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Magnetocardiography Scoring System to Predict the Presence of Obstructive Coronary Artery Disease

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Abstract

BACKGROUND: Magnetocardiography (MCG) has been proposed as a non-invasive and functional technique with high accuracy for diagnosis of myocardial ischemia.

OBJECTIVE: This study sought to develop a novel scoring system of MCG for predicting the presence of significant obstructive coronary artery disease (CAD).

METHODS: In a training set of 108 subjects, predictors of ≥ 70% stenosis in at least one major coronary vessel were prospectively identified from MCG variables. The final model was then retrospectively validated in a separate set of 45 subjects.

RESULTS: In the multivariable logistic regression, among those in the training set, elevated scores were predictive of ≥ 70% stenosis in all subjects (OR: 40.85; 95% CI: 6.28-265.90; p <0.001). In the validation set, the score had an area under the receiver-operating characteristic curve of 0.91 (p <0.001) for ≥ 70% stenosis. At an optimal cutoff, the score had 89% sensitivity, 77% specificity, 74% positive predictive value (PPV), 91% negative predictive value (NPV), and 82% accuracy for ≥ 70% stenosis. Partitioning the score into three levels of predicted risk, 91% of subjects could be identified or excluding CAD (81% PPV and 84% NPV).

CONCLUSION: We described an MCG score with high accuracy for predicting the presence of anatomically significant CAD.

1. Introduction

Despite efforts to improve early diagnosis and the development of preventive therapies, the prevalence of coronary artery disease (CAD) in the general population remains high and is the leading cause of death for both men and women. It is estimated that one third of adults in the United States have some form of CAD, including more than 17 million with CAD and nearly 10 million with angina pectoris (1). Also, as ischemic events constantly occur after revascularization in CAD, the early detection of this is important for lifelong prognosis (2). Nevertheless, the detection of myocardial ischemia in patients with presumed CAD is still a challenge in routine cardiological diagnostics. Although non-invasive stress testing to detect inducible ischemia has been used to diagnose CAD (3), less than half of patients are evaluated non-invasively before percutaneous coronary intervention (PCI) (4). This is because of the testing limitation caused by low diagnostic accuracy and radiation hazard in coronary CT or SPECT.

Magnetocardiography (MCG) is a non-invasive, non-contact, and radiation-free multichannel mapping technique to record cardiac electromagnetic activity with high resolution (between 10^{-11} Tesla and 10^{-14} Tesla) (5-7). Both electrocardiography (ECG) and MCG provide information about the same electrical activities of the heart and thus a magnetocardiogram can be viewed as the magnetic equivalent of an electrocardiogram. However, the magnetic signal is much less influenced by the variations of conductance in body tissues than electric currents. Various clinical studies have already shown superior sensitivity of MCG than ECG for ischemic myocardium at rest, as well as under stress (8-12). MCG has been recognized for its outstanding ability to detect patients with CAD (13-16). Moreover, MCG accurately detects functionally significant CAD as defined by using FFR and provides an assessment of ischemic status in agreement with the percent change of ST-segment fluctuation score (17). Recently, our study found that the incorporation of non-dipole phenomenon (qualitative variable of

MCG) into the percent change of ST-segment fluctuation score (a quantitative variable of MCG) significantly improved the diagnostic performance of CAD detection. In the present study, we attempted to develop a novel MCG score to predict the presence of significant CAD.

2. Methods

2.1. Study population

The study was conducted as a prospective registry at Coburg Hospital, Coburg, Germany with the approval of the institutional review board and in accordance with the ethical guidelines of Clinical Hemorheology and Microcirculation (18). The written informed consent was obtained from all subjects. They were patients who were admitted to the hospital with an indication for coronary angiography due to chest pain or suspected CAD and were older than 18 years and suited for stress testing with MCG.

For the purposes of this analysis, we characterized significant coronary stenosis as ≥ 70% luminal obstruction. Although less severe stenoses might be associated with risk for cardiovascular events, we elected to use a widely accepted standard for defining angiographic significance. Exclusion criteria were acute coronary syndromes or recent (< 3 months) acute myocardial infarction, coronary artery bypass grafting, chronic total coronary occlusion, significant valvular heart disease, end stage renal failure, or refusal to enter the registry. After enrollment, simultaneous recordings of ECG and MCG at rest as well as under stress and echocardiography were performed in a standardized schedule within 24 hours. All MCG data were recorded before coronary angiography.

