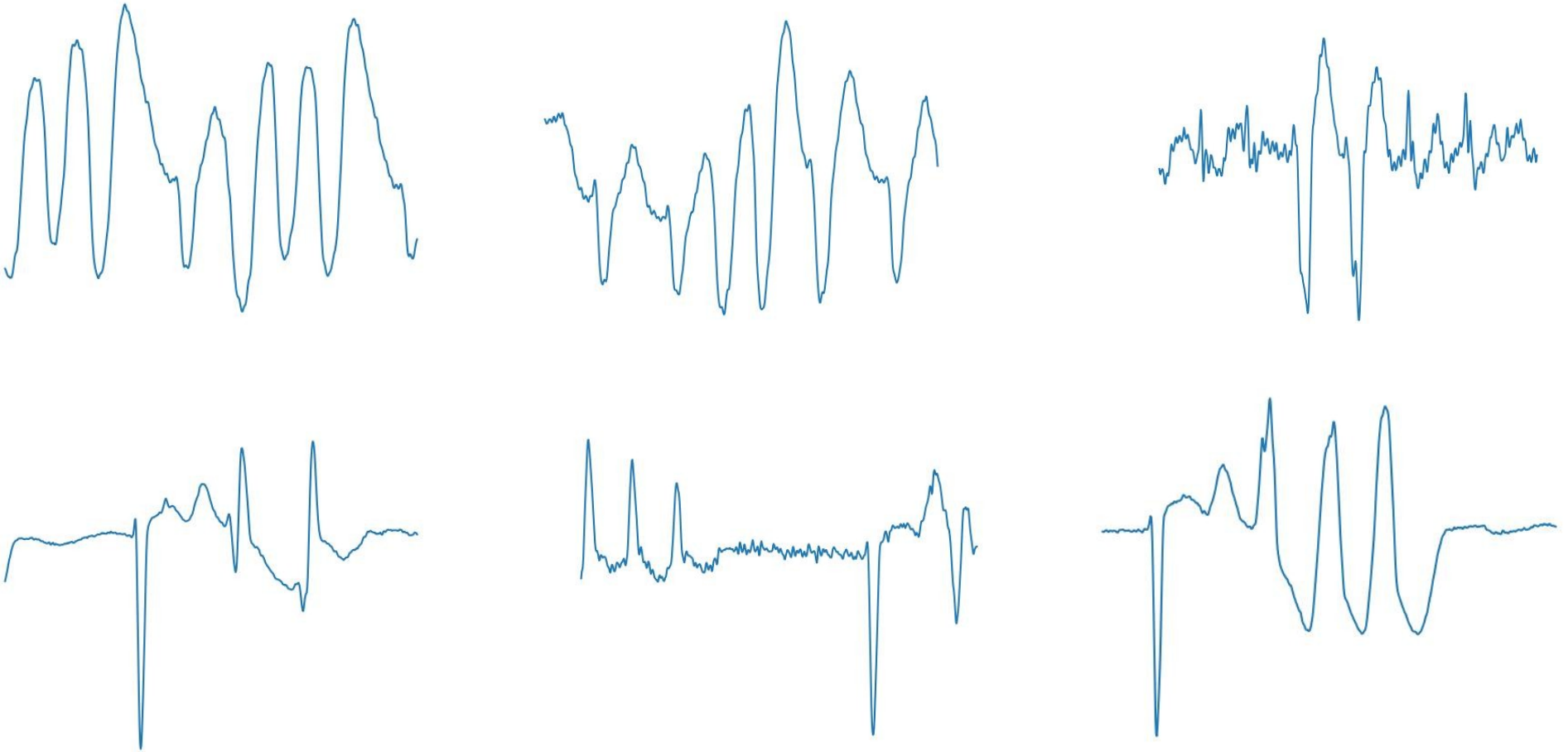




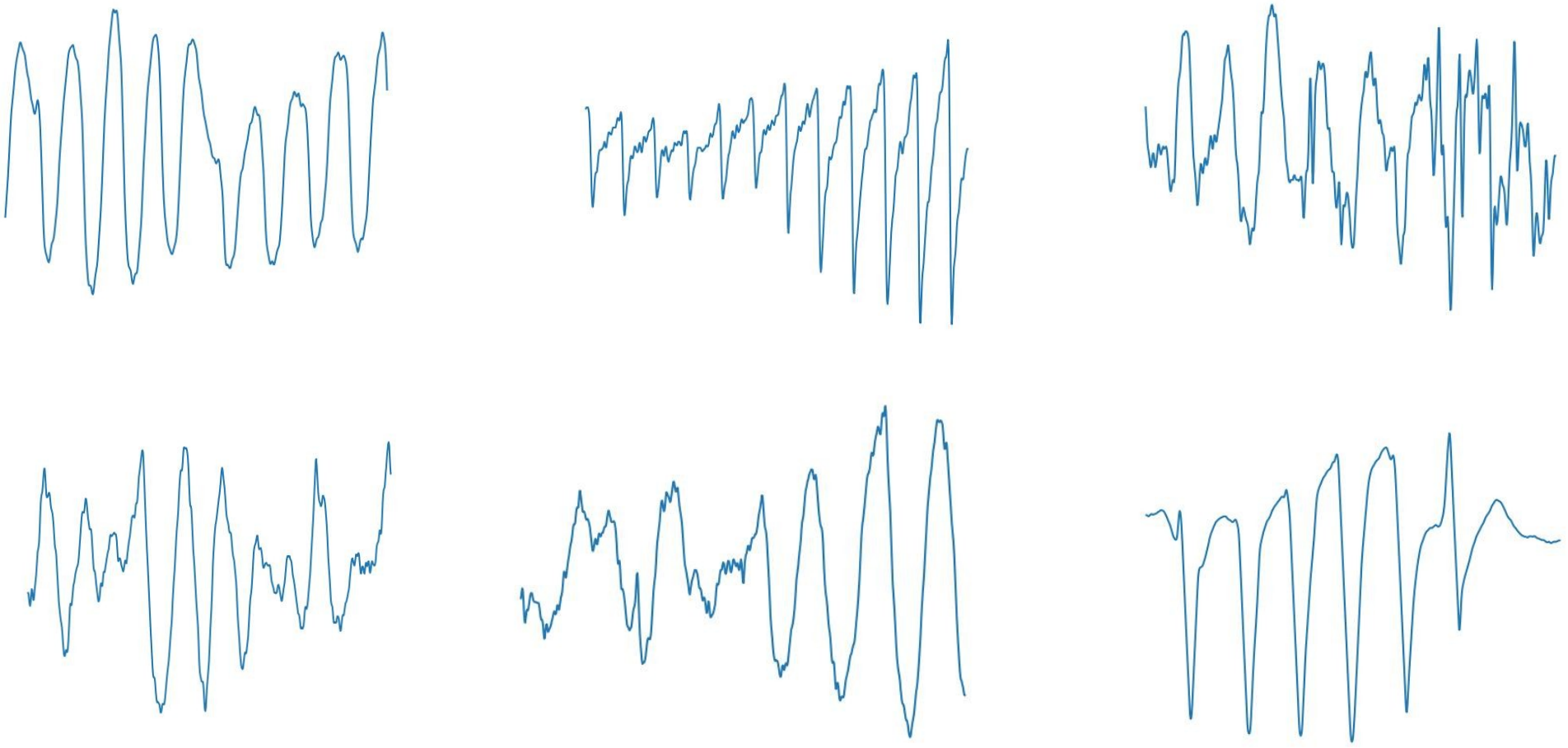
Dangerous Ventricular Flatter



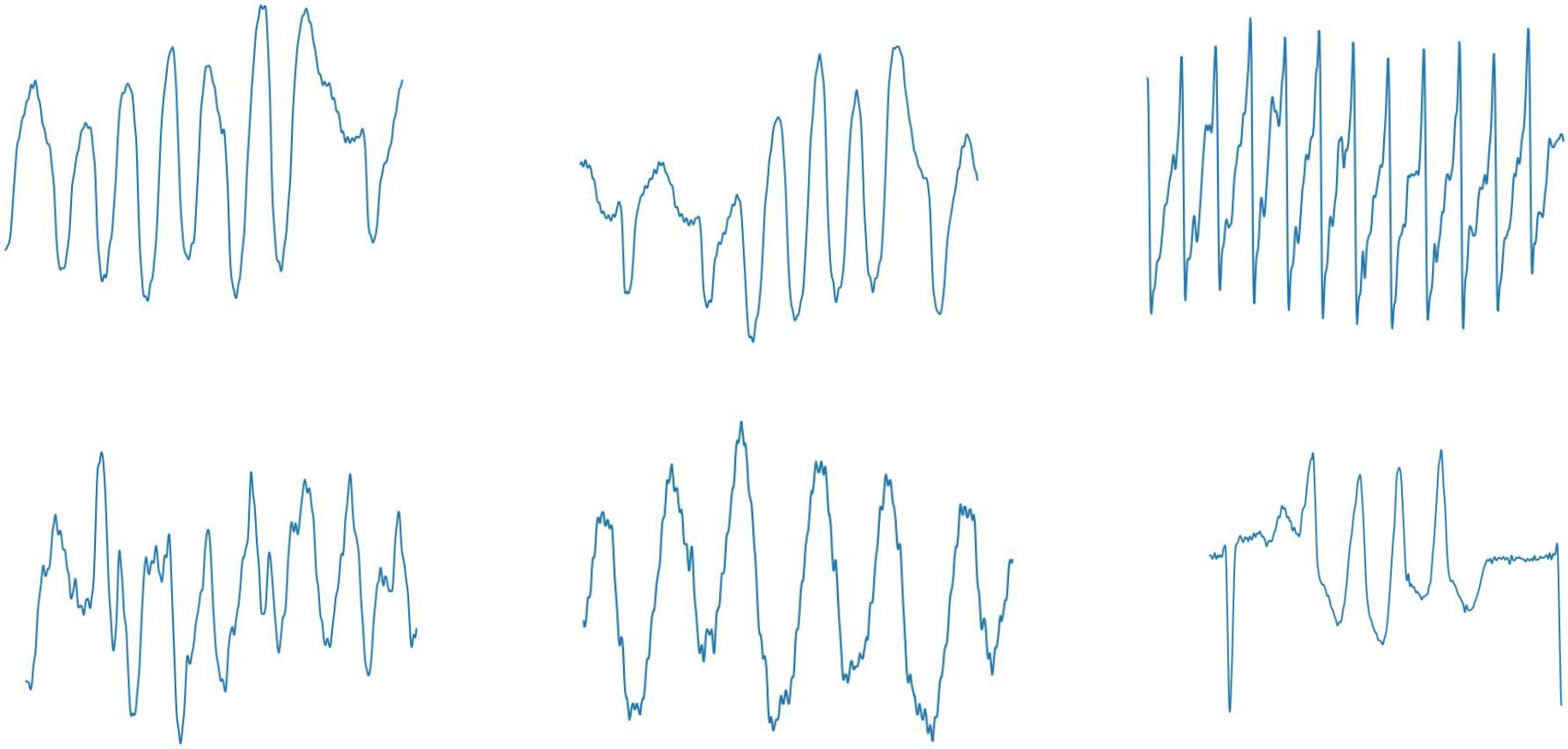
Potentially dangerous high degree of ventricular ectopic activity



A special form of life-threatening arrhythmias: ventricular tachycardia torsade de pointes



Life-threatening ventricular arrhythmias: high rate ventricular tachycardia (monomorphic and polymorphic)



The specifics of SCD diagnosis

- There are some pitfalls in the traditional method of electrocardiogram recognition.
- Different diseases can have similar patterns of cardiac cycles
- Similar patterns of cardiac cycles can occur in different diseases
- Predictors of sudden cardiac death can occur rarely and only for a short period of time, making them easy to miss during routine medical examinations.
- The solution lies in combining two approaches:
- 1) online monitoring of the cardiovascular system
- 2) post-processing of long-term ECG measurements

Motivation and Aim

- The purpose of the proposed study was to develop software designed to recognize potentially dangerous physiological conditions (predictors of sudden cardiac death) by analyzing digitized electrocardiograms. The software should have the ability to detect predictors of sudden cardiac death of short duration (2-3 seconds), and it should also generate a report on the detected potentially dangerous physiological conditions.

