Innovations in Artificial Intelligence enables device in Day-1 prediction of 95% of all diagnosable heart diseases

Dr. Istvan Kecskes[1], Dr. xxx[2], Dr. xxx[3], Marc Bisnaire[1]

[1]Cardiology Research and Scientific Advancements, UVA Research, Toronto, Canada

Abstract

CHART is a breakthrough technology that uses novel bio-signals (Phonocardiogram and Mechanocardiogram besides ECG) to diagnose significant heart diseases to reduce instances of "inconclusive ECG". In addition to diagnosing standard 12-lead ECG findings, CHART can predict 14 significant heart diseases that typically are only diagnosed by Echocardiography in Secondary Care. These findings are equivalent with echocardiography-based conclusions, which found to be a good indicator as to what kind of heart problems can be expected, revealed by a previous and published clinical utility study. The AI enables device in Day-1 prediction of 95% of all heart diseases including heart failure, its structural and functional comorbidities, heart-valve diseases, MI and wall motion abnormalities. By comparison the standard ECG findings cover only 45% according to prevalence-based calculation. The sensitivity of wall motion abnormality is almost doubled by CHART compared the ECG-based myocardial infarction diagnosis, with similar specificity level.

1 Introduction

According to the CDC, nearly 800,000 Americans die each year from cardiovascular diseases -- that's one in every three deaths in the US. In a recent John Hopkins study [1], medical error is the 3rd leading cause of death in the United States. Further studies from Baylor University and John Hopkins reported that medical diagnostic errors are the most common and costly type of medical error, annually impacting more than 12 million patients.

Data from the Institute of medicine [2] reports preventable medical errors account for 4% of national healthcare costs, or $29Bn annually (2016). Unsurprisingly, the number of reported malpractice claims has soared, from 225,00 to as high as 440,000.

A review of malpractice claims in the United States reveals that 41% of all claims result from a failure to diagnose, a category of claims with three causes, a failure to detect, delays in detecting or an incorrect diagnosis. Scratching the surface however reveals that “human error” might have a root cause, the “inconclusive ECG”, which leaves clinicians without diagnostic support at a critical patient pathway decision point. AI can help, either indirectly, via decision support tools based on similar cases or, more directly, by addressing diagnostic effectiveness intrinsic to the medical device itself.

Motivated by the cost of claims but mainly from a desire to improve diagnostic certainty and accuracy, cardiovascular medicine is increasingly turning to AI to address issues related to failure to diagnose, for example heart failure is notoriously challenging. Yet, the clinical application of AI as an integral element of a medical device is still in its infancy, it largely remains a short-sighted use of off-the-shelf CNNs applied to institutional data more relevant to academic research purposes. Real diagnostic innovation focused on clinically meaningful outcomes remains a rarity - because it’s hard.

One company is using AI to address one of the most insidious, yet burdensome, medical problems in clinical practice, the diagnostic source of failure to diagnose. The AI is integral to the innovation that binds three bio-signals with the aim of outputting not only better ECG findings but also output breakthrough Echo equivalent findings, effectively increasing the diagnostic range and effectiveness of the device similarly to that of echocardiography.

This innovation reduces the “failure to diagnose” by directly addressing the issues related to an “inconclusive ECG”. CHART is a game changer as this AI powered device is indicated for use in primary care, and creates a new class of cardiac diagnostic device [3]. It is for use as a direct substitute for 12-Lead resting ECG.

2 Breakthrough AI Technology in Heart Diagnostics

Cardio-HART (“CHART”) not only provides AI enhanced ECG findings, but also 14 of the most prevalent Echocardiography findings, such as dilated cardiomyopathy (DCM), left-ventricular hypertrophy (LVH), left and right atrial enlargement (LAE, RAE), pulmonary hypertrophy (PH), etc. called HART findings[1], see Table 1. HART findings, are disease equivalent to Echo-findings, only derived from bio-signals instead of images. The AI uniquely enables the early detection of 95% of all common heart diseases including Heart Failure and heart valve diseases, see statistical analysis in next section.

For the clinician faced with confounding and ambiguous symptoms, CHART's AI acts as the clinician's cardiac assistant, to deliver superior 1st visit diagnostic accuracy and immediacy. This greatly shortens clinical diagnostic timelines and decreases instances of "inconclusive ECG", the source of most "failure-to-diagnose" claims. For example, heart failure can be diagnosed Day-1 on patient presentation, rather than the typical months of costly testing and clinical visits. Greatly underappreciated, is that CHART also reveals any co-morbidities that might additionally be present such as heart valve disease, MI or Atrial fibrillation [5], that can lead to a more comprehensive understanding of a patient's actual cardiac status.

