Comparing MultiFunction-CardioGram™ and Coronary Angiography for Detection of Hemodynamically Relevant Coronary Artery Stenosis (>70%) in Women

a report by John E. Strobeck,[1] Norbert Rainford,[2] Bonnie Arkus[3] and Michael Imhoff[4]

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Introduction

Cardiovascular disease is the leading cause of death for women in the United States.[1] Coronary heart disease—which includes coronary artery (or atherosclerotic) disease (CAD), myocardial infarction (MI), acute coronary syndromes, and angina pectoris—is the largest subset of this mortality.[1] According to the American Heart Association (AHA), approximately one in three female adults has some form of cardiovascular disease. Since 1984, the number of deaths attributed to cardiovascular disease in women has exceeded that in men, reaching 454,613 in 2005, more than deaths from all forms of cancer combined.[2] It is estimated that 8.1 million women alive today have a history of heart attack, angina pectoris or both, and that in this year alone an estimated 370,000 women will have a new or recurrent MI. Overall, women who have had an acute MI—particularly those older than 55 years of age—have a worse prognosis than men, with a greater recurrence of MI and higher mortality.[1] More women (5.5 million) than men (4.3 million) have angina in total numbers. Among women older than 20 years of age, non-Hispanic black women have the highest incidence of angina (6.7%) when compared to non-Hispanic whites (4.3%) and Mexican Americans (4.5%)[2]. However, the prevalence of CAD in women with chest pain is only about 50%, as compared to 80% in men, which complicates accurate diagnosis in women.[3]

The American Heart Association suggests that there is evidence showing that women at risk for CAD are less often referred for the appropriate diagnostic test than men.[1] Coronary anatomy and pathology have traditionally been defined and identified by coronary angiography.[4] The major benefits of invasive coronary angiography over non-invasive diagnostic techniques are that the use of a catheter makes it possible to visualize the coronary arteries in greater detail and to combine diagnosis and treatment in a single procedure. The limitations of coronary angiography include the skill of the interventionist and the inability to provide data on the functional impact of a luminal obstruction. These limitations are generally considered to be minor when compared with the benefits of the procedure, and coronary angiography is now the standard for diagnosis and clinical care of patients who have chest pain suggestive of obstructive CAD.

Electrocardiographic methods are routinely used as the first tools for initial screening and diagnosis in clinical practice. The low sensitivity and specificity of these methods makes them less than ideal diagnostic and prognostic indicators of CAD, however.[6] When used by non-specialists, the 12-lead resting ECG shows a sensitivity of less than 50% in diagnosing myocardial infarction.[40]

For women even worse diagnostic performance of rest-ECG is described with less frequent occurrence of specific ECG changes in women with CAD reported in other studies.[32]

Sensitivity, and to a lesser extent specificity, can be enhanced by different exercise or stress test methods, such as ECG stress testing, nuclear stress testing, or stress echocardiography. Nevertheless, even their sensitivity and specificity are limited, especially in single-vessel CAD.[46] Moreover, stress testing requires significant personnel and time resources, is contraindicated in relevant patient populations, and bears a small but measurable morbidity and mortality.[19,20] Also for stress testing reduced diagnostic yield has been reported for female patient populations.[17,32]

ECG-based methods are even less sensitive in patients after coronary revascularization[23,36,44] and may be contraindicated immediately after intervention. Finally, in a recently published cohort study of 8176 consecutive patients presenting with chest pain,[43] designed to determine whether the resting and exercise ECG provided prognostic information incremental to medical history, in accurately identifying those at higher

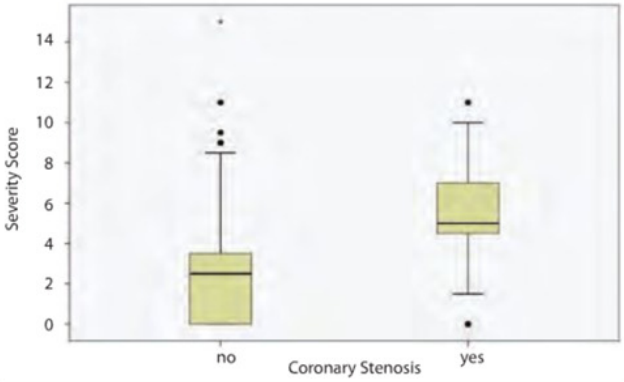

Figure 1. Severity Score vs. coronary stenosis (all patients).
Boxplots of MCG severity scores in all patients with and without relevant coronary stenosis. The boundaries of the box are Tukey's hinges. The median is identified by the line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*). Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (•). Whiskers show high/low values. Outliers and Extremes were included in the overall statistical analysis because the assumptions about the distribution of the data (normal distribution) were not violated.

risk of Acute Coronary Syndrome and death during a median follow-up of 2.46 years, showed that 47% of all events during follow-up occurred in patients with a negative exercise-ECG result. This study emphasized the limitations of resting or stress-ECGs for risk assessment and highlighted the need for new tests to assess this patient population.

Coronary angiography remains the gold standard for the morphologic diagnosis of CAD and also allows revascularization during the same procedure.[8,18] Coronary angiography is a relatively safe and effective intervention, yet it is resource-intensive, expensive, and invasive with

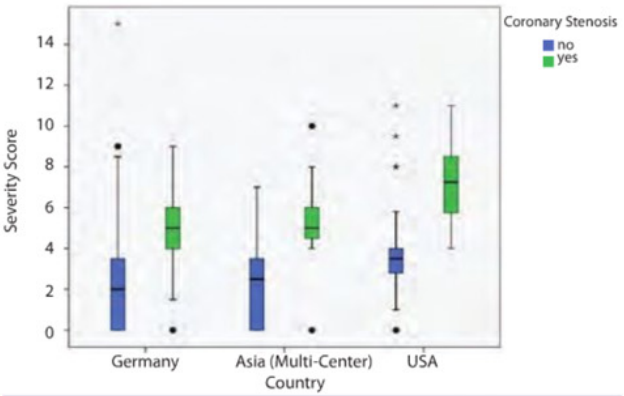

Figure 2. Severity Score vs. coronary stenosis vs. geographical location.
Boxplots of MCG severity scores in all patients with and without relevant coronary stenosis. The boundaries of the box are Tukey's hinges. The median is identified by the line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*). Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (•). Whiskers show high/low values. Outliers and Extremes were included in the overall statistical analysis because the assumptions about the distribution of the data (normal distribution) were not violated.

