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ORIGINAL PAPER

Computerized 2-Lead Resting ECG Analysis for the Detection of Relevant Coronary Artery Stenosis in Comparison With Angiographic Findings

To assess the sensitivity and specificity of a new computer-enhanced resting electrocardiographic analysis device for the detection of coronary stenosis, 189 patients (aged 61.3±12.9 years, 57 women) scheduled for coronary angiography from 4 Asian centers were included in an observational study. Angiographic results were independently classified for hemodynamically relevant stenosis by 2 angiographers. The device calculated a severity score from 0 to 20. The score was significantly higher for patients with coronary stenosis (5.4±1.8 vs 1.7±2.1). The study device (cutoff 4.0) identified 73 of 77 patients with stenosis (sensitivity 94.8%, specificity 86.6%). Adjusted positive and negative predictive values were 78.4% and 97.1%, respectively (receiver operating characteristic area under the curve, 0.914 [95% confidence interval, 0.868–0.961]). Subgroup analysis showed no significant influence of sex, age, previous revascularization procedures, or participating center. The new computer-enhanced, resting electrocardiographic analysis device appears to identify patients with relevant coronary stenosis with high sensitivity and specificity. Congest Heart Fail. *2008;14:251–260.* ©*2008 Le Jacq*

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Coronary artery disease (CAD) is the leading single cause of death in the developed world and is responsible for more than 30% of all deaths in most Organisation for Economic Co-operation and Development (OECD) countries.[1] Between 15% and 20% of all hospitalizations are the direct result of CAD.[1] CAD is responsible for 17 million deaths annually worldwide and is also an increasing cause of concern in the developing world, where it causes a direct disease burden of 10%.[2] In the United States alone the prevalence of CAD is estimated at 5.9% of all Caucasians aged 18 years and older.[3]

Accurate, noninvasive diagnosis of and screening for CAD and restenosis after coronary revascularization has been an elusive challenge. Electrocardiography (ECG)-based methods are routinely used as the first tools for initial screening and diagnosis in clinical practice. The low sensitivity of these methods, however, makes them less than ideal diagnostic and prognostic indicators of CAD. Their sensitivity of 20% to 70% is especially unsatisfactory.[4] When used by nonspecialists, the 12-lead resting ECG shows a sensitivity <50% in diagnosing myocardial infarction.[5]

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.[6] Moreover, stress testing requires significant personnel and time resources, is contraindicated in relevant patient populations, and bears small but measurable morbidity and mortality rates.[7,8] ECG-based methods are even less sensitive in patients after coronary revascularization[9–11] and may be contraindicated immediately after intervention.

Coronary angiography remains the gold standard for the morphologic diagnosis of CAD and also allows revascularization during the same procedure.[12,13] Due to both high levels of standardization and training, coronary angiography is a relatively safe and effective intervention. Yet, it is resource-intensive, expensive and invasive, and bears a relevant procedure-related complication rate (<2%) and morbidity (0.03%–0.25%) and mortality (0.01%–0.05%) rates.[14,15] Noninvasive imaging techniques such as multislice computed tomography (CT), high-resolution magnetic resonance imaging/angiography, electron beam angiography, and positron-emission tomography with CT (PET-CT) have an alleged high sensitivity and specificity for detecting morphologic coronary lesions, and some findings even claim that these methods permit the functional assessment of myocardial perfusion. Yet these techniques are also not ideal because they, among other things, are expensive, require significant staff and time resources, and lead to relevant

x-ray radiation exposure of the patient (CT, PET-CT).[16,17]

Several methods have been proposed and developed to enhance sensitivity and specificity of resting ECG for diagnosis of symptomatic and asymptomatic CAD. In theory, such methods may improve diagnostic quality for nonspecialists. Diagnostic ECG computer programs, however, have not been shown to be equal or superior to specialist physicians' judgment.[18] Moreover, studies comparing computerized with manual ECG measurements in patients with acute coronary syndrome have shown that computerized measurements have diagnostic cutoffs that differ from manual measurements and that they may not be used interchangeably.[19] This is likely one of the reasons that underlie the limited acceptance of such techniques in clinical practice.

The present study compared a new computer-enhanced resting ECG analysis device (multiphase functional electromyocardial tomography [mfEMT]), with coronary angiography to evaluate the device's accuracy in detecting hemodynamically relevant CAD.

Methods and Materials

The study was performed in 5 medical centers in Asia after it was approved by the respective local institutional review boards. Written informed consent was waived by each participant as a result of the disclosed nonrisk designation of the study device. All patients received a full explanation and gave verbal consent to the study and the use of their deidentified data.

The following centers participated in the study:

- Cardiovascular Center, Seoul National University Bundang Hospital, Gyeonggi-do, South Korea (center A)
- Mount Elizabeth Medical Centre, Singapore (center B)
- Tokyo Heart Center, Tokyo, Japan (center C)
- Wockhardt Heart Hospital, Mumbai, India (center D)
- HSC Medical Center, Kuala Lumpur, Malaysia (center E)

Patients. Patients scheduled for coronary angiography (N=222) between June 1 and October 18, 2004, were included in the study. These represented a convenience sample of patients in the respective institutions in that each patient was already scheduled for coronary angiography for any indication. Thirty patients from center E had to be excluded from the study because angiograms were not available for second external review due to unforeseen legal limitations. Moreover, 3 patients (1.6%) were excluded during the study due to poor ECG tracing quality. The patient population had no overlap with any previous study or with the actual mfEMT database. The mfEMT database was not modified or updated during the study period. Patient demographics, medical history, and risk factors apart from sex and age were not recorded because they are not required for mfEMT analysis.

