

## **Pain scales enhance diagnostic accuracy of coronary artery disease-an observational study.**

**Kai-Chun Cheng<sup>1,2,3#</sup>, Kai-Yuan Cheng<sup>4#</sup>, Mei-Chu Lai<sup>5</sup>, Tsung-Hsien Lin<sup>6,7</sup>, Ho-Ming Su<sup>5,6,7</sup>, Wen-Ter Lai<sup>8</sup>, Kai-Hung Cheng<sup>6,7,9\*</sup>**

<sup>1</sup>Department of Ophthalmology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

<sup>2</sup>Department of Ophthalmology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan

<sup>3</sup>Department of Optometry, Shu-Zen Junior College of Medicine and Management, Kaohsiung, Taiwan

<sup>4</sup>Department of Otolaryngology-Head and Neck Surgery, Ministry of Health and Welfare Pingtung Hospital, Pingtung, Taiwan

<sup>5</sup>Department of Cardiology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Taiwan

<sup>6</sup>Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

<sup>7</sup>Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

<sup>8</sup>Department of Internal Medicine, Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan

<sup>9</sup>Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA

#These authors contributed equally to this work

### **Abstract**

**Background:** Hypoalgesia has been identified in patients with DM and hypertension. In addition, endogenous opioid system has been proven to be activated during myoischemia. The aim of the study was to test if pain scales could enhance the diagnostic accuracy of CAD.

**Methods:** Patients (n=249) with symptomatic chest pain with Myocardial Infarction (MI) suspicion, or with positive stress test were prospectively enrolled for diagnostic coronary angiography by the left trans-radial approach. The pain elicited by arterial puncture was assessed using 3 different pain-scale questionnaires, namely the Numerical Rating Scale (NRS), Verbal Rating Scale (VRS), and Visual Analogue Scale (VAS), immediately after the procedure. The pain scales were compared between patients with CAD and non-CAD to find the associations.

**Results:** All the values of pain scales, including NRS, VRS, and VAS were significantly lower in patients with CAD (n=138) compared to those without CAD (n=111). The optimal cut-off points (sensitivity/specificity) of pain scales were 3.25 (0.74/0.75) in NSR, 1.5 (0.69/0.79) in VRS, and 4.25 (0.68/0.78) in VAS. In addition, these three pain scales improved c-statistics for CAD prediction from 0.50 to 0.73~0.75. Patients with low pain scales of NSR 3.25 (or 3) had >8-fold higher risk of CAD than those with NSR>3.25 (or 3).

**Conclusions:** These findings suggest that low pain scales can enhance diagnostic accuracy in patients with symptomatic chest pain suspicious of MI or with positive stress tests. NSR was the best pain scale among these three for enhancing diagnosis of CAD.

**Keywords:** Hypoalgesia, Coronary artery disease, Transradial access, Angina pectoris, Pain scales.

*Accepted on December 19, 2017*

### **Introduction**

Hypoalgesia, a decreased sensitivity to painful stimuli, occurs when nociceptive (painful) stimuli are interrupted or decreased. It is noted in patients with DM (as a Coronary Artery Disease (CAD) equivalent) [1-4] and hypertension (one of major risk

factor for CAD) [5], and it can be mediated by some chemicals such as opioids. The endogenous opioid system consists of 3 three opioids, beta-endorphin, enkephalins, and dynorphins, and 3 families of receptors,  $\mu$  (MOR),  $\delta$  ( $\lambda$ , DOR), and  $\kappa$  (KOR). The endogenous opioid system including beta-

endorphin and opioid receptors is being activated and increased during myoischemia [6-11]. The CAD is reported to be the most common type of heart disease, which is the leading cause of death for both men and women. (CDC, NCHS. Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015.). Chest pain is a common complaint in patients, with one of the relevant causes being coronary artery disease. While many studies were focused on how to differentiate what patterns of chest pain responsible for CAD relevant chest pain in the past [12-14], it is interesting and is a reverse thinking to find out if the sensitivity to painful stimuli is helpful to improve the diagnostic accuracy of CAD. Since little is known about the influence of pain assessment for CAD prediction, the aim of the study is to test the pain scales on the diagnostic accuracy of CAD in patients with symptomatic chest pain.