associated mortality and morbidity.[31,41]

Several methods have been proposed and developed to enhance sensitivity and specificity of the resting ECG for diagnosis of symptomatic and asymptomatic CAD. In theory, such methods may improve diagnostic quality for non-specialists. Yet, diagnostic ECG computer programs have not been shown to be equal or superior to specialist physician's judgement.[25] Moreover, studies comparing computerized with manual ECG measurements in patients with acute coronary syndrome have shown that computerized measurements have diagnostic cut-offs that differ from manual measurements, and they may not be used interchangeably.[15] This is likely to be one of the reasons underlying the limited acceptance of such techniques in clinical practice.

As the non-invasive testing for CAD in women seems to be an even greater challenge than in men, we performed a meta-analysis of all female subjects enrolled in three prospective studies[21,22,24,45,48] comparing the diagnostic accuracy of the non-invasive MultiFunction CardioGram (MCG), a new mathematical ECG signal analysis tool, with coronary angiography.

Materials and Methods

Data from three published trials of the use of MCG in the identification of relevant coronary stenosis was used in this meta-analysis. For the analysis we had access to the detailed study data. A detailed description of the studies can be found in the respective publications.[21,22,24,45,48] For the analysis data for female patients was extracted from the original data sets.

Patients

A total of 390 female patients scheduled for coronary angiography were included in the meta-analysis. These represented a convenience sample of patients in the respective institutions in that each patient was already scheduled for the reference coronary angiography for any indication. Coronary angiographic data was reviewed by two independent interventional cardiologists. The included patient population had no overlap with any other previously published or un-published study or with the actual independently validated MCG clinico-pathologic reference database of 40,000 patients accumulated over more than two decades. The MCG reference database used in the computer-database comparative analysis of each patient's data, was not modified or updated during the study period. Patient demographics, medical history, and risk factors apart from sex, age, height, weight and three samples of 82 second resting two ECG data were not recorded because they are not required for the MCG analysis.

Study Device

The study device used in all patients in each included trial, MCG, is

manufactured in the US by Premier Heart, LLC, Port Washington, NY, and records simultaneous 2-lead resting ECG signals from leads II and V5 for 82 seconds using proprietary hardware and software. The analog MCG ECG signal is amplified, digitized, and down-sampled to a sampling rate of 100 Hz to reduce data transmission size; subsequent data transformations performed on the data do not require higher than 100 Hz/sec resolution. The digitized MCG ECG data was encrypted by the device at each study location and securely transmitted over the Internet to a central server located in New York, NY for final analysis and reporting.

At the central server location in New York, a series of Discrete Fourier Transformations (DFT) and post DFT signal averaging are performed on the data from the two ECG leads during the 82 second sampling period followed by signal averaging. The final averaged digital data, obtained from multiple cardiac cycles, is then subjected to six mathematical transformations (auto power spectrum, coherence, phase angle shift, impulse response, cross correlation, and transfer function – thus the trademark MultiFunction CardioGram in addition to an amplitude histogram, which generates a large inventory of normalized mathematical indexes of abnormality. It is the pattern of these mathematical indexes of abnormality, obtained from analysis of multiple cardiac cycles of the resting ECG not a specific time-based segment of data (i.e. ST segment), that contains the deviations from normal that are measured by the MCG device. The resulting mathematically integrated patterns of the abnormal indexes are then compared for their degree of abnormality to the abnormal index patterns in the reference database to reach a final diagnostic output. The diagnostic output is represented as a combination of the disease severity score from 0 to 20 and the presence of local or global ischemia, which indicates the level of coronary obstruction/myocardial ischemia that is present in the study patient.

The reference database against which the patient's MCG index patterns are compared, originated from data-gathering trials conducted from 1978 to 2000 in more than 30 institutions in Europe, Asia, and North America on individuals of varying ages, in both genders, and degrees of coronary disease state including 10,000 normal subjects with no definable coronary disease[16,48] (age range 14-99, 49% females; no statistically significant demographic differences between normal subjects and CAD patients). All MCG data and spectral analysis included in the database were performed using the same "made in USA" equipment as in the included trials and were analyzed using the same software and hardware located at the central server location in New York. All MCG analysis in this database have been validated against the final medical and angiographic diagnoses, confirmed by two US independent academic angiographers having access to all the diagnostic tests including angiography results, lab, and cardiac enzyme test results.

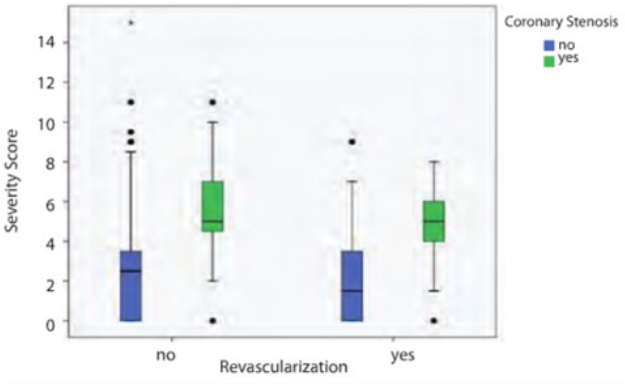

Figure 3. Severity Score vs. coronary stenosis vs. prior revascularization. Boxplots of MCG severity scores in all patients with and without relevant coronary stenosis. The boundaries of the box are Tukey's hinges. The median is identified by the line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*). Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (•). Whiskers show high/low values. Outliers and Extremes were included in the overall statistical analysis because the assumptions about the distribution of the data (normal distribution) were not violated.