The secret was the development of a sophisticated AI algorithm that could address the unique aspects of extracting relevant medical information from novel bio-signals. This engineered approach to AI greatly reduces False Positives [FP] and False Negatives [FN] inherent in the use off-the-shelf CNNs typically used for academic research purposes, see examples, various recent CNN results [10]-[15]. Rather the AI is intrinsic to the innovation that first complemented and augmented ECG with phonocardiogram and mechano-cardiogram (mechano-physiological bio-signal) mapping them to Echo equivalent disease findings. This required years of data collection as this type of data didn't exist – the device simply had not been invented yet. The result, the cardiologists in the clinical study found that CHART's AI was 94.2% in agreement with their echocardiography assessment – an astonishing achievement attributable to its engineered AI design [4].

Proven in a clinical study designed with the assistance of the FDA, the AI was instrumental in guiding clinicians in understanding when to send the patient to cardiology, and just as importantly, when not to. As well, it helped them prioritize patients based on severity of condition, allowing cardiologist to better triage referrals based on urgency, rather than first come first served. In that study, the AI propelled clinicians to similar diagnostic accuracy as those of the overreading cardiologist (ORC), (PPA=70.3%, NPA=81%) a remarkable equivalency, with wide-ranging clinical implications. Conversely, their peers using rule-based ECG were far less accurate than the ORC (PPA=51.6%, NPA=77%), a disparity that translates directly into higher FP and FN outcomes. Clinicians using CHART saw

[1] FDA insisted the term HART findings be used instead of Echo findings, to distinguish their underlying nature, HART findings being bio-signal based, and Echo findings being image based.

their positive diagnostic rate improve by over 250% compared to their ECG using peers. Overall, there was a clinically meaningful reduction in false positives by 5% and a stunning 16% reduction in false negatives [4] in referral decision. Such clinical reductions translate directly into meaningful cost reductions that will ripple throughout the healthcare ecosystem.

3 Analysis results

Todo

3.1 14 HART findings definition

CHART analyses and diagnoses 14 significant heart diseases that are critical in patient management. See more details in [5].

Table 1 – List of 14 HART Findings and baseline ECHO Criteria

	HART findings	ECHO Criteria for "Mild"	ECHO Criteria for Abnormal	Abbr.
1.	Concentric LVH	IVSd≥[10/11*]mm and LVMI>[100/115*]g/m^2	IVSd≥[13/14*]mm and LVMI>[115/131*]g/m^2	LVH
2.	Dilated Cardiomyopathy, (Eccentric LVH)	LVIDd>[53/59*]mm	LVIDd>[56/63*]mm	DCM
3.	RV Enlargement	RVOTprox>30mm	RVOTprox>36mm	RVE
4.	LA Enlargement	LAVI>30ml/m^2	LAVI>40ml/m^2	LAE
5.	RA Enlargement	RAVI>30ml/m^2	RAVI>40ml/m^2	RAE
6.	Wall motion abnormality	Mild Hypokinesis (WMscore≥1)	Hypokinesis, Akinesis, Dyskinesis (WMscore≥2 and LVEF<[54/52*]%)	WMA
7.	LV Systolic Dysfunction	LVEF<[54/52*]%	LVEF<40%	LVSD
8.	Diastolic Dysfunction (Impaired Relaxation)	E/A<0.85	E/A<0.70	LVDD
9.	Aortic Valve Stenosis	AVpV>2.0m/s	AVpV>3.0m/s	AS
10.	Mitral Valve Stenosis	MVA<3.0cm^2 (MVGEm>3.7mmHg)	MVA<1.5cm^2 (MVGEm>5.0mmHg)	MS
11.	Aortic Valve Insufficiency	ARgrade≥1	ARgrade≥2	AR
12.	Mitral Valve Insufficiency	MRgrade≥1, MRjet/LAA>20%	MRgrade≥2, MRjet/LAA>30%	MR
13.	Tricuspid Valve Insufficiency	TRgrade≥1, TRjet/RAA>20%	TRgrade≥2, TRjet/RAA>30%	TR
14.	Pulmonary Hypertension	RVSP>40mmHg	RVSP>50mmHg	PH