2.2. MCG recording

The MCG recordings were performed using a 64-channel gradiometer system in a magnetically shielded room (MSR) (CS-MAG II, BMP GmbH, Hamburg, Germany) (19). The MCG system utilizes double relaxation oscillation superconducting quantum interference device (DROSQUID) sensors (20, 21). The average noise spectral density of the entire system in the MSR room is 10 fT/√Hz at 1 Hz and 5 fT/√Hz over 100 Hz. Tangential components of the cardiomagnetic fields were measured, which were effective in obtaining the overall heart information with a relatively small area of the sensor array (22). However, in order to apply the well-known magnetic field map variables, the tri-polar field map patterns were changed into ordinary dipolar field maps using minimum norm estimation (23). The signal processing software provided automatic digital filtering, averaging, synthetic gradiometer formation and baseline correction of the acquired recordings.

2.3. MCG data acquisition

The MCG signals were digitally recorded at rest for 100 s at a sampling rate of 500 Hz, with the patient in the supine position and the SQUID's 2-D arrayed sensors positioned close to, but not in contact with the left chest wall. Stress recordings were acquired by bicycle exercise test. An independent investigator performed quality evaluation and analysis of ECG and MCG.

2.4. MCG variables

We compared twelve arbitrarily chosen variables which are T-wave score at rest and stress, T-wave dispersion at rest and stress, T-wave vector-MCG (VMCG) at rest and stress, 1/2RT-interval VMCG rest and stress, ST-segment fluctuation score, %change of T-wave

dispersion, %change of T-wave VMCG, and %change of 1/2RT-interval VMCG between subjects with CAD and without CAD. The definition of the T-score and ST-segment fluctuation score has been published previously (6). The T-wave dispersion is automatically detected and the temporal standard deviation is calculated in milliseconds by the aforementioned automatic algorithm. VMCG is based on vector-ECG (24, 25). Our implementation follows existing literature. The tool shows the time-evolution of the main current vector, creating a closed loop for each wave in the heart signal. We measured the area of the T-wave loop between T-wave begin and max. The area is expected to increase during conductive problems, since areas of reduced conductivity effect the main current vector. 1/2RT-interval is the midpoint between R-wave peak and T-wave max. All the %change is calculated [(stress-rest) x 100/rest] between rest and stress conditions.

2.5. Statistical analysis

One hundred eight patients and 45 patients from the Coburg Hospital were selected as a training set prospectively and a validation set retrospectively. All the studies for MCG variable selection and the development of a diagnostic model were conducted exclusively on the training set. The starting sets of variables consisted of all twelve variables and were tested using the Wilcoxon Rank Sum test (Levene's test ≤ 0.05), student T test (Levene's test > 0.05), and the Fisher's exact test. The nine variables, which were significantly different between patients with and without CAD, were selected to build an optimal model for predicting the presence of obstructive CAD from the twelve variables selected for the statistical analysis above. An optimal model of multivariable logistic regression was chosen from 511 combinations of nine variables by Hosmer-Lemeshow goodness of fit test, Akaike information Criterion (AIC), Bayesian information Criterion (BIC), and area under the curve (AUC) with their receiver-

operating characteristic (ROC) analyzing with confidence of the score based on the predicted probability in the validation set. If the new variable did not improve the performance, it was removed from the panel, and the next-best variable was selected. This method was repeated until there were no options left that satisfy the algorithm's goodness-of-fit requirements. When we reached the point where we had the final panel, the final model was built by using the entire training set, validating it on the validation set. Candidates were subjected to further analysis of discrimination via iterative model building, assessing change in area under the curve (AUC) with the addition of variables to the base model, along with assessment of improvement in calibration from their addition through minimization of the Akaike or Bayesian information criteria and goodness-of-fit in Hosmer-Lemeshow testing.