## Methods

### *Study populations and the protocol*

In total, 249 patients with symptomatic angina pectoralis with positive findings in stress tests, treadmill and Th-201 SPECT studies, or with suspicion of myocardial infarction, were prospectively enrolled for coronary angiography. All diagnostic coronary angiography procedures were performed percutaneously *via* the left trans-radial approach, and pain scales including the numerical rating, verbal rating, and visual analogue scales were assessed immediately following the procedures. After being verified by angiography, patients were allocated into CAD and Non-CAD groups respectively. This study was approved by the Institutional Review Board at Kaohsiung Medical University Hospital (Approval No. KMHIRB-E(I)-20150178). The flow of the cohort is outlined in Figure 1.

### *Pain scales*

The Numerical Rating Scale (NRS) used a scale of 1-10 to assess the degree of pain; the Verbal Rating Scale (VRS) of 0-3 was determined by patients' subjective responses in the words "no", "mild", "moderate", and "severe" in referring to pain intensity; and the Visual Analogue Scale (VAS) was based on patients' marks on a horizontal 10 cm line indicating their pain intensity, in which 0 indicated "no pain" and 10 indicated "worst pain" [15] (Figure 2).

### *Statistical analysis*

Demographic and clinical data were presented as mean  $\pm$  SD. Categorical variables were compared using contingency tables (Pearson chi-square test) and continuous variables using student t-test. Spearman's correlation coefficients were calculated. Multiple logistic regression analysis with Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were calculated to evaluate the independence property of the association between CAD and pain scales. The discriminatory capacity of the risk scores were assessed by using AUC (c-statistic) as an index of model performance [16] and optimal

cut-off points by maximal values of Youden index (Youden index=sensitivity+specificity-1) between pain scales and CAD. The c-statistic reflected the concordance of predictions with actual outcomes in rank order, with a c-statistic of 1.0 indicating perfect discrimination. The P value<0.05 was considered statistically significant. Statistical analysis was performed by SPSS 12.0 software (Chicago, IL, USA).

## Results

### *Patient characteristics*

The demographic and clinical characteristics at baseline of the study patients are summarized in Table 1. The traditional atherosclerotic risks including male gender, concomitant diabetes, End-Stage Renal Disease (ESRD), dyslipidemia, and habit of cigarette smoking were significantly higher in patients with CAD.

### *Correlation analysis between pain scales and number of stenotic coronary arteries*

All study parameters of the pain scales, including numerical rating, verbal rating and visual analogue scales were significantly lower in patients with CAD (Table 2). In addition, significantly negative correlations among numerical rating, verbal rating, and visual analogue scales with number of affected coronary vessels in CAD group were found ( $r=-0.308$ ,  $-0.338$  and  $-0.342$  respectively, all  $p<0.001$ ).

### *Performance of pain-scale models prediction in CAD-free population using c-statistics and cut-off points through Youden index*

C-statistics of pain-scales for predicting CAD-free group and optimal cut-off points of pain-scales are presented in Table 3. The c-statistics (ROC index) (and its 95% Confidence Interval (CI)) were 0.5 (0.43-0.57) for stress test alone (data not shown), 0.73 (0.67-0.80) when incorporating NRS, 0.73 (0.66-0.79) when incorporating VRS, and 0.75 (0.69-0.82) when incorporating VAS respectively. The optimal cut-off point (sensitivity/specificity) of pain scales were 3.25 (0.74/0.75) in NSR, 1.5 (0.69/0.79) in VRS and 4.25 (0.68/0.78) in VAS. These pain scale results appeared able to predict CAD-free status with good sensitivity and specificity. Taking gender into consideration, the sensitivity and the specificity were relatively lower in women's treadmill testing [17], and our results compensated for this discrepancy with better sensitivity and specificity in the women's group. While the optimal cut-off points (sensitivity/specificity) of pain scales were 3.5 (0.62/0.76) in NSR, 1.5 (0.56/0.79) in VRS, and 4.15 (0.60/0.75) in VAS for the men's group, the cut-off points (sensitivity/specificity) of pain scales were 3.25 (0.74/0.73) in NSR, 1.5 (0.68/0.77) in VRS, and 4.15 (0.68/0.76) in VAS for the women's group (Table 3).