IVSd - End-diastolic Interventricular Septum Thickness, LVMI - Left Ventricular Mass Index, LVIDd - End-diastolic Left Ventricular Diameter (internal), RVOT - Right Ventricular Outflow Tract Proximal, LAVI - Left Atrial Volume Index, RAVI - Right Atrial Volume Index, EF – LV Ejection Fraction, AVpV - Aortic maximum Velocity, MVA – Mitral Valve Area, ARgrade - Rate of Aortic Regurgitation, MRgrade - Rate of Mitral Regurgitation, MRjet/LAA - Mitral Regurgitant Jet Area in LA area, TRgrade - Rate of Tricuspid Regurgitation, TRjet/RAA – Tricuspid Regurgitant Jet Area in RA area, RVSP - Right Ventricular Systolic Pressure

3.2 Common heart diseases coverage

CHART predicts the HART-, ECG-, PCG- and MCG-findings, which is a select subset of the analyzed ECG and ECHO findings. (In the CHART system the ECHO-findings are represented by the HART findings.) Fig. 1 illustrates the prevalence graphically.

- Green background color represents findings that the CHART system predicts.
- Yellow background colour, findings it does not predict.
- Purple coloured bars represent ECHO findings, it predicts
- Orange coloured bars, represents ECG findings it predicts.
- Blue background colour represents integrated findings, a group of findings that are combined to reduce system complexity to the clinician (in accordance with Intended Use).

The accumulated prevalence of detected cardiac abnormalities by CHART results 95% compared to the all listed prevalence - compare yellow prevalence (5%) to green + blue prevalence (95%) in Fig. 1.

