Original Studies

Noninvasive Mathematical Analysis of Spectral Electrocardiographic Components for Coronary Lesions of Intermediate to Obstructive Stenosis Severity–Relationship with Classic and Functional SYNTAX Score

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Objectives: The aim of this study was to evaluate the relationship between the multifunction cardiogram (MCG), and SYNTAX score (SS) and functional SYNTAX score (FSS) in detecting the presence of intermediate to obstructive coronary lesions. Background: Performing coronary angiography (CAG) and measuring fractional flow reserve (FFR) to calculate the SS and FSS is inherently invasive and adds complexity. Methods: The MCG was obtained and analyzed before performing CAG in 87 consecutive subjects with suspected coronary artery disease who were scheduled for elective CAG. The patients were divided into three groups according to risk based on high, borderline, and low MCG scores. The SS was determined, as well as FSS but only by counting lesions prone to functional ischemia (FFR $\leq$ 0.8). The relationship between the MCG and the SS and FSS was evaluated. Results: The MCG was the only test significantly associated with the SS (odds ratio, 2.92 [1.60 – 5.31], $P < 0.001$) and FSS (odds ratio, 3.66 [1.95 – 6.87], $P < 0.001$). A high MCG score had a specificity of 92.6% (89.0–96.2%) and 92.3% (89.0–95.6%), and a predictive accuracy of 72.4% (67.6–77.2%) and 82.8% (78.7–86.8%) for the prediction of SS and FSS, respectively. Conclusions: The MCG showed high specificity and predictive accuracy especially for the FSS, suggesting that it is useful not only in identifying functionally significant ischemia but also in reducing unnecessary CAGs.

Key words: multifunction cardiogram; functional SYNTAX score; fractional flow reserve

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INTRODUCTION

The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score (SS) is an anatomic scoring system based the coronary angiographic (CAG) findings, which not only quantifies lesion complexity but also predicts adverse events after percutaneous coronary intervention (PCI) [1–4]. The potential benefit of revascularization depends on the presence of myocardial ischemia; therefore, careful identification of ischemia-inducing stenosis allows for a greater benefit from revascularization [5–10]. Hence, a recent study demonstrated the superiority of a functional SS (FSS), a fractional flow reserve (FFR)-guided SS, to a classic SS regarding the predictive value of clinical outcome in patients with multivessel coronary artery disease (CAD) who underwent PCI [11]. However, these scores have several inherent limitations because they are obtained using invasive modalities such as CAG and FFR.

The multifunction cardiogram (MCG) is a new computer-enhanced, multiphase, resting electrocardiographic (ECG) analysis device that improves the quality of noninvasive tests. It has been used to determine the optimal decision-making algorithm for the evaluation of suspected obstructive CAD [12–14]. Recently, we reported the association between noninvasive MCG and classic coronary lesion scores [15]. However, the prognostic impact of the reference for ischemia in our previous study has not been established in contrast with SS and FSS.

The aim of this study, therefore, was to evaluate the accuracy of the MCG in relation to the SS and FSS in a relatively high-risk population who were scheduled for elective CAG, taking into account standard ECG and Framingham risk scores (FRSs).

METHODS

Patients and Study Design

This prospective study was designed to evaluate the accuracy of the MCG in diagnosing CAD patients with relevant ischemia as defined by classic SS and FSS reference standards. Our target population consisted of 103 consecutive subjects with or without known CAD who were scheduled for elective CAG between October 2012 and December 2013. Thirteen patients with no significant coronary lesion (<50%) in any of the three coronary trees on CAG and 3 patients with poor-quality MCG results were excluded, leaving 87 patients for the evaluation. This study was approved by the institutional review board at Chubu Rosai Hospital; all the patients provided written informed consent, and the study complied with the principles of the Declaration of Helsinki. (Clinical Trial Registration–UMIN ID: 000009992).