**Multivariate regression analysis for clarifying the independent association among pain scales for the CAD-free population**

Independence of association among all pain scales in the CAD population were found to be significant after being adjusted for risk factors including age, gender, DM, hypertension, smoking, dyslipidemia, and ESRD. Compared to NSR>3.25, NSR ≤ 3.25 was the strongest predictor among the pain scales for CAD (OR, 8.291; 95% CI, 4.227~15.981, p<0.001). Since NSR was not a continuous scale, NSR value of 3.0 was further analysed, and the same result was found with NSR ≤ 3.25. The ORs (95% CI) of VRS ≤ 1.5 and VAS ≤ 4.25 (compared with VRS>1.5 and VAS>4.25) were 7.943 (4.120~15.315) and 6.781 (3.572~12.873) respectively (both p<0.001). The ORs of these 3 scales were almost double or even more than doubled compared to other risk factors (Table 4). In addition, 3-vessel disease (3VD) was differentiated from single-vessel disease (1VD), NSR ≤ 3.25 (3.0), VRS ≤ 1.5, and VAS ≤ 4.25 had significantly and independently higher risks of 3-vessel disease than did NSR>3.25 (3.0), VRS>1.5 and VAS>4.25 with ORs (95% CI) of 4.922 (2.123~11.409), 5.403 (2.190~13.330) and 5.627 (2.283~13.868) respectively (all p<0.001) (Table 5).

**Table 1.** The baseline characteristics of patients with CAD and Non-CAD.

	CAD (n= 138)	Non-CAD (n=111 )	P value
Male gender, n (%)	106 (76.8)	55 (49.5)	<0.001#
Age (y)	61.0 ± 11.1	58.8 ± 11.9	0.14
DM, n (%)	63 (45.7)	22 (19.8)	<0.001#

**Table 3.** Performance of free of CAD prediction pain-scale models using c-statistics and cut-off points through Youden index.

ROC curves of 3 pain-scale questionnaires for diagnosing free of CAD in whole population					
Pain-scale questionnaire	c-statistics (ROC index)	95% CI	Optimal cut-off point	Sensitivity	Specificity
Numerical rating scale	0.73	0.67-0.80	3.25	0.74	0.75
Verbal rating scale	0.73	0.66-0.79	1.5	0.69	0.79
Visual analogue scale	0.75	0.69-0.82	4.25	0.68	0.78
ROC curves of 3 pain-scales for diagnosing free of CAD in male population					
Pain-scale questionnaire	c-statistics (ROC index)	95% CI	Optimal cut-off point	Sensitivity	Specificity
Numerical rating scale	0.67	0.59-0.76	3.5	0.62	0.76
Verbal rating scale	0.67	0.58-0.76	1.5	0.56	0.79
Visual analogue scale	0.89	0.60-0.78	4.15	0.6	0.75
ROC curves of 3 pain-scales for diagnosing free of CAD in female population					
Pain-scale questionnaire	c-statistics (ROC index)	95% CI	Optimal cut-off point	Sensitivity	Specificity
Numerical rating scale	0.72	0.65-0.79	3.25	0.74	0.73
Verbal rating scale	0.72	0.65-0.79	1.5	0.69	0.77
Visual analogue scale	0.75	0.68-0.82	4.25	0.69	0.76

ROC: Receiver Operating Characteristic; CI: Confidence Interval. All P<sub>(trend)</sub>-values<0.001

Hypertension, n (%)	97 (70.3)	70 (63.1)	0.28
Current smoking, n (%)	86 (62.3)	44 (39.6)	<0.01*
Dyslipidemia, n (%)	73 (52.9)	42 (37.8)	0.02*
ESRD history, n (%)	11 (8)	2 (2)	0.04*

Data are displayed as mean ± SD or n (%). \*p<0.05, #p< 0.001; CAD: Coronary Artery Disease; DM: Diabetes Mellitus; ESRD: End Stage Renal Disease.