  To implement the project, the following steps need to be taken:

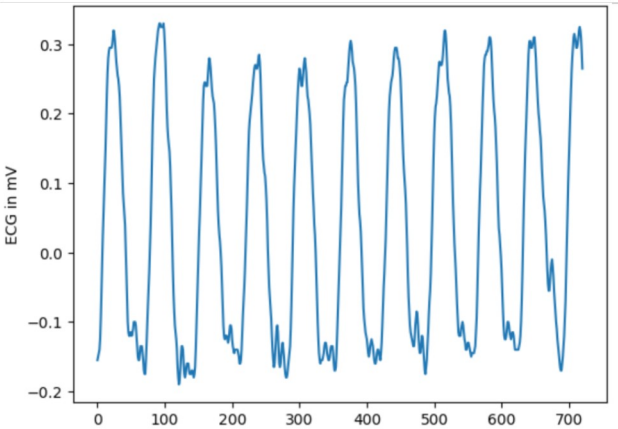
- 1. Preparing a training data set
- 2. Extracting features
- 3. Training a model for feature classification
- 4. Testing the model on an alternative dataset
- 5. Deploying the application.

1. Training dataset preparation

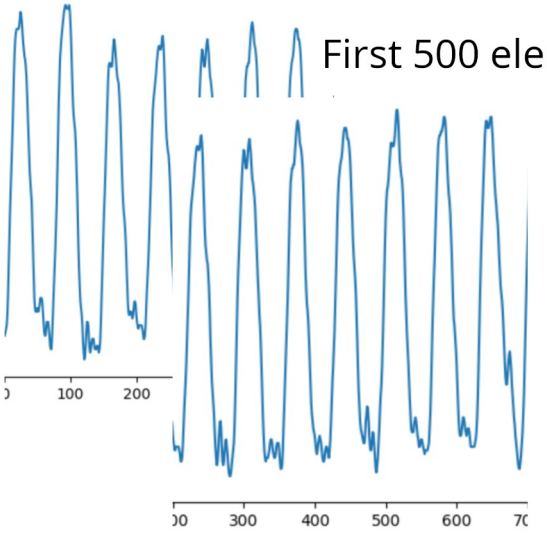
- ECG Fragment Database for the Exploration of Dangerous Arrhythmia, developed by scientists from INCART based on the MIT-BIH Malignant Ventricular Ectopy Database dataset.
- The dataset contains ECG fragments consisting of 721 elements (sampling rate of 250 Hz, signal duration of 2.884 seconds). There are 16 diagnostic classes (ventricular flutter, ventricular fibrillation, torsade de pointes ventricular tachycardia, high-frequency ventricular tachycardia (monomorphic and polymorphic), low-frequency ventricular tachycardia (monomorphic and polymorphic), ventricular bigeminia, high degree of ventricular ectopic activity, ventricular replacement rhythm, atrial fibrillation, supraventricular tachycardia, sinus bradycardia, first degree cardiac blockade, nodular (a-b) rhythm, sinus rhythm with blockage of the bundle of His, normal sinus rhythm, normal rhythm with a single extrasystole).

Feature extraction

- We decided not to rely on cardiac cycles, but to use short ECG fragments of fixed duration (2 seconds).
- When implementing this approach, it is necessary to take into account the possible time shift between the ECG fragments used in the model training and the ECG fragments that need to be recognized. To solve the shift problem, a sliding window was used, where a sample of 500 elements is selected from the left part of an array containing 721 elements (500/250 = 2 seconds), then the window is shifted one position to the right, and the selection is repeated 221 times (721-500).



