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Detection of myocardial ischemia due to clinically asymptomatic coronary artery stenosis at rest using supervised artificial intelligence-enabled vectorcardiography – A five-fold cross validation of accuracy☆

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ABSTRACT

Background: Coronary artery disease (CAD) is a leading cause of death and disability. Conventional non-invasive diagnostic modalities for the detection of stable CAD at rest are subject to significant limitations: low sensitivity, and personal expertise. We aimed to develop a reliable and time-cost efficient screening tool for the detection of coronary ischemia using machine learning.
Methods: We developed a supervised artificial intelligence algorithm combined with a five lead vectorcardiography (VCG) approach (i.e. Cardisiography, CSG) for the diagnosis of CAD. Using vectorcardiography, the excitation process of the heart can be described as a three-dimensional signal. A diagnosis can be received, by first, calculating specific physical parameters from the signal, and subsequently, analyzing them with a machine learning algorithm containing neuronal networks. In this multi-center analysis, the primary evaluated outcome was the accuracy of the CSG Diagnosis System, validated by a five-fold nested cross-validation in comparison to angiographic findings as the gold standard. Individuals with 1, 2, or 3- vessel disease were defined as being affected.
Results: Of the 595 patients, 62·0% ($n = 369$) had 1, 2 or 3- vessel disease identified by coronary angiography. CSG identified a CAD at rest with a sensitivity of 90·2 ± 4·2% for female patients (male: 97·2 ± 3·1%), specificity of 74·4 ± 9·8% (male: 76·1 ± 8·5%), and overall accuracy of 82·5 ± 6·4% (male: 90·7 ± 3·3%).
Conclusion: These findings demonstrate that supervised artificial intelligence-enabled vectorcardiography can overcome limitations of conventional non-invasive diagnostic modalities for the detection of coronary ischemia at rest and is capable as a highly valid screening tool.

Introduction

Coronary artery disease (CAD) is a leading cause of death and disability [1–19]. Conventional non-invasive diagnostic modalities for the detection of stable CAD are subject to significant limitations: low sensitivity, local availability, and personal expertise [2]. Myocardial perfusion scintigraphy, dobutamine stress echocardiography, stress cardiac magnetic resonance imaging, and coronary computed tomography demonstrate excellent diagnostic accuracy [3,4]. However, results depend on local availability, personal expertise, and are cost- intensive because they require considerable equipment, personnel expenditure, and the presence of a physician representing further significant costs. Exercise testing is easy to perform but has a sensitivity of only 50% since results are highly dependent on exercise capacity [5]. One major complication of undetected CAD is an acute coronary syndrome, resulting in disability or death. Therefore, there is a need for a non-invasive, easy-to-perform, affordable, and reliable screening tool for the diagnosis of stable CAD.

☆ Short tweet summarizing the "take-home" message of the provided manuscript: Cardisiography - a non-invasive, highly valid screening tool for the detection of coronary ischemia at rest - combines a five lead vectorcardiography approach with supervised artificial intelligence. #cardisiography #ischemia.

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Recent experience demonstrates that modified vector analysis possesses the potential to overcome the limitations of conventional diagnostic modalities for the diagnosis of stable CAD [6,7]. In addition, artificial intelligence-enabled electrocardiograph algorithms showed promising results and envisaged new diagnostic possibilities [8,9].We hypothesized that we could develop a supervised machine learning algorithm, based on modified vectorcardiography analysis, to identify coronary ischemia at rest. Such a diagnostic test (hereinafter referred to as Cardisiography, CSG) could serve as a reliable screening tool for the diagnosis of CAD at rest.

Materials and methods

Principles of Cardisiography

Cardisiography consists of various components being responsible for data acquisition and analysis: a) a receiver that is used to process, and transform analogue to digital signals, b) a software that estimates and interprets signal vectors from the VCG measurement, and finally, c) a central server where the statistically vector data is analyzed and stored anonymously.