**Table 2.** The association of pain scales with Coronary Artery Disease (CAD).

Independent Student t-test			
Variables	CAD (n=138)	Non-CAD (n=111 )	P value
Numerical rating scale	3.4 ± 2.0	4.8 ± 1.8	<0.001#
Verbal rating scale	1.2 ± 0.6	1.8 ± 0.6	<0.001#
Visual analogue scale	3.7 ± 2.0	5.4 ± 2.0	<0.001#

Data are displayed as mean ± SD or n (%). \*p<0.05, #p<0.001

Correlation analysis between pain scales and involved CAD number		
Variables	correlations coefficient	P value
Numerical rating scale	-0.308	<0.001#
Verbal rating scale	-0.338	<0.001#
Visual analogue scale	-0.342	<0.001#

\*p<0.05, #p<0.001

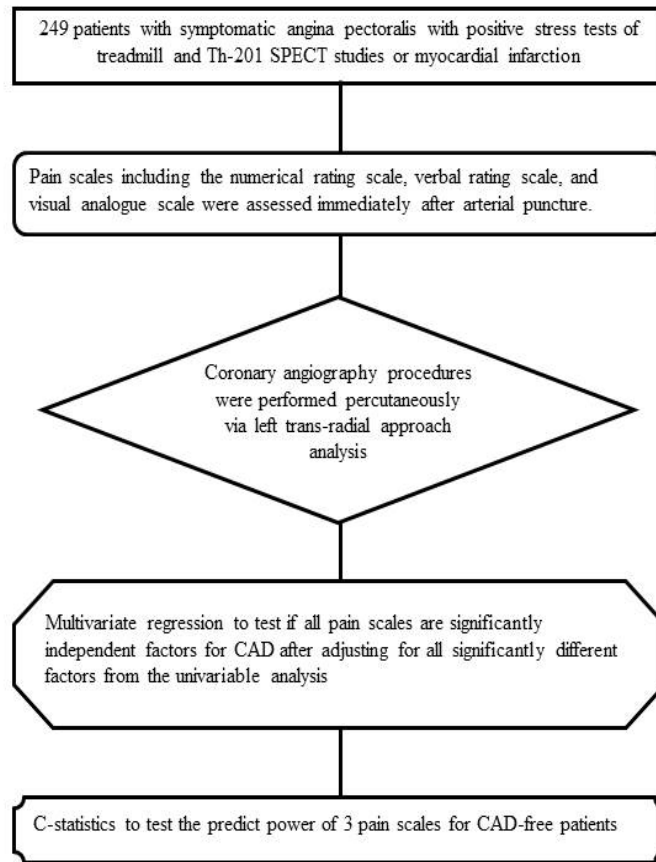


Figure 1

Figure 1. Flow of the study cohort. Patients with symptomatic angina pectoralis with positive stress tests of treadmill and Th-201 SPECT studies or myocardial infarction were prospectively enrolled for diagnostic Coronary Angiography (CAG) by the left trans-radial approach. Three pain scales were assessed immediately after the procedures. Multivariate regression tested if all pain scales were significantly independent factors for CAD after adjusting for all significantly different factors from the univariable analysis. If these 3 pain scales were independent for CAD, c-statistics and cut-off points through the Youden index were applied to test the predictive power with adequate sensitivity and specificity of 3 pain scales for CAD-free patients.

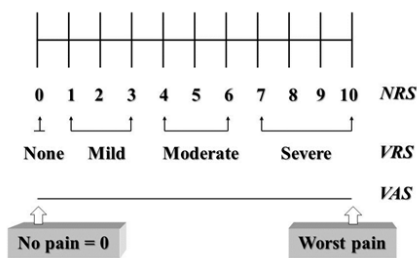


Figure 2. Pain-scale questionnaire evaluated immediately after CAG. The three common one-dimensional pain intensity scales are: (1) the 11-point Numerical Rating Scale (NRS); (2) the Visual Analogue Scale (VAS), indicating a position along a continuous line between two end-points, from no pain (=0) to worst pain imaginable (=10 cm (or 100 mm)); and (3) the four-point categorical Verbal Rating Scale (VRS).

Table 4. Multiple logistic regression analysis for prediction of CAD by three pain scale cut-off points.

Variables	OR	95% Confidence Interval (CI)	P-value
<b>NSR 3.25 (or 3)</b>	8.219	(4.227~15.981)	<0.001#
DM	3.587	(1.747~7.364)	<0.001#
Current smoking	2.776	(1.313~5.868)	0.008*
Gender	1.69	(0.782~3.652)	0.182
Dyslipidemia	2.028	(1.057~3.888)	0.033*
ESRD	4.445	(0.737~26.811)	0.073
Age	1.018	(0.989~1.048)	0.235
Hypertension	1.248	(0.608~2.562)	0.547
<b>VRS 1.5</b>	7.943	(4.120~15.315)	<0.001#
DM	3.783	(1.834~7.801)	<0.001#
Current smoking	2.521	(1.199~5.298)	0.015*
Gender	1.926	(0.896~4.139)	0.093

