

# The Effect of Slow Coronary Artery Flow on Microvolt T-Wave Alternans

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**Background:** Slow coronary artery flow (SCF) is characterized by angiographically confirmed delayed vessel opacification in the absence of any evidence of obstructive epicardial coronary artery disease. Microvolt T-wave alternans (MTWA) is defined as beat-to-beat changes in shape, amplitude, or timing of ST segments and T waves, and is utilized in predicting sudden cardiac death and life-threatening malignant ventricular arrhythmias in high-risk patients. In our study, we aimed to evaluate the effects of slow coronary artery flow on MTWA.

**Methods:** Thirty-nine consecutive patients (SCF group: 6 women and 33 men; mean age,  $49 \pm 10$  years) with angiographically documented SCF in at least 1 major epicardial artery and 39 patients (control group: 13 women and 26 men; mean age,  $50 \pm 10$  years) with normal coronary arteries were included in the study. Coronary flow rates of all patients were calculated by thrombolysis in myocardial infarction frame count (TFC). The MTWAs of all patients were analyzed using the time-domain modified moving average method by means of a treadmill exercise stress test.

**Results:** The age distribution, body mass index, and diastolic and systolic blood pressure (BP) were similar in the SCF and control group. In the SCF group, the three epicardial coronary artery corrected TFCs and mean TFCs were significantly higher than in the control group (for all,  $p < 0.001$ ). MTWA positivity in the SCF group was statistically significant compared to the control group ( $p = 0.006$ ). Spearman's correlation analysis, showed a positive correlation between MTWA and right coronary artery (RCA) TFC and mean TFC ( $r = 0.368$ ,  $p = 0.001$  and  $r = 0.271$ ,  $p = 0.016$ , respectively). In linear regression analysis, only the right coronary artery TFC was correlated with positive MTWA ( $p = 0.001$ ).

**Conclusions:** The results of our study suggest that diagnosed SCF is associated with MTWA positivity. Furthermore, we determined that only RCA TFC was predictive of positive MTWA.

**Key Words:** Microvolt T-wave alternans • Slow coronary flow

## INTRODUCTION

Angiographically normal coronary arteries are ob-

served in approximately 10-30% of patients being evaluated for typical angina or angina-like pain.<sup>1</sup> The pathophysiology of angina pectoris in patients with angiographically normal coronary anatomy is not well understood.<sup>2,3</sup> The slow coronary artery flow (SCF) phenomenon is described as delayed opacification of coronary vessels in the absence of occlusive epicardial coronary artery disease.<sup>4</sup> Clinical series and individual case reports have shown that SCF may be associated with angina, infarction, and ischemia.<sup>5,6</sup>

Microvolt T-wave alternans (MTWA) is defined as beat-to-beat changes in shape, amplitude, or timing of

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ST segments and T waves. The usefulness of exercise-induced MTWA in predicting sudden cardiac death and life-threatening malignant ventricular arrhythmias in high-risk patients has been investigated in several studies.<sup>7,8</sup> These studies consisted of patient groups with a high risk of malignant ventricular arrhythmias, such as impaired left ventricular function,<sup>9</sup> congestive heart failure,<sup>10</sup> ischemic cardiomyopathy,<sup>11</sup> or prior myocardial infarction (MI).<sup>12</sup> Despite these studies, however, there is not enough information about the prognostic significance of MTWA in patient populations such as those with SCF. As such, in our study, we aimed to evaluate the effect of SCF on MTWA.

## METHODS

### Study population

Thirty-nine consecutive patients (SCF group: 6 women and 33 men; mean age,  $49 \pm 10$  years) with angiographically documented SCF in at least 1 major epicardial artery and 39 patients (control group: 13 women, 26 men; mean age,  $50 \pm 10$  years) with normal coronary arteries were included. We included patients older than 18 years who had at least one Canadian Cardiovascular Society class 3 angina and/or proven myocardial ischemia according to noninvasive diagnostic tests. We excluded patients with a history of acute MI, serious valvular heart disease, rhythm disturbances, heart failure, inflammatory diseases, peripheral arterial diseases, renal failure, liver failure, acute coronary syndrome, and left ventricular hypertrophy, as well as pregnant patients and those with a history of use of drugs or chemicals such as marijuana, antiarrhythmic drugs, digitalis,  $\beta$ -blockers, and non-dihydropyridine calcium channel blockers. We also excluded patients subjected to air embolization during coronary angiography or complications during catheterization.