The final model included the MCG variables of five (T-wave score at stress, T-wave dispersion at stress, T-wave VMCG at rest, %change of T-wave VMCG, and %change of 1/2RT-interval VMCG). Multivariable logistic regression was used to evaluate the performance of the model in the training set as a whole as well as in several relevant subgroups; diagnostic odds ratios (ORs) with 95% confidence intervals (CIs) were generated. Subsequently, the final model was evaluated with the validation set: To do so, we generated the score distribution within the validation cohort, followed by receiver-operating characteristic (ROC) testing with the score as a function of the AUC. Operating characteristics of the score were calculated, with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) generated. The range of the diagnostic model was then partitioned into three different risk levels, corresponding to multiple levels of CAD risk. All statistics were performed by using R software, version 3.3 (R Foundation for Statistical Computing, Vienna, Austria). P values are 2-sided and with a value < 0.05 was considered significant.

3. Results

3.1. Study patients

Baseline characteristics of study subjects, dichotomized as a presence or absence of significant CAD, are detailed in Table 1. There were numerous baseline characteristics that differed between those in the training set who had at least one coronary stenosis ≥ 70% and those who did not. The validation set came from the previous data (17).

Table 1. Baseline Characteristics

	Subjects with CAD (n = 35)	**Subjects without CAD (n =73)**	**p-value**
Men	13 (37.1)	41 (56.2)	0.050
Age (years)	65.2 ± 12.1	63.7 ± 9.6	0.519
Hypertension	27 (77.1)	60 (82.2)	0.353
Diabetes mellitus	21 (60.0)	31 (42.5)	0.067
Hypercholesterolemia	12 (34.3)	28 (38.4)	0.424
Previous CAD	8 (22.9)	4 (5.5)	0.011
Clinical manifestations			<0.001
Typical chest pain	26 (74.3)	27 (37.0)	
Atypical chest pain	9 (25.7)	46 (63.0)	
Ejection fraction (%)	48.9 ± 5.9	58.0 ± 6.4	<0.001
Multivessel disease	8 (22.9)	0	<0.001
MCG variables			
Positive T-wave score at stress	26 (74.3)	1 (1.4)	<0.001
T-wave dispersion at stress	8.7 ± 1.6	6.2 ± 1.2	<0.001
T-wave VMCG at rest	0.025 ± 0.014	0.017 ± 0.014	0.006

%change of T-wave VMCG	281.1 ± 281.2	111.2 ± 149.2	0.002
%change of 1/2RT-interval VMCG	278.5 ± 213.7	60.3 ± 112.1	<0.001

Data are mean ± SD or number (percentage) or median (interquartile range). CAD = coronary artery disease; NSTEMI = non-ST segment elevation myocardial infarction; MCG = magnetocardiography; VMCG = vector magnetocardiography

3.2. MCG scoring system

In the training cohort, independent predictors of CAD ≥70% in any one vessel included five MCG variables (T-wave score at stress, T-wave dispersion at stress, T-wave VMCG at rest, %change of 1/2RT-interval VMCG, and %change of T-wave VMCG). Model fitting performed on the validation cohort (Table 2) shows that the addition of MCG variables improved discrimination, while simultaneously improving the calibration for coronary stenosis of ≥70%, as evidenced by minimization of the Akaike or Bayesian information criteria and with concomitant goodness of fit through Hosmer-Lemeshow testing. With respect to the variables, candidates were retained if they strengthened the model and/or improved calibration.

Table 2. Validation cohort: Model fitting

	AUC	**AIC**	**BIC**	**Hosmer-Lemeshow p Value**
T-Ss + T-Ds + T-VMCGr + %Δ 1/2RT-VMCG + %Δ T-VMCG	0.91	53.1655	69.2583	0.59
T-Ss + T-Ds + T-VMCGr + %Δ T-D + %Δ T-VMCG	0.91	61.5748	77.6676	0.16
T-Ss + T-Ds + T-VMCGr + %Δ T-D + %Δ 1/2RT-VMCG + %ΔT-VMCG	0.91	54.6688	73.4437	0.95

T-Ss + T-Ds + T-VMCGr + T-VMCGs + %Δ T-VMCG	0.87	56.4208	72.5136	0.09
T-Ss + T-Ds + %Δ T-D + %Δ 1/2RT-VMCG + %Δ T-VMCG	0.87	53.1029	69.1957	0.80

T-Ss = T-wave score at stress; T-Ds = T-wave dispersion at stress; T-VMCGr = T-wave VMCG at rest; %Δ 1/2RT-VMCG = %change of 1/2RT-interval VMCG; %Δ T-VMCG = %change of T-wave VMCG; %Δ T-D = %change of T-wave dispersion; T-VMCGs = T-wave VMCG at stress; AIC = Akaike information criterion; AUC = area under the curve; BIC = Bayesian information criterion.