Cardisiography focuses on spatial and temporal heterogeneity of cardiac excitation using vectorcardiography (VCG). The VCG is determined using five electrodes; four signal electrodes and one grounding electrode are placed on the thorax defining two orthogonal planes (Fig. 1A (2)). Each electrode provides a signal from which the lead vectors (potential differences) H_0, A, V_e, I, and D are derived. Considering the heart, respectively the dipole sum vector of the heart is orientated 45° from the body axis, it would be advisable to use a coordinate system aligned the same. To realize this, the leads are transformed (orthogonal projection) as invented by Sanz [10]. Given the five leads, the three-dimensional spatial vector **V** of the excitation propagation of the heart can be described through the projections:

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} D\cdot \cos(45\ ^\circ) - I \\ D\cdot \sin(45\ ^\circ) + A \\ \sin(45\ ^\circ)\cdot(V_e - H_0) \end{pmatrix} = \boldsymbol{V}$$

in Cartesian space (Fig. 1A (1)). While the orientation of the vector in the coordinate system corresponds to the direction, the length of the vector corresponds to the intensity of the electrical field of the heart [10]. Thus, the VCG is directly computed from the leads, and not derived

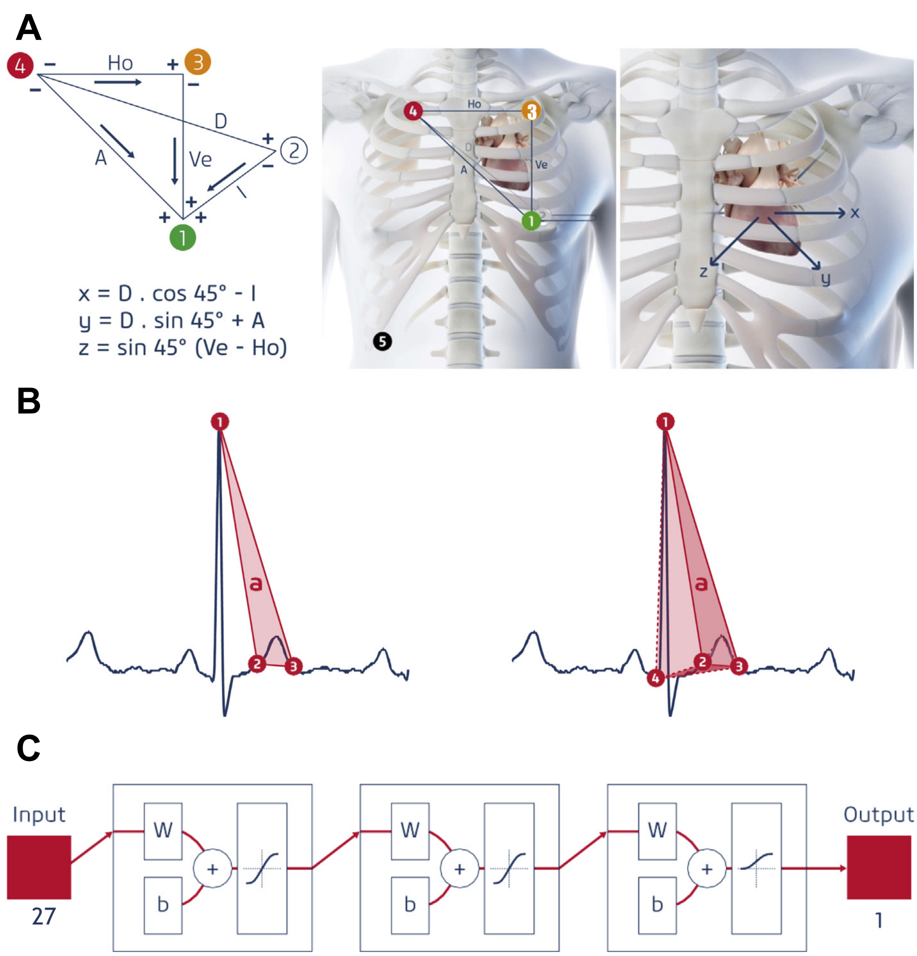

Fig. 1. Principles of Cardisiography. A) Electrode positioning and Cartesian derivate directions. Only four thoracic electrodes are required, positioned in a predefined geometric configuration, additionally to a ground electrode. This electrode positioning provides a three-dimensional reading and spatial display of the cardiac potentials over a period of 4 min. Measurable potentials, based on electric heart impulses, are converted into digital values using bipolar leads (A, I, H_0, D, V_e). This bipolar derivation is transformed into an orthogonal derivation, as shown by the axes x, y, z. While the x- and y-axis represent the diagonal sagittal plane, the z-axis is aligned orthogonally to the sagittal plane. Thus, compared to Frank's system [18], the frontal plane is rotated by 45° compared to the body axis. The figure is modified according to Schuepbach et al. [19]. B) Excerpt of characteristic parameters detected by Cardisiography. In a derivation period of four minutes, CSG documents and analyses automatically a set of 290 parameters including the start and end of the QRS complex, R-peak, start and end of the T-wave, T-peak, as well as the area and superposition of the T-wave and QRS complex in the transverse plane of the vector loop. C) Architecture of the neural network. The machine learning model is an ensemble of five feedforward neural networks. Each neural network is a feed-forward neural network. It comprises an input layer of 27 input neurons, two hidden layers of 22 and 20 neurons and one output neuron. A back-propagation algorithm trains the network, which is optimized for sensitivity and specificity, with 1.5-weighted sensitivity.

from a conventional twelve channel ECG (e.g. through an inverse transformation).

By detecting various significant signal points (e.g. QRST) in the VCG, in total 290 parameters are calculated. The set of 290 parameter series includes commonly known parameter such as: beginning and ending of the QRS complex, R-peak, beginning and ending of the T-wave, T-peak, the area of the T-wave, and the superposition of T-wave and QRS complex in the transverse plane of the vector loop. For example, a well-known parameter is the spatial angle α:

$$\alpha(i) = arcos\left[\frac{(x_R \cdot x_T + y_R \cdot y_T + z_R \cdot z_T)}{\sqrt{(x_R^2 + y_R^2 + z_R^2)\ (x_T^2 + y_T^2 + z_T^2)}}\right]$$

between the R- and T-wave vectors for each heartbeat i (Fig. 1B), where, x, y, and z are the representative Cartesian coordinates of $\boldsymbol{V_{T,R}}$.

All measurements are recorded at rest and are automatically analyzed in a derivation period of four minutes (Cardisiograph). Each parameter deviating from a permissible range reflects impaired repolarization owing to an affective cardiac perfusion.

Feature generation

The characteristic parameters, named above, are detected by CSG for each heartbeat and patient. The time series consisting of i heartbeats allow to extract different statistics; mean, median, range and variance 5%, 15%, 85%, and 95% quantile skewness, kurtosis. They contain dispersion information about time differences, morphology, electric energy density, magnitudes and direction information. A feature is thus described as one statistical moment of a specific parameter. For example, the feature *mean* of a parameter P can be calculated considering the total number of heartbeats i as:

$$\overline{P} = \frac{1}{i}\sum_{k}^{i} P_k.$$

These statistics i.e. features, are used to train the ensemble of neural networks as described in the following section.

Neural network and five-fold nested cross-validation

The machine learning model is an ensemble of five feedforward neural networks. This has the benefit, that by combining the networks together the bias can be reduced significantly. Each neural network is a feedforward multilayer perceptron comprising an input layer of 27 input neurons, two hidden layers of 20 and 22 neurons and one output neuron. However, before the features are weighted using a multi-layer perceptron, they are selected by their level of discriminative power (Area Under Curve, (AUC)) so that only 27 input neurons were selected out of all 2320 features. Since only single values and not time series can serve as input (see Feature Generation), a feature is calculated from each parameter series resulting in total $290 \cdot 8 = 2320$ features per patient. Furthermore, the features were filtered for a maximum correlation of 90%, aiming to establish significant but independent features. The network gives a binary classifier (healthy, sick) as well as the Cardisio Index (range 0 to 1, respectively 0 to −1 for the likelihood that the algorithm decides correctly) as output. It was trained by a back-propagation algorithm and was optimized for sensitivity and specificity, with 1.5-weighted sensitivity (Fig. 1C). The data was split in 80% for training and 20% for testing. 16% of the training data set was randomly taken as validation data. Each neural network corresponds to one split of a five-fold cross-validation. The five-fold cross-validation ensures that every single measurement is used for all the purposes (training, validation, testing) while the groups do not overlap during the process (Fig. 2). Negative patients were weighted with a factor of two to correct for the imbalance in the testing set, as the cohort of available measurements contained a bias to positive values (patients with ischemia).