Study Device. The study device, mfEMT (Premier Heart, LLC, Port Washington, NY), records a 2-lead resting ECG from leads II and V5 for 82 seconds each using proprietary hardware and software. The analog ECG signal is amplified, digitized, and downsampled 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/s resolution. The digitized ECG data is encrypted and securely transmitted over the Internet to a central server.

At the server, a series of discrete Fourier transforms (DFT) are performed on the data from the 2 ECG leads followed by signal averaging. The final averaged digital data segment is then subjected to 6 mathematic transformations (power spectrum, coherence, phase angle shift, impulse response, cross correlation, and transfer function), in addition to an amplitude histogram, which generate indexes of abnormality. The resulting mathematically integrated patterns of the indexes are then compared for abnormality to the patterns in the reference database to reach a final diagnostic output. In addition to the automatic differential diagnosis and also based on the database comparison, a severity score from 0 to 20 is calculated that indicates the level of myocardial ischemia (if present) resulting from coronary disease.

The database against which the incoming ECG results are compared originated from data-gathering trials conducted from 1978 to 2000 in more than 30 institutions in Europe, Asia, and North America on persons of varying ages and with varying degrees of disease states, including normal populations.[20,21] All ECG analyses in this database have been validated against the final medical diagnoses and confirmed by 2 independent experts who had access to all the diagnostic tests, including results of angiography and enzyme tests. The current diagnostic capability for identification of local or global ischemia and the disease severity score used in this clinical study are based on mfEMT's large proprietary database of validated ECG analyses accumulated since 1990.

One important difference between mfEMT and other ECG methods is that the ECG is locally recorded but remotely analyzed at a central data facility due to the size and complexity of the reference database. Further aspects of the underlying technology and methodology have been described elsewhere.[20–22]

ECG Acquisition and Processing. mfEMT tests were conducted as follows by a trained trial site technician as part of a routine electrophysiologic workup received by each patient prior to angiography:

- Patients were tested while quietly lying supine following 20 minutes of bedrest.
- Five ECG wires with electrodes were attached from the mfEMT machine to the patient at the 4 standard limb lead and precordial lead V5 positions.
- An automatic 82-second simultaneous 2-lead (leads V5 and II) ECG sample was acquired with amplification and digitization.
- During the sampling, the ECG tracings displayed on the mfEMT screen were closely monitored for tracing quality.

The digital data was then de-identified, encrypted, and sent via a secure Internet connection to http://www.premierheart.com. A second identical copy of the data was saved on the remote mfEMT 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 idiopathic extrema that deviate from the baseline by ≥2 mm and appear ≥10 times
- Two or more 5.12-second segments of ECG data containing idiopathic extrema that deviate from the baseline by ≥5 mm
- A waveform that strays from the baseline by ≥3 mm in a 25-mm section of waveform in any 5.12-second segment of the ECG data
- A radical deviation away from the baseline angle of at least 80° with peak amplitude of ≥2 mm measured from the baseline, occurring 2 or 3 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. Tracings consistently graded as poor after repeat sampling were excluded from the present study. All other tracings were included in the study.

mfEMT provided automatic diagnosis of regional or global ischemia, including silent ischemia, due to CAD 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 mfEMT manufacturer's recommendation, a cutoff of 4.0 for the severity score was used in this study; a score of ≥4.0 was considered indicative of a hemodynamically relevant coronary artery stenosis of >70% in at least 1 large vessel.

Angiographers and staff at the study site were blinded to all mfEMT findings. The mfEMT technicians and all Premier Heart personnel were blinded to all clinical data, including pretest probabilities for CAD or angiography findings from the study patients.

Angiography. After the mfEMT test, coronary angiography was performed at the discretion of the attending physicians and following the standards of the institution. Angiographers were blinded to the mfEMT test results. Angiographic findings were classified by the respective angiographer and independently by a second interventional cardiologist within 4 weeks after the angiogram. If the 2 investigators did not agree on the results, they discussed the angiographic findings until agreement was reached. Angiographic results were classified as follows:

- Nonobstructive CAD: angiographic evidence of coronary artery stenosis ≤70% in a single or multiple vessels. Evidence included demonstrable vasospasm, delayed clearance of contrast medium indicating potential macrovascular or microvascular disease, documented endothelial abnormality (as indicated by abnormal contrast staining), or CAD with at least 40% luminal encroachment observable on angiograms. These patients were classified as being negative for hemodynamically relevant CAD ("stenosis: no").
- Obstructive CAD: angiographic evidence of coronary artery sclerosis >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 being positive for hemodynamically relevant CAD ("stenosis: yes").

The results from the angiograms represent the diagnostic end point against which mfEMT was tested.

Statistical Methods. The data acquisition process, all angiography reports, and all mfEMT test results were monitored by an independent study monitor who verified the double-blindness of the study and the data integrity.

