The AMPS Insider

An AMPS LLC Magazine

The AMPS Insider is a quarterly magazine dedicated to all AMPS' partners and customers.
Published by AMPS, it provides news and information about AMPS' products and initiatives.

#8 - 4Q2022

Executive Overview

Incorporation of Serial 12-Lead Electrocardiogram with Machine Learning to Augment the Out-of-Hospital Diagnosis of Non-ST Elevation Acute Coronary Syndrome. Consumer-Led Screening for Atrial Fibrillation. Deep learning predicts atrial fibrillation – with low precision. Product news. AMPS People.

Editorial

We are continuing the **AMPS**' tradition of participation in research projects in this **TAI** issue, as we feature one new paper published in the past quarter:

Incorporation of Serial 12-Lead Electrocardiogram with Machine Learning to Augment the Out-of-Hospital Diagnosis of Non-ST Elevation Acute Coronary Syndrome. The abstract reads:

Study objective

Ischemic electrocardiogram (ECG) changes are subtle and transient in patients with suspected non-ST-segment elevation (NSTE)-acute coronary syndrome. However, the out-of-hospital ECG is not routinely used during subsequent evaluation at the emergency department. Therefore, we sought to compare the diagnostic performance of out-of-hospital and ED ECG and evaluate the incremental gain of artificial intelligence-augmented ECG analysis.

Methods

This prospective observational cohort study recruited patients with out-of-hospital chest pain. We retrieved out-of-hospital-ECG obtained by paramedics in the field and the first ED ECG obtained by nurses during in hospital evaluation. Two independent and blinded reviewers interpreted ECG dyads in mixed order per practice recommendations. Using 179 morphological ECG features, we trained, cross-validated, and tested a random forest classifier to augment non-ST-elevation acute coronary syndrome (NSTE-ACS) diagnosis.

Results

Our sample included 2,122 patients (age 59 [16]; 53% women; 44% Black, 13.5% confirmed acute coronary syndrome). The rate of diagnostic ST elevation and ST depression were 5.9% and 16.2% on out-of-hospital-ECG and 6.1% and 12.4% on ED ECG, with ~40% of changes seen on out-of-hospital-ECG persisting and ~60% resolving. Using expert interpretation of out-of-hospital-ECG alone gave poor baseline performance with area under the receiver operating characteristic (AUC), sensitivity, and negative predictive values of 0.69, 0.50, and 0.92. Using expert interpretation of serial ECG changes enhanced this performance (AUC 0.80, sensitivity 0.61, and specificity 0.93). Interestingly, augmenting the out-of-hospital-ECG alone with artificial intelligence algorithms boosted its performance (AUC 0.83, sensitivity 0.75, and specificity 0.95), yielding a net reclassification improvement of 29.5% against expert ECG interpretation.

Conclusion

In this study, 60% of diagnostic ST changes resolved prior to hospital arrival, making the ED ECG suboptimal for the in hospital evaluation of NSTE-ACS. Using serial ECG changes or incorporating artificial intelligence-augmented analyses would allow

correctly reclassifying one in 4 patients with suspected NSTE-ACS.

You will find the full article here: https://www.annemergmed.com/article/S0196-0644(22)00579-0/fulltext

Another interesting article appeared on Circulation, titled: "*Consumer-Led Screening for Atrial Fibrillation: Frontier Review of the AF-SCREEN International Collaboration*". The article provides a critical appraisal of this rapidly evolving field to increase awareness of the complexities and uncertainties surrounding consumer-led AF screening. The abstract reads:

The technological evolution and widespread availability of wearables and handheld ECG devices capable of screening for atrial fibrillation (AF), and their promotion directly to consumers, has focused attention of health care professionals and patient organizations on consumer-led AF screening. In this Frontiers review, members of the AF-SCREEN International Collaboration provide a critical appraisal of this rapidly evolving field to increase awareness of the complexities and uncertainties surrounding consumer-led AF screening. Although there are numerous commercially available devices directly marketed to consumers for AF monitoring and identification of unrecognized AF, health care professional–led randomized controlled studies using multiple ECG recordings or continuous ECG monitoring to detect AF have failed to demonstrate a significant reduction in stroke. Although it remains uncertain if consumer-led AF screening reduces stroke, it could increase early diagnosis of AF and facilitate an integrated approach, including appropriate anticoagulation, rate or rhythm management, and risk factor modification to reduce complications. Companies marketing AF screening devices should report the accuracy and performance of their products in high- and low-risk populations and avoid claims about clinical outcomes unless improvement is demonstrated in randomized clinical trials. Generally, the diagnostic yield of AF screening increases with the number, duration, and temporal dispersion of screening sessions, but the prognostic importance may be less than for AF detected by single–time point screening, which is largely permanent, persistent, or high-burden paroxysmal AF. Consumer-initiated ECG recordings suggesting possible AF always require confirmation by a health care professional experienced in ECG reading, whereas suspicion of AF on the basis of photoplethysmography must be confirmed with an ECG. Consumer-led AF screening is unlikely to be cost-effective for stroke prevention in the predominantly young, early adopters of this technology. Studies in older people at higher stroke risk are required to demonstrate both effectiveness and cost-effectiveness. The direct interaction between companies and consumers creates new regulatory gaps in relation to data privacy and the registration of consumer apps and devices. Although several barriers for optimal use of consumer-led screening exist, results of large, ongoing trials, powered to detect clinical outcomes, are required before health care professionals should support widespread adoption of consumer-led AF screening.