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Dyslipidemia	1.886	(0.989~3.598)	0.054	Dyslipidemia	1.752	(0.928~3.305)	0.084
ESRD	4.882	(0.821~29.017)	0.081	ESRD	3.588	(0.627~20.515)	0.151
Age	1.018	(0.989~1.048)	0.214	Age	1.108	(0.989~1.047)	0.23
Hypertension	1.182	(0.578~2.418)	0.646	Hypertension	1.176	(0.582~2.375)	0.651
<b>VAS 4.25</b>	6.781	(3.572~12.873)	<0.001 <sup>#</sup>	*p<0.05, <sup>#</sup> p<0.001; Parameters calculated using risk factors including age, gender, DM, hypertension, smoking, dyslipidemia, ESRD and each of these 3 pain scales entering the models. CAD: Coronary Artery Disease; NSR: Numerical Rating Scale; VRS: Verbal Rating Scale; VAS: Visual Analogue Scale; DM: Diabetes Mellitus; ESRD: End Stage Renal Disease.			
DM	3.705	(1.817~7.555)	<0.001 <sup>#</sup>				
Current smoking	2.494	(1.195~5.206)	0.015 <sup>*</sup>				
Gender	1.985	(0.930~4.239)	0.076				

**Table 5.** Multiple logistic regression analysis for prediction of single or 3-vessel CAD by three pain scale cut-off points.

Variables	OR	95% Confidence Interval (CI)	P-value
<b>NSR 3.25 (or 3)</b>	4.922	(2.123~11.409)	<0.001 <sup>#</sup>
DM	2.943	(1.425~6.079)	0.004 <sup>*</sup>
Current smoking	1.088	(0.471~2.510)	0.844
Gender	1.722	(0.658~4.509)	0.268
Dyslipidemia	1.738	(0.841~3.591)	0.136
ESRD	0	-	0.998
Age	1.014	(0.983~1.045)	0.393
Hypertension	1.886	(0.818~4.353)	0.137
<b>VRS 1.5</b>	5.403	(2.190~13.330)	<0.001 <sup>#</sup>
DM	3.069	(1.490~6.320)	0.002 <sup>*</sup>
Current smoking	1.02	(0.439~2.366)	0.964
Gender	1.88	(0.719~4.914)	0.198
Dyslipidemia	1.693	(0.820~3.496)	0.154
ESRD	0	-	0.998
Age	1.015	(0.984~1.046)	0.342
Hypertension	1.831	(0.797~4.211)	0.154
<b>VAS 4.25</b>	5.627	(2.283~13.868)	<0.001 <sup>#</sup>
DM	3.051	(1.475~6.315)	0.003 <sup>*</sup>
Current smoking	1.072	(0.465~2.467)	0.871
Gender	1.743	(0.675~4.505)	0.251
Dyslipidemia	1.616	(0.784~3.333)	0.194
ESRD	0	-	0.998
Age	1.102	(0.982~1.044)	0.436
Hypertension	1.815	(0.788~4.178)	0.161

\*p<0.05, <sup>#</sup>p<0.001; Parameters calculated using risk factors including age, gender, DM, hypertension, smoking, dyslipidemia, ESRD and each of these 3 pain scales entering the models. CAD: Coronary Artery Disease; NSR: Numerical Rating Scale; VRS: Verbal Rating Scale; VAS: Visual Analogue Scale; DM: Diabetes Mellitus; ESRD: End Stage Renal Disease.

## Discussion

All pain scales, including NSR, VRS and VAS were significantly lower in patients with CAD, and all showed

significant negative correlations with CAD. To the best of our knowledge, this is the first study to investigate the pain scales on improvement of diagnostic accuracy of CAD. It validated that low pain scales could further enhance CAD diagnostic

accuracy in patients with symptomatic chest pain of suspicion of MI or with positive stress tests. The optimal cut-off points (sensitivity/specificity) of pain scales were 3.25 (0.74/0.75) in NSR, 1.5 (0.69/0.79) in VRS, and 4.25 (0.68/0.78) in VAS. In addition, these three pain scales improved c-statistics for CAD prediction from 0.50 to 0.73~0.75. All pain scales were significantly associated with CAD after adjusting for risk factors including age, gender, DM, hypertension, smoking, dyslipidemia, and ESRD. The ORs of these 3 scales were almost double or even more than doubled compared to other risk factors. Compared to  $NSR > 3.25$ ,  $NSR \leq 3.25$  was the strongest predictor among these pain scales for CAD (OR, 8.291; 95% CI, 4.227~15.981,  $p < 0.001$ ). In addition, these pain scales might be independently helpful in differentiating multi-vessel disease (MVD) from single-vessel disease (1VD).

