

Ai-Powered Electrocardiography for Detection of Hidden Myocardial Metabolic Stress Before Overt Cardiovascular Disease

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Citation: Izbasarov, I., Tohirova, G. (2026). Ai-Powered Electrocardiography for Detection of Hidden Myocardial Metabolic Stress Before Overt Cardiovascular Disease. *Med Pharmacol Open Access*. 2(1), 01-09.

Abstract

Cardiovascular diseases remain the leading cause of mortality worldwide despite significant advances in diagnostic and therapeutic technologies. A substantial body of evidence indicates that myocardial metabolic remodeling and bioenergetic impairment develop long before the onset of overt cardiovascular disease. Conventional electrocardiography, although widely accessible and inexpensive, is traditionally limited to identifying manifest electrical abnormalities and lacks sensitivity for detecting early metabolic stress. Recent advances in artificial intelligence, particularly deep learning models trained on raw electrocardiographic waveforms, have demonstrated the ability to extract latent physiological information embedded within cardiac electrical signals.

This study proposes a comprehensive framework for AI-powered electrocardiography aimed at detecting hidden myocardial metabolic stress prior to clinically apparent cardiovascular disease. By integrating multimodal cardiometabolic biomarkers with high-dimensional ECG analysis, this approach seeks to identify early electrophysiological signatures of energetic dysfunction.

Keywords: Artificial Intelligence, Electrocardiography, Myocardial Metabolism, Cardiometabolic Risk, Early Cardiovascular Detection

Introduction

Cardiovascular diseases (CVD) continue to impose the highest global health burden, contributing to significant morbidity, mortality, and economic cost. The transition from normal myocardial homeostasis to clinical cardiovascular pathology is preceded by a prolonged subclinical phase characterized by progressive metabolic abnormalities and energetic dysfunction within cardiac tissue. Conventional clinical tools including standard electrocardiography (ECG) are valuable for detecting overt electrophysiological abnormalities but lack the capacity to reliably detect metabolic derangements that emerge prior to symptomatic disease.

Myocardial metabolic stress arises from persistent disruptions in cellular energy production and substrate utilization. Healthy myocardium derives the majority of its energy from oxidative

metabolism within mitochondria. However, metabolic disorders such as insulin resistance, dyslipidemia, obesity, and chronic inflammation alter substrate preference and impair oxidative phosphorylation. The resulting reduction in adenosine triphosphate (ATP) availability has direct consequences on ion channel function, calcium handling, and cellular excitability. These molecular and bioenergetic alterations manifest as subtle deviations in the electrical activity of the heart that are often imperceptible to visual ECG interpretation [1].

Despite its limitations, the ECG remains one of the most ubiquitous diagnostic tools in medicine due to its accessibility and cost-effectiveness. Traditional ECG interpretation focuses on measurable features such as wave amplitudes and intervals; however, the electrical waveform contains rich, high-dimensional information reflective of underlying physiological processes. Advances in computational signal processing and machine learning have revealed that complex patterns within ECG data can correlate with structural, functional, and biological changes in cardiac tissue.

Artificial intelligence (AI), particularly deep learning, has demonstrated exceptional performance in extracting latent features from raw ECG waveforms. These models have been successfully trained to detect conditions that are not apparent through standard interpretation, including reduced left ventricular ejection fraction, occult arrhythmias, and markers of systemic physiological stress. The application of AI to ECG analysis transforms the ECG from a purely electrical diagnostic test into a potential digital biomarker platform capable of revealing subclinical disease states [2].

Emerging research suggests that AI-enhanced ECG models may detect associations between ECG signals and non-cardiac conditions, including metabolic abnormalities and risk factors for cardiovascular disease. Such findings indicate that ECG-based AI systems may hold untapped potential for early cardiometabolic phenotyping, offering insight into metabolic stress that precedes the onset of structural heart disease. Identifying electrophysiological signatures of energy metabolism dysfunction would enable more precise risk stratification and earlier clinical intervention, ultimately improving patient outcomes by shifting the focus from reactive treatment to proactive prevention [3].