One important difference between MCG and other ECG methods is that the MCG digitized analog electrocardiogram signals are locally recorded, but remotely analyzed at a central US data facility, due to the size and complexity of the digital signal processing, the analysis by multiple mathematic functions, and the required comparison to the reference clinico-pathologic database. Further aspects of the underlying technology and methodology have been described elsewhere.[16,21,22,48]

MCG ECG Acquisition and Processing

MCG tests were conducted as follows by a trained trial site technician as

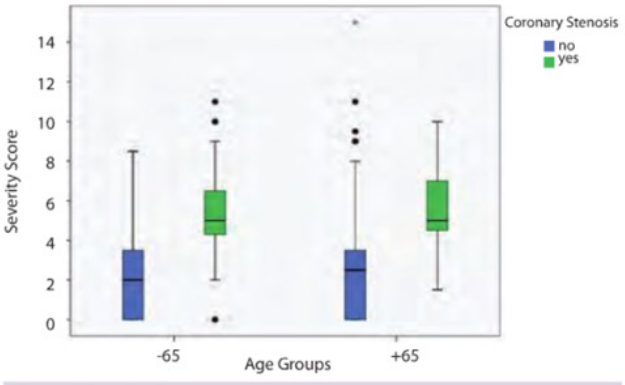

Figure 4. Severity Score vs. coronary stenosis vs. age groups. Boxplots of MCG severity scores in all patients with and without relevant coronary stenosis. The boundaries of the box are Tukey's hinges. The median is identified by the line inside the box. The length of the box is the interquartile range (IQR) computed from Tukey's hinges. Values more than three IQR's from the end of a box are labeled as extreme, denoted with an asterisk (*). Values more than 1.5 IQR's but less than 3 IQR's from the end of the box are labeled as outliers (•). Whiskers show high/low values. Outliers and Extremes were included in the overall statistical analysis because the assumptions about the distribution of the data (normal distribution) were not violated.

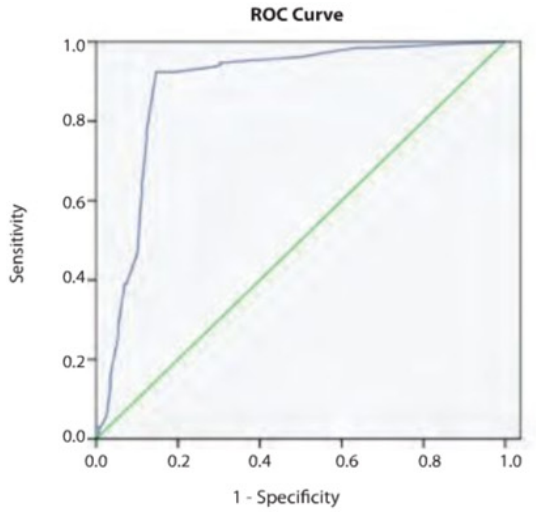

Figure 5. Receiver Operating Characteristics Curve (ROC) for MCG severity score against coronary stenosis detected in coronary angiography.

part of a routine electrocardiographic workup received by each patient<24 hours (average 2.5 hrs) prior to angiography. Patients were tested while quietly lying supine following 20 minutes of bed rest. Five ECG wires with electrodes were attached from the MCG machine to the patient at the four standard limb lead and precordial lead V5 positions. An automatic 82-second simultaneous two-lead (leads V5 and II) ECG sample was acquired with amplification and digitization. During the sampling, the ECG tracings displayed on the MCG screen were closely monitored for tracing quality.

The digital data was then de-identified, encrypted, and sent via a secure Internet connection to the central server in New York. A second identical copy of the data was saved on the site MCG machine for post-study verification purposes before the data analysis was carried out. The quality of the tracing was visually rechecked and graded as "good," "marginal," or "poor". A poor tracing was defined by one of the following:

- Five or more 5.12-second segments of ECG data containing baseline artefact that deviated from the baseline by ≥2 mm and appears ≥10 times,
- Two or more 5.12-second segments of ECG data containing baseline artefact that deviated from the baseline by ≥5 mm,
- In a 25-mm section of waveform in any 5.12-second segment of the ECG data, the waveform strays from the baseline by ≥3 mm,
- A radical deviation away from the baseline angle of at least 80° with peak amplitude of ≥2 mm measured from the baseline, occurring two or more times,
- A single episode of radical deviation away from the baseline angle of at least 80° with peak amplitude of ≥5 mm measured from the baseline.

A marginal tracing was defined by significant baseline fluctuations that did not meet the above criteria. A good tracing had no significant baseline artifact or baseline fluctuation. Tracings consistently graded as poor after repeated sampling were excluded from the present study, as noted above. All other tracings were included in the study.

MCG provided automatic diagnosis of regional or global ischemia, including silent ischemia, due to coronary artery disease and calculated a severity score ranging from 0 to 20 where a higher score indicated a higher likelihood of myocardial ischemia due to coronary stenosis. Following the MCG manufacturer's recommendation, a cut-off of 4.0 for the severity score was used in this meta-analysis; a score of 4.0 or higher and the presence of a moderate, moderate to severe, or severe Local and/or Global ischemia indicator was considered indicative of a hemodynamically relevant coronary artery stenosis of >70% in at least one large-sized vessel.

Angiographers and staff at each study site were blinded to all MCG results and findings. The MCG technicians and all Premier Heart staff were blinded to all clinical data including pre-test probabilities for CAD and the coronary angiography findings from the study patients.

			Age (years)
Country	Germany	Mean	65.3
		SD	10.6
		n	276
	Asia (Multi-Center)	Mean	65.1
		SD	10.8
		n	57
	USA	Mean	63.2
		SD	12.5
		n	57
Total		Mean	65.0
		SD	10.9
		n	390

Table 1. Listing of average age by geographical location.
SD=standard deviation, n=number of patients in each group.