Initial signal



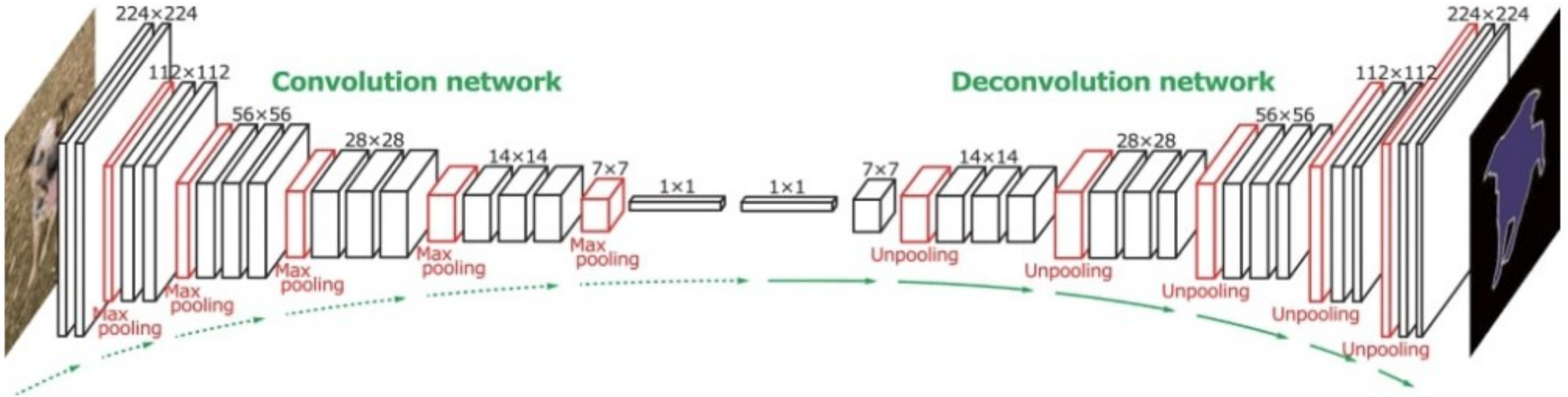
First 500 elements

Last 500 elements

Shift by 221 positions

3. Training a model

A fully connected convolutional neural network was used for feature classification. The accuracy metric on 16 classes was 0.99.



4. Testing the model on an alternative dataset

- The effectiveness of the proposed approach was evaluated using the Sudden Cardiac Death Holter Database [13]. The accuracy metric was 0.95 (Sudden Cardiac Death Holter Database. https://physionet.org/content/sddb/1.0.0/. July 2, 2004). The effectiveness was evaluated by Professor I. Shaybakov, Head of the Cardiology Department at the Republican Clinical Hospital No. 2.