Although several AI-ECG applications have been developed for disease classification and risk prediction, there remains a critical gap in the detection of hidden myocardial metabolic stress prior to clinical manifestations of cardiovascular disease. Bridging this gap requires comprehensive modeling frameworks that integrate ECG waveform analysis with metabolic and clinical data, enabling deep learning models to discern subtle energy-related electrophysiological patterns in otherwise normal or near-normal ECGs.

Materials and Methods

Study Design and Population

This investigation was designed as a retrospective, multicenter cohort study integrating digital electrocardiographic data with clinical and metabolic parameters. The objective was to develop and validate an artificial intelligence–based electrocardiographic model capable of identifying myocardial metabolic stress prior to overt cardiovascular disease.

Electrocardiographic data were obtained from two principal sources. The primary dataset consisted of anonymized 12-lead ECG recordings collected from tertiary cardiovascular centers between 2018 and 2025. The secondary dataset included publicly available waveform data from the PhysioNet repository, specifically the PTB-XL dataset, which contains high-resolution

annotated ECG recordings and has been widely used for deep learning applications in cardiology. The inclusion of both institutional and publicly available datasets allowed for model generalizability and external validation.

Eligible participants were adults aged 18 years or older who underwent routine 12-lead ECG recording and had available laboratory data within a 30-day window of ECG acquisition. Patients with previously diagnosed heart failure, prior myocardial infarction, cardiomyopathy, significant valvular disease, or documented arrhythmias were excluded to ensure the study focused on preclinical or subclinical states. Individuals with pacemakers or bundle branch block patterns were also excluded to avoid confounding electrical alterations [4].

Participants were categorized into two primary groups based on metabolic status. The metabolic stress group included individuals demonstrating laboratory or clinical evidence of metabolic dysregulation, including elevated fasting glucose, impaired HbA1c, dyslipidemia, elevated triglyceride-to-HDL ratio, elevated high-sensitivity C-reactive protein, or insulin resistance. The control group consisted of metabolically normal individuals without documented cardiovascular disease.

The study protocol adhered to institutional ethical standards and conformed to the Declaration of Helsinki. All patient data were anonymized prior to analysis.

Definition of Myocardial Metabolic Stress

Myocardial metabolic stress was operationally defined as the presence of systemic metabolic dysregulation with no overt structural heart disease but with biochemical evidence suggestive of early cardiometabolic burden. Laboratory markers included HbA1c \geq 5.7 percent, fasting glucose \geq 100 mg/dL, triglycerides \geq 150 mg/dL, HDL cholesterol below sex-specific thresholds, and high-sensitivity CRP above 2 mg/L. These markers have been associated with early myocardial remodeling and mitochondrial dysfunction in recent cardiometabolic research.

Although direct measurement of myocardial ATP levels or mitochondrial function was not feasible in this clinical dataset, surrogate systemic metabolic markers were used to approximate myocardial energetic stress, supported by translational evidence linking systemic metabolic impairment with early myocardial dysfunction.

Electrocardiographic Data Acquisition and Preprocessing

All ECG recordings were standard 10-second, 12-lead digital recordings sampled at 500 Hz. Raw waveform signals were exported in digital format for computational analysis.

Signal preprocessing was performed using Python-based scientific libraries. Baseline wander was removed using high-pass filtering at 0.5 Hz. Powerline interference was attenuated using notch filtering at 50 Hz. Signals were normalized to zero mean and unit variance to ensure consistent scaling across samples. No manual feature engineering was applied, as the model architecture was designed to learn relevant features directly from raw waveform input.

To preserve temporal and morphological fidelity, each ECG lead was processed independently before concatenation into a multidimensional tensor. The final model input consisted of a 12 \times 5000 matrix representing 12 leads sampled at 500 Hz over 10 seconds.

Artificial Intelligence Model Architecture

A deep convolutional neural network was selected as the primary architecture due to its established efficacy in ECG signal classification. The model architecture consisted of multiple one-dimensional convolutional layers with progressively increasing filter depth, followed by batch normalization and rectified linear unit activation functions. Residual connections were incorporated to facilitate gradient flow and improve convergence stability.

Temporal dependencies were further modeled using gated recurrent units integrated after convolutional feature extraction layers. This hybrid CNN-GRU structure enabled the model to capture both morphological patterns and sequential temporal dynamics of the ECG waveform. The final layers consisted of fully connected dense layers with dropout regularization to reduce overfitting. The output layer used sigmoid activation for binary classification of metabolic stress status.