### Coronary artery angiography

Coronary angiography was performed with a femoral approach using Judkins catheters. Coronary arteries were visualized in the left and right oblique planes and cranial and caudal angles. Left ventriculography was performed in the left and right anterior oblique views. Injection of contrast medium (Iopromide, Ultravist-370;

Schering AG, Berlin, Germany) was conducted by an automatic injector at rates of 3-4 mL/sec for the left coronary artery and 2-3 mL/sec for the right coronary artery. Arteriographies were recorded at a rate of 30 frames/sec.

Coronary blood flow rates were measured quantitatively by using the thrombolysis in myocardial infarction frame count (TFC) method, which was derived from the number of cine-frames recorded from the first entrance of contrast to its arrival at the distal end of either the left anterior descending artery (LAD), the left circumflex artery (LCX), or the right coronary artery (RCA).<sup>13</sup> For purposes of our study, the first frame was defined as the frame in which the concentrated dye fills the full width of the proximal coronary artery lumen, touching both borders of the lumen, and proceeds in a forward motion down the artery. The final frame was defined as the frame in which the leading edge of the contrast column initially arrived at the distal landmark. In the LAD coronary artery, the landmark was defined as the most distal branch nearest to the apex of the left ventricle. The LAD is usually longer than the other major coronary arteries, and the thrombolysis in TFC for this vessel is usually higher. Therefore, to obtain a corrected TFC for the LAD, the TFC was divided by 1.7.<sup>14</sup> The RCA distal landmark is the first branch of the posterolateral RCA after the origin of the posterior descending artery, regardless of the size of this branch. The branch of the left circumflex (LCX), which encompassed the greatest total distance traveled by the contrast dye, was used to define the distal landmark of the LCX artery. The TFCs of the LAD and LCX were assessed in the right anterior oblique projection with caudal angulation and RCA left anterior oblique projection with cranial angulation. TFC of  $36 \pm 2.6$  frames for LAD,  $22.2 \pm 4.1$  frames for LCX, and  $20.4 \pm 3.0$  frames for RCA were defined as the cutoff values for slow coronary artery blood flow.<sup>14,15</sup> For the purposes of our study, any values obtained above these thresholds were considered to be SCF. TFCs were evaluated by two experienced observers blinded to the study design.

### Exercise test protocol

Before beginning the exercise test, all patients were asked to lay down in the supine position for 10 minutes and resting electrocardiography (ECG) was digitally recorded. The upright exercise test was performed on a treadmill. The lead system used was the Mason-Likar

modification of the standard 12-lead system. We used a modified Bruce protocol to increase the workload every 3 minutes. Continuous ECGs were digitally recorded at 500 Hz using the Cardiosoft version 4.14 exercise system (GE Healthcare) and completely automatically analyzed by the Cardiosoft version 4.14 exercise system using the modified moving averaged (MMA) method. During the exercise test, heart rate was recorded continuously via ECG, and systolic and diastolic arterial pressure was measured with a brachial cuff every 2 minutes.

### Measurement of MTWA

The algorithm used in the identification and quantification of MTWA is based on time-domain MMA analysis. An update is calculated for every incoming beat, which results in continuous moving averages of odd and even beats. In addition, algorithms have been incorporated to reduce the influence of noise and artifacts, such as those caused by running and respiration. MTWA values were calculated continuously during the entire exercise test, from rest to recovery, using all standard leads (I, II, III, aVR, aVF, aVL, and V1-V6). Maximum MTWA values at heart rates < 125 bpm were recorded, and MTWA values at higher heart rates were excluded. The analyses were performed in 1/32 incremental update factors. We designated 65  $\mu$ V as the cutoff point, as it had been shown to predict cardiac arrest and arrhythmic death in a prior study.<sup>16</sup> Patient characteristics were compared between those with MTWA < 65  $\mu$ V as negative and  $\geq$  65  $\mu$ V as positive.<sup>16-18</sup>

### Statistical analysis

Statistical analysis was performed using SPSS software version 17. The variables were investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods to determine whether they were normally distributed. Descriptive analyses were presented as mean  $\pm$  standard deviation (SD), and categorical variables were expressed as percentages. Demographic information between the groups (age, hematocrit, total cholesterol, low-density lipoprotein, and body mass index) was compared using Student's t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test, where appropriate. While investigating the associations between non-normally distributed and/or ordinal variables, correlation coefficients

and their significance were calculated using the Spearman test. A multiple linear regression model was used to identify independent predictors of MTWAs, and inter-observer agreement between the two observers in determining the TFC values were investigated using the Kappa test. An overall 5% type-I error level was used to infer statistical significance.