Patients

From April 2017 to February 2019 cardisiographic results were obtained from 595 unselected adult patients (male: 355, female: 240) who had undergone coronary angiography at three centers in Germany (Evangelisches Krankenhaus Duisburg-Nord, Herzzentrum Duisburg, and St. Bernhard Hospital Kamp-Lintfort). Angiographic findings were evaluated blindly. Importantly, cardisiographic results were obtained prior to coronary angiography. Patients fulfilled the following criteria: aged 18 years or older, clinical indication for conventional coronary angiography in absence of acute myocardial infarction (inclusion criteria). In addition, signs of coronary ischemia were not detectable in the electrocardiogram of the enrolled patients. Individuals with less than 30 parsable heart beats within the measurement were excluded (exclusion criteria). By analyzing conventional coronary angiography, individuals with 1, 2, or 3-CAD with a stenosis were defined as being affected, regardless of the size and location of the stenosis. Individuals without CAD were defined as healthy. Informed patient consent was obtained prior to the examination, thus written consent has been given by all patients.

Statistical analysis

Accuracy of the Cardisio Diagnosis System was measured by sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) with coronary angiography as the standard of reference. We estimated P(sick|red) and P(healthy|green) of CSG by using the Bayes' theorem taking into account an expected prevalence of coronary artery disease of 30% in male and 15% in female patients as given by the 2017 German patients Guideline to the National Supply Guideline [11]. Furthermore, Receiver Operator Characteristic (ROC) and AUC are considered. In addition, the F1 score, representing the harmonic average of the precision and recall, was calculated.

Results

In total 639 patients were examined, however, after applying the exclusion criteria, 595 patients were included. Their age ranged from 39 to 84 years for male patients ($n = 355$) and from 28 to 88 years for female patients ($n = 240$). Impaired coronary perfusion was identified in 369 out of 595 patients by coronary angiography (male patients: 246/355, 69·3%; female patients: 123/240, 51·3%). The diagnostic accuracy was evaluated by applying a five-fold cross validation. Each neural network of the five-fold cross-validation was trained with 192 female patients (284 male patients) and tested with 48 female patients (71 male patients). From the training data set, 16% is randomly taken as validation.

Based on the five-fold nested cross-validation, the sensitivity of the Cardisio index for positive female patients was 90·2% (SD 4·2) while negative predictive value was 87·9% (SD 8·4), specificity 74·4% (SD 9·8), and positive predictive value 78·7% (SD 8·6, Fig. 3A). By using the Bayes' Theorem, P(sick|red) was 38·3% (SD 3·9) and P(healthy|green) 97·7% (SD 1·3). Receiver operating characteristic curve analysis showed an area under curve of 85·0 (SD 5·9) for female patients (Fig. 3B). The supervised artificial intelligence algorithm yielded a F1 score of 83·6 (SD 5·1) in the female cohort.

For male patients, the CSG yielded a sensitivity of 97·2% (SD 3·1), negative predictive value of 92·2% (SD 6·9), specificity of 76·1% (SD 8·5), and positive predictive value of 90·2% (SD 3·0, Fig. 3C). P(sick|red) was 63·6% (SD 3·5) and P(healthy|green) 98·4% (SD 2·9) in this cohort. An area under curve of 90·0 (SD 3·1) and a F1 score of 93·5 (SD 2·3) were calculated for male patients (Fig. 3D).

