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Diagnostic accuracy of the magnetocardiograph for patients with suspected acute coronary syndrome

Steve Goodacre¹, Stephen J Walters¹, Hasan Qayyum², Frank Coffey³, Edward Carlton⁴, Timothy Coats⁵, William Glazebrook⁶, Lynda Unitt⁷

¹ School of Health and Related Research, University of Sheffield, Sheffield, UK

²Emergency Department, Sheffield Teaching Hospitals NHS Foundation Trust, Northern General Hospital, Sheffield, UK

³Department of Research and Education in Emergency Medicine, Acute Medicine and Major Trauma, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK

⁴Emergency Department, North Bristol NHS Trust, Southmead Hospital, Bristol, UK

⁵Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

⁶St George's Emergency Department Clinical Research Unit, St George's University Hospitals NHS Foundation Trust, London, UK

⁷Clinical Affairs Department, Creavo Medical Technologies, Coventry, UK

Corresponding author: Steve Goodacre, School of Health and Related Research, Regent Street, Sheffield S1 4DA, s.goodacre@sheffield.ac.uk, 0114 2220842

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Abstract

Background

To estimate the diagnostic accuracy of the VitalScan magnetocardiograph (MCG) for suspected acute coronary syndrome (ACS).

Methods

We undertook a prospective cohort study evaluating the diagnostic accuracy of the MCG in adults with suspected ACS. The reference standard of ACS was determined by an independent adjudication committee based on 30-day investigations and events. The cohort was split into a training sample, to derive the MCG algorithm and an algorithm combining MCG with a modified Manchester Acute Coronary Syndrome (MACS) clinical probability score, and a validation sample, to estimate diagnostic accuracy.

Results

We recruited 756 participants and analysed data from 680 (293 training, 387 validation), of whom 96 (14%) had ACS. In the training sample the respective area under the receiving-operator characteristics (AUROC) curves were: MCG 0.66 (95% confidence interval (CI) 0.58 to 0.74), MACS 0.64 (0.54 to 0.73) and MCG+MACS 0.70 (0.63 to 0.77). MCG specificity was 0.16 (0.12 to 0.21) at the threshold achieving acceptable sensitivity for rule out (>0.98).

In the validation sample (N=387) the respective AUROCs were: MCG 0.56 (95% CI 0.48 to 0.64), MACS 0.69 (0.61 to 0.77) and MCG+MACS 0.64 (0.56 to 0.72). MCG sensitivity was 0.89 (95% CI 0.77 to 0.95) and specificity 0.15 (0.12 to 0.20) at the rule-out threshold. MCG+MACS sensitivity was 0.85 (95% CI 0.73 to 0.92) and specificity 0.30 (0.25 to 0.35).

Conclusion

The VitalScan MCG is currently unable to accurately rule out ACS and is not yet ready for use in clinical practice. Further developmental research is required.

Key messages

What is already known about this subject?

- Magnetocardiography (MCG) is a non-contact imaging technique that detects the magnetic fields generated by the electrical activity of the heart.
- MCG can differentiate between patients with ischaemic heart disease and those without, and has potential to be used to rule out acute coronary syndrome (ACS).

What does this study add?

- This is the first clinical evaluation to be undertaken of the VitalScan MCG for ACS. It showed that the MCG is currently unable to accurately discriminate between people with and without ACS in a cohort with suspected ACS, and unable to accurately rule out ACS.

Introduction

Chest pain accounts for around 6% of adult emergency department (ED) attendances.[1] The main reason for attendance and most common diagnostic assessment is for suspected acute coronary syndrome (ACS). Most people investigated for suspected ACS do not ultimately have a diagnosis of ACS, but investigation takes time and resources, and is an important contributor to ED crowding.

Magnetocardiography (MCG) is a non-contact imaging technique that detects the magnetic fields generated by the electrical activity of the heart. The MCG technology has been evaluated in a number of clinical studies, demonstrating its potential usefulness in the detection of patients with stable angina and ACS including non-ST elevation myocardial infarction (NSTEMI).[2-11] These studies have not evaluated the use of MCG to rule-out of ACS in the ED, which requires the sensitivity and negative predictive value of the test to approach 100%. A portable MCG device could be used in the ED to assist with ACS rule-out, with potential savings of time and cost, and reductions in ED crowding. Specifically, early triage with the MCG could be used to identify patients with a very low risk of ACS who could be discharged without further investigation.