Descriptive statistics were calculated for all variables. Differences between paired or 2 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 >2 mean values were analyzed with the Scheffé test, where homogeneity of variances was assessed with the Levene statistic. For 2-way and multiway tables, Fisher exact test was used to calculate significance levels.

Odds ratios including 95% confidence intervals were calculated. Sensitivity and specificity were calculated, as were receiver operating characteristic (ROC) curves, including an estimate of the area under the curve. Positive and negative predictive values for the assessment of coronary stenosis were calculated with adjustment to prevalence of stenosis.[23] Moreover, to assess the performance of the prediction of stenosis independent of the prevalence of stenosis, the positive and negative likelihood ratios (LRs) were calculated.[24] A *P* value of <.05 was considered statistically significant. All analyses were performed with SPSS for Windows version 15 (SPSS Inc, Chicago, IL).

Results

Final analysis was performed on 189 of the original 222 patients: 33 patients were excluded, 3 due to poor ECG tracings and 30 because of unavailability of angiograms for secondary analysis. The excluded patients were not significantly different from the included patients with respect to age (59.4±10.7 vs 61.3±12.9 years; *P*=.909) and sex (18% female vs 30%; *P*=.210). Available patients comprised 132 men and 57 women, with an average age of 61.3±12.9 years (21–88 years). Women were significantly older than men (65.1±10.8 vs 59.6±13.4 years; *P*<.05).

Sex distribution was not significantly different between the medical centers (*P*=.340). Patients from center C were significantly older than those in all other centers (*P*<.05) (Table I). Women were

Table I. Age and Sex of Study Population: Total and Grouped By Medical Center

	Sex (Age, y)		
	Female	Male	Total
Center A			
Mean	63.4	60.1	61.1
SD	9.3	13.4	12.4
No.	19	46	65
%	30.3	69.7	100.0
Center B			
Mean	59.1	56.5	57.5
SD	8.6	10.5	9.7
No.	7	12	19
%	37.9	62.1	100.0
Center C			
Mean	73.3	70.0	71.1
SD	8.6	9.7	9.4
No.	15	29	44
%	35.2	64.8	100.0
Center D			
Mean	62.1	53.2	55.5
SD	11.6	12.2	12.6
No.	16	45	61
%	29.4	70.6	100.0
Total			
Mean	65.1	59.6	61.3
SD	10.8	13.4	12.9
No.	57	132	189
%	32.1	67.9	100.0

Abbreviation: SD, standard deviation.

Table II. Previous Revascularization by Age, Sex, and Medical Center

	Revascularization in Medical History	
	No	Yes
Age, y		
Mean	60.0	65.6
Standard deviation	12.5	13.5
Sex		
Female		
No.	48	9
%	84.2	15.8
Male		
No.	98	34
%	74.2	25.8
Medical Center		
Center A		
No.	52	13
%	80.0	20.0
Center B		
No.	10	9
%	52.6	47.4
Center C		
No.	28	16
%	63.6	36.4
Center D		
No.	56	5
%	91.8	8.2
Total		
No.	146	43
%	77.2	22.8

Table III. Coronary Stenosis by Age, Sex, and Medical Center

	Coronary Stenosis	
	No	Yes
Age, y		
Mean	60.6	62.2
Standard deviation	13.8	11.6
Sex		
Female		
No.	34	23
%	59.6	40.4
Male		
No.	78	54
%	59.1	40.9
Revascularization in medical history		
No		
No.	82	64
%	56.2	43.8
Yes		
No.	30	13
%	69.8	30.2
Medical center		
Center A		
No.	40	25
%	61.5	38.5
Center B		
No.	9	10
%	47.4	52.6
Center C		
No.	30	14
%	68.2	31.8
Center D		
No.	33	28
%	54.1	45.9
Total		
No.	112	77
%	59.3	40.7

older in all centers, although differences did not always reach statistical significance.

Forty-three patients (23%) had a percutaneous coronary intervention for revascularization at least 6 weeks before inclusion in the study. All other patients had no coronary revascularization procedure in their medical history. Patients with previous revascularization were significantly older ($P<.05$) and more frequently male, although this difference was not statistically significant ($P=.185$). There were significant differences in the frequency of patients with revascularization between the centers (Table II).

Hemodynamically relevant coronary stenosis was diagnosed by angiography in 77 patients (40.7%). Although the percentage varied between centers, these differences were not significant ($P=.563$). There were no significant age differences between patients with and without stenosis ($P=.389$). There were also no significant sex differences ($P=1.000$). Patients with revascularization procedures in their medical history were less frequently diagnosed with coronary stenosis, although this difference was also not statistically significant ($P=.117$) (Table III).

The severity score ranged from 0 to 10.5, mean 3.2 (±2.7), with 54% of all patients having a severity score <4. For patients with relevant coronary stenosis as diagnosed by angiography, the severity score was significantly higher than that for patients without stenosis (5.4±1.8 vs 1.7±2.1; $P<.001$) (Figure 1). These significant differences could be observed in each center (Figure 2) and between patients with or without previous revascularization procedure (Figure 3).