Multifunctional Cardiogram

The MCG test was performed and analyzed before performing CAG. The angiographers were blinded to the test results. The MCG (Toray Medical) and associated computer with the MCG version 2.1.1 software (Premier Heart Japan) were used. An ECG was performed with leads II and V5 for 82 sec, and 3–5 tests were performed at each session. Only those tests with a marginal or better quality trace, which was checked automatically by the system, were sent for analysis to the PH LLC data center via the Internet. The MCG device and database used were previously described [16]. In brief, the database against which the incoming MCG data were compared originated from data-gathering trials conducted from 1978 to 2000 in more than 30 institutions in Europe, Asia, and North America, among ~100,000 individuals of varying ages and degrees of coronary disease. The MCG reports also indicate the level of myocardial damage and severity integrated into a score; other information such as coronary damage, area of damage, and myocardial pathological and pathophysiological conditions are included in the report. An MCG score of 4 was used as the cutoff score in most published clinical trials [12,17]. In this study, we used the cut-off score of 4 but investigated the scoring method further. The patients were divided into three groups as follows: high MCG score, minimum MCG score of ≥ 4.0 per session among the 3-5 tests; borderline MCG score, $4.0 >$ all scores ≥ 3.0; low MCG score, maximum score of < 3.0 per session among the 3–5 tests.

CAG and Measurements of SS and FSS

Before performing CAG, an intracoronary injection of 0.5 mg isosorbide dinitrate was administered to prevent coronary spasms. Cineangiograms were analyzed by an independent angiographer who was blinded to the MCG test results. The SS and FSS for each patient was calculated by 2 independent interventional cardiologists (M.T. and N.S.) to assess interobserver variability. The lesion selected for this calculation were those producing $\geq 50\%$ diameter stenosis in vessels ≥ 1.5 mm according to visual estimation from the baseline diagnostic CAG and scored separately using the SS score algorithm from its website. FSS was calculated by separately adding the individual scores of lesions with an actual FFR value ≤ 0.80 and ignoring lesions with FFR values >0.80 [11]. FFR was calculated as previously described [5,9,10]. In brief, equalization was performed with the guide wire sensor positioned at the guiding catheter tip. The 0.014-in pressure guide wire (St. Jude

TABLE I. Baseline Clinical and Angiographic Data

		MCG level			
Variable		Low $n=30$	Borderline $n=40$	High $n=17$	P value
Clinical					
Age (years)		65.8 ± 10.3	70.7 ± 9.0	74.3 ± 5.9	0.008
Male sex		22 (73)	24 (60)	14 (82)	0.22
Diabetes		18 (60)	14 (35)	6 (35)	0.090
Hypertension		26 (87)	30 (75)	15 (88)	0.42
Systolic blood pressure (mm Hg)		133 ± 15	130 ± 14	137 ± 15	0.28
Dyslipidemia		26 (87)	32 (80)	12 (71)	0.38
Total-cholesterol (mg/dL)		185 ± 36	189 ± 32	187 ± 33	0.91
HDL-cholesterol (mg/dL)		54 ± 16	54 ± 13	48 ± 14	0.31
Chronic kidney disease					
0		0 (0)	2 (5)	0 (0)	0.86
1		2 (7)	3 (8)	2 (12)	–
2		20 (67)	25 (63)	9 (53)	–
3		8 (27)	10 (25)	6 (35)	–
Smoking		9 (30)	8 (20)	3 (18)	0.60
CCS class					
0		12 (40)	10 (25)	6 (35)	0.38
1		10 (33)	13 (33)	2 (12)	–
2		5 (17)	11 (28)	7 (41)	–
3		3 (10)	6 (15)	2 (12)	–
Ejection fraction (%)		71.4 ± 6.1	70.5 ± 8.2	71.5 ± 6.6	0.84
Left ventricular hypertrophy		7 (23)	7 (19)	9 (53)	0.034
BNP (pg/mL)		23.4 [17.4–37.3]	25.2 [14.8–39.4]	48.4 [20.4–66.8]	0.25
hs-CRP (mg/dL)		0.12 [0.06–0.34]	0.13 [0.04–0.45]	0.11 [0.06–0.29]	0.97
Calcium channel blocker		11 (37)	21 (53)	6 (35)	0.31
Beta blocker		7 (23)	7 (18)	4 (24)	0.78
ACEI/ARB		22 (73)	16 (40)	6 (35)	0.009
Statin		26 (87)	34 (85)	11 (65)	0.19
Angiography					
Indicated lesions per patient		2.2 ± 1.3	1.9 ± 1.2	3.1 ± 1.2	0.006
50–75% narrowing		33 (43)	33 (43)	11 (14)	0.60
75–90% narrowing		24 (33)	26 (36)	23 (32)	0.23
90–99% narrowing		8 (22)	15 (42)	13 (36)	0.054
Total occlusion		0 (0)	0 (0)	5 (100)	0.001
Proximal LAD lesion		7 (21)	17 (52)	9 (27)	0.090
Diagnosis test					
ECG	Negative	24 (80)	35 (88)	11 (65)	0.14
	Positive	6 (20)	5 (13)	6 (35)	–
FRS	Low	1 (3)	2 (5)	0 (0)	0.040
	Intermediate	9 (30)	19 (48)	2 (12)	–
	High	20 (67)	19 (48)	15 (88)	–
SS	Low (≤6)	12 (40)	10 (25)	2 (12)	0.005
	Medium (7–12)	12 (40)	16 (40)	2 (12)	–
	High (≥13)	6 (20)	14 (35)	13 (76)	–
FSS	Low (≤6)	20 (67)	20 (50)	3 (18)	<0.001
	Medium (7–12)	7 (23)	13 (33)	2 (12)	–
	High (≥13)	3 (10)	7 (18)	12 (71)	–

