ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–3
doi:10.1093/eurheartj/ehab611

EDITORIAL

Long QT syndrome, artificial intelligence, and common sense

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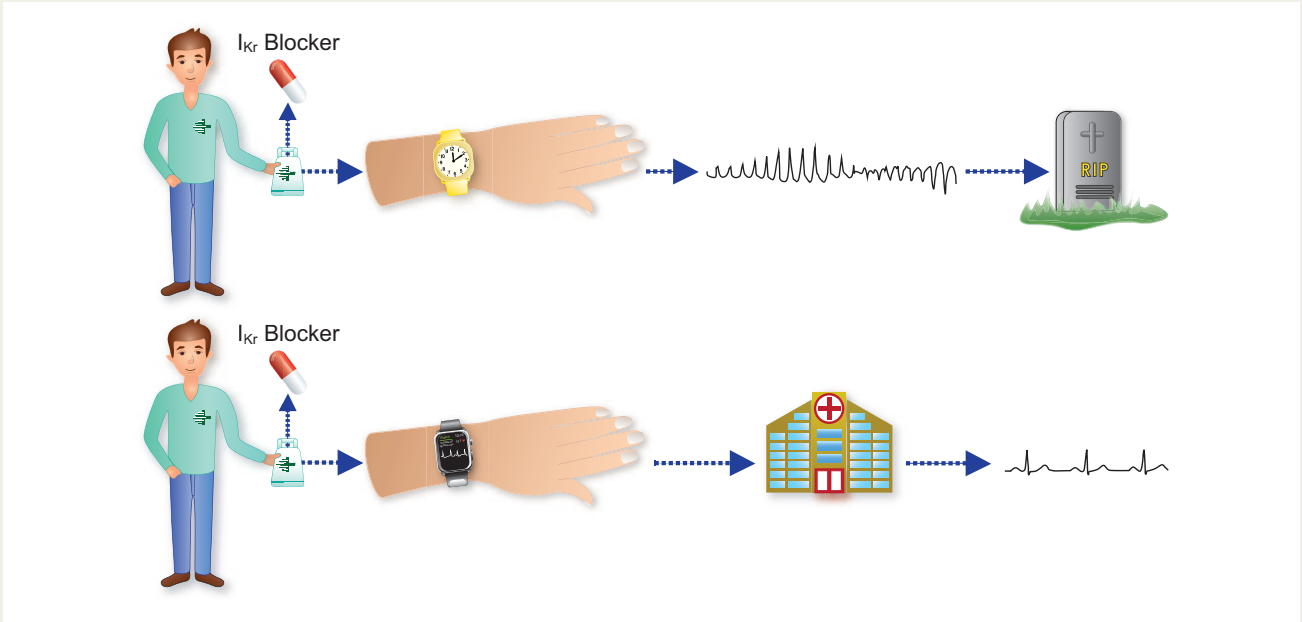
This editorial relates to 'Deep learning analysis of electrocardiogram for risk prediction of drug-induced arrhythmias and diagnosis of long QT syndrome' by E. Prifti et *al.*, doi:10.1093/eurheartj/ehab588.



Graphical Abstract Top: current situation. A patient receives an I_{Kr} blocker from his/her doctor, develops TdP, and dies. Bottom: possible future. A patient receives an I_{Kr} blocker from his/her doctor but he/she wears a device operated by AI. This device recognizes a significant rise in the footprint of I_{Kr} block (TdP footprint) in a timely manner. This offers the patient sufficient time to alert his/her doctor, who can then act in time to avert the risk of TdP.