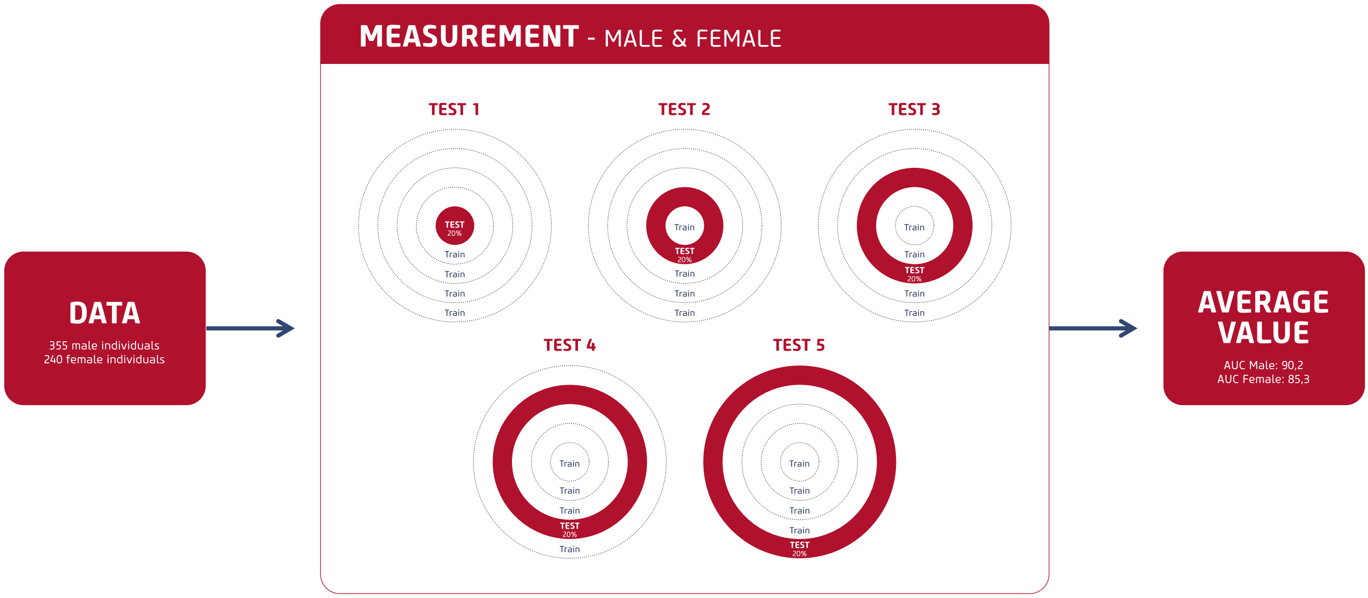

Fig. 2. Measurement of the performance of Cardisiography by five-fold nested cross-validation. Once an Artificial Intelligence system has been trained, its target accuracy needs to be validated, even with regard to data the system has not seen before. To generate a meaningful validation, a sufficient amount of testing data is necessary. The data must first be split into distinct groups: Testing (80%) and training (20%). 16% of the testing data set is randomly taken as validation. Cross validation ensures that every single measurement is used for all three purposes while the groups do not overlap during the process. Each neural network corresponds to one split of a five-fold cross-validation. By combining the results of the five neural networks, the target accuracy can be evaluated.

Overall, the diagnostic accuracy was 82·5% (SD 6·4) for female and 90·7% (SD 3·3) for male patients for the diagnosis of coronary artery disease at rest, using coronary angiography as reference method. A summary of the parameters displaying the diagnostic performance of CSG is presented in Table 1.