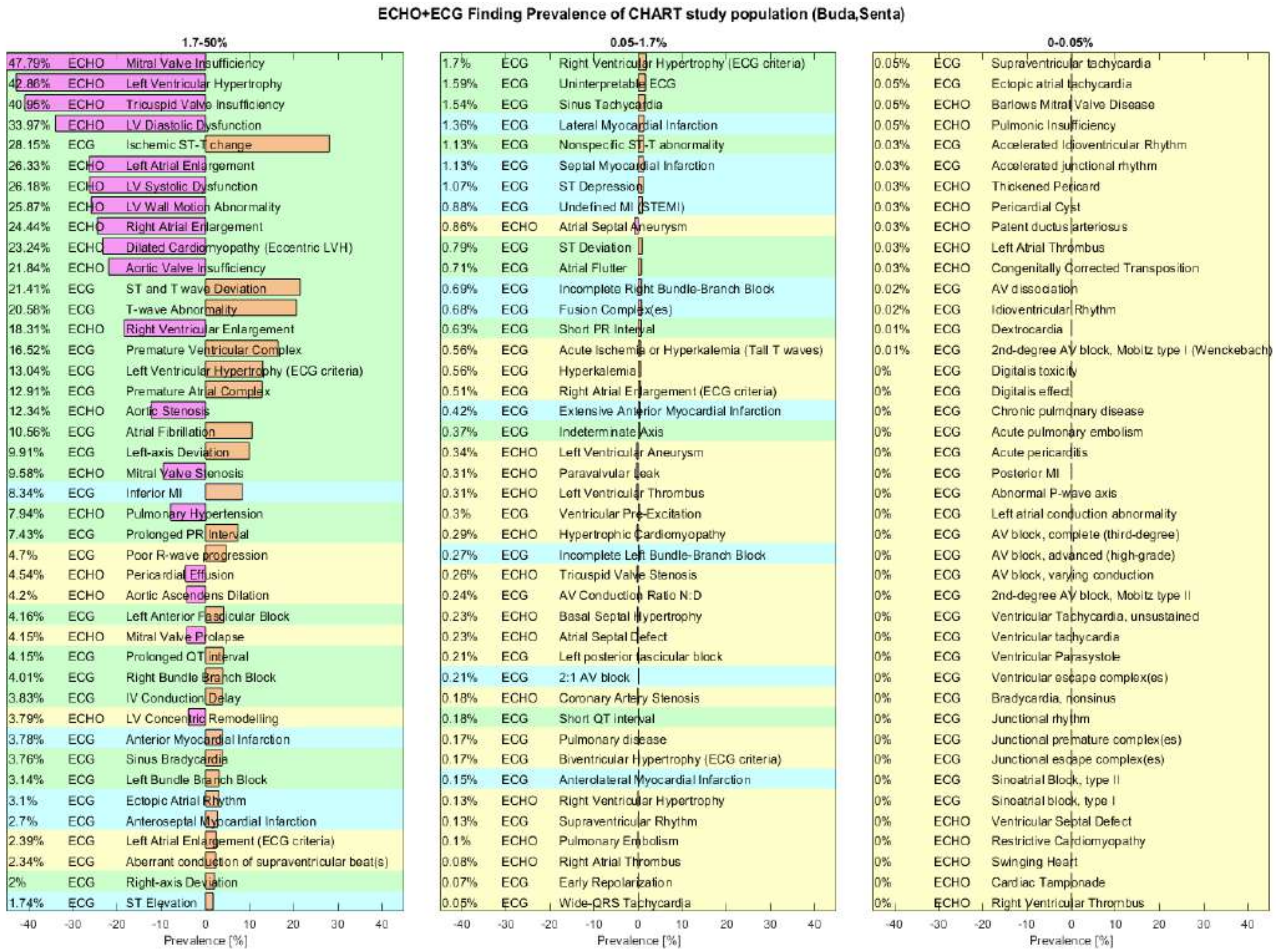

Figure 1 - ECG and ECHO-findings prevalence analysis of CHART study population

The interpretation of the prevalence analysis are follows:

The summarized ECHO-findings show higher prevalence (64%) compared to ECG-findings (36%). It confirms that ECHO-findings includes the high-prevalence mild abnormalities beside the moderate/severe, however, ECG typically become abnormal in case of lower-prevalent moderate/severe diseases on average.

Most significant heart diseases are detected by ECHO, not ECG.

- CHART system predicts most of the significant heart diseases (prevalence>1%)
- CHART system does not predict the very rare heart diseases (prevalence<0.1%)
- CHART system predicts 95% of occurred heart diseases according to the available 25 ECG and 14 ECHO-findings

This analysis does not include the PCG and MCG findings, which is also provided by CHART report. However, PCG and MCG findings are integrated into HART findings and provide critical morphological information about the hearts functioning.

3.3 Comparison Performance of Ischemic Wall Motion Abnormality

This performance comparison demonstrates the limitation of ECG -based criteria in detection of wall motion abnormality confirmed by ECHO. Thee rule-based ECG findings are included in the comparison analysis: Ischemic ST-T changes – as the best ECG finding for ischemia, standard MI criteria – as the best ECG finding for MI, and general ST-T deviation (including non-ischemic) – as the subsidiary ECG finding for comparison.

The AI supported HART – WMA finding reaches significantly higher performance: 71.5% sensitivity with 88.7% specificity, AUC=0.88, compared to the best ECG finding, the standard myocardial infarction (MI) criteria on ECG shows only 44.5% sensitivity with 86.8% specificity, AUC=0.75