In multivariable logistic regression, among those in the training cohort, our score strongly predicted severe CAD in all subjects (OR: 40.85; 95% CI: 6.28 to 265.90; $p < 0.001$). Individual scores were then calculated for patients in the validation cohort, and results were expressed as a function of CAD presence. In doing so, a bimodal score distribution was revealed (Figure 1), with higher prevalence of severe CAD in those with higher scores and lower prevalence among those with lower scores.

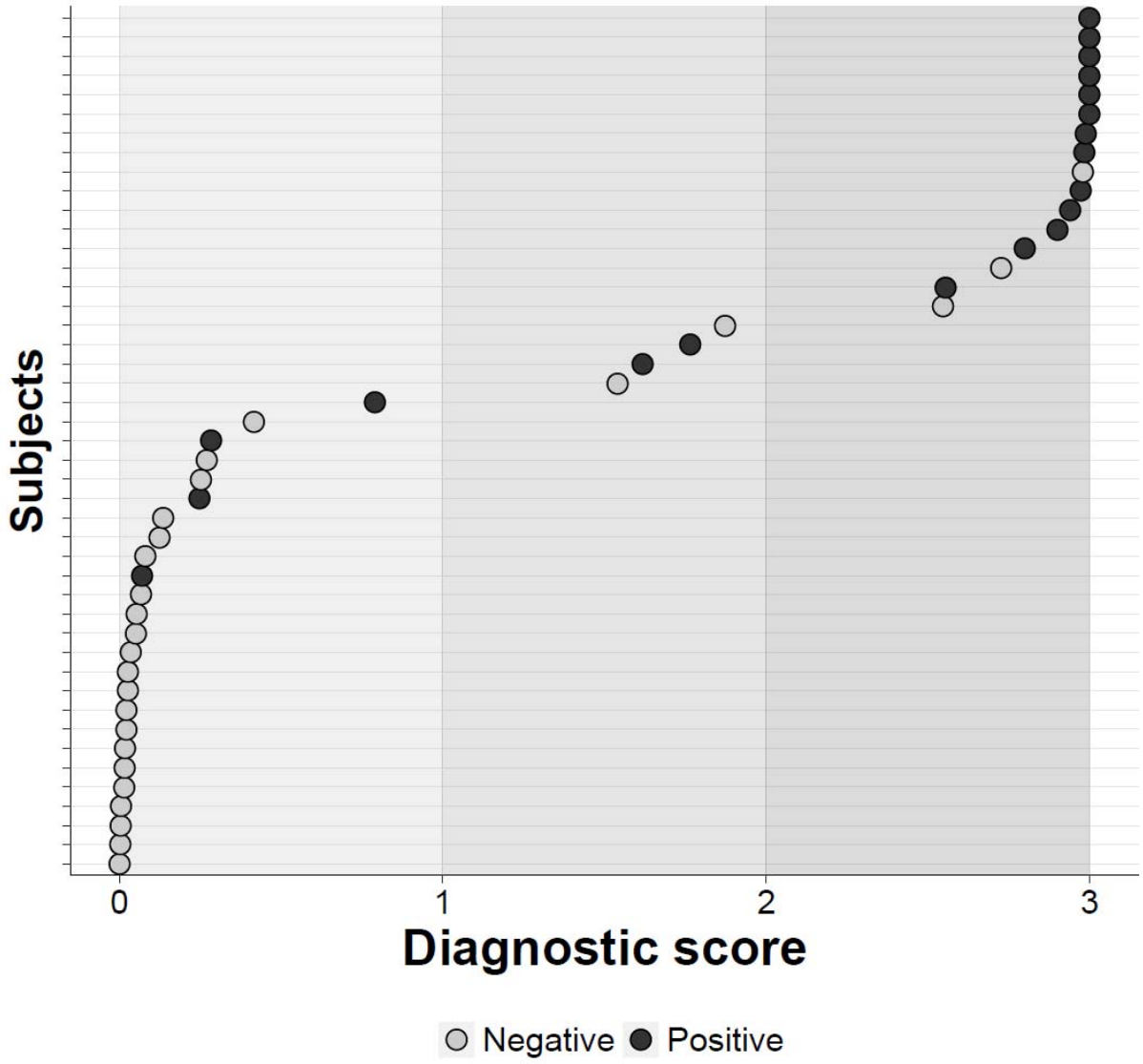

Fig. 1. Distribution of the CAD score to predict severe CAD. A bimodal distribution of the magnetocardiography score is noted in the validation set (n = 45), with preponderance of those with significant CAD distributed at higher scores. Positive = subjects with at least one coronary stenosis ≥ 70% (definition of significant); negative = subjects without coronary stenoses ≥ 70%.