The area under the ROC curve for the entire study population was calculated to be 0.914 (0.868–0.961). The coordinates of the curve confirmed that a cutoff of 4.0 provides the best combination of sensitivity and specificity for the prediction of coronary stenosis from the mfEMT test.

Patients without coronary stenosis had a severity score <4.0 significantly more frequently than those with stenosis by a wide margin ($P<.001$). The results indicate that mfEMT showed a sensitivity of 94.8% and a specificity of 86.6% for the prediction of coronary stenosis. The positive predictive value was 0.784, and the negative predictive value was 0.971. A positive LR >7 and a negative LR <0.1 indicate a good to strong diagnostic value for this test (Table IV).

Sensitivity and specificity showed slight differences between participating centers, age, and sex groups, as well as between patients with and without a history of revascularization procedures. For every group, however, sensitivity was always >90% and specificity >80% (Table IV).

Analysis of ROC also showed that for each subgroup and each center, the best cutoff was 4.0, as it was for the entire study population (Table IV).

Discussion

The overall sensitivity of 95% and specificity of 87% of the mfEMT device confirms the results of the studies from Weiss and colleagues[21] and Grube and colleagues.[22] Resting ECG analysis, including 12-lead ECG, typically has significantly less sensitivity in detecting ischemia. Clinical studies report a wide range for sensitivity, from 20% to 70% for acute myocardial infarction,[4] and typically less for hemodynamically significant CAD ischemia.[25]

Diagnostic yield from ECG can be improved by exercise testing. Whereas exercise ECG has a reported specificity of >80% under ideal conditions, the sensitivity utilizing exercise-based ECG is typically not better than 50% in routine clinical use.[6,26–28]

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 to excellent sensitivity in men and women (83% and 70%, respectively) and specificity (93% and 89%, respectively).[29,30] These results were confirmed by a second group of researchers[31] and are similar to our findings with mfEMT. Other researchers used different statistical approaches and models of multivariate stress ECG analysis with different sets of variables included in the models.[32–35] 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 a commercial product. It should also be noted that none of the above studies included patients with previous coronary revascularization.

Stress echocardiography performed by experienced investigators may provide better sensitivity and specificity than stress ECG. Numerous studies into exercise echocardiography as a diagnostic tool for CAD have been performed. Reported sensitivity rates range from 31% to <90% and specificity rates range from 46% to nearly 100%.[36–38] With experienced investigators, sensitivities >70% and specificities >85% can be expected.

In a comprehensive systematic review of 16 prospective studies, myocardial perfusion scintigraphy showed better positive and negative LRs than exercise ECG testing.[39] Wide variation between studies was reported, however, with positive LRs ranging from 0.95 to 8.77 and negative LRs from 1.12 to 0.09. Another review of stress scintigraphy studies showed similar results, with a

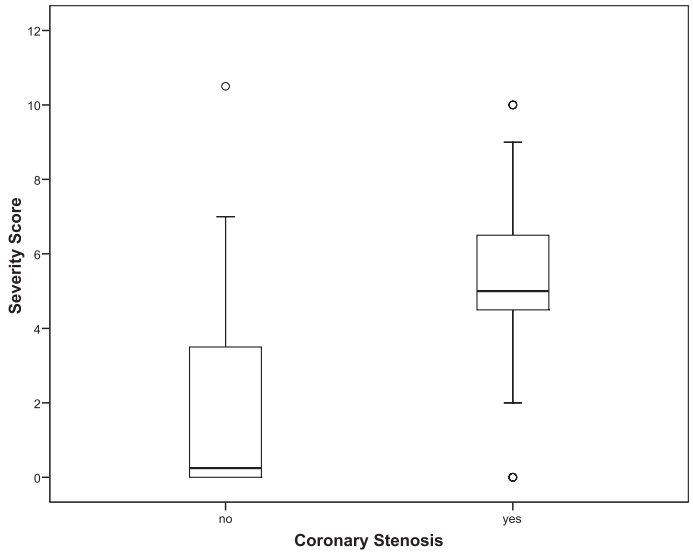

Figure 1. Severity score vs coronary stenosis. Boxplots of severity score. Boxes indicate first to third quartile; line within box, median; whiskers, high/low; circles, outliers.