We are being inundated by so many articles dealing with artificial intelligence (AI) to the point that one begins to wonder about what happened to natural intelligence. Clinical cardiologists are following these rapid developments with mixed feelings. They struggled in the 1990s to survive the assault by the genetic jargon and still shiver recalling how they survived the jungle populated by introns and stop codons, and are now cowed by the new army of 'machine learning', 'convolutional neural networks', and 'deep learning algorithms'.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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These fears, however, are unjustified. Under the cover of Latin, most of these new methodologies are just complex and elegant ways to use a rather old instrument: pattern recognition. This essentially is what we all use to recognize other human beings, not by measuring the distance between their eyes or the size of their ears, but by simply recognizing 'a face'. Cardiologists are not new to this approach as already several years ago, using natural intelligence, they wrote 'one does not measure the QT interval, one looks at it'.[1]

The use of the term AI has skyrocketed during the last few years and it has recently also entered the field of cardiac arrhythmias.[2,3] These AI applications are largely based on the analysis of signals representing cardiac electrical activity, specifically ECG and photo plethysmography, the latter being used in wearable devices, including watches and smart phones. One area that presents many facets for potential reward by the use of AI technology is the one related to prolongation of the QT interval, be it due to genetic mutations such as the congenital long QT syndrome (cLQTS),[4] or secondary to drugs[5] (drug-induced long QT syndrome, di-LQTS) or conditions such as hypokalaemia[5] and acute myocardial infarction.[6] The importance of QT prolongation is related to its established association with life-threatening arrhythmias, especially Torsades de Pointes (TdP) ventricular tachycardia, and sudden death.[7] It is thus not surprising that investigators, knowledgeable in the field of LQTS,[8,9] have started to apply AI methodologies to this intriguing disorder, which probably represents the best example of a tight correlation between genotype and phenotype.[10] These studies by Ackerman's group focused primarily on the detection of cLQTS and the apparent superiority of AI compared with the simple assessment of QTc.[8,9]

A major progress in this rapidly developing field is presented in this issue of the *European Heart Journal*, where the group led by Prifti and Salem reports its AI-driven model developed to detect ECG patterns that reflect diLQTS.[11] This study is also important for cLQTS, but goes well beyond it. They used a convolutional neural network (CNN) trained with one dataset (and validated in another independent similar dataset) to analyse ECGs from healthy individuals before and after the intake of sotalol, a blocker of I_{Kr}, the cardiac ion current impaired in cLQTS type 2 (LQT2). In effect, this novel AI-driven model is designed to recognize ECG patterns associated with I_{Kr} block, independently of its origin. Prifti *et al.* demonstrate that their model has high accuracy in identifying not only ECGs of healthy individuals taking sotalol, but also of LQT2 patients. Furthermore, their model correctly also identified ECGs of LQT1 and LQT3 patients, albeit with somewhat lower accuracy compared with LQT2. Even though the shape of the T-wave already differs upon visual inspection between the cLQTS types,[12] it is clear that some elements of the ECG are shared between the various types of cLQTS, most importantly obviously QT prolongation.

The main advance of this novel AI model probably lies in its ability to recognize I_{Kr} block from a simple ECG. This is important, because I_{Kr} block underlies the vast majority of diLQTS cases[7], as I_{Kr} is blocked by a wide range of drugs prescribed for the treatment of both cardiac conditions (class Ia and III antiarrhythmic drugs, for which I_{Kr} block is their designed mode of action) or non-cardiac conditions (e.g. antidepressant, anticancer, antiemetic, antibiotic drugs, for which I_{Kr} block is an off-target effect).[7] diLQTS has great clinical relevance because of the widespread use of these drugs. This AI model may be of particularly great significance for the prescription and follow-up of non-cardiac QT-prolonging drugs, which are mostly prescribed by physicians (typically non-cardiologists) who have less knowledge and experience with ECG analysis, and often less access to tools for ECG recording. Indeed, the real-life risk of sudden cardiac arrest of non-cardiac QT-prolonging drugs actually exceeds that of cardiac QT-prolonging drugs.[13] Of particular interest, there are two features of the novel AI tool that seem to render it suitable for application as a QT-monitoring tool, which may change clinical practice: its ability to detect changes in the ECG pattern at least 24 h before TdP actually occurs, and the fact that its diagnostic accuracy is equally high in a one-lead ECG recording as in a 12-lead recording. These features are key assets for the development of an easy-to-use (possibly operated by the patient) remote monitoring system to detect potentially hazardous ECG changes in time to take actions to avert arrhythmic risk. Such a novel risk-monitoring system may not only be superior to current methods, but it may also change the way we utilize QT-prolonging drugs. This system may replace our strategy of pre-prescription risk prediction, currently used but far from perfect, with more accurate real-time monitoring. This may not only reduce the risk of adverse arrhythmic events, but it may also give us more confidence when prescribing these drugs, thereby allaying our fears and, in some patients, lifting our overprotective inhibition to prescribe these drugs on which large patient groups with a wide variety of medical conditions have to rely.