In ROC testing, for the gold standard diagnosis of ≥70% stenosis of any major epicardial coronary artery, the scores generated had an AUC of 0.91 ($p < 0.001$) (Figure 2). At optimal cutoff, the score had 89% sensitivity, 77% specificity, 74% positive predictive value, 91%

negative predictive value and accuracy of 82% for ≥ 70% stenosis. When the score was divided into 3 categories of predicted risk, 91% of subjects could be ″ruled in" or "ruled out" for severe CAD with an NPV of 84% and a PPV of 81%, respectively.

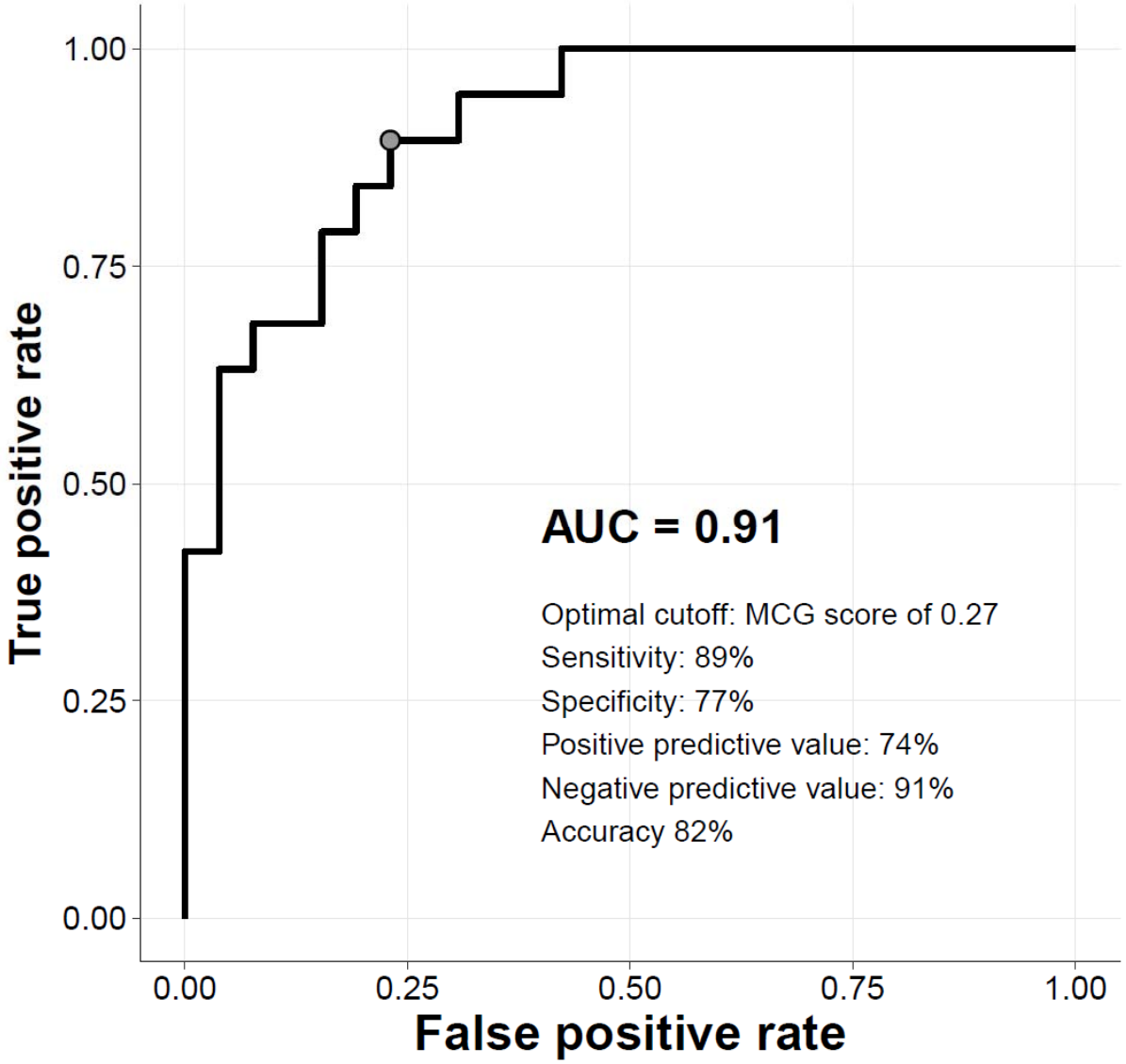

Fig. 2. Receiver-operating characteristic curve. The magnetocardiography score had a very robust area under the curve (AUC). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy at the optimal cutoff are included.

4. Discussion

This study describes a novel scoring system to predict the presence of severe epicardial CAD (≥ 70% stenosis in at least one major vessel). The main results obtained from this study are as follows. This score combined five relevant MCG variables. For the diagnosis of ≥ 70% stenosis of any major epicardial coronary artery, the score generated had an area under the ROC curve of 0.91 in the validation set and, at the optimal cutoff point (MCG score of 0.27), the score had 89% sensitivity, 77% specificity, 74% positive predictive value, 91% negative predictive value, and accuracy of 82%.

For non-invasive diagnosis of CAD, to our knowledge, such efforts are not sufficiently explored. After derivation of a candidate list of assays with MCG plausibility for the detection of underlying CAD, we performed a broad search of >12 variables; in doing so, five variables (T-wave score at stress, T-wave dispersion at stress, T-wave VMCG at rest, %change of 1/2RT-interval VMCG, and %change of T-wave VMCG) were found. Each either added to model discrimination and/or calibration for predicting epicardial stenoses ≥ 70%. Our data suggest that this MCG scoring method is useful for predicting the presence of angiographically significant CAD.

MCG is a non-contact and non-invasive technique to assess the electromagnetic activity of a human heart particularly for ischemic myocardium both at rest and under stress with superior sensitivity (5, 7). Transient myocardial ischemia causes well-recognizable changes in a variety of MCG variables (8, 9, 13). Electrophysiological alteration is the first consequence of myocardial hypoxia occurring in less than a minute after the reduction of blood flow or unmet metabolic demand. The changes of the magnetic field under hypoxia are due to the