Values are mean ± SD or median [interquartile] or number (percentage of total).
The P values were obtained from the analysis of variance, Kruskal-Wallis test, or Fisher exact test.
HDL: high-density lipoprotein; CCS: Canadian cardiovascular society; BNP: brain natriuretic peptide; hs-CRP: high sensitivity C-reactive protein; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II type 1 receptor antagonists; LAD: left anterior descending; ECG: electrocardiogram; FRS: Framingham risk score.

Medical, Minneapolis, MN) was then advanced distally to the stenosis, and FFR was measured at maximal hyperemia induced by intravenous adenosine triphosphate administered at 150 μg/kg/min through a central or forearm vein. It was then calculated as the mean distal coronary pressure divided by the mean aortic pressure during maximal hyperemia. Functional significance was defined as FFR values ≤ 0.80. FFR measurements

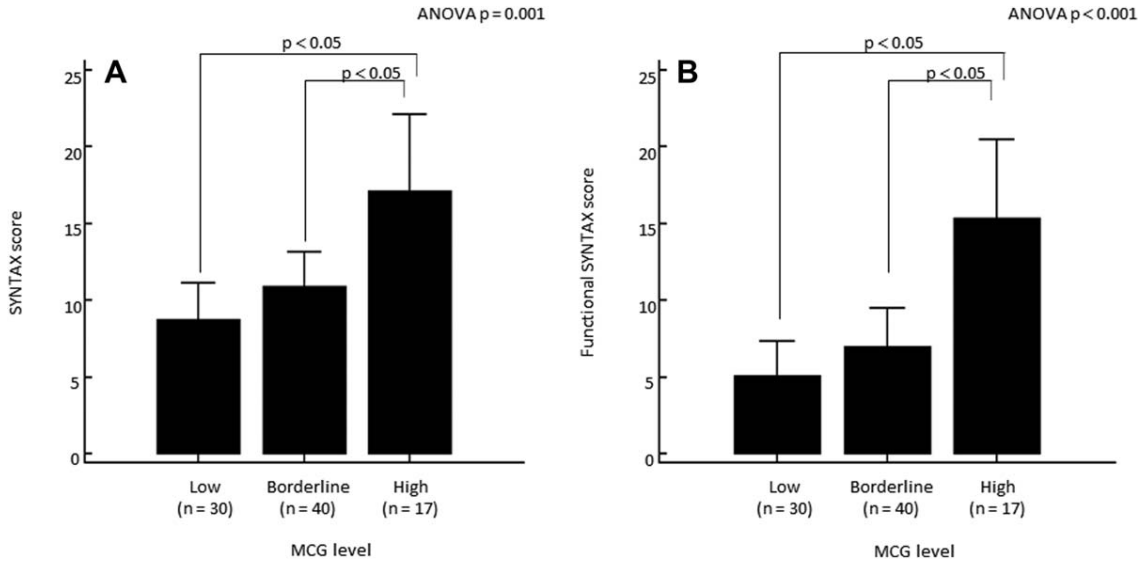

Fig. 1. The SS and FSS according to increasing risks based on the MCG scores. The SS in A and FSS in B were significantly associated with an increasing risk of the MCG score (ANOVA, $P = 0.001$ and ANOVA, $P < 0.001$). The SS and FSS for the individual low, borderline, and high MCG scores were 8.8 ± 6.1 and 5.1 ± 6.0, 10.9 ± 7.0, and 7.0 ± 7.9, and 17.2 ± 9.7 and 15.4 ± 10.0, respectively. SS: SYNTAX score; FSS: functional SYNTAX score; MCG: multifunction cardiogram; ANOVA: analysis of variance.

were deferred when vessels had obvious severe lesions (>99%) with a delayed coronary flow or had no significant stenosis (<50%) as observed on CAG.