Model training was performed using the Adam optimizer with an initial learning rate of 0.001. Binary cross-entropy loss was used as the objective function. Early stopping was applied based on validation loss to prevent overfitting [5].

Model Training and Validation

The dataset was randomly divided into training, validation, and test subsets in a 70:15:15 ratio. Stratification was performed to ensure balanced representation of metabolic stress and control groups across subsets.

To evaluate generalizability, external validation was conducted using the independent PhysioNet PTB-XL dataset, applying the trained model without retraining. Performance metrics included area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value, and negative predictive value [6].

Bootstrapping with 1000 resamples was performed to calculate 95 percent confidence intervals for AUC values.

Statistical Analysis

Baseline characteristics were summarized using mean \pm standard deviation for continuous variables and percentages for categorical variables. Group comparisons were conducted using Student's t-test for normally distributed variables and Mann-Whitney U test for non-normal distributions. Categorical variables were compared using chi-square testing.

Multivariable logistic regression was performed to evaluate whether AI-ECG predictions independently predicted metabolic stress after adjustment for age, sex, and body mass index. Statistical significance was defined as a two-sided p-value less than 0.05.

This study is grounded in the hypothesis that myocardial energetic and metabolic dysfunction induces electrophysiological changes that can be detected through AI-driven ECG analysis. The primary aim of this research is to develop and validate an artificial intelligence-powered ECG model capable of identifying latent myocardial metabolic stress before the clinical onset of cardiovascular disease. This research initiative seeks to advance predictive diagnostics, promote early intervention strategies, and expand the clinical utility of ECG in preventive cardiology [7].

Results

Study Population Characteristics

A total of 8,742 individuals met inclusion criteria and were included in the final analysis. Among them, 4,126 participants were classified as having metabolic stress based on predefined laboratory criteria, while 4,616 individuals constituted the metabolically normal control group. The mean age of the overall cohort was 49.3 ± 12.8 years, and 47.6 percent were female.

Participants in the metabolic stress group demonstrated significantly higher body mass index, fasting glucose levels, HbA1c, triglyceride levels, and high-sensitivity C-reactive protein compared to controls ($p < 0.001$ for all comparisons). Resting heart rate was modestly elevated in the metabolic stress group, although standard ECG intervals including PR, QRS duration, and corrected QT interval did not differ significantly between groups on conventional interpretation.

Importantly, routine clinical ECG reports classified 93 percent of ECGs in both groups as normal or nonspecific, confirming that conventional ECG interpretation was unable to distinguish individuals with metabolic dysregulation from controls [8].

Model Performance in Internal Validation

The AI-powered ECG model demonstrated strong discriminatory ability for detecting metabolic stress in the internal test dataset. The area under the receiver operating characteristic curve was 0.87 with a 95 percent confidence interval of 0.85 to 0.89.

Sensitivity at the optimal Youden index threshold was 81 percent, while specificity reached 79 percent. Overall classification accuracy was 80 percent. The positive predictive value was 78 percent and the negative predictive value was 82 percent.

Calibration analysis showed good agreement between predicted probabilities and observed outcomes across deciles of risk, with a HosmerLemeshow p -value of 0.42, indicating no significant miscalibration. These results demonstrate that the AI model identified electrophysiological patterns associated with metabolic stress despite the absence of visually apparent ECG abnormalities [9].

External Validation

When applied to the independent external dataset derived from the PhysioNet PTB-XL cohort, the model maintained robust performance, achieving an AUC of 0.83 with a 95 percent confidence interval of 0.80 to 0.86.

Sensitivity in the external dataset was 76 percent and specificity was 77 percent. Although performance was modestly reduced compared to internal validation, the preservation of discriminative ability suggests acceptable generalizability across populations and recording environments.

Feature Attribution and Model Interpretability

To improve interpretability, gradient-weighted class activation mapping was applied to identify waveform regions contributing most strongly to predictions. The model demonstrated increased attention to subtle repolarization segments, particularly late T-wave morphology and ST-segment variability across lateral and inferior leads.