Angiography

After the MCG test, coronary angiography was performed at the discretion of the attending physicians and following the standards of the institution. Angiographers were blinded to the MCG test results. Angiograms were classified by the respective angiographer and independently by two US based academic research angiographers within four weeks after the angiogram. If the two independent investigators did not agree on the results, they discussed the angiograms and conferred with the US study monitor until agreement was reached. Angiograms were classified as follows:

• Non-obstructive CAD: angiographic evidence of coronary artery stenosis of ≤70% in a single or multiple vessels. Evidence included demonstrable vasospasm, delayed clearance of contrast medium indicating potential macro- or micro-vascular disease, or CAD with at least 40% luminal encroachment observable on angiograms. These patients were classified as negative for hemodynamically relevant CAD (= "stenosis: no").
• Obstructive CAD: angiographic evidence of coronary artery sclerosis of>70% in a single or multiple vessels, with the exception of the left main coronary artery, where≥50% was considered obstructive. These patients were classified as positive for hemodynamically relevant CAD (="stenosis: yes").

The results from the angiograms represent the diagnostic endpoint against which MCG was tested.

Statistical Methods

The data acquisition process, all angiography reports, and all MCG test results were monitored by an independent, US cardiologist, study monitor based at the National Institutes of Health, who verified the double-blindness of the study and the data integrity. Two, independent, academic research cardiologists from US, reviewed the coronary angiographic data for each patient. In the event of disagreement among the academic research cardiologists, discussion with the study monitor occurred until agreement was achieved.

Descriptive statistics were calculated for all variables. Differences between paired or two unpaired mean values were analyzed with the t-test, and degrees of freedom were adjusted according to a variance estimate if the F-test could not show equality of variances. Differences between more than two mean values were analyzed with the Scheffé test where homogeneity of variances was assessed with the Levene statistic. For two-way and multi-way tables, Fisher's exact test was used to calculate significance levels.

Odds ratios were calculated. Sensitivity and specificity were calculated as were receiver operating characteristic (ROC) curves including an estimate of the area under the curve (AUC). Positive and negative predictive values (PPV, NPV) for the assessment of coronary stenosis were calculated. 95% confidence intervals were computed. Moreover, to assess the performance of the prediction of stenosis independent of the prevalence of stenosis, the positive and negative likelihood ratios (LR) were calculated.[12] A value of $p<0.05$ was considered statistically significant. All analyses were done with SPSS for Windows Version 17 (SPSS Inc., Chicago, Illinois, USA).

Results

Final analysis was performed on 390 women with an average age of 65.0 +/- 10.9 (Table 1). There were no statistically significant differences in age between geographical locations.

Seventy-six patients (19.5% of those included in the analysis) had either percutaneous coronary intervention (PCI) (63 or 16.2%) or coronary artery bypass grafting (13 or 3.3%) for revascularization six or more weeks before inclusion in the study. All other patients (314 or 80.5%) had no coronary revascularization procedure in their medical history. There were no statistically significant differences in age between patients with or without prior revascularization (details in Table 2).

Hemodynamically relevant coronary stenosis was diagnosed by angiography in 131 patients (33.6%) with a significantly lower incidence in the German center. Patients with coronary stenosis were significantly older than those without (67.7 years vs. 63.6). Patients with revascularization procedures in their medical history were less frequently diagnosed with relevant coronary stenosis, although this difference was not statistically significant (Table 3).

The severity score calculated by MCG was significantly higher for patients with relevant coronary stenosis (5.5 ± 1.9 vs. 2.3 ± 2.3; Figure 1). Also within age groups, geographical locations, and without or with prior revascularization, patients with coronary stenosis consistently showed significantly higher Severity Scores (Figures 2-4).

				Revascularization			
			Age (years)	None	PCI	CABG	Total
Country	Germany	Mean	65.3	64,3	68,9	66,3	65,3
		SD	10.6	11,1	7,7	10,1	10,6
		n	276	209	54	13	276
	Asia (Multi-Center)	Mean	65.1	64,6	68,0		65,1
		SD	10.8	10,2	13,7		10,8
		n	57	48	9	0	57
	USA	Mean	63.2	63,2			63,2
		SD	12.5	12,5			12,5
		n	57	57	0	0	57
Total		Mean	65.0	64,2	68,7	66,3	65,0
		SD	10.9	11,2	8,7	10,1	10,9
		n	390	314	63	13	390

Table 2. Average age and number of patients by geographical location and prior revascularization status. *n=number of patients in each group, SD=standard deviation.*

Patients without a significant coronary stenosis had a severity score<4.0 more frequently than those with a relevant coronary stenosis by a wide, highly significant margin. The results indicate that MCG showed a sensitivity of 92.4% and a specificity of 85.3% for the prediction of coronary stenosis. The positive predictive value (PPV) was 0.76, and the negative predictive value (NPV) was 0.96. A positive likelihood ratio of over 6 and a negative likelihood ratio of less than 0.1 indicate a good to strong diagnostic value for this test (Table 4).

Sensitivity and specificity showed slight differences between participating centers, and age groups, as well as between patients with and without revascularization procedures in their history. But for every group, sensitivity was always 85% or better and specificity better than 80% (detailed results in Table 4), even for those in the revascularization group with a lower angiographic a priori pretest probability of 0.3.

The area under the receiver operator curve (ROC) for the entire study population was calculated to be 0.885 (0.849-0.920) (see Figure 5). The coordinates of the curve confirmed that a cut-off score of 4.0 provides the best combination of sensitivity and specificity for the prediction of relevant coronary stenosis from the MCG test that was reproducible throughout the participating regions.