Wide variations in the sensitivity and specificity of treadmill testing have been reported in the related literature. In a large-scale analysis, the reported sensitivities ranged from 23-100% (mean, 68%), and the specificities ranged from 17-100% (mean, 77%) [17]. Dipyridamole-thallium testing has a reported sensitivity of 67-95% (mean, 86%) and a specificity ranging from 41-100% (mean, 71%) [17,18]. Our study showed a gain of 68%-74% in sensitivity and 75%-78% in specificity on top of these stress tests including treadmill and dipyridamole-thallium tests (Table 3). In addition to the estimation of CAD risks (Table 4), physicians can also easily estimate the risk of MVD through the pain scale assessments (Table 5). The sensitivity was relatively lower in treadmill testing in the women's group [17], and our study results provide a solution for this discrepancy (Table 3).

The possible mediator for low pain scales in CAD is the activated endogenous opioid system through increased beta-endorphin and opioid receptor activations in the situation of myoischemia [6-11]. In addition to generalized hypoalgesia to visceral and somatic stimulations mechanism [19], competitive inhibition from visceral nociception transmitted through sympathetic afferent fibers entering the dorsal root ganglions might compete with and reduce peripheral painful stimuli intensity [20-23]. This competitive inhibition has been verified and used in a reverse way for many clinical neuromodulation therapies, such as acupuncture, spinal cord stimulation, and transcutaneous electrical nerve stimulation, and all of which have been proven to reduce symptoms of visceral pain induced by angina pectoris [20,23-25] by competing against the visceral nociception inputs.

Factors such as concomitant DM, smoking habit, and male gender were significantly higher in patients with CAD in our study, which are also major CAD risk factors documented in previous studies [26-28]. From the viewpoint of these risk factors, hypoalgesia has been documented in patients with DM (CAD equivalent) [1-3]. In addition, smoking is an important source of acrylamide exposure, which is a possible cause of hypoalgesia by interrupting inputs from demyelinating and axonal changes in peripheral nerves [29]. Current human findings regarding gender differences in experimental pain indicate greater pain sensitivity among females as compared

with males for most pain modalities and hypoalgesia [30-34]. This advantage of higher pain sensitivity in female population led to a greater pain test sensitivity in our study that compensated for the relatively low sensitivity in treadmill testing.

## Study Limitations

There are limitations regarding this study that are worth noting. The study population was relatively small, and the findings can only be applied to patients suspected of having CAD based on positive findings of stress tests. A large prospective study might be warranted to see if the power of pain scales can enhance the detection accuracy of CAD.

## Conclusion

This is the first study to unveil the lower pain in patients with myoischemia through assessment of the pain during arterial puncture procedure. The low-pain scale improved the diagnostic accuracy of CAD in patients with symptomatic chest pain suspicious of MI or with positive stress tests; consequently, it would also assist physicians in being aware of the possibility of MVD. NSR value of 3.25 presents as the best cut-off point for predicting the risk of CAD.

## Acknowledgments

The authors thank the volunteers and staff who participated in this study.

## Conflict of Interests

No potential conflicts of interest relevant to this article were reported. Funding/Supports

None

## Author Contributions

The authors, Dr. Kai-Chun Cheng and Dr. Kai-Yuan Cheng, participated in generating original ideas, in study design and analysis of data, in drafting of the manuscript, in revising it critically for important intellectual content and in final approval of the manuscript submitted. All the authors were involved in 1) making substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) reviewing and providing final approval of the version to be published. Kai-Chun Cheng and Kai-Hung Cheng wrote the manuscript, researched data and held the meetings for discussion. Kai-Chun Cheng and Kai-Hung Cheng (guarantors) take responsibility for the content of this article.

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**\*Correspondence to**

Kai-Hung Cheng

Division of Cardiology

Department of Internal Medicine

Kaohsiung Medical University Hospital

Taiwan