reduction of the transmembrane action potential of cardiomyocytes (26-28), which can be demonstrated by MCG (29).

Through this study, we introduce a noble MCG score approaches for cardiac magnetic field analysis in order to detect CAD. In our previous study, we showed the change of ST-segment fluctuation score accurately predicted the presence of hemodynamically significant CAD when compared to FFR (17). As a qualitative variable, the non-dipole phenomenon showed better accuracy to detect CAD than the quantitative variable, the change of ST-segment fluctuation score. However, two variables were removed during the model fitting process.

To our knowledge, this is the first description of MCG score system as a diagnostic tool for coronary atherosclerosis in humans. Our data suggest that this score can be useful for predicting the presence of angiographically significant CAD.

Clearly, the score we have developed deserves critical validation in other unique cohorts, including potentially in patients with suspicious of CAD for whom a physician is considering the risk/benefit ratio of sending the patient for coronary angiography. A score like this could aid in such decisions. Further exploration of the score in patients with different pre-test probabilities for significant CAD will be the next step.

4.1. Study limitations

There are some limitations that should be acknowledged. Firstly, the current study has limitations inherent to its retrospective nature of patients in a limited number for the validation. Secondly, this study investigated a population with high disease prevalence, and thus further studies are required to establish the diagnostic performance of MCG in lower-risk patients. In spite of these limitations, this is the first study to determine the diagnostic value of the MCG score system to detect CAD.

5. Conclusion

We have developed an MCG scoring system to reliably diagnose severe epicardial CAD. Advantages of such a reliable MCG score are that it can be widely disseminated, it can be easily interpreted, and it can be associated with a well-defined sequence of therapeutic steps to reduce the risk of CAD-related complications, such as antiplatelet or lipid-lowering therapy. Further studies using our scoring system are planned.

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Disclosures

None of the authors report any conflict of interest with the specific subject of the study.

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