Discussion

The overall sensitivity of 92.4% and specificity of 85.3% of the MCG device in this meta-analysis in female patients is consistent with earlier reports on this technology. There was little variation between different geographical regions and age groups. Also prior revascularization did not seem to have an impact on the diagnostic performance of MCG. These results compare favorably to results reported in the literature from resting ECG analysis and ECG stress testing. Resting ECG analysis, including 12-lead ECG, typically has significantly less sensitivity in detecting ischemia or obstructive coronary disease in patients with a low pre-test risk of disease. Clinical studies report a wide range for sensitivity from 20% to 70% for acute myocardial infarction (AMI) (review in[6]) and less for hemodynamically significant CAD ischemia.[29] Diagnostic yield from a resting ECG can be improved by exercise testing. Whereas exercise ECG has a reported specificity of over 80% under ideal conditions, in routine clinical use the sensitivity utilizing exercise-based ECG is typically not better than 50-60%.[7,9,10,46]

			Coronary Stenosis	
			No	Yes
Age (years)		Mean	63,6	67,7
		SD	11,3	9,6
Revascularization	no	n	206	108
		%	65,6	34,4
	yes	n	53	23
		%	69,7	30,3
Country	Germany	n	192	84
		%	69,6	30,4
	Asia (Multi-Center)	n	34	23
		%	59,6	40,4
	USA	n	33	24
		%	57,9	42,1
Total		n	259	131
		%	66,4	33,6

Table 3. Incidence of coronary stenosis detected by coronary angiography. Average age, prior revascularization, and geographical location.

Performance of exercise ECG testing can be further enhanced by multivariate analysis of ECG and clinical variables. First studies into computerized, multivariate exercise ECG analysis showed good sensitivity in women (70%) and specificity (89%).[13,38] These results were confirmed by a second group of researchers[11] and are similar to our findings with MCG, though MCG may have superior sensitivity. Other researchers used different statistical approaches and models of multivariate stress ECG analysis with different sets of variables included in the models.[26,27,37,39] Although these approaches provided significantly better diagnostic performance than did standard exercise ECG testing, it appears that none of these methods has been implemented in broad clinical practice or as a commercial product. It should also be noted that none of the above referenced studies included patients with previous coronary revascularization.

Stress echocardiography performed by experienced investigators may provide better sensitivity and specificity than does stress ECG. Numerous studies into exercise echocardiography as a diagnostic tool for CAD have been done. Reported sensitivities range from 31% to over 90% and specificities from 46% to nearly 100%.[17,30,44] With experienced investigators, sensitivities of over 70% and specificities better than 85% can be expected. In a comprehensive systematic review of 16 prospective studies, myocardial perfusion scintigraphy showed better positive and negative likelihood ratios than did routine exercise ECG testing.[34] However, wide variation between studies was reported. Another review of stress scintigraphy studies showed similar results, with a diagnostic accuracy of 85% but wide variation between studies (sensitivity 44%-89%, specificity 89%-94% for 2+ vessel disease).[14] In one study, the combination of stress ECG testing with myocardial scintigraphy using multivariate analysis provided only limited improvement of diagnostic accuracy.[33] Whereas the reported diagnostic performance of stress echocardiography, myocardial scintigraphy, and stress scintigraphy are not dissimilar to what we found for MCG, imaging modalities can provide additional information such as spatial localization that a resting ECG method cannot.

MCG's sensitivity and specificity for the detection of coronary stenosis was good to excellent in all women groups included in this meta-analysis, with only moderate differences between groups. Moreover, there were only small differences in the results between the different geographical regions. The optimal cut-off for the device-determined severity score was not different between patient groups or regions. These results indicate that MCG generates reproducible and stable results in diverse populations of female patients with suspected CDA and different medical settings. Although the number of patients with a revascularization procedure in their medical history was small, the findings may further indicate that MCG provides reliable results in this patient group where other ECG or stress modalities often perform unsatisfactorily.[23,36,44] The endpoint of this study was the morphologic diagnosis of CAD on coronary angiography, whereas the investigated electro-physiologic method (MCG) assesses functional changes of electro-myocardial function secondary to changes in resting coronary blood flow, including both local and global forms of ischemia. Therefore, even under ideal conditions, a 100% coincidence between angiographic findings and MCG results could not be expected. The disagreements mainly stem from under- or over-estimation of disease severity by MCG or the angiographer. Technicians' misidentifying poor quality tests as "acceptable" for MCG interpretation is a source for potential discordance of MCG data and angiographic data. Finally, microvascular disease, not associated with definable epicardial vessel lesions on angiography, resulting in myocardial ischemia can create a false positive result, and critical stenosis of an epicardial vessel with a well-established collateral circulation resulting in a reduction of myocardial ischemia may result in a false negative result. Clinical correlation of MCG data will always be required by the treating physician.

Resting and stress ECG analyses in CAD patients primarily focus on time-dependent ST-segment analysis and the detection of other abnormalities, such as Q-wave abnormalities, Q-T interval, etc. This is not comparable to the MCG concepts and technology, which performs a coronary disease/ischemia assessment from a complex mathematical analysis performed in both the frequency and the time domains.