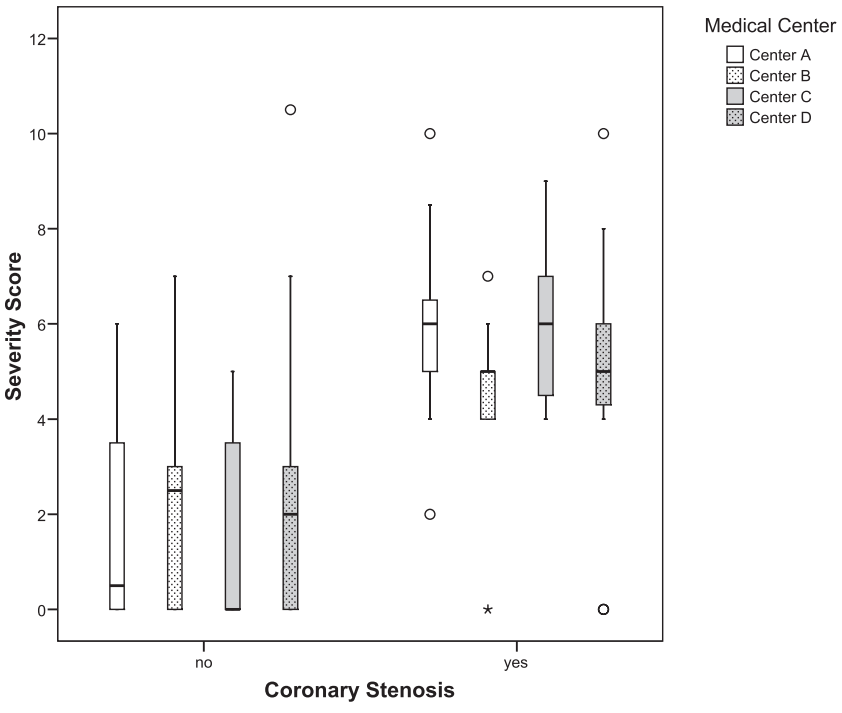

Figure 2. Severity score vs coronary stenosis grouped by medical center. Boxplots of severity score. Boxes indicate first to third quartile; line within box, median; whiskers, high/low; circles, outliers; asterisk, extremes.

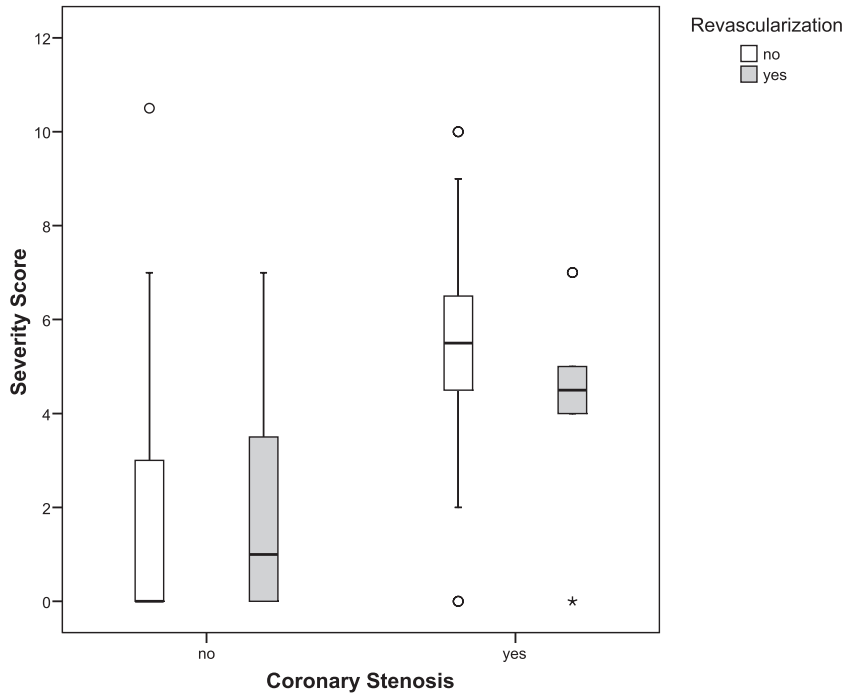

Figure 3. Severity score vs coronary stenosis grouped by revascularization procedure in medical history. Boxplots of severity score. Boxes indicate first to third quartile; line within box, median; whiskers, high/low; circles, outliers; asterisk, extremes.

diagnostic accuracy of 85% but wide variation between studies (sensitivity 44%–89%, specificity 89%–94% for 2+ vessel disease).[40] In one study, the combination of stress ECG testing with myocardial scintigraphy using multivariate analysis provided only limited improvement of diagnostic accuracy.[41]

Whereas the reported diagnostic performance of stress echocardiography, myocardial scintigraphy, and stress scintigraphy are not dissimilar to what we found for mfEMT, imaging modalities can provide additional information such as spatial localization, which a resting ECG method cannot.

mfEMT's sensitivity and specificity for the detection of coronary stenosis was good to excellent in all patient groups included in this study, with only moderate differences between groups. Moreover, there were only small differences in the results between the different centers. The optimal cutoff for the severity score was not different between patient groups or medical centers. These results may indicate that mfEMT generates reproducible and stable results in diverse patient populations and different medical settings. Although the number of patients with a revascularization procedure in their medical history was small, the findings may indicate that mfEMT also provides reliable results in this patient group where other ECG methods often perform unsatisfactorily.[9–11]

The end point of this study was the morphologic diagnosis of CAD in coronary angiography, whereas the investigated electrophysiologic method (mfEMT) assesses functional changes of electrical myocardial function secondary to changes in coronary blood flow including local and global ischemia. Therefore, even under ideal conditions, a 100% coincidence between angiographic findings and mfEMT results could not be expected. This is probably true for every electrophysiologic diagnostic method.

Resting and stress ECG in patients with CAD primarily focuses on ST-segment analysis and the detection of other abnormalities, such as Q-wave abnormalities and Q–T interval. This is not comparable to the mfEMT approach, which calculates a severity score (for CAD) from a complex mathematic analysis. A comparison between mfEMT, 12-lead resting ECG, and coronary angiography in another study showed a higher sensitivity and specificity for mfEMT than 12-lead ECG in the detection of coronary stenosis.[21]

Limitations

One limitation of the present study was that the angiographic results were not explicitly quantified using a suitable scoring system such as the bypass angioplasty revascularization investigation system.[42] Still, the assessment of coronary lesions in the present study was consistent between 2 experienced angiographers who independently evaluated the angiographic results. Since the target criterion was hemodynamically relevant coronary stenosis, implying an indication for therapeutic intervention, borderline lesions may have been classified as nonrelevant. This may have artificially reduced the calculated specificity of the mfEMT method.