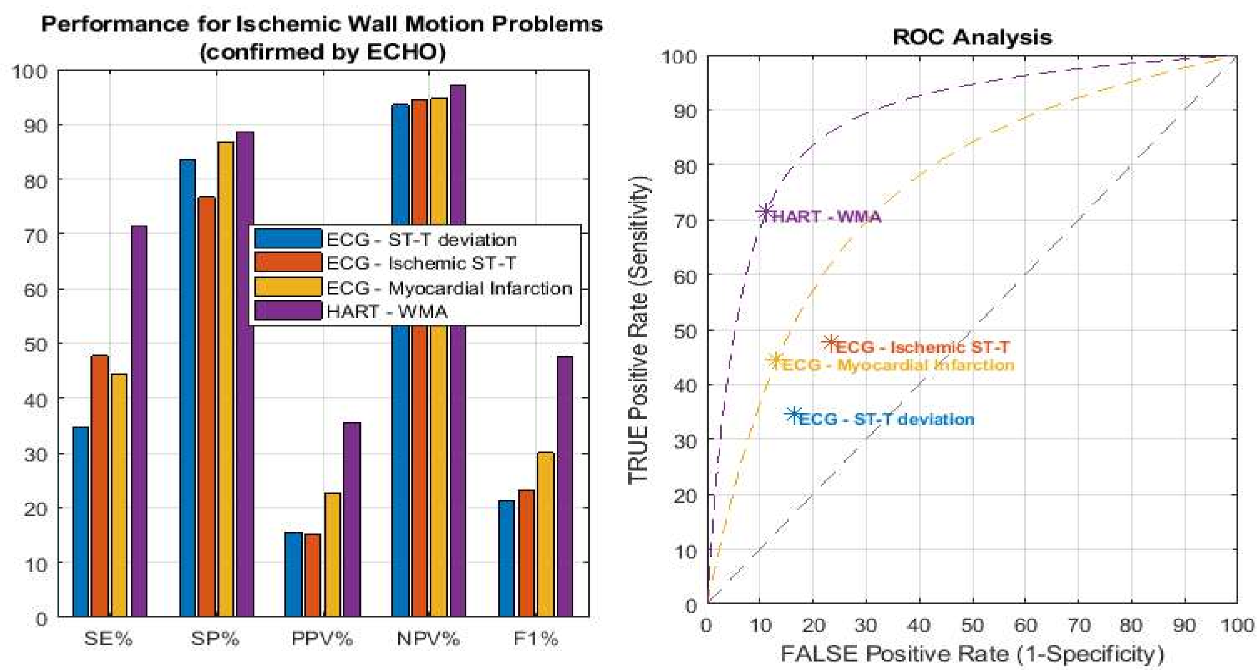

Figure 2 – Performance evaluation of HART - WMA compared to ECG for ECHO-confirmed WMA. Various ECG findings are included: ECG - Myocardial Infarction, ECG - Ischemic ST-T, ECG - ST-T deviation

4 Discussion

With Echocardiography readily available in Cardiology, how could an AI powered CHART benefit cardiology? First, as a direct substitute for the 12-Lead ECG examination on initial patient presentation, aside from producing all the relevant ECG outcomes, the CHART AI can help identify True Negative [TN] patients that don't need Echocardiography confirmation, with an NPV of 99%, saving time and costs. An often-overlooked benefit is that the AI also provides a "big picture" of co-morbidities that might not be indicated in the patient referral, such as the presence of heart failure or heart valve disease – conditions that are better known before the echo examination. The big-picture also serves to establish a clear Echo examination start point, reducing cold-starts, increasing examinations effectiveness and accuracy, yet reducing the time needed for testing [4].

A novel use of the AI is in identifying MI or ischemia in patients with classic anginal chest pain that may have normal or non-specifically abnormal ECG, which may lead to delayed treatment or even death [9]. When ECG is nondiagnostic or inconclusive, Echocardiography can help identify high-risk patients among those presenting with chest pain, as 91% of patients with wall motion abnormalities (WMA) eventually suffered a cardiac event [9], MI or Ischemia, compared to only 2.4% of those with normal wall motion. The AI's WMA finding is disease equivalent to Echo WMA finding.

As such, the AI appreciably increases CHART's sensitivity for ischemic problems compared to the traditional ECG criteria with better specificity, boosting 1st visit accuracy. Wall motion abnormality by HART models reaches 71.5% sensitivity with 88.7% specificity, AUC=0.88, but the standard myocardial infarction (MI) criteria on ECG shows only 44.5% sensitivity with 86.8% specificity, AUC=0.75 (see details in Figure 2 in supplementary material). This is possible because the AI uniquely diagnoses **MI or ischemia** two ways: 1) as defined by ECG standards and, 2) as defined by wall motion abnormalities as similarly diagnosed by echocardiography.

Medical malpractice claims data out of the USA, shows that women are on average more likely to be misdiagnosed for MI in their 1st visit, whether in Cardiology (28%) [6] or Primary Care (28%) [7], than men. Attesting to this, during the FDA designed clinical study, two patients, both women, attending primary care with minor chest discomfort were actually experiencing MI's in progress. In both cases the clinicians using traditional ECG failed to detect the MI, whereas the clinicians assisted with the AI's WMA findings readily detected the MI. What ECG didn't detect, CHART's AI did, and two lives were saved.

5 Conclusion

The use of AI in front-line patient care settings, in particular primary care settings, can significantly reduce instances of inconclusive ECG that lead to "failure to diagnose". The AI in CHART is instrumental in enabling the early detection of a broader range of heart diseases, similarly to those diagnosable with Echocardiography, boosting 1st visit accuracy. Not only will this lead to better patient outcomes but also result in significant cost savings, and reduced wait-times that plague healthcare. As a direct substitute for traditional ECG, the AI enabled CHART fits directly into the existing standard of care and clinical workflows, whether primary or cardiology care. In CHART, the AI is clinician's trusted heart diagnostic assistant.