You will find the full article here: https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.121.058911

Finally, we are pleased to host in our quarterly newsletter a contribution by Dr. Jonas L. Isaksen PhD, a postdoctoral researcher at the University of Copenhagen, who is focusing on the use of big data to identify novel associations within the cardiometabolic area using both large Danish registers of population studies and deep learning models for powerful ECG analysis with explainable AI.

A Noteworthy Contribution:

Deep learning predicts atrial fibrillation – with low precision

Jonas L. Isaksen,1 Dominik Linz,2,3 Michael A. Riegler,4 Jørgen K. Kanters 1.

1 Laboratory of Experimental Cardiology, Department of Biomedical Sciences, University of Copenhagen, Denmark

2 Department of Biomedical Sciences, University of Copenhagen, Denmark

3 Department of Cardiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht, The Netherlands

4 Department of Holistic Systems, SimulaMet, Oslo, Norway

Deep learning enables powerful hypothesis-free pattern recognition at the expense of a need for large and well labelled data sets. In electrocardiogram (ECG) analysis, most deep learning models are based on convolutional layers, which act as filters on the ECG to identify and utilize unspecified features for a given task (1). As such, any given model architecture may learn to focus on QRS-specific features for predicting response to cardiac resynchronization therapy, T wave specific features for identification of HERG-blockage in a novel drug candidate, or P wave morphology in the prediction of atrial tachycardia. The three hypothetical models would be identically specified, but the convolutional layers adapt (train) to specific ECG analysis based on the problem and data – i.e., they are data-driven (2). The algorithm is inherently a "black box", but various post-processing analyses allow us to learn how the models approximately operate (3).

In this commentary, we will examine the current state of the art of deep-learning enabled ECG-based prediction of atrial fibrillation (AF), the most common sustained cardiac arrhythmia. We will critically review two important landmark studies and discuss the usefulness of top-performing models, the causes underlying the short-comings of the models, and potential strategies to mitigate these issues in the future.

Identification of AF with ECG and deep learning has been fairly successful; however, prediction is much more difficult (4). In 2019, Attia and colleagues presented a deep learning-based model, which predicted (presumed) incident atrial fibrillation based on analysis of sinus-rhythm ECGs before any known AF. The paper was published in The Lancet (5) and has been cited more than 600 times before the end of 2022. The paper utilized up to 1,000,000 ECGs from 210,414 patients to train one model, and the often-used area under then receiver-operator characteristics curve (AUROC) was an impressive 0.87 with a sensitivity of 79% and specificity of 80%. However, sensitivity and specificity are artificially high for rare outcomes4, and the more appropriate F1 score (the harmonic mean of sensitivity and positive predictive value [PPV]) was only 39%. Indeed, only 26% of those predicted to develop AF actually did develop AF during follow-up, a PPV that was not reported. Notwithstanding, the paper was a major step forward although the model may not readily be used in the clinic. The group evaluated the model on patients with embolic stroke of unknown source (i.e., high risk of AF) of which 6% were found to have AF (6). The model had a negative predictive value of 94% (corresponding to predicting everyone as negative) and a PPV of only 23% - i.e., lower than the original study. Indeed, as we shall see, it is common that deep learning models generalize poorly to new populations (out-of-distribution data).

In 2022, Khurshid and colleagues presented their model to predict AF in Circulation (7). They developed the model using ECGs from 45,770 individuals in primary care within the Mass General Brigham network. The model was evaluated in 4,166 patients from the same network, and in 37,963 patients from Brigham and Women's Hospital and 41,033 people from the UK Biobank. The authors combined deep learning-based ECG analysis with the existing CHARGE-AF score for 5-year risk of AF (8) and showed that ECG-analysis was comparable to clinical risk factors, but that the combination was better than either model. Despite the improvement, the PPVs at 85% sensitivity ranged from 5.7% down to 1.3% in the UK Biobank. Indeed, the authors had to recalibrate the model for use in the UK Biobank, which means that the model cannot be used as-is in new populations. Despite that, the authors should be commended for their efforts to delineate how their model works, and their attention maps suggest that the model operates by analyzing the P wave somehow.