Another limitation may have been the recruitment of patients. The patient population 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 herein, the demographic distribution of this sample matches very well with the distributions reported in the literature for patients with CAD. In addition, 59% of the participants did not have hemodynamically significant CAD, with mfEMT severity scores ranging from normal (0.0–0.5) to abnormal (<4.0). Therefore, it appears justified to assume that the study findings from the investigated patient group are valid for a general population of CAD patients.

Finally, mfEMT was compared with angiography but not with any other noninvasive diagnostic technology in this study. Therefore, inference about the potential superiority or inferiority of mfEMT against other ECG-based methods can only be indirectly drawn from other studies. Even with this important caveat, however, sensitivity and specificity of mfEMT for the detection of CAD must be considered

at least as good as the best currently used ECG-based methods. Future research shall also include direct comparisons between mfEMT and other noninvasive diagnostic methods.

Conclusions

The mathematic analysis of ECG performed in the mfEMT method appears to provide a sensitivity and specificity for the prediction of relevant CAD as diagnosed by coronary angiography that may be at least as good as those of any other resting or stress ECG method currently used in clinical practice.

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Appendix I—Premier Heart mfEMT Technology

Overview. The Premier Heart mfEMT technology investigated in this study is based on systems theory, in which mathematic modeling is used in the analysis of complex systems and the interactions of internal and external environments with those systems. In the case of the heart, analysis is performed on the signals emitted by the heart, such as the surface resting electrical signal recorded by an ECG.

In systems analysis, the ECG signals are therefore not conventionally analyzed, such as when each individual cardiac cycle (P–QRS–T complex) of each ECG lead is measured and analyzed in a single time domain (milliseconds vs millivolts) in sequence. Rather, multiple cardiac cycles from both ECG leads are individually sampled, digitized, and analyzed in relation to each other. This means that analysis focuses not only on the variations of heart harmonics in the frequency domain from each lead independently but also on other linear or nonlinear correlations between the 2 leads in both frequency and time domains, in combination.

Table IV. Prediction of Coronary Stenosis by Severity Score (Cutoff 4.0) for Total Population, Medical Centers, Sex, Age Groups, and Previous Revascularization Procedure

	No.	TP	TN	FP	FN	A Priori	Correct	Sensitivity	Specificity	PPV	NPV	LR+	LR–	OR	OR 95% CI		ROC AUC	ROC AUC 95% CI	
															Lower	Upper		Lower	Upper
Total	189	73	97	15	4	0.407	0.899	0.948	0.866	0.784	0.971	7.09	0.06	118.02	37.59	370.48	0.914	0.868	0.961
Center A	65	24	34	6	1	0.385	0.892	0.960	0.850	0.730	0.981	6.41	0.05	136.00	15.37	1203.75	0.942	0.886	0.997
Center B	19	9	8	1	1	0.526	0.895	0.900	0.889	0.909	0.878	8.10	0.11	72.00	3.84	1349.55	0.828	0.604	1.052
Center C	44	14	24	6	0	0.318	0.864	1.000	0.800	0.587	1.000	5.00	0.00	NaN	NaN	NaN	0.963	0.916	1.010
Center D	61	26	31	2	2	0.459	0.934	0.929	0.939	0.917	0.948	15.32	0.08	201.50	26.51	1531.30	0.893	0.793	0.993
Female	57	22	28	6	1	0.404	0.877	0.957	0.824	0.713	0.976	5.42	0.05	102.67	11.50	916.81	0.904	0.813	0.995
Male	132	51	69	9	3	0.409	0.909	0.944	0.885	0.814	0.969	8.21	0.06	130.33	33.59	505.70	0.918	0.864	0.972
<65 years	113	43	58	8	4	0.416	0.894	0.915	0.879	0.820	0.943	7.55	0.10	77.94	22.03	275.69	0.890	0.820	0.960
>65 years	76	30	39	7	0	0.395	0.908	1.000	0.848	0.782	1.000	6.50	0.00	NaN	NaN	NaN	0.962	0.925	1.000
No revasc	146	61	72	10	3	0.438	0.911	0.953	0.878	0.831	0.968	7.82	0.05	146.40	38.54	556.06	0.925	0.876	0.974
Revasc	43	12	25	5	1	0.302	0.860	0.923	0.833	0.583	0.980	5.60	0.08	60.00	6.29	571.93	0.859	0.727	0.991

Abbreviations: a priori, a priori probability of stenosis; correct, fraction of correctly predicted cases; FN, false negatives; FP, false positives; lower, lower boundary of 95% confidence interval (CI); LR–, negative likelihood ratio; LR+, positive likelihood ratio; NaN, not a number; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; revasc, coronary revascularization in medical history; ROC AUC, receiver operating curve area under the curve for continuous severity score; Sens, sensitivity; Spec, specificity; TN, true negatives; TP, true positives; upper, upper boundary of 95% CI.