A portable MCG device has been developed for cardiac magnetic field mapping, focused upon rapid chest pain assessment in the ED.[12] Evaluation of the device in 70 patients with ischaemic heart disease, 69 controls and 37 healthy volunteers showed that a logistic regression model based on MCG predictors could differentiate patients from controls with a specificity of 35.0%, sensitivity of 95.4%, and negative predictive value of 97.8% (area under the curve 0.78).[13] This suggested potential for the portable MCG to have a role in ruling out ACS, but further research was required to derive an algorithm for the MCG to diagnose ACS, determine the threshold used to indicate a positive test and then validate the algorithm and threshold in a separate cohort. The MCG measures a number of parameters that can be combined in an algorithm to predict the probability of ACS. This information is operationalised by setting a threshold above which further investigation is recommended and below which ACS can be considered to be ruled out. This threshold needs to be set to optimise sensitivity and thus allow safe ACS rule out. The algorithm and threshold then need to be validated in a separate cohort to determine the diagnostic accuracy for ACS.

We aimed to: (1) Derive an algorithm and an appropriate rule-out threshold for the MCG; (2) Estimate the diagnostic accuracy of the MCG algorithm for ACS across its range of values and at the rule-out threshold; (3) Derive and estimate the diagnostic accuracy of an algorithm combining MCG parameters with a clinical probability score – the modified Manchester Acute Coronary Syndromes

(MACS) score;[14,15] (4) Estimate the diagnostic accuracy of the MCG in different risk strata, determined by the MACS score; and (5) Estimate the prognostic accuracy of the MCG for subsequent major adverse cardiac events (MACE).

Methods

We undertook a prospective, multi-centre cohort study comparing the VitalScan MCG (index test) to independent panel adjudication of ACS (reference standard) in patients presenting to the ED with chest pain symptoms suggestive of ACS. We collected data for training and validation samples, analysts from Creavo Technologies derived the algorithms and optimal threshold using the training sample, and we then independently estimated diagnostic accuracy of the algorithms using the validation sample. The authors were therefore responsible for study design, data collection, data analysis and interpretation of the findings, but played no role in developing the MCG algorithm. LU is an employee of Creavo Medical Technologies but played no role in developing the MCG algorithm. Throughout this paper “we” refers to the authors rather than anyone involved in developing the technology or the algorithm.

We recruited adults (age 18 years or above) presenting to the EDs of five English hospitals with suspected ACS who were willing and able to provide written informed consent. We excluded people with atrial fibrillation, ST-segment Elevation MI (STEMI), a clear non-cardiac cause, haemodynamic instability (BP>220mmHg systolic, >110mmHg diastolic, <80mmHg systolic, <40mmHg diastolic, HR>160bpm), ventricular tachycardia or fibrillation, thoracic metal implants (including pacemaker or internal defibrillator), pregnancy or lactation, inability to lie down (i.e. supine position) or stay still on the examination bed, inability to understand the informed consent process and/or poor understanding of English, and inability to comply with the requirements of the protocol.

The index test was the VitalScan MCG, which is shown in Figure 1. Participants underwent a resting MCG scan within 30 minutes (\pm 15 minutes) of the standard resting 12-lead ECG being completed in the ED. All scans were performed at the patient’s bedside by a trained operator in accordance with the Manufacturer’s Instructions for Use manual. Results were stored and transferred to the research team, and were not revealed to the operator or any member of the clinical team.