Discussion

Aiming at developing a new non-invasive alternative method in the diagnosis of stable CAD, this study verified the diagnostic accuracy of Cardisiography, a de novo development in the field of modified vectorcardiography together with artificial intelligence based supervised machine learning algorithms. Based on a sensitivity of 97·2% for male patients CSG excludes stable coronary vascular disease with a high probability. For female patients, the sensitivity is slightly lower (90·2%).The Bayes' probability P(healthy|green) of 97·7% for the female and 98·4% for the male cohort indicates, that only one out of 43 women (one out of 63 men) receives a green test result, although coronary perfusion is detectable by coronary angiography. The specificity of 74·4% for female and 76·1% for male patients correspond to a P(sick|red) of 38·3% for female and 63·6% for male patients, indicates that a positive test result requires further cardiological workup justifying angiography. Besides high diagnostic accuracy, CSG provides additional benefits compared to existing non-invasive methods for detecting coronary artery disease. For example, whereas those methods are correlated with a low sensitivity, specificity, or with high expenses with, and require the presence of a physician, CSG is easy to perform, time-cost-efficient, and investigator-independent.

Undetected, stable CAD is a main risk factor for acute coronary ischemia, resulting in disability or death. By defining people with a 1-, 2- or 3-CAD, regardless of the size of the stenosis, as being affected, CSG is qualified as a screening tool. Therefore, the provided Cardisio Index could serve as a biomarker: A high Cardisio Index could implicate a high risk for cardiac events (e.g. myocardial infarction). By applying further cariological workup after a positive CSG result, adverse events could be prevented. We also note, that the applicability of CSG is not limited to the detection of stable CAD. The combination of a neural network with the measurement of electric potential is implementable to many scientific applications. In addition, the threshold for a positive test result (e.g. size of the stenosis) could be modified for different clinical approaches. However, prospective studies are warranted.

One limitation of the provided study is the limited number of analyzed cases. Compared to other already published studies analyzing the combination of machine learning and electrocardiogram [9], the number of 595 analyzed patients is low. However, we correlate these measurements to a 100% reliably gold standard (coronary angiography), ensuring an appropriate development and validation of the algorithm. Another limitation is the selection of the study population. By just including patients, who already have been obtained a cardiologic workup by receiving a coronary angiography, deductions for the total population have to be discussed critically. However, by including a sufficient number of patients without coronary artery disease as well as considering of different hospitals, a proper variety of analyzed individuals could be achieved. Due to the retrospective character of the presented study, statements on the clinical applicability and on the diagnostic performance in the primary setting have to be treated with caution.

The interpretation of the neuronal network's output is not trivial, and therefore the second limitation of the provided study. Making a clinically important decision without knowing, what the networks interpretation drives, has to be discussed critically. Furthermore, information on the affected vessel, the clinical relevance of the stenosis or on potential arrythmia are lacking. However, this is beyond of the studies. Hence, further research could deal with the interpretation and representation of the neuronal network decisions. Moreover, the analysis and comparison of the CSG to a typical twelve channel ECG approach in combination with this neural network design possibly enhance the results of CSG. Therefore, future studies could examine how the findings of this study correlate with pathological twelve channel ECG results, for example.

Nonetheless, in comparison to other, already published studies presenting artificial intelligence-enabled electrocardiograph algorithms [8,9], Cardisiography offers two advantages: First, we developed a screening tool which is based on vector analysis, not electrocardiography. By considering three dimensions in our artificial intelligence algorithm, we could select the features from a broader, more physiological