mfEMT records a short (82-second) resting analog ECG signal from 2 left ventricular leads (V5 and II). The use of leads V5 and II has been empirically tested over many years and confirmed to provide the information required to build the analysis software. Following the principles of systems analysis, this approach is considered adequate, as one only needs an input and output of the systems of interest. The signal is amplified and digitized at a sampling rate of 100 Hz in multiple time series. Because it could consistently be demonstrated that far more than 90% of the power output of the autopower spectra of the human ECGs in the mfEMT database fall within 50 Hz, 100 Hz are an adequate sampling rate as they are the respective Nyquist frequency. The signal is then converted to the frequency domain via DFT intervals.[43] These frequency intervals are then averaged following DFT procedures. The result is a signal-averaged digital data segment in the frequency domain with maximum signal-to-noise ratio. In the next step, post-averaging digital signal deconstruction takes place using a series of signal analysis functions. A sequence of abnormal indexes from a total of 166 discovered thus far is derived from each analysis, which quantify abnormalities in the ECG signals that are not expressed by conventional ECG methods. Over the years, an accumulation of abnormal elements or indexes has been discovered. The efforts to verify, validate in clinical trials, and quantify the thresholds of each index are largely complete. Clusters of indexes and their permutations, representing potential diagnoses, are probalistically compared with a proprietary database containing the abnormal index patterns of tens of thousands of patients with known and clinically verified diagnoses as well as with the patterns of several thousand normal individuals, male and female, from ages 14 to 91 years. The primary focus has been on the automatic detection of myocardial ischemia. The final diagnosis produced by the system includes the presence (or absence) of local or global myocardial ischemia and an associated severity score.

History and Development of mfEMT. Research into the theoretic models underlying mfEMT began in 1976 in the People's Republic of China in a project that investigated the effect of noise exposure on cardiac function under the auspices of the Academia Sinica, Institute of Dynamics, Beijing. ECG analysis was found to be inadequate because, although previous clinical observations correlated with noise exposure, ECG waveforms were consistently unremarkable.

The Chinese research group focused on ECG analysis and transformations and used a mathematic model of the myocardium and blood to address this problem. The first models of ECG transformations were tested using an animal model of acute myocardial infarction. This showed the potential of this mathematic approach to ECG analysis for detecting myocardial ischemia and stimulated further experimental and clinical research (Presented at the 11th International Congress on Acoustics: Paris July 19–27, 1983: "Effect of Noise on EKG [with Computer Analysis]"). Several very ambitious clinical studies were conducted in the 1980s to test the system's ability to detect and differentiate 8 differential diagnoses. As a result of these studies and from a better understanding of the mathematic approach, the research concentrated more and more on myocardial ischemia. The first DOS stand-alone PC version received US Food and Drug Administration (FDA) approval in 1995 (FDA 510(k) K953470).

After 1983, research continued outside China until the present day. An initial PC (DOS)-based version of the analytical system was used in clinical trials in 30 hospitals. Further research with this version was done in France, Belgium, and the United States. During these trials, data from approximately 23,000 patients (7000 patients qualified as normal, 16,000 patients with confirmed cardiac pathologies) were collected for the construction of the initial mfEMT database (unpublished data).

Since then, the system has evolved from a stand-alone version due to the need for an expanding centralized database and new algorithmic developments to prioritize the differential diagnosis of myocardial ischemia detection along with other secondary clinical diagnoses, such as myocardial infarction. A new quantitative scoring system has also been created and added to the analysis. The most recent version of the mfEMT system has been developed on a web-based paradigm, which allows the analysis of remote ECGs on a centralized database. This new version of mfEMT, which also uses relational database architecture, received FDA clearance in 1999 (FDA 510(k) K992703). This version has been used in all current trials including the one in Siegburg, Germany, reported herein.

Basic Principles of mfEMT. mfEMT is based on a purely mathematic approach to ECG description that is validated against a very large clinical database. Whereas Einthoven historically presumed the myocardium to be a single-point electrical generator, research leading to the development of mfEMT began by using 2 mathematic descriptions of 2 intrinsic physiologic properties of the heart: (1) the myocardium is a viscoelastic solid,[44] and (2) blood is a non-Newtonian fluid at low and intermediate shearing states.[45]

To unify these 2 properties, the 2 mathematic relations can be fused into one using the Laplace transform.

Mathematic Transformations of ECG Data. The mfEMT ECG analysis employs 6 mathematic transformations. All these transformations are based on the power spectrum of the recorded ECG leads (G*xx* for lead V5 and G*yy* for lead II). The power spectrum uses both real and imaginary number sets where the domain of the coordinate plane is the set of real numbers [*R*] and the range encompasses the imaginary number set [*I*]. The autopower spectrum remains within the respective lead (V5 or II) and the cross-power spectrum (G*xy*) is used when the attributes of each lead are to be compared. Empirical observation has elicited patterns among the 6 transformations that have consistently correlated with specific patient conditions.