All participants underwent routine clinical assessment including resting 12-lead electrocardiograph (ECG) and one or more high sensitivity cardiac troponin measurement as per standard practice at the

hospital. The protocol did not specify any additional interventions other than the MCG. The modified MACS score, which includes several clinical variables taken from history and clinical examination but doesn't take account of troponin, [Unpublished data, Body R, University of Manchester, July 2016] was calculated following all baseline procedures and each participant was assigned to a low (<7%), intermediate (7-25%) or high risk (>25%) subgroup for secondary analysis, based on producing meaningful numbers in each strata. We used a modified MACS score that excludes troponin to determine whether clinical and MCG assessment could allow ACS rule-out without troponin testing. Hospital electronic records were reviewed at 3 months and each participant was contacted by telephone, email or text message to identify any MACE (death, non-fatal acute myocardial infarction (AMI), emergency revascularisation, hospitalisation for myocardial ischaemia, life threatening arrhythmia).

An independent adjudication committee consisting of two emergency physicians and one cardiologist determined whether or not each participant had a reference standard diagnosis of ACS by reviewing all available ED and in-patient medical records, including high sensitivity troponin results. A standardised definition for ACS was used that classified cases as: (1) AMI, based upon the third universal definition and divided into type 1 and type 2; [16] (2) Unstable angina, based upon clinical symptoms consistent with ACS but without criteria for AMI, taking into account results from functional or anatomical testing and/or subsequent MACE. The committee were blinded to MCG results.

The sample size was determined on the basis of estimating diagnostic sensitivity for ACS with acceptable precision. We split the sample on the basis of date of recruitment across the whole sample to an early training sample and a later validation sample. For the training sample we estimated that, assuming ACS prevalence of 15%, 300 participants (45 with ACS) would provide a 95% confidence interval (CI) ranging from 0.72 to 0.88 for an MCG algorithm with an AUROC of 0.8, or 0.84 to 0.96 for an AUROC of 0.9. For the validation sample, we estimated that, assuming ACS prevalence of 15%, 426 participants (64 with ACS) would provide a 95% CI ranging from 0.91 to 1.0 for sensitivity of 0.98 and 0.35 to 0.45 for specificity of 0.4.

Training sample: Analysts from Creavo Medical Technologies extracted the MCG parameters from the MCG data by applying signal processing algorithms to extract the MCG waveform for each channel (sensor), selecting intervals on the MCG waveform from which the MCG parameters were calculated, and applying algorithms to determine the MCG parameters. All MCG parameters that

could be potentially used for predictors of diagnostic status (ACS & non-ACS) were identified and the most pertinent parameters for predicting ACS determined. Methods used included, but were not limited to, dimensionality reduction, univariate and multivariate analysis. Using the pertinent predictors, a supervised classification model was fitted to the training dataset. Assessment of the training model was conducted using several key performance indicators including receiving-operator characteristic (ROC) analysis. An appropriate threshold for rule-out was selected by identifying the point on the ROC curve where sensitivity exceeded 98%. Another model was created using a combination of MCG parameters and clinical MACS score to estimate the probability of ACS.

During derivation it was found that a number of scans were too complex for meaningful analysis and interpretation. These scans were automatically coded as MCG positive (i.e. ACS probability = 1). We felt this best reflected clinical practice, whereby an uninterpretable scan would require further investigation rather than allowing ACS rule-out.

Validation sample: An independent statistician applied the MCG and MCG+MACS algorithms to the validation sample data to construct ROC curves, estimate the area under the ROC (AUROC) and estimate the sensitivity and specificity of each algorithm at the rule-out threshold. We also undertook stratified analysis of MCG sensitivity and specificity in low, moderate and high-risk groups. We estimated the prognostic accuracy of the MCG by calculating the relative risk of MACE with a positive MCG result compared to a negative result.

All participants provided written informed consent. The protocol was approved by the Sheffield Research Ethics Committee (reference 16/YH/0454). The study was prospectively registered at ClinicalTrials.gov (NCT02921438), see <https://clinicaltrials.gov/ct2/show/NCT02921438> .

Patient and Public Involvement

Development of the research question and outcome measures was informed by previous studies undertaken by the research team that involved patient representatives and evaluation of patient experience.[17,18] A patient representative on the Study Steering Committee (David Houghton) advised on the design and conduct of the study, and interpretation of results. Patients were not involved in the recruitment to and conduct of the study. We have no plans to disseminate the findings to study participants.