6 References

[1] Makary M A, Daniel M., Medical error—the third leading cause of death in the US BMJ 2016; 353 :i2139 doi:10.1136/bmj.i2139

[2] Institute of Medicine (US) Committee on Quality of Health Care in America; Kohn LT, Corrigan JM, Donaldson MS, editors. To Err is Human: Building a Safer Health System. Washington (DC): National Academies Press (US); 2000. 2, Errors in Health Care: A Leading Cause of Death and Injury. Available from: https://www.ncbi.nlm.nih.gov/books/NBK225187/Kohn, LT, Corrigan JM,

[3] Cardio-HART™ - a Breakthrough Cardiac-Telemedicine™ device, now CE-Marked. (2021). Retrieved 20 December 2021, from https://www.cardiophoenix.com/news/cardio-hart-a-breakthrough-cardiac-telemedicine-device-now-ce-marked

[4] Calcagno, S., Biondi Zoccai, G., Stankovic, T., Szabo, E., Berta-Szabo, A., Kecskes, I. (2021) Novel Tech throws knock-out punch to ECG improving GP referral decisions to cardiology, accepted by Open Heart

[5] Zaman, A., Calcagno, S., Zoccai, G. B., Campbell, N., Koulaouzidis, G., Tsipas, D., & Kecskes, I. (2021). Unraveling diagnostic co-morbidity makeup of each HF category as characteristically derived by ECG-and ECHO-findings, a prevalence analysis. *medRxiv*.

[6] David B, Troxel, MD, Medical Director, American College of Cardiology, Feature Article, Nurse Practitioner Closed Claims Study, April 9, 2018. ACC, Advanced Practice Provider Claims, September 2019.

[7] Taking the risks to heart: misdiagnosis of heart disease, The doctors company, accessed on February 20th, 2017. Sandeep S. Mangalmurti, MD, JD, cardiologists, American

College of Cardiology, The Cardiologists Closed Claims Study, November 8th, 2017. Women and heart disease fact sheet. Centers for Disease Control and Prevention, CDC, January 11, 2017.

[8] Sia, Y. T., O'Meara, E., & Ducharme, A. (2008). Role of echocardiography in acute myocardial infarction. *Current heart failure reports*, *5*(4), 189-196.

[9] Brady, W. J., Roberts, D., & Morris, F. (1999). The nondiagnostic ECG in the chest pain patient: normal and nonspecific initial ECG presentations of acute MI. *The American journal of emergency medicine*, *17*(4), 394-397.

[10] Goto, S., Kimura, M., Katsumata, Y., Goto, S., Kamatani, T., Ichihara, G., ... & Sano, M. (2019). Artificial intelligence to predict needs for urgent revascularization from 12-leads electrocardiography in emergency patients. *PloS one*, *14*(1), e0210103.

[11] Attia, Z. I., Kapa, S., Lopez-Jimenez, F., McKie, P. M., Ladewig, D. J., Satam, G., ... & Friedman, P. A. (2019). Screening for cardiac contractile dysfunction using an artificial intelligence–enabled electrocardiogram. *Nature medicine*, *25*(1), 70-74.

[12] Ullah, A., Anwar, S. M., Bilal, M., & Mehmood, R. M. (2020). Classification of arrhythmia by using deep learning with 2-D ECG spectral image representation. *Remote Sensing*, *12*(10), 1685.

[13] Acharya, U. R., Fujita, H., Oh, S. L., Hagiwara, Y., Tan, J. H., & Adam, M. (2017). Application of deep convolutional neural network for automated detection of myocardial infarction using ECG signals. *Information Sciences*, *415*, 190-198.

[14] Porumb, M., Iadanza, E., Massaro, S., & Pecchia, L. (2020). A convolutional neural network approach to detect congestive heart failure. *Biomedical Signal Processing and Control*, *55*, 101597.

[15] Hughes, J. W., Olgin, J. E., Avram, R., Abreau, S. A., Sittler, T., Radia, K., ... & Tison, G. H. (2021). Performance of a convolutional neural network and explainability technique for 12-Lead electrocardiogram interpretation. *JAMA cardiology*.