CNNs were introduced by LeCun *et al.*[14] in 1990 with the objective to automatically extract abstract features from the data while preserving their spatial configuration as well as ensuring the property of translation invariance, which is the ability to recognize the objects even when the appearance varies under a number of transformations. These characteristics made CNN models very popular in many fields where shapes are important, including image and signal analysis. The basic architecture of CNNs is composed of three types of layers, i.e. convolutional, pooling, and fully connected layers[14] combined together multiple times. Different declinations of CNNs have greatly improved their performances, including residual based architectures such as the most recent DenseNet.[15] Unlike traditional linear convolutional architectures, DenseNet, also used by Prifti *et al.*, extracts ECG features and reuses them later in the network. Therefore, each layer receives inputs from all the preceding ones and passes its own output to all subsequent layers. As a consequence, the final output layer has direct information from every preceding layer, which optimizes computation, while allowing complex multilevel representation of the features detected anywhere on the input signals.

At variance with most previous studies, where CNN models are applied to pre-processed (e.g. filtered) heart beat data, Prifti *et al.* applied their DenseNet model on 10 seconds of unprocessed ECG data without any additional inputs. While often categorized as black boxes, deep neural networks such as CNNs can be probed with the proper set of tools to inform the user of how they see the data, and what part of the signal contributed most to their decision, e.g. the initial part of the ST segment in the present algorithm.[11] A whole field in AI is focusing on making these models more interpretable.

Prifti *et al.* are the first to demonstrate what risk footprints on ECG could look like.[11] This principle lies in the fact that ECGs may contain subtleties not always readily interpretable by humans. It is likely that several other risk conditions such as ischaemia or heart

failure may be similarly identified from the ECG. Thus, the ability to recognize underdiagnosed, potentially treatable conditions from an ECG in a cost-effective manner holds the potential to improve population health.

There is a possibility that in the near future AI will replace rule-based expert systems, since deep learning approaches result in better recognition of complex patterns hidden in high dimensional medical data. However, there are limitations that need to be considered and overcome. Deep learning approaches, as others, require large training datasets to achieve high quality and unbiased results. Also, data are often obtained from specific populations, which may introduce bias and limit the generalization of the models. Another potential stumbling block is represented by interpretability of the results. In general, it is difficult to interpret non-linear features of deep neural networks because results depend on complex interactions with features from other layers. Making these models more robust, unbiased, and interpretable for clinical use will require large clinical studies where the same concepts of evidence-based medicine should apply. This should also tackle legal and ethical issues in using them in clinical practice.

At the end of the day, one has to recognize that the study by Prifti *et al.*[11] has the potential to be ground-breaking conceptually and in its translational impact. Indeed, the possibility that the risk of life-threatening arrhythmia might be reduced by involving patients in monitoring their own risk with an easy-to-use wearable device that uses AI to detect tell-tale ECG changes well in time for them to call on their physician and for the physician to take appropriate life-saving actions may no longer belong to science fiction.

Acknowledgments

The authors are grateful to Davide Gentilini, PhD, for useful suggestions, and to Pinuccia De Tomasi, BS, for expert editorial support.

Funding

This work has received funding from the European Union's Horizon 2020 research and innovation programme under acronym ESCAPE-NET, registered under grant agreement no. 733381, and the COST Action PARQ (grant agreement no. CA19137) supported by COST (European Cooperation in Science and Technology), and from the Leducq Foundation for Cardiovascular Research grant 18CVD05 'Towards Precision Medicine with Human iPSCs for Cardiac Channelopathies'.

Conflict of interest: none declared.

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