Results

We recruited 756 eligible participants between 6 February 2017 and 30 April 2018 across five sites, of whom 746 completed the study. Figure 2 shows the flow of participants. We were unable to record a usable MCG scan for 52 (7%, 28 training, 24 validation) or adjudicate a reference standard for 16 (2%, 6 training, 10 validation), with 2 participants having neither MCG scan nor reference standard. This left 293 training and 387 validation cases in the analysis. The mean age of participants was 59 years (58 training, 59 validation) and mean MACS score was 19 (training 17, validation 21). Table 1 compares other characteristics. Participants in the validation sample had a higher prevalence of previous cardiac history, risk factors for coronary artery disease and high risk MACS score, but the prevalence of reference standard ACS was similar in the two samples (15% (43/293) v 14% (53/387)).

Table 1: Baseline characteristics of participants included in the training and validation samples

		Training sample		Validation sample		Combined sample	
		n	%	n	%	n	%
Female		111	38%	139	36%	250	37%
Ethnicity	Asian / Asian British	15	5%	30	8%	45	7%
	Black / African / Caribbean / Black British	8	3%	7	2%	15	2%
	Declined to answer	0	0%	2	1%	2	0%
	Mixed multiple ethnic groups	3	1%	1	0%	4	1%
	Other ethnic group	1	0%	5	1%	6	1%
	White / Caucasian	266	91%	342	88%	608	89%
Patient has previous cardiac history		98	33%	156	40%	254	37%
Known family history of CAD and/or MI <60yrs old		119	41%	167	43%	286	42%
Known dyslipidaemia		92	31%	177	46%	269	40%
Known diabetes		38	13%	71	18%	109	16%
Known hypertension		117	40%	185	48%	302	44%
Current smoker (within 4 weeks)		48	16%	77	20%	125	18%
Presence of acute ischaemia on ECG		10	3%	33	9%	43	6%
Pre-test probability score (MACS)	High risk (> 25%)	56	19%	105	27%	161	24%
	Intermediate risk (7-25%)	176	60%	210	54%	386	57%
	Low risk (< 7%)	60	20%	72	19%	132	19%
Relevant patient diagnosis as recorded on the discharge summary	Non-cardiac cause	177	60%	229	59%	406	60%
	NSTEMI	30	10%	40	10%	70	10%
	Other cardiac cause	71	24%	103	27%	174	26%
	Unstable angina (UA)	14	5%	15	4%	29	4%
Reference standard positive for ACS		43	15%	53	14%	96	14%

ACS categorisation	Type 1 MI	34	12%	42	11%	76	11%
	Type 2 MI	0	0%	2	1%	2	0%
	Unstable Angina	9	3%	9	2%	18	3%

The training sample was used to derive an algorithm for the MCG and identify a threshold for positivity that provided acceptable sensitivity for rule-out, and derive an algorithm that combined the MCG and MACS score. A total of 293 participants in the training sample had both a valid MCG index test result and a reference standard diagnosis. One participant did not have a valid MACS score. The ROC curves for these algorithms and the MACS score are shown in Figure 3. The respective AUROCs were: MCG 0.66 (95% CI 0.58 to 0.74), MACS 0.64 (0.54 to 0.73) and MCG+MACS 0.70 (0.63 to 0.77). The specificity of the MCG was 0.16 (0.12 to 0.21) at the rule-out threshold that achieved sensitivity of 0.98 (0.88 to 1.0).

The validation sample was used to estimate diagnostic accuracy. 387 participants had both a valid MCG index test result and a reference standard diagnosis. Figure 4 shows the ROC curves for the MCG algorithm, MACS and MCG+MACS combined in the validation sample. The respective AUROCs were: MCG 0.56 (95% CI 0.48 to 0.64), MACS 0.69 (0.61 to 0.77) and MCG+MACS 0.64 (0.56 to 0.72). Table 2 shows the 2x2 table comparing the MCG algorithm to the ACS reference standard. Sensitivity was 0.89 (95% CI 0.77 to 0.95), specificity 0.15 (0.12 to 0.20), positive predictive value 0.14 (0.11 to 0.18) and negative predictive value 0.89 (0.79 to 0.95).