		Stenosis in Angiography		Stenosis predicted by MCG		Test Classification					Sensitivity			Specificity		
	n	yes	no	yes	no	TP	TN	FP	FN	Correct	Sens.	LCI	UCI	Spec.	LCI	UCI
Total	390	131	259	159	231	121	221	38	10	342	0.924	0.864	0.963	0.853	0.804	0.894
Germany	276	84	192	98	178	75	169	23	9	244	0.893	0.806	0.950	0.880	0.826	0.923
Asia (multi-center)	57	23	34	28	29	22	28	6	1	50	0.957	0.781	0.999	0.824	0.655	0.932
USA	57	24	33	33	24	24	24	9	0	48	1.000	0.858	1.000	0.727	0.545	0.867
<65 yoa	184	51	133	55	129	43	121	12	8	164	0.843	0.714	0.930	0.910	0.848	0.953
65+ yoa	206	80	126	104	102	78	100	26	2	178	0.975	0.913	0.997	0.794	0.712	0.861
No revasc	314	108	206	130	184	101	177	29	7	278	0.935	0.871	0.974	0.859	0.804	0.904
Revasc of any kind	76	23	53	29	47	20	44	9	3	64	0.870	0.664	0.972	0.830	0.702	0.919
PCI	63	16	47	21	42	13	39	8	3	52	0.813	0.544	0.960	0.830	0.692	0.924
CABG	13	7	6	8	5	7	5	1	0	12	1.000	0.590	1.000	0.833	0.359	0.996

	Positive Predictive Value			Negative Predictive Value			Likelihood Ratio		Odd Ratio			Correct			a piori			ROC AUC		
	PPV	LCI	UCI	NPV	LCI	UCI	LR+	LR-	OR	LCI	UCI	Correct	LCI	UCI	a piori	LCI	UCI	AUC	LCI	UCI
Total	0.761	0.687	0.825	0.957	0.922	0.979	6.296	0.089	70.4	33.9	146.2	0.877	0.840	0.908	0.336	0.289	0.385	0.885	0.849	0.920
Germany	0.765	0.669	0.845	0.949	0.906	0.977	7.453	0.122	61.2	27.0	138.6	0.884	0.840	0.919	0.304	0.251	0.362	0.880	0.836	0.923
Asia (multi-center)	0.786	0.590	0.917	0.966	0.822	0.999	5.420	0.053	102.7	11.5	916.8	0.877	0.763	0.949	0.404	0.276	0.542	0.904	0.813	0.995
USA	0.727	0.545	0.867	1.000	0.858	1.000	3.667	0.000	NaN	NaN	NaN	0.842	0.721	0.925	0.421	0.291	0.559	0.893	0.802	0.985
<65 yoa	0.782	0.650	0.882	0.938	0.881	0.973	9.345	0.172	54.2	20.8	141.5	0.891	0.837	0.932	0.277	0.214	0.348	0.896	0.838	0.953
65+ yoa	0.750	0.656	0.830	0.980	0.931	0.998	4.725	0.032	150.0	34.5	651.3	0.864	0.810	0.908	0.388	0.321	0.459	0.857	0.803	0.911
No revasc	0.777	0.696	0.845	0.962	0.923	0.985	6.643	0.075	88.1	37.2	208.3	0.885	0.845	0.918	0.344	0.292	0.399	0.893	0.855	0.932
Revasc of any kind	0.690	0.492	0.847	0.936	0.825	0.987	5.121	0.157	32.6	8.0	133.4	0.842	0.740	0.916	0.303	0.202	0.419	0.849	0.754	0.944
PCI	0.619	0.384	0.819	0.929	0.805	0.985	4.773	0.226	21.1	4.9	91.7	0.825	0.709	0.909	0.254	0.153	0.379	0.820	0.700	0.940
CABG	0.875	0.473	0.997	1.000	0.478	1.000	6.000	0.000	NaN	NaN	NaN	0.923	0.640	0.998	0.538	0.251	0.808	0.917	0.000	1.000

Table 4. Updated Summary of study results – detection of coronary stenosis by MCG.
n=number of cases; TP=true positives; TN=true negatives; FP=false positives; FN=false negatives; a priori=a priori probability of stenosis; Correct=fraction of correctly predicted cases; Sens=sensitivity; Spec=specificity; PPV=positive predictive value; NPV=negative predictive value; LR+=positive likelihood ratio; LR-=negative likelihood ratio; OR=odds ratio; ROC AUC=receiver operating curve area under the curve for continuous severity score; 95% CI=95% confidence interval; LCI=Lower boundary of 95% CI; UCI=Upper boundary of 95% CI; NaN=not a number; Revasc=coronary revascularization in medical history.

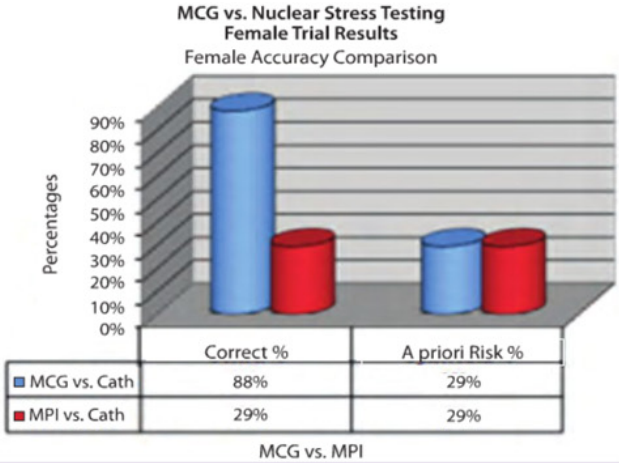

Figure 6. Accuracy (%) of MCG vs Nuclear Stress Testing Compared to Cardiac Catheterization in detecting the presence of >70% coronary stenosis in a cohort of 34 Females.

One limitation of the included studies, with the exception of one,[48] was that the angiographic results were not explicitly quantified using a suitable scoring system such as the BARI (bypass angioplasty revascularization investigation) system in all studies.[5] Still, the assessment of coronary lesions in the present study was consistent between two experienced angiographers who independently evaluated the angiograms. As the target criterion was hemodynamically relevant coronary stenosis (>70%), implying an indication for therapeutic intervention, borderline lesions may have been classified as non-relevant. This may have further artificially reduced the calculated specificity of the MCG method. Another limitation may have been the recruitment of patients. The patient population in all studies included in the meta-analysis represented a convenience sample of patients from a larger group of consecutive patients scheduled for coronary angiography in the respective centers. Although this may limit the generalizability of the patient sample employed, the demographic distribution of this sample matches very well with the distributions reported in the literature for female patients with CAD.