Definition of Clinical Characteristics

Diabetes mellitus was defined as the patient was taking any antihyperglycemic medication or had previously been diagnosed with diabetes mellitus. Hypertensive patients were those with documented blood pressure >140/90 mm Hg on two or more occasions, or who were already on antihypertensive therapy. A positive smoking status was defined as the patient currently smoking or had quit less than a year before entering the study. Chronic kidney disease stages were defined according to estimated glomerular filtration rate levels [18].

STATISTICAL ANALYSES

On clinical, angiographic, and diagnostic characteristics, variables were stratified according to SS tertiles, and three groups of FSS were divided by the same cutoff score based on SS tertiles. Categorical data were summarized as frequency (%) and continuous data were expressed as mean and standard deviation, or median and interquartile range as appropriate. The reproducibility of SYNTAX scoring was evaluated by calculating interobserver reliability using intraclass correlation. For evaluating the relationship between the ischemia level and three tests as predictors, the odds ratio (OR) was calculated by applying a cumulative logit regression model on each of the three tests. We also conducted a logistic regression analysis to estimate the OR for the need for revascularization. The Akaike Information Criterion was used to compare the goodness of fit between the three models [19,20]. Dichotomized data were used to calculate the accuracy, sensitivity, specificity, and positive (PPV) and negative predictive values (NPV), with their 95% confidential intervals (CIs). Agreement between the SS and FSS, and the three tests was evaluated by using Cohen's kappa coefficient. Sensitivity was calculated by dividing the number of patients with positive test results and high SS and FSS (considered as a true positive) by the total number of patients with high SS and FSS. Specificity was calculated by dividing the number of patients with a negative test results and patients with low to intermediate SS and FSS (considered as a true negative) by the total number of patients with low to intermediate SS and FSS. We constructed receiver operating curve (ROC) plots to determine the best cutoff MCG scores for the prediction of high SS and FSS. Three MCG score groups (low, borderline, and high) were evaluated using analysis of variance (ANOVA), and Fisher least significant difference test for multiple comparisons to determine their associations with the SS and FSS. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SAS 9.3 software (SAS institute, Cary).

TABLE II. Cumulative Logit Model Analysis of the Results of the Three Tests for the Prediction of SS and FSS

	Classic SS			Functional SS		
Test	OR (95%CI)	*P* value	AIC	OR	*P* value	AIC
MCG	2.92 (1.60–5.31)	<0.001	182.5	3.66 (1.95–6.87)	<0.001	169.9
ECG	1.58 (0.59–4.26)	0.37	194.9	1.60 (0.60–4.28)	0.35	186.8
FRS	1.16 (0.58–2.32)	0.68	195.5	1.09 (0.54–2.22)	0.81	187.5

SS: SYNTAX score; FSS: functional SYNTAX score; OR: odds ratio; AIC: Akaike information criterion; MCG: multifunction cardiogram; ECG: electrocardiogram; FRS: Framingham risk score.

RESULTS

Baseline Characteristics

Table I outlines the baseline clinical characteristics of all the 87 patients with low ($n = 30$), borderline ($n = 40$), and high MCG scores ($n = 17$). Patients with high MCG scores were significantly older and had a high prevalence of left ventricular hypertrophy. Based on CAG findings, 191 lesions were selected for the calculation of SS. The indicated lesions per patient in the low, borderline, and high MCG score groups were 2.2 ± 1.3, 1.9 ± 1.2, and 3.1 ± 1.2, respectively ($P = 0.006$). The high MCG scores were significantly associated with the increasing severity of diameter stenosis.

Reproducibility of the SYNTAX Score (SS)

The mean values of the SS calculated by 2 cardiologists were 11.4 ± 7.9 and 11.8 ± 8.4, whereas those of FSS were 7.8 ± 8.7 and 7.5 ± 8.4, respectively. An interobserver reliability of classic SS using the intraclass correlation analysis was 0.749, 95% CI: 0.412 to 0.875, and that of FSS was 0823, 95% CI: 0.434 to 0.922.