Table 2: Comparison of the MCG algorithm to the ACS reference standard in the validation sample using the derived rule-out threshold

	Reference standard		
	ACS	No ACS	Totals
MCG positive	47	283	330
MCG negative	6	51	57
Totals	53	334	387

Table 3 shows the 2x2 table comparing the MCG+MACS algorithm to the ACS reference standard. Sensitivity was 0.85 (95% CI 0.73 to 0.92), specificity 0.30 (0.25 to 0.35), positive predictive value 0.16 (0.12 to 0.21) and negative predictive value 0.93 (0.86 to 0.96).

Table 3: Comparison of the MCG+MACS algorithm to the ACS reference standard in the validation sample using the derived rule-out threshold

	Reference standard		
	ACS	No ACS	Totals
MCG+MACS positive	45	235	280
MCG+MACS negative	8	99	107
Totals	53	334	387

We estimated the diagnostic accuracy of the MCG algorithm in the validation sample stratified by MACS score into low, moderate and high risk strata. Sensitivity and specificity were 0.50 (95% CI 0.15 to 0.85) and 0.15 (0.08 to 0.25) respectively in the low risk strata, 0.90 (0.70 to 0.97) and 0.17 (0.12 to 0.23) respectively in the moderate risk strata, and 0.93 (0.78 to 0.98) and 0.11 (0.06 to 0.20) in the high risk strata.

There were only 4 MACE in the training sample and 11 MACE in the validation sample, providing very limited power to analyse prediction of MACE. Analysis showed that all relative risks had wide confidence intervals with no evidence that MCG results predicted MACE. There were no adverse device effects from performing the MCG scan.

Discussion

This study is the first clinical investigation of a new device, the VitalScan MCG, for ruling out ACS in patients presenting to the ED with suspected ACS. The training sample was used to derive an algorithm for predicting the probability of ACS and to derive an appropriate threshold for the algorithm to achieve high sensitivity for rule-out. The ROC analysis showed how the device performed, in terms of sensitivity and specificity, across the range of cut-offs for the predicted probabilities of ACS from the algorithm. An AUROC exceeding 0.7 indicates a model that is good at discriminating between patients at high and low risk of ACS, and an AUROC exceeding 0.8 a strong model. Our findings indicate that the MCG only just achieved good discrimination when combined with modified MACS in the training sample. Estimates from the training sample should not be used to indicate how test will perform in practice because the algorithm will have been over-fitted to the

data. The validation sample provides a better estimate of performance in practice. The AUROC estimates from the validation sample indicated that MCG discrimination of ACS was not significantly better than chance. It is notable that the performance of MCG+MACS combined appeared to be worse than modified MACS alone in the validation sample. This is probably explained by classification of complex MCG scans as positive, which eliminates any potential discriminant value associated with modified MACS in such cases.

Analysis of sensitivity and specificity at the optimal threshold for ruling out showed that the MCG algorithm achieved 98% sensitivity as intended in the training sample, but this was at the expense of specificity of 16%. Statistical shrinkage (which is when a fitted relationship appears to perform less well on a new dataset (the validation set) than on the data set used for fitting (the training dataset)) resulted in sensitivity falling to 89% in the validation sample, which is not acceptable for ACS rule-out. This emphasises the importance of estimating diagnostic parameters in a validation cohort rather than relying on estimates from the data set in which the algorithm or threshold for positivity were derived.

This study had a number of strengths that assist our confidence in the validity and generalisability of the findings. Separation of the training and validation samples was carefully maintained, and analysis of the validation sample was undertaken by a statistician (SJW) who was independent of the manufacturers and not involved in developing the technology or deriving the algorithm. Reference standard adjudication was undertaken by an independent adjudication committee, who were blind to the results of the index test. The results of the index test were also not available to treating clinicians, thus removing the potential for work-up bias (i.e. the index test results influencing ordering of the investigations used to determine the reference standard). The study was conducted across five sites, thus ensuring a wide spectrum of patients and enhancing generalisability.