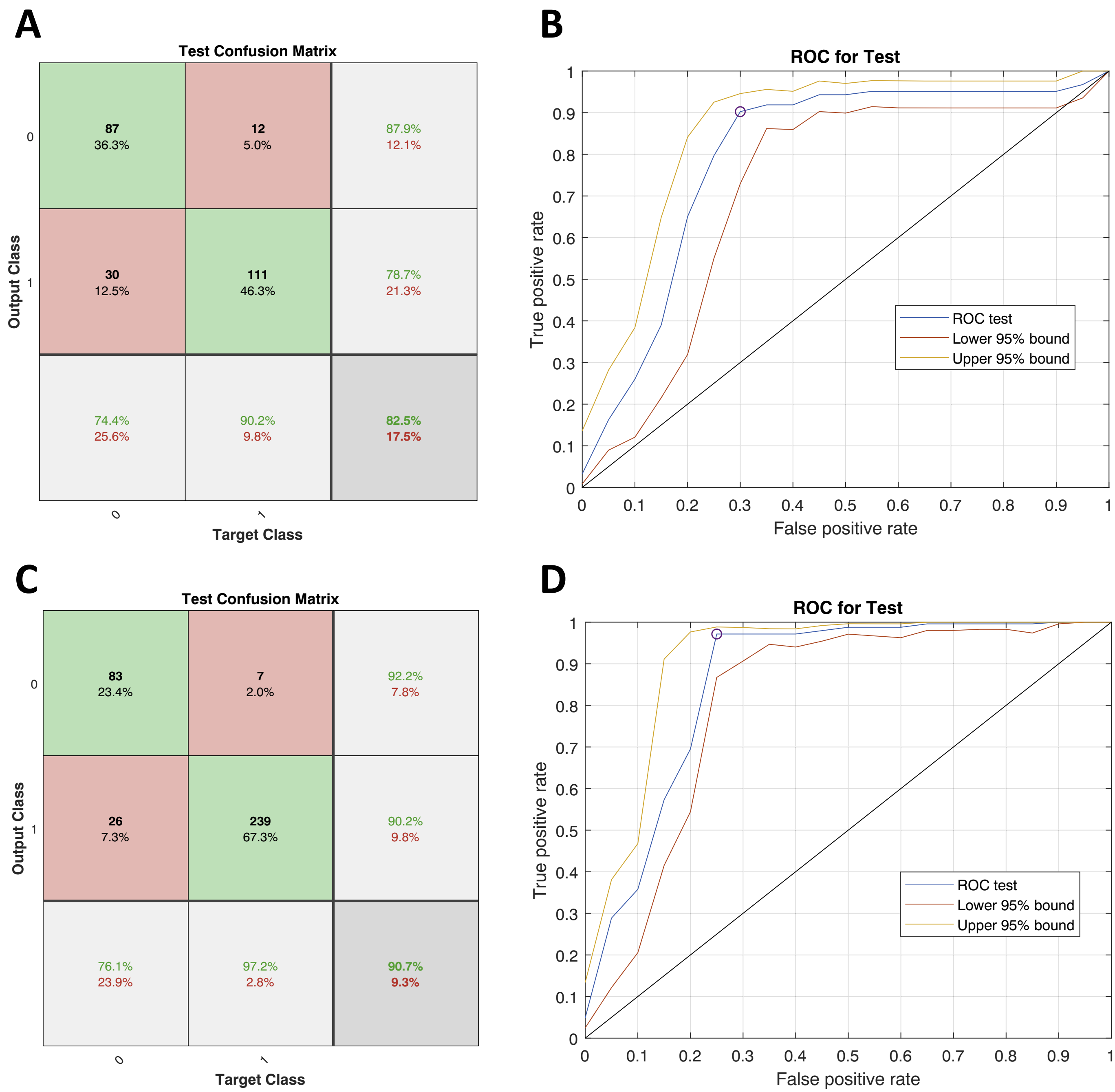

Fig. 3. Confusion matrix and ROC-Curve showing the diagnostic accuracy of Cardisiography. The diagnostic accuracy was determined in a cohort of 240 female (a) and 355 male (c) patients. In the confusion matrix the rows represent the CSG result and the columns the result of the coronary angiography, whereas"0″ means no event and"1″ means CAD. In summary for female patients the sensitivity of Cardisio Index is 90·2% (a) and for male patients 97·2% (c), the specificity 74·4% and 76·1%, respectively. The area under curve (AUC) for female patients (b) is 0·85 and for male (d) 0·90.

range. Second, we used an artificial intelligent, but also supervised machine learning algorithm for the detection of CAD at rest. This facilitates the possibility to analyze each of the selected features for its clinical relevance.