5. Application Deployment

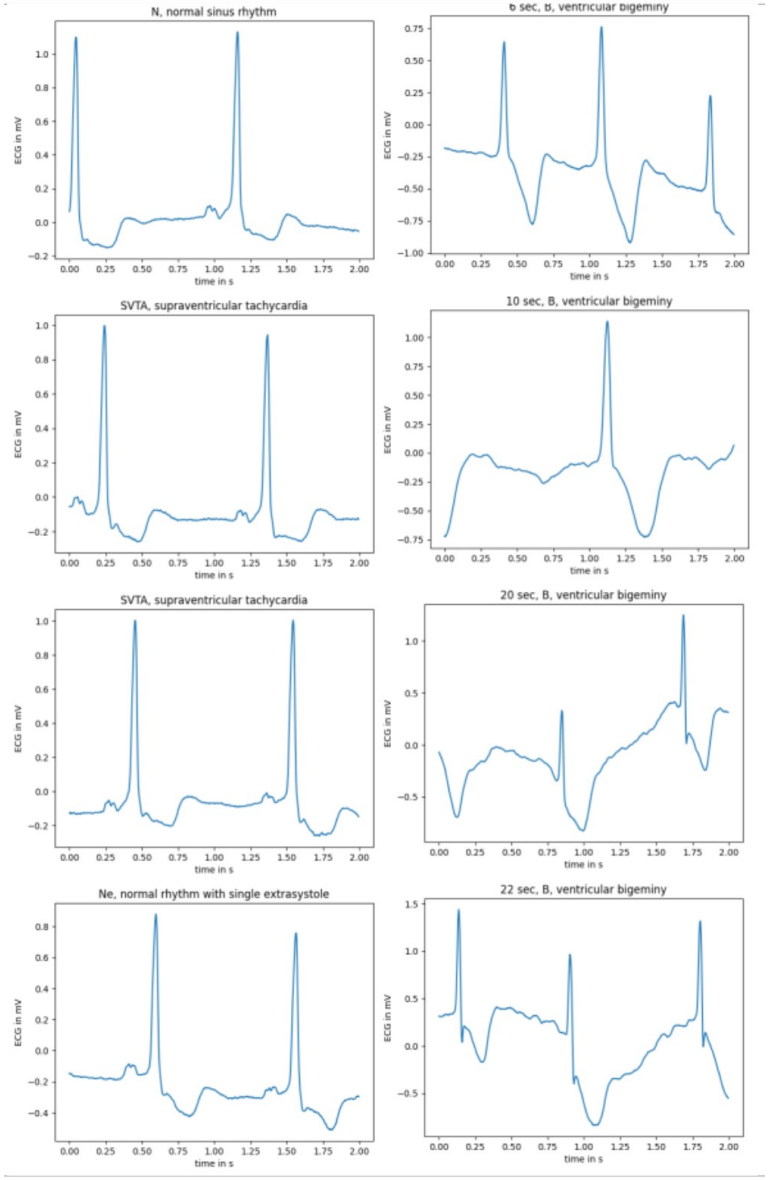
- To train the electrocardiogram classification model, software was developed in Python to detect potentially dangerous physiological conditions. The Tensorflow (Keras) framework was used. The FCN model was trained on a computer with an Intel Core i9 processor, 256 GB of RAM, and an NVIDIA 3080 Ti.
- Several deployment scenarios are being considered.

1. Postprocessing

A server application based on the FastAPI framework has been developed (available at: github.com/Fakek0f3sT/CardioRiskRecognizer). The application allows you to upload digitized electrocardiograms in waveform database format, cut them into two-second fragments, and recognize each fragment individually. Below is the result of recording recognition from the Sudden Cardiac Death Holter Database (https://physionet.org/content/sddb/1.0.0/). The summary table shows the number of fragments for each detected diagnosis. The app also allows you to display the classification results frame by frame or by selected diagnosis.

Postprocessing results of Holter ECG

Diagnosys	Fragments number
Ventricular fibrillation	492
Ventricular tachycardia of the "pirouette" type	26
High-frequency ventricular tachycardia	1313
Low-frequency ventricular tachycardia	1
Ventricular bigeminy	674
High degree of ventricular ectopic activity	226
Ventricular replacement rhythm	1570
Atrial fibrillation	183
Supraventricular tachycardia	4
First degree heart block	127
Nodal atrioventricular rhythm	559
Sinus rhythm with bundle branch block	25
Normal sinus rhythm	1386
Normal rhythm with single extrasystole	3824
Total:	10410



An example of the software operation. The left column shows the results of recognition of 2-second time intervals of the ECG, the right column shows statistics on ventricular bigeminy

2. Online monitoring

From our point of view, smartwatch technology has great potential. These devices work in conjunction with smartphones. Unfortunately, Google has been inconsistent in its support for ECG recording in Android. Currently, this feature is not supported. If it were possible, the TensorFlow/keras model could be converted to TensorFlow Lite, and the smartwatch could potentially function as a single-channel electrocardiograph in conjunction with a smartphone.

3. Using edge computing

A very interesting solution, in our opinion, is the use of small autonomous computing modules used in the Internet of Things, smart cameras, and so on. NVIDIA provides an example of successful recognition of artemia using an NVIDIA Jetson device. In the future, it would be possible to connect ECG sensors to an NVIDIA Jetson Nano Orin and run a recognition model on this device, creating an analog of a clinical electrocardiograph.

Results

The proposed approach allows you to recognize 16 classes of potentially dangerous physiological conditions with an efficiency of 0.95, using two-second fragments of electrocardiograms. The FCN model was trained in the tensorflow/keras format. A web service was implemented using FastAPI technology, and it can be deployed as a mobile app or an app running on edge AI devices.

Thank you for your attention!