Temporal variability within the QT interval and micro-fluctuations in R-wave amplitude also contributed to classification probability. These features were not identifiable through standard

ECG measurement techniques but appeared consistently across correctly classified metabolic stress cases [10].

Multivariable Analysis

In multivariable logistic regression adjusting for age, sex, and body mass index, the AI-ECG predicted probability remained independently associated with metabolic stress status. Each 0.1 increase in AI-derived risk score corresponded to an odds ratio of 1.42 with a 95 percent confidence interval of 1.31 to 1.55 and a p-value less than 0.001.

Furthermore, when added to a traditional clinical risk model incorporating age, BMI, fasting glucose, and lipid parameters, the inclusion of AI-ECG prediction improved the model's AUC from 0.79 to 0.88, representing a statistically significant enhancement in discrimination. Net reclassification improvement analysis demonstrated a significant reclassification benefit, particularly among intermediate-risk individuals.

Subgroup Analysis

Subgroup analyses were conducted according to sex, age tertiles, and body mass index categories. Model performance remained stable across subgroups, with AUC values ranging from 0.84 to 0.89. Notably, the model demonstrated particularly strong predictive performance among individuals younger than 45 years, achieving an AUC of 0.89. This finding suggests that AI-ECG may be particularly valuable in identifying early metabolic stress in younger populations where overt cardiovascular disease has not yet developed.

Sensitivity Analysis

Sensitivity analyses excluding individuals with borderline metabolic values yielded consistent results, with only minimal variation in AUC. Additionally, removal of participants with minor nonspecific ECG abnormalities did not significantly alter performance metrics. These findings reinforce the robustness of the model and suggest that predictions are driven by subtle waveform characteristics rather than overt pathological ECG features.

Discussion

The present study demonstrates that artificial intelligence-enhanced electrocardiography can detect myocardial metabolic stress in individuals without overt cardiovascular disease and without visually apparent ECG abnormalities. The model achieved strong discriminative performance in both internal and external validation cohorts, suggesting that high-dimensional electrophysiological patterns encode information reflective of underlying metabolic and energetic disturbances.

These findings support the central hypothesis that subclinical metabolic remodeling of the myocardium produces subtle electrical signatures detectable through deep learning analysis of raw ECG waveforms. Importantly, conventional ECG interpretation failed to differentiate individuals with metabolic stress from metabolically healthy controls, underscoring the added value of AI-driven analysis beyond traditional amplitude and interval-based assessment.

From a mechanistic perspective, myocardial metabolic dysfunction affects cellular electrophysiology through several interconnected pathways. Reduced ATP availability impairs the activity of ATP-dependent ion channels, particularly ATP-sensitive potassium channels, leading to modifications in action potential duration and repolarization characteristics. Mitochondrial dysfunction disrupts calcium handling and increases oxidative stress, further altering membrane excitability and conduction properties. These processes may produce micro-

variations in repolarization heterogeneity, ST-segment morphology, and T-wave dynamics that remain below the threshold of human visual detection but are identifiable by deep neural networks trained on large datasets.

The model's attention to late repolarization phases and subtle QT variability is consistent with experimental evidence linking metabolic stress to repolarization instability. Previous translational research has demonstrated that metabolic disorders such as insulin resistance and dyslipidemia alter ventricular repolarization reserve even before structural cardiomyopathy develops. AI-based ECG analysis appears capable of capturing these nuanced electrophysiological consequences.

Recent advances in AI-enabled electrocardiography have primarily focused on structural heart disease detection, including reduced left ventricular ejection fraction and hypertrophy. However, several recent clinical investigations have suggested that AI-ECG can also detect systemic physiological states beyond overt cardiac pathology. Studies have shown associations between deep learning-derived ECG phenotypes and age-related biological changes, diabetes status, and incident heart failure. These findings align with the concept that ECG signals represent an integrative biomarker reflecting the cumulative effect of metabolic, structural, and autonomic influences on the myocardium.

The current study extends this paradigm by specifically targeting myocardial metabolic stress prior to structural disease. The improvement in discrimination when AI-ECG predictions were added to traditional clinical risk models highlights the potential of electrophysiological biomarkers as complementary tools in cardiometabolic risk stratification. The observed increase in area under the curve from 0.79 to 0.88 after integration of AI predictions suggests meaningful incremental value beyond conventional laboratory parameters alone.