Autopower Spectrum. The autopower spectrum, $Gxx=Sx(f) \cdot Sx(f)i$ and $Gyy=Sy(f) \cdot Sy(f)I$, where S(*f*) and S(*f*)i represent the real and imaginary components of the FFT (*f*) function, respectively, depicts the power distribution along a frequency range of 0.1 to 50 Hz. G*xx* is obtained from V5; thus, "x" represents the lead V5 input. G*yy* is obtained from lead II; thus, "y" represents the lead II input. The autopower spectrum is a measure of the power in watts of each frequency of an ECG signal. The peak with the lowest frequency in the autopower spectrum represents the heart rate, which is generally around 1.2 Hz (72 beats per minute); higher frequency peaks will generally have less power than lower frequency peaks, with the signal generally fading out at approximately 35 Hz. On the basis of analysis of 23,000 ECGs with confirmed clinical diagnoses, it has been established that approximately 80% of the power exerted by the myocardium is represented in the first 10 peaks of the autopower spectrum graphic output. Based on the power spectra, mf-EMT uses the remaining transformations, described below. The autopower spectrum data can be used to identify physiologic or pathologic conditions such as fast or slow heart rate, arrhythmias,

and fibrillation. In addition, various peak-to-peak power amplitude abnormal distributions correlated well with clinical conditions such as myocardial ischemia, hypertensive heart disease, congestive heart failure, and cardiogenic shock.

Transfer Function. The transfer function $Txy=Gxy/Gxx$, $Txy=A, \varphi$ has 2 components or phases. Dividing the cross-power spectrum (Gxy) by the lead V5 autopower spectrum (Gxx) yields 2 complementary components of phases of the frequency and power axes, namely amplitude and phase angle. The amplitude of this result is referred to as the transfer function. Transfer function is a measure of deviations away from 1, where 1 is the ideal ratio between Gxy and Gxx. Deviations from 1 may reflect myocardial abnormalities.

Phase Angle Shift of Transfer Function. The phase shift angle $\theta xy=tan^{-1}\{Txy(I)/Txy(R)\}=tan^{-1}[\{Gxy/Gxx(I)\}/\{Gxy/Gxx(R)\}]$ is a comparison of an actual waveform (the combined autopower spectra of each lead) to an ideal waveform (the cross-power spectrum of the 2 leads). This is expressed as the angle in degrees of the phase shift for each frequency: essentially, the relative angles of the harmonics at a specific frequency to each other. The angle represents the delay between the 2 leads, so that a greater angle is evidence of higher degrees of asynchronization; positive angles indicate angle shift favoring the input lead (V5), and negative angles indicate angle shift favoring the output lead (II). Asynchrony between the leads may be due to infarction, myocardial ischemia, and myocardial hypertrophies.

Impulse Response. The impulse response function $Pih=F^{-1}Txy$ measures the continuous activation and response of the cardiac system between input (lead V5) and output (lead II). It is derived from the transfer function using a reverse DFT and is expressed in the time domain as the latency for each amplitude peak in millivolts. The impulse response function uses the V5 lead as system input and lead II as system output. This makes the impulse response function as an idealized system, which generates lead II from lead V5 in response to a unit impulse. Changes in myocardial compliance correlate with changes in impulse response. Increased compliance as represented in the impulse-response graph can be associated with ventricular dilatation and overall system quality, ie, better signal-to-noise ratio. Decreased compliance may indicate left ventricular hypertrophy or damage due to ischemia or infarction.

Coherence Function. The coherence function $\gamma^2=(Gxy)^2/\{(Gxx)(Gyy)\}$ generates a unitless number that reflects the net disparity between the cross-power spectrum and the product of the 2 power spectra of leads II and V5. It represents the correspondence of the amplitude, frequency, and phase shift of the 2 ECG leads. Coherence is expressed as the amplitude ratio of the 2 leads squared for each frequency. The result is a measure of the correspondence of the output energy of the 2 leads. The coherence function is primarily useful in the frequency band of the heart harmonics because higher frequencies show little variation in amplitude ratio. The distortion of the myocardial coherence function away from a predefined threshold is reflected here. This is a universal threshold of degree of coherence for the autopower spectra and the cross-power spectrum of both ECG leads at the system's fundamental frequency. A value of 1 would indicate a theoretically perfect spherical order (where the products of auto- and cross-power spectra from both leads are equal), whereas a value of 0 is undefined and clinically represents chaotic ventricular interaction.

Cross-Correlation. Cross-correlation $Vxy=F^{-1}Gxy$ is the reciprocal of the cross-power spectrum. It provides the linear relation between the R waves of the ECG signals, expressed as the measure of amplitude in millivolts over time. Only the shared qualities of both leads are studied here. The commonalties of both leads are compared during one 5.12-second cycle, and this inversion is reflected in the cross-correlation graph.

Final Diagnostic Output. Each of these transformations generates numerous indexes that can be related to certain pathologic changes in the myocardium. Whereas each transformation or single index by itself does not have sufficient diagnostic significance to allow a conclusive diagnosis, the combination of these 6 transformations and the resulting 166 indexes does. To reach the final diagnosis, the index patterns of the individual subject or patient are compared with the patterns stored in a database of healthy subjects and patients with confirmed, detailed diagnoses. The end result is a confirmed and verified diagnostic report that is typically transmitted back to the remote ECG site within 2 minutes after reception of the ECG data.

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