Association between Various Tests and SS and FSS

Figure 1 shows the association between the three MCG score groups and the SSs and FSSs. The SSs and the FSSs in the low, borderline, and high MCG score groups were 8.8 ± 6.1 and 5.1 ± 6.0, 10.9 ± 7.0, and 7.0 ± 7.9, and 17.2 ± 9.7 and 15.4 ± 10.0, respectively. The high MCG score was related to the increasing SSs (ANOVA, $P = 0.001$) and FSSs (ANOVA, $P < 0.001$). Table II shows the cumulative logit model analysis of the results of three tests for the prediction of SS and FSS. The MCG was the only test significantly associated with SS (OR, 2.92 [1.60–5.31], $P < 0.001$) and FSS (OR, 3.66 [1.95–6.87], $P < 0.001$).

Predictive Values of MCG, ECG, and FRS for SS and FSS

Table III shows the values predictive of high SS and FSS that were measured using the MCG (high vs. borderline/low), ECG (positive vs. negative), and FRS (high vs. intermediate/low). The high MCG scores ($\geq$ 4.0) had specificity rates of 92.6% (89.0–96.2%) and

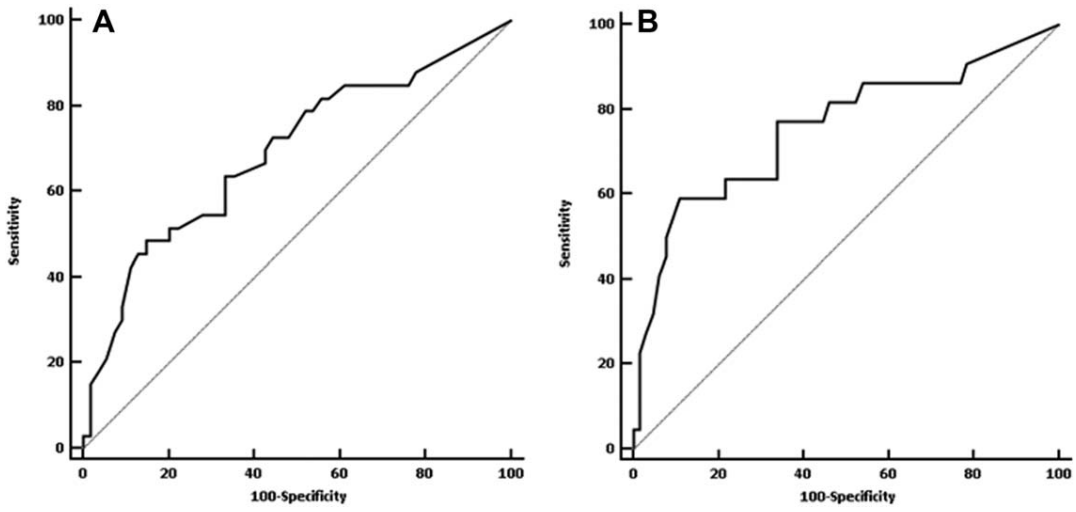

Fig. 2. ROC analyses of the MCG scores for the prediction of high SS and FSS. The area under the ROC curve of the MCG scores for the prediction of high SS (> 13) in A and high FSS (> 13) in B were 0.69 (0.58–0.77) and 0.76 (0.65–0.84), respectively. The optimal cutoff value identified though the ROC analysis was 4.4 and 4.8, respectively, which produced a sensitivity of 48.5 and 59.1%, and a specificity of 85.2 and 89.2%, respectively. ROC: receiver operating curve; MCG: multifunction cardiogram; SS: SYNTAX score; FSS: functional SYNTAX score.