The study also had some limitations. Exclusion of patients with atrial fibrillation, inability to lie down and inability to speak English may have limited the generalisability of findings. Splitting the sample on the basis of time (with the training sample being recruited before the validation sample) may have resulted in systematic differences between the two samples, with the validation sample having a higher prevalence of previous cardiac history, risk factors for coronary artery disease and high risk modified MACS score. The study was designed to evaluate diagnostic accuracy for ACS rather than prognostic accuracy for MACE, and the sample size estimate was determined on this basis. As a consequence the study was under-powered to estimate prognostic accuracy for MACE. New

technologies could provide useful prognostic information without adding useful diagnostic information, but we are unable to determine this for the MCG in this study.

We were not involved in development of the device or derivation of the algorithm, so we are unable to provide details of the methods used. An inevitable consequence of our independence is that we had to treat the algorithm as a “black box” and limit our analysis to determining diagnostic performance. We are therefore unable to provide insights as to why the device performed as it did or how performance could be improved. Communication with the analysts from Creavo Technologies suggests that operation of the device may have been suboptimal. Diagnostic parameters are obtained from both the ECG-like signal and from markers placed on the magneto-cardiac image. Extracting these accurately is critical to the performance of the device. Therefore, positioning of the scan head so that the magneto-cardiac image lies in the centre of the field of view of the scan head is critical to the functioning of the device. Misalignment of the scan creates two problems. Firstly, magnetic signals can be missed, resulting in a lower (or even absent) signal strength and secondly, the field pattern becomes distorted. Both of these lead to inaccuracies in the parameters extracted. As there was no feedback given to the operators to allow re-positioning of scans, from the device or following analysis, there was no ability to improve the operation. This has been corrected in the next iteration of the device, and has been combined with improvements in the ergonomics and technology.

In conclusion, this study was conducted to evaluate the real world performance of a first-generation bedside MCG device. We have shown that the VitalScan MCG cannot yet meet the high accuracy required to rule out ACS for use in clinical practice. Further developmental research is being undertaken to understand failure of the MCG to identify ACS and improve diagnostic performance within the next iteration of the device which will be evaluated in further clinical studies.

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Steering Committee: Prof Richard Body (Chair), Prof John Camm, Prof Rod Stables, Mr David Houghton, Dr Richard Charles

Adjudication Committee: Dr Janet McComb (Chair), Dr Daniel Horner, Dr Andrew Webster

Local site investigators and research staff:

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Creavo Medical Technologies analysts: Prof Ben Varcoe, Dr Abbas Al-Shimary, Dr Shima Ghasemi-Roudsari

Competing interests

The University of Sheffield received funding from Creavo Medical Technologies for the time committed to the study by its employees (SG, SJW). The authors have no financial interests in the company, other than LU who is an employee of Creavo Medical Technologies.

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Contribution of authors

LU conceived the study. SG and SJW designed the study. HQ, FC, EC, TC, WG and LU collected the data. SJW analysed the data. All authors contributed to interpretation of the data and drafting the paper, and all authors approved the final draft.

Data sharing

Data are available upon request from the authors.

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Figure1: The VitalScan Magnetocardiograph