MCG performed very well in the group of women who had prior revascularization (Table 4). Despite the fact that in these patients there was a low *a priori* pre-test risk of coronary stenosis of 30%, MCG correctly identified 84% of these patients as either having relevant stenosis or not. If the MCG score was below 4.0 in this group, the negative predictive value of the test was 93.6%. Finally, MCG was compared to angiography, but not directly to any other non-invasive diagnostic technology in the studies included in this meta-analysis. Therefore, any inference about the potential superiority or inferiority of MCG compared to other ECG-based methods can only be drawn indirectly from other studies. Recently, the results of a direct paired-comparison of MCG with nuclear SPECT myocardial perfusion imaging in 116 patients was presented at the annual meeting of the American College of Cardiology.[49] In this study MCG performed at least as good if not better than SPECT imaging at correctly identifying relevant coronary stenosis in the female cohort (34 patients). MCG accurately classified 30/34 (88%) women in this study as either having or not having relevant coronary stenosis while SPECT nuclear MPI accurately classified only 10/34 (29%) women as either having or not having relevant coronary stenosis (Figure 6). This recent additional study[49] confirms that the data presented in this meta-analysis on sensitivity and specificity of MCG for the detection of relevant CAD in women is at least as good if not better than the published sensitivity, specificity, and negative predictive value of the most widely used stress ECG-based methods, including combined stress-nuclear imaging techniques.Additionally, the reported sensitivity, specificity, and negative predictive value of 97%, 79%, and 98% respectively, for females 65 years of age or older is superior to published data for stress ECG and stress perfusion or wall motion imaging.[19,20,46]

In conclusion, the multi-functional, mathematical, systems analysis of the resting ECG in the frequency and time domains done using the MCG device appears to provide a high sensitivity and specificity for the identification of relevant CAD in female subjects, as diagnosed by coronary angiography, in patients with a low or high pre-test risk of coronary disease, that appears to be equal to or better than those of any other resting or stress ECG/imaging methods currently used in clinical practice. Future research should include further direct comparisons between MCG and other commonly used or new non-invasive or invasive diagnostic and monitoring methods (PET Imaging, Coronary CT Angiography, Cardiac MR Angiography) as well as studies designed to determine the accuracy and outcomes of a diagnostic strategy where the MCG score is the primary determinant of whether an invasive treatment pathway is used.

References

1. Mieres JH, Shaw LJ, Arai A, *et al*. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation 2005;111(5):682-96.

2. Lloyd-Jones D, Adams RJ, Brown TM, *et al*. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010;121(7):e46-e215.

3. Stangl V, Witzel V, Baumann G, *et al*. Current diagnostic concepts to detect coronary artery disease in women. European Heart Journal 2008; 29(6):707-17.

4. Matchar DB, Mark DB, Patel MR, *et al*. Non-invasive imaging for coronary artery disease. Technology Assessment. Rockville, MD: Agency for Healthcare Research and Quality, October 2006. Available at: http://www.cms.gov/determinationprocess/downloads/id34TA.pdf. Accessed February 10, 2011.

5. Alderman E, Stadius M. The angiographic definitions of the bypass angioplasty re-vascularization investigation. Coron Artery Dis. 1992;3:1189-1207