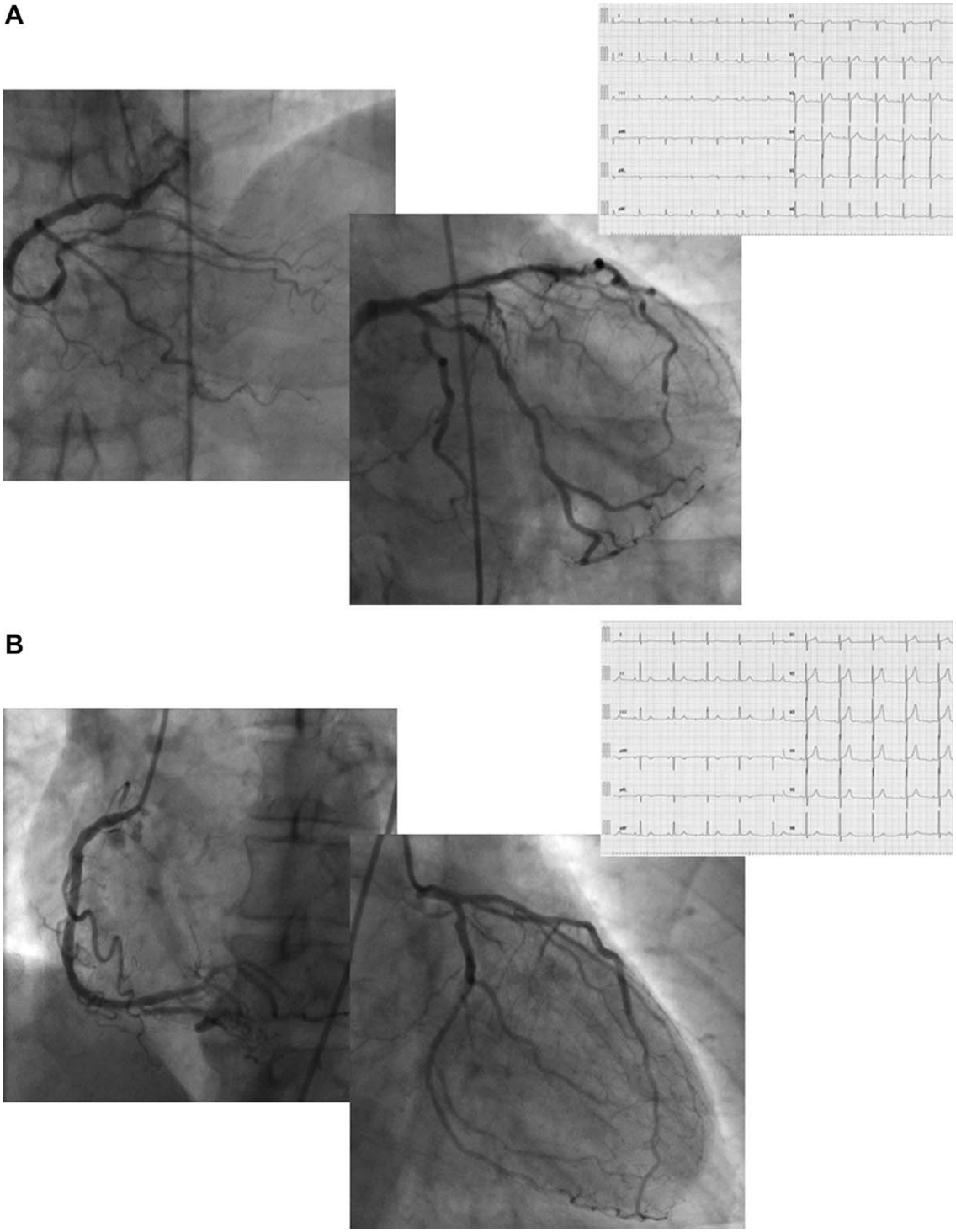

Fig. 3. Representative images of CAG from the patient who showed no resting ECG abnormality with functional ischemia in A and without functional ischemia in B. The resting ECG of both patient A and patient B showed no abnormality. The average MCG score of patient A was 5.0 and the multivessel disease was found on CAG. The SS and FSS of patient A were 26 and 19, respectively. The average MCG score of patient B was 0.0, and no significant stenosis was found on CAG. The SS and FSS of patient B were 15 and 0, respectively. CAG: coronary angiography; ECG: electrocardiography, MCG: multifunction cardiogram; SS: SYNTAX score; FSS: functional SYNTAX score.

TABLE III. Predictive value of the SS and FSS measured using the MCG, ECG, and FRS