Notably, the model demonstrated particularly strong performance among younger individuals. This observation is clinically relevant because early metabolic dysfunction often progresses silently for years before manifesting as symptomatic cardiovascular disease. Identifying high-risk individuals at a younger age could facilitate earlier lifestyle and pharmacologic interventions, potentially altering long-term disease trajectories.

The external validation results confirm acceptable generalizability across independent datasets. Although a modest reduction in performance was observed compared to internal validation, the preservation of discriminative capacity indicates robustness of the learned electrophysiological features. Differences in signal acquisition hardware, population demographics, and labeling criteria likely contributed to this performance variation.

Despite promising findings, several limitations must be acknowledged. First, myocardial metabolic stress was defined using systemic metabolic biomarkers rather than direct myocardial energetic measurements. While translational evidence supports the association between systemic metabolic dysregulation and myocardial bioenergetic impairment, future studies incorporating cardiac imaging modalities such as phosphorus magnetic resonance spectroscopy or positron emission tomography would strengthen biological validation.

Second, the retrospective design limits causal inference. Prospective longitudinal studies are required to determine whether AI-ECG-detected metabolic stress predicts future cardiovascular events independently of established risk factors. Third, although interpretability techniques were

applied, deep learning models remain partially opaque, and further research is needed to enhance explainability for clinical adoption.

Additionally, the study population consisted primarily of individuals undergoing routine ECG evaluation in tertiary centers. Broader validation in community-based populations and diverse ethnic groups is necessary to ensure equitable performance and prevent algorithmic bias.

Future research directions should include longitudinal follow-up to assess predictive value for incident heart failure, myocardial infarction, and cardiovascular mortality. Integration of additional data modalities such as wearable device signals, continuous glucose monitoring, and metabolomics may further refine predictive performance. Moreover, deployment studies evaluating real-world clinical implementation and cost-effectiveness are essential before widespread adoption.

From a preventive cardiology perspective, AI-powered ECG screening offers several advantages. ECG is inexpensive, widely available, non-invasive, and easily repeatable. Embedding AI algorithms into standard ECG machines or cloud-based platforms could enable large-scale cardiometabolic risk assessment without additional hardware or imaging requirements. Such an approach aligns with the growing emphasis on early detection and personalized medicine.

In conclusion, this study provides evidence that artificial intelligence–enhanced electrocardiography can detect hidden myocardial metabolic stress prior to overt cardiovascular disease. By uncovering latent electrophysiological signatures associated with energetic dysfunction, AI-ECG may serve as a scalable digital biomarker for early cardiometabolic risk identification. Continued prospective validation and mechanistic investigation will determine its ultimate role in clinical practice.

Conclusion

The findings of this study demonstrate that artificial intelligence–enhanced electrocardiography has the capacity to detect myocardial metabolic stress in individuals without overt cardiovascular disease and without visually apparent ECG abnormalities. By leveraging deep learning analysis of raw waveform data, subtle electrophysiological signatures associated with metabolic and energetic dysfunction can be identified with meaningful discriminative performance.

The ability of AI-based ECG models to capture high-dimensional patterns beyond traditional amplitude and interval measurements suggests that the electrocardiogram contains latent information reflective of underlying myocardial bioenergetics. The observed improvement in risk stratification when AI-derived predictions were integrated with conventional clinical and metabolic markers highlights the potential of AI-ECG as a complementary diagnostic tool in preventive cardiology.

Importantly, the model demonstrated consistent performance across demographic subgroups and maintained generalizability in external validation. These results support the feasibility of implementing AI-enhanced ECG as a scalable screening modality for early cardiometabolic risk assessment.

While further prospective and mechanistic studies are required to validate predictive value for long-term cardiovascular outcomes, this research establishes a conceptual and methodological framework for detecting hidden myocardial metabolic dysfunction before structural disease becomes clinically manifest. The integration of artificial intelligence into routine

electrocardiographic analysis may shift the paradigm of cardiovascular diagnostics from reactive detection of established disease toward proactive identification of early pathophysiological change.

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