6. Ammar KA, Kors JA, Yawn BP, Rodeheffer RJ. Defining unrecognized myocardial infarction: a call for standardized electrocardiographic diagnostic criteria. Am Heart J. 2004; 148:277-284.
7. Anthony D. Diagnosis and screening of coronary artery disease. Prim Care. 2005; 32:931-946.
8. Braunwald E, Antman EM, Beasley JW, *et al.*; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). Circulation. 2002; 106:1893-1900.
9. Cox JL, Teskey RJ, Lalonde LD, Iles SE. Noninvasive testing in women presenting with chest pain: evidence for diagnostic uncertainty. Can J Cardiol. 1995; 11:885-890.
10. Curzen N, Patel D, Clarke D, ete al. Women with chest pain: is exercise testing worthwhile? Heart. 1996; 76:156-160.
11. Deckers JW, Rensing BJ, Tijssen JG, *et al.* A comparison of methods of analysing exercise tests for diagnosis of coronary artery disease. Br Heart J. 1989; 62:438-444.
12. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ. 2004; 329:168-169.
13. Detry JM, Robert A, Luwaert RJ, *et al.* Diagnostic value of computerized exercise testing in men without previous myocardial infarction. A multivariate, compartmental and probabilistic approach. Eur Heart J. 1985; 6:227-238.
14. Elhendy A, Bax JJ, Poldermans D. Dobutamine stress myocardial perfusion imaging in coronary artery disease. J Nucl Med. 2002; 43:1634-1646.
15. Eskola MJ, Nikus KC, Voipio-Pulkki LM, *et al.* Comparative accuracy of manual versus computerized electrocardiographic measurement of J-, ST- and T-wave deviations in patients with acute coronary syndrome. Am J Cardiol. 2005; 96:1584-1588.
16. Feng G. EKG and EEG Multiphase Information Analysis (A collection of unpublished notes, thesis, papers and published articles from mid seventies to the late eighties translated into English from Chinese). First Edition. U.S.A., American Medical Publishers; 1992.
17. Geleijnse ML, Krenning BJ, Soliman OI, *et al.* Dobutamine stress echocardiography for the detection of coronary artery disease in women. Am J Cardiol. 2007;99:714-717.
18. Gibbons RJ, Abrams J, Chatterjee K, *et al.*; American College of Cardiology; American Heart Association Task Force on practice guidelines (Committee on the Management of Patients With Chronic Stable Angina). ACC/AHA 2002 guideline update for the management of patients with chronic stable angina--summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). J Am Coll Cardiol. 2003;41: 159-168.
19. Gibbons RJ, Balady GJ, Beasley JW, *et al.* ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol. 1997;30:260-311.
20. Gibbons RJ, Balady GJ, Bricker JT, *et al.*; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines).Circulation. 2002; 106:1883-1892.
21. Grube E, Bootsveld A, Buellesfeld L, *et al.* Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis after coronary revascularization. Int J Med Sci. 2008 Mar 2; 5:50-61.
22. Grube E, Bootsveld A, Yuecel S, *et al.* Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis. Int J Med Sci. 2007 Oct 16; 4:249-63.
23. Hecht HS, Shaw RE, Chin HL, *et al.* Silent ischemia after coronary angioplasty: evaluation of restenosis and extent of ischemia in asymptomatic patients by tomographic thallium-201 exercise imaging and comparison with symptomatic patients. J Am Coll Cardiol 1991;17:670-677.
24. Hosokawa J, Shen JT, Imhoff M. Computerized 2-lead resting ECG analysis for the detection of relevant coronary artery stenosis in comparison with angiographic findings. Congest Heart Fail. 2008 Sep-Oct;14:251-60.
25. Hurst JW. Current status of clinical electrocardiography with suggestions for the improvement of the interpretive process. Am J Cardiol. 2003;92:1072-1079.
26. Koide Y, Yotsukura M, Yoshino H, Ishikawa K. A new coronary artery disease index of treadmill exercise electrocardiograms based on the step-up diagnostic method. Am J Cardiol. 2001;87:142-147.
27. Lehtinen R, Sievänen H, Uusitalo A, *et al.* Performance characteristics of various exercise ECG classifiers in different clinical populations. J Electrocardiol. 1994;27:11-22.
28. Mackay J, Mensah G. Atlas of Heart Disease and Stroke. Geneva: WHO Press; 2004.
29. Mant J, McManus RJ, Oakes RA, *et al.* Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care. Health Technol Assess. 2004;8:iii, 1-158.
30. Marwick TH, Shaw L, Case C, *et al.* Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice. Eur Heart J. 2003;24:1153-1163.
31. Mason JJ, Owens DK, Harris RA, *et al.* The role of coronary angiography and coronary revascularization before noncardiac vascular surgery. JAMA. 1995;273:1919-1925.
32. Mieres JH, Shaw LJ, Arai A, *et al.* Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation. 2005;111:682-696.
33. Morise AP, Diamond GA, Detrano R, Bobbio M. Incremental value of exercise electrocardiography and thallium-201 testing in men and women for the presence and extent of coronary artery disease. Am Heart J. 1995;130:267-276.
34. Mowatt G, Vale L, Brazzelli M, *et al.* Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction. Health Technol Assess. 2004;8:1-207.
35. OECD. OECD Health Data 2005: Statistics and Indicators for 30 Countries. Paris: OECD Publishing; 2005.
36. Pirelli S, Danzi GB, Alberti A, *et al.* Comparison of usefulness of high-dose dipyridamole echocardiography and exercise electrocardiography for detection of asymptomatic restenosis after coronary angioplasty. Am J Cardiol 1991;67:1335-1338.
37. Pruvost P, Lablanche JM, Beuscart R, *et al.* Enhanced efficacy of computerized exercise test by multivariate analysis for the diagnosis of coronary artery disease. A study of 558 men without previous myocardial infarction. Eur Heart J. 1987;8:1287-1294.
38. Robert AR, Melin JA, Detry JM. Logistic discriminant analysis improves diagnostic accuracy of exercise testing for coronary artery disease in women. Circulation. 1991;83:1202-1209.
39. Rodriguez M, Moussa I, Froning J, *et al.* Improved exercise test accuracy using discriminant function analysis and "recovery ST slope". J Electrocardiol. 1993;26:207-218.
40. Salerno SM, Alguire PC, Waxman HS. Competency in interpretation of 12-lead electrocardiograms: a summary and appraisal of published evidence. Ann Intern Med. 2003;138:751-760.
41. Scanlon PJ, Faxon DP, Audet AM, *et al.* ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation. 1999;99:2345-2357.
42. Schroeder E, Marchandise B, De Coster P, *et al.* Detection of restenosis after coronary angioplasty for single-vessel disease: how reliable are exercise electrocardiography and scintigraphy in asymptomatic patients? Eur Heart J 1989;10 Suppl G:18-21.
43. Sekhri N, Feder GS, Junghans C, *et al.* Incremental prognostic value of the exercise electrocardiogram in the initial assessment of patients with suspected angina: cohort study. BMJ. 2008;337:a2240.
44. Smart SC, Bhatia A, Hellman R, *et al.* Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. J Am Coll Cardiol. 2000;36:1265-1273.
45. Strobeck JE, Shen JT, Singh B, *et al.* Comparison of a two-lead, computerized, resting ECG signal analysis device, the MultiFunction-CardioGram or MCG (a.k.a. 3DMP), to quantitative coronary angiography for the detection of relevant coronary artery stenosis (>70%) - a meta-analysis of all published trials performed and analyzed in the US. Int J Med Sci. 2009;6(4):143-55.
46. Tak T, Gutierrez R. Comparing stress testing methods. Available techniques and their use in CAD evaluation. Postgrad Med. 2004;115:61-70.
47. Thom T, Haase N, Rosamond W, *et al.*; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113:e85-e151.
48. Weiss MB, Narasimhadevara SM, Feng GQ, Shen JT. Computer-enhanced frequency-domain and 12-lead electrocardiography accurately detect abnormalities consistent with obstructive and nonobstructive coronary artery disease. Heart Dis. 2002;4:2-12.
49. Strobeck, JE, Mangieri, A, Rainford, N, Imhoff, M. A Paired-Comparision of the MultiFunction CardioGramsm (MCG) and Sestamibi SPECT Myocardial Perfusion Imaging to Quantitative Coronary Angiography for the Detection of Relevant Coronary Artery Stenosis (>70%) - A Single-Center Study of 116 Consecutive Patients Referred for Coronary Angiography. J Am Coll Cardiol, 57 (14 Suppl S), p. E48