Test	Kappa coefficient (95%CI)	*P* value	Accuracy	Sensitivity	Specificity	PPV	NPV
Classic SYNTAX score							
MCG	0.35		72.4	39.4	92.6	76.5	71.4
(H vs. B/L)	(0.16–0.55)		(67.6–77.2)	(30.9–47.9)	(89.0–96.2)	(66.2–86.8)	(66.0–76.8)
ECG	0.14	0.14	63.2	27.3	85.2	52.9	65.7
(P vs. N)	(−0.06–0.33)		(58.0–68.4)	(19.5–35.0)	(80.4–90.0)	(40.8–65.0)	(60.0–71.4)
FRS	0.02	0.002	48.3	63.6	38.9	38.9	63.6
(H vs. I/L)	(−0.16–0.21)		(42.9–53.6)	(55.3–72.0)	(32.3–45.5)	(32.3–45.5)	(55.3–72.0)
Functional SYNTAX score							
MCG	0.51		82.8	54.5	92.3	70.6	85.7
(H vs. B/L)	(0.29–0.72)		(78.7–86.8)	(43.9–65.2)	(89.0–95.6)	(59.5–81.6)	(81.5–89.9)
ECG	0.18	0.017	71.3	31.8	84.6	41.2	78.6
(P vs. N)	(−0.05–0.41)		(66.4–76.1)	(21.9–41.7)	(80.1–89.1)	(29.2–53.1)	(73.7–83.5)
FRS	0.01	<0.001	44.8	63.6	38.5	25.9	75.8
(H vs. I/L)	(−0.14–0.17)		(39.5–50.2)	(53.4–73.9)	(32.4–44.5)	(20.0–31.9)	(68.3–83.2)

SS: SYNTAX score; FSS: functional SYNTAX score; OR: odds ratio; AIC: Akaike information criterion; MCG: multifunction cardiogram; ECG: electrocardiogram; FRS: Framingham risk score.

92.3% (89.0–95.6%), and relatively high NPVs of 71.4% (66.0–76.8%) and 85.7% (81.5–89.9%) for the prediction of high SS and FSS, respectively. The MCG showed a predictive accuracy of 72.4% (67.6–77.2%) for SS and 82.8% (78.7–86.8%) for FSS. The areas under the ROC curve (AUC) for the MCG scores in the prediction of high SS and FSS were 0.69 (0.58–0.77) and 0.76 (0.65–0.84), and the optimal cutoff value identified though the ROC analysis was 4.4 and 4.8, with a sensitivity of 48.5 and 59.1%, respectively, and a specificity of 85.2 and 89.2%, respectively (Fig. 2). Figure 3 shows the representative images of CAG from the patient who showed no resting ECG abnormality with functional ischemia in A and without functional ischemia in B. The average MCG score of patient A was 5.0 and the multivessel disease was found on CAG. The SS and FSS of this patient were 26 and 19, respectively. The average MCG score of patient B was 0.0, and no significant stenosis was found on CAG. The SS and FSS of this patient were 15 and 0, respectively.

DISCUSSION

The major findings in this study are that the MCG score was significantly associated with not only the SS but also the FSS in a relatively high-risk population with or without known CAD. Furthermore, the high MCG scores showed relatively high predictive accuracy for high FSS. These findings could have significant clinical implications on the improvement of noninvasive diagnosis tests in terms of the diagnosis of relevant ischemic heart disease.

Recently the SS, which is based on coronary anatomy and lesion characteristics, was introduced to quantify lesion complexity and to predict clinical outcomes after PCI in patients with multivessel CAD [1–4]. However, the potential benefit of revascularization depends on the presence of myocardial ischemia; therefore, careful identification of ischemia-inducing stenosis allows for a greater benefit from revascularization, especially in patients with stable angina pectoris [5–10]. In this regard, the FSS, which is the modified SS after counting only lesions prone to ischemia with $FFR \leq 0.80$, has been advocated regarding decision making in the choice of revascularization strategies [11]. Nevertheless, performing CAG and measuring FFR to calculate the SS and FSS is inherently invasive and adds complexity. Hence, in the clinical setting, many unnecessary CAGs are often performed, resulting in increased risks of safety and economic problems. Meanwhile, the MCG has been studied as an innovative computational electrophysiological signal analysis tool for the noninvasive diagnosis of relevant ischemia [12–15]. In the present study, we related the relatively high accuracy of the MCG to the FSS, therefore providing an alternative for contemporary noninvasive diagnostic modalities for the detection of relevant ischemia as a gatekeeper for CAG, especially in patients who are not able to perform exercise and have low kidney function.

In this study, the SSs and FSSs were significantly associated with an increasing from the low- and borderline-risk groups to the high-risk group based on MCG scores. This difference seemed to be greater for the FSS compared with the SS. In addition, the predictive accuracy of the MCG also tended to be higher for the FSS (82.8%) compared with the SS (72.4%). The information provided by the MCG indicates the level of myocardial damage and other information such as coronary damage, area of damage, and myocardial

pathological and physiopathological conditions are indicated in the report. Therefore, the predictive ability of the MCG might be greater for the FSS, which is obtained by counting ischemia-provoking lesions, than for the SS, which is simply angiography based.