Pre-clinical findings already demonstrated, that mapping the spatial heterogeneity of coronary blood flow enabled the detection of clinically unapparent resting ischemia. The regional differences of flow in individual areas of the myocardium, called micro-heterogeneities, were first described by Yipinsoi et al. [12] and confirmed by numerous investigations in different species and by using various methods [13]. A review of local myocardial perfusion using microspheres at a resolution of 300 μm shows that about one tenth of areas receive less than 50% of average flow (called low-flow areas), and a further one tenth receives more than 150% (high-flow areas). Blood flow within a particular area can vary by a factor of 10 [14]. Loncar et al. showed that high-flow areas do not represent luxury perfusion, but that local flow actually reflects the surrounding tissue's perfusion requirement [15]. According to Austin et al., the resting blood flow is determined by metabolic factors, while the maximum flow is dependent on factors such as coronary pressure, diastole length, and extra-luminal tissue pressure. For regions with a lower coronary reserve (such as coronary vascular disease) an increased vulnerability to ischemia is postulated [16]. Regional differences of the duration of the action potential are associated with spatial heterogeneity of myocardial blood flow and can be determined using

Table 1
Diagnostic performance of CSG.

Male/female: accuracy	Male CSG (n = 355)	Female CSG (n = 240)
Sensitivity	97·2 ± 3·1	90·2 ± 4·2
Specificity	76·1 ± 8·5	74·4 ± 9·8
Positive Predictive Value (PPV)	90·2 ± 3·0	78·7 ± 8·6
Negative Predictive Value (NPV)	92·2 ± 6·9	87·9 ± 8·4
P (sick | red)	63·6 ± 3·5	38·3 ± 3·9
P (healthy | green)	98·4 ± 2·9	97·7 ± 1·3
Accuracy	90·7 ± 3·3	82·5 ± 6·4
Area Under Curve (AUC)	90·0 ± 3·1	85·0 ± 5·9
F1-score	93·5 ± 2·3	83·6 ± 5·1

Table 1: Diagnostic performance of CSG: Parameters displaying the diagnostic performance of CSG are calculated for the test data set, presented for male ($n = 355$) and female patients ($n = 240$). P(sick|red), showing the probability to be sick after getting a "red" test result, and P (healthy|green), showing the probability to be healthy after getting a" green" test result, were estimated by taking into account an expected prevalence of coronary artery disease of 30% in male and 15% in female patients [11]. The F1 score represents the harmonic average of the precision and recall. Summing up, CSG achieved a strong diagnostic performance with slightly better parameters in the male cohort.

Activation Recovery Intervals (ARIs) via unipolar electrograms utilizing a neutral reference electrode [17]. These pre-clinical findings support the hypothesis that modified vector analysis, in combination with an artificial intelligence-enabled algorithm, possess the potential to identify regional differences in blood flow and thereby can be used to identify coronary ischemia.

Conclusion

In essence of the presented study, we demonstrate that the Cardisiography, a supervised machine learning algorithm, based on vectorcardiography analysis, can classify myocardial ischemia with a high diagnostic performance, compared with personal expertise-dependent and uneconomical methods as stress echocardiography. If confirmed in clinical studies, Cardisiography could serve as a first line non-invasive diagnostic modality for the detection of CAD in primary clinical settings, emergency departments, or remote areas, since it is time-cost efficient and user friendly. Consequently, this result could have important implications for the screening of CAD at rest.

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CRediT authorship contribution statement

Till Braun: Writing - original draft, Visualization. **Sotirios Spiliopoulos:** Resources, Visualization. **Charlotte Veltman:** Resources. **Vera Hergesell:** Resources. **Alexander Passow:** Resources. **Gero Tenderich:** Conceptualization, Methodology, Investigation, Formal analysis, Funding acquisition, Supervision. **Martin Borggrefe:** Writing - review & editing. **Michael M. Koerner:** Writing - review & editing, Project administration, Supervision.

Declaration of competing interest

T. Braun, C. Veltman, A. Passow and G. Tenderich are consultants to Cardisio GmbH. None of the other authors have potential conflicts of interest.

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