Current deep learning-based models suffer from low precision (PPV). Attia and colleagues had to compromise an unequal age distribution to get a high number of events. Age is associated with both AF and the ECG (9), which may lead the model to predict age implicitly. Khurshid and colleagues tried to combat this effect by explicitly predicting age as a secondary output.

We have discussed two recent studies, which aimed to use deep learning to identify subtle ECG changes to predict AF before it develops. Unfortunately, the

precision was low for both models – perhaps because even if subtle ECG changes occur in an individual they may remain within normal variation of the population. We speculate that biological between-person variation may mask pathophysiological changes to the predictive models, and perhaps that masking is what complicates the AF prediction task for deep learning models.

To uncover such subtle changes, perhaps serial ECG analysis could provide the answer. In that way, an individual's ECG is not compared to the population mean, but rather to that individuals' previous ECG(s). That approach would lie within the personalized medicine framework and may very well be the next step towards reliable ECG-based prediction of atrial fibrillation and other arrhythmias.

Indeed, as we have seen, deep learning cannot solve any task given any data. A substrate must be present for the algorithm to pick up on, and the amount of data must be sufficient for the algorithm to identify the substrate. The labelling of the data must be adequate as to not introduce too much noise. Finally, some questions require a carefully planned study setup to overcome the epidemiological challenges that may mask the yet unknown associations of interest. Deep learning is far from a plug-and-play application, but with the correct approaches, deep learning can continue to facilitate ground-breaking discoveries.

References:

1. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521:436–444.

2. Somani S, Russak AJ, Richter F, Zhao S, Vaid A, Chaudhry F, De Freitas JK, Naik N, Miotto R, Nadkarni GN, Narula J, Argulian E, Glicksberg BS. Deep learning and the electrocardiogram: review of the current state-of-the-art. Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol. 2021;23:1179–1191.

3. Hicks SA, Isaksen JL, Thambawita V, Ghouse J, Ahlberg G, Linneberg A, Grarup N, Strümke I, Ellervik C, Olesen MS, Hansen T, Graff C, Holstein-Rathlou N-H, Halvorsen P, Maleckar MM, Riegler MA, Kanters JK. Explaining deep neural networks for knowledge discovery in electrocardiogram analysis. Sci Rep. 2021;11:10949.

4. Isaksen JL, Baumert M, Hermans ANL, Maleckar M, Linz D. Artificial intelligence for the detection, prediction, and management of atrial fibrillation. Herzschrittmachertherapie Elektrophysiologie. 2022.

5. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, Carter RE, Yao X, Rabinstein AA, Erickson BJ, Kapa S, Friedman PA. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. The Lancet. 2019;394:861–67.

6. Rabinstein AA, Yost MD, Faust L, Kashou AH, Latif OS, Graff-Radford J, Attia IZ, Yao X, Noseworthy PA, Friedman PA. Artificial Intelligence-Enabled ECG to Identify Silent Atrial Fibrillation in Embolic Stroke of Unknown Source. J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2021;30:105998.

7. Khurshid S, Friedman S, Reeder C, Di Achille P, Diamant N, Singh P, Harrington LX, Wang X, Al-Alusi MA, Sarma G, Foulkes AS, Ellinor PT, Anderson CD, Ho JE, Philippakis AA, Batra P, Lubitz SA. ECG-Based Deep Learning and Clinical Risk Factors to Predict Atrial Fibrillation. Circulation. 2022;145:122–133.

8. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens ACJW, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kääb S, Couper D, Harris TB, Soliman EZ, Stricker BHC, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. J Am Heart Assoc. 2013;2:e000102.

9. Attia ZI, Friedman PA, Noseworthy PA, Lopez-Jimenez F, Ladewig DJ, Satam G, Pellikka PA, Munger TM, Asirvatham SJ, Scott CG, Carter RE, Kapa S. Age and Sex Estimation Using Artificial Intelligence from Standard 12-Lead ECGs. Circ Arrhythm Electrophysiol. 2019;12:e007284.

Products News

We are pleased to announce the release of the new certified version of CER-S v4.5.0. The most notable features of this release include the improvements to:

- security and traceability
- the graphical user interface
- report customization: it is now possible to modify the graphics of the report such as fonts, colors, and displayed report elements.

AMPS People

We are very pleased to announce that Gianluca Generali joined AMPS in December 2022. Gianluca holds a PhD in Electronic Engineering (Biomedical applications) and started his professional path in Computer Graphics (Tesak SRL - Florence), and soon moved to medical devices R&D where he found a passion that never stopped. He managed the R&D departments in Esaote (Cardiology, Neurology & Imaging - Florence), Mortara Instrument (Cardiology - Milwaukee, US), Cardioline (Cardiology - Trento), and Schiller (Cardiology, Resuscitation & Respiratory - Baar, CH). His focus is driving the full product development of innovative medical devices for the competitive global market, with special attention given to real-time ECG analysis algorithms.

Gianluca Generali