Compared with the ischemia level in the previous reports [12–15], the SS and FSS in the present study have better prognostic values [1–3,11]. Therefore, the relationship between the MCG, and the SS and FSS observed in this study might contribute not only to the reduction of unnecessary CAGs but also in providing the potential risk stratification, especially in patients who are not able to exercise and have low kidney function.

STUDY LIMITATIONS

Even the FSS used ischemia severity score as a reference for functional ischemia still does not include patient characteristics. Recent studies have demonstrated the superiority of the incorporation of clinical risk factors into scoring systems, such as the clinical SS [21,22]. However, this was not the subject of this study; the main focus rather was the comparison between the MCG and clinical risk factors such as FRS for the prediction of SS and FSS.

CONCLUSIONS

The MCG could have relatively high predictive values for functional cardiac ischemia as assessed by the FSS and thus could contribute to the risk stratification of patients who are not suitable to undergo invasive diagnosis tests.

REFERENCES

1. Wykrzykowska JJ, Garg S, Girasis C, de Vries T, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW. Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (limus eluted from a durable versus ERodable stent coating) trial. J Am Coll Cardiol 2010;56:272–277.
2. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the syntax study. EuroIntervention 2009;5:50–56.
3. van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, Banning AP. The syntax score predicts periprocedural myocardial necrosis during percutaneous coronary intervention. Int J Cardiol 2009;135:60–65.
4. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. SYNTAX Investigators Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–972.
5. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001. [PMC][10.1056/NEJMoa1205361] [22924638]
6. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: Results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (courage) trial nuclear substudy. Circulation 2008;117:1283–1291.
7. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the defer study. J Am Coll Cardiol 2007;49:2105–2111. [PMC][10.1016/j.jacc.2007.01.087] [17531660]
8. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107:2900–2907.
9. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703–1708.
10. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993;87:1354–1367.
11. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PAL, De Bruyne B, Pijls NH, Fearon WF. On behalf of the FAME Study Investigators Functional SYNTAX score for risk assessment in multivessel coronary artery disease. J Am Coll Cardiol 2011;58:1211–1218. [PMC][10.1016/j.jacc.2011.06.020] [21903052]
12. Strobeck JE, Shen JT, Singh B, Obunai K, Miceli C, Sacher H, Ritucci F, Imhoff M. 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;6:143–155.
13. Grube E, Bootsveld A, Buellesfeld L, Yuecel S, Shen JT, Imhoff M. Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis after coronary revascularization. Int J Med Sci 2008;5:50–61.
14. 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 (Hagerstown, Md.) 2002;4:2–12.
15. Amano T, Shinoda N, Kunimura A, Harada K, Uetani T, Takashima H, Ando H, Kumagai S, Gosho M, Murohara T.

Non-invasive assessment of functionally significant coronary stenoses through mathematical analysis of spectral ECG components. Open Heart 2014;1:e000144 doi:10.1136.
16. Strobeck JE, Mangieri A, Rainford N. A paired-comparision of the multifunction cardiogram (MCG) and sestamibi SPECT myocardial perfusion imaging (MPI) to quantitative coronary angiography for the detection of relevant coronary artery obstruction ($\geq$70%) - a single-center study of 116 consecutive patients referred for coronary angiography. Int J Med Sci 2011; 8:717–724.
17. Grube E, Bootsveld A, Yuecel S, Shen JT, Imhoff M. Computerized two-lead resting ECG analysis for the detection of coronary artery stenosis. Int J Med Sci 2007;4:249–263.
18. National Kidney FoundationK/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002;39 (2 Suppl 1):S1–S266.
19. Akaike H. A new look at statistical model identification. IEEE Trans Automat Contr 1974;19:716–723.
20. Akaike H. Prediction and entropy. In: Atkinson AC, Fienberg SE, editors. A Celebration of Statistics. Springer; 1985. pp 1–24.
21. Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW. ARTS-II Investigators A new tool for the risk stratification of patients with complex coronary artery disease: The clinical SYNTAX score. Circ Cardiovasc Interv 2010;3:317–326.
22. Chen SL, Chen JP, Mintz G, Xu B, Kan J, Ye F, Zhang J, Sun X, Xu Y, Jiang Q, Zhang A, Stone GW. Comparison between the NERS (new risk stratification) score and the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score in outcome prediction for unprotected left main stenting. JACC Cardiovasc Interv 2010; 3:632–641.