Figure 2: Flow of participants through study

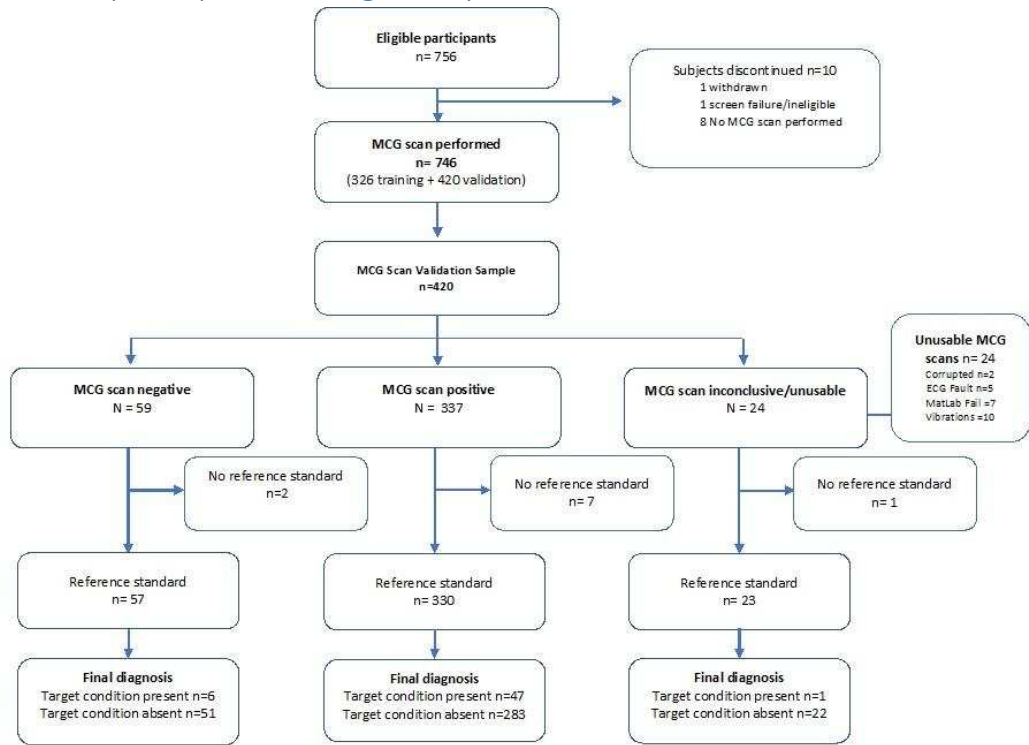


Figure 3: Receiver Operating Characteristic (ROC) Curves for MCG, MACS and MCG+MACS combined in the training sample

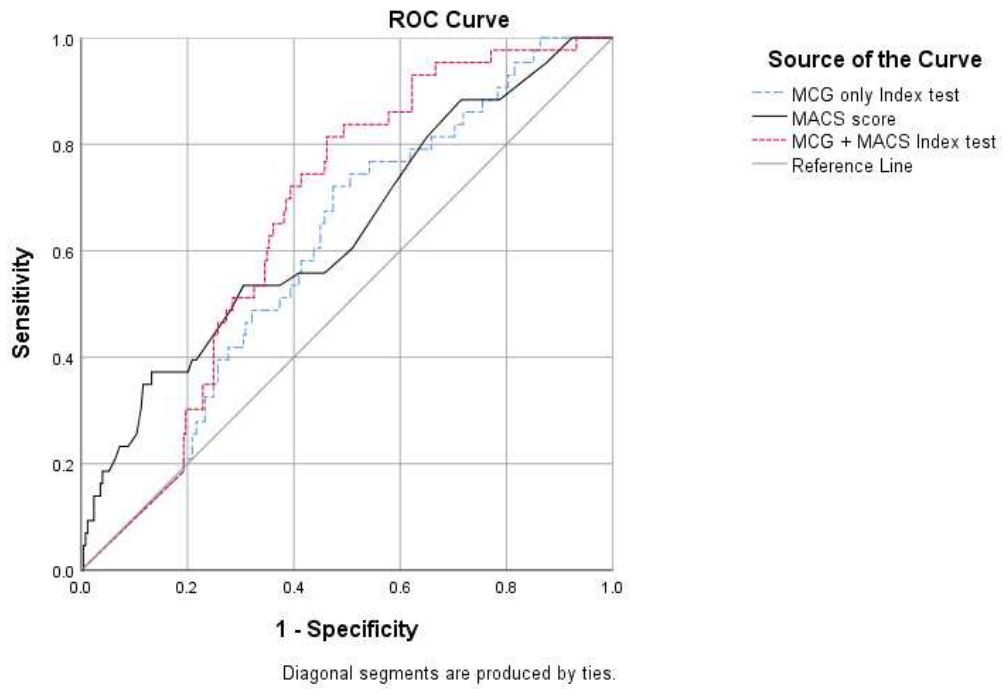


Figure 4: Receiver Operating Characteristic (ROC) Curves for MCG, MACS and MCG+MACS combined in the validation sample