## RESULTS

The distribution of age, body mass index, diastolic and systolic blood pressure (BP), heart rate, and cardiac risk factors was similar in the SCF and control group. The general characteristics of the study groups are listed in Table 1. In the SCF group, the three epicardial coronary artery corrected TFC and mean TFC were significantly higher (for all,  $p < 0.001$ ). MTWA positivity in the SCF group was statistically significantly different from the control group ( $p = 0.006$ ). In Spearman's correlation analysis, there was a positive correlation between MTWA and RCA TFC (Figure 1) and mean TFC ( $r = 0.368$ ,  $p = 0.001$  and  $r = 0.271$ ,  $p = 0.016$ ), respectively (Table 2). In linear regression analysis, only RCA TFC correlated with positive MTWA ( $\beta = 0.537$ ,  $p = 0.001$ ). At MTWA values above 65  $\mu$ V, SCF patients' sensitivity was 59%, specificity was 71.8%, positive predictive value was 67.6%, and negative predictive value was 63.7%. Our TFC results showed excellent agreement between independent observers (Kappa = 0.91).

## DISCUSSION

The main findings of this study were that MTWA was significantly higher in patients with SCF documented by TFC than in those with normal coronary flow. Additionally, RCA TFC correlated with positive MTWA. To the best of our knowledge, this is the first study to demonstrate the relationship of SCF with positive MTWA.

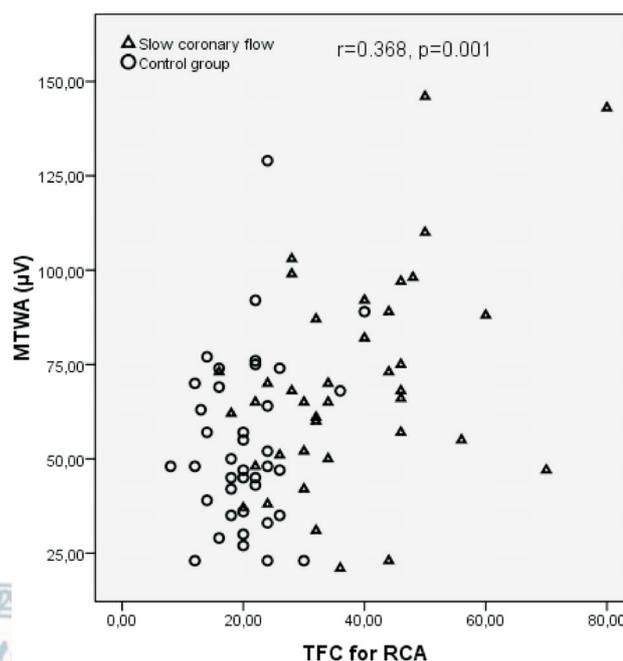
The pathogenesis of SCF is still not well understood. There are some histopathological features associated with SCF. Reduction of luminal diameter and functional obstruction are thought to be the key events in its pathogenesis. Mosseri et al. found medial hypertrophy, myointimal proliferation, and endothelial degeneration

**Table 1.** Clinical and laboratory findings between slow coronary flow and control groups

	Coronary slow flow (n = 39)	Control group (n = 39)	p value
Age (year)	49 ± 10	50 ± 9	.503
Sex, (male %)	84.6	66.7	.065
Body mass index (kg/m <sup>2</sup> )	29 ± 3	28 ± 4	.362
Diastolic pressure (mmHg)	74 ± 7	74 ± 7	.728
Systolic pressure (mmHg)	124 ± 8	125 ± 12	.851
Heart rate (beat/min)	79 ± 8	76 ± 8	.093
Smokers (%)	43.6	38.5	.645
Diabetes mellitus (%)	7.7	12.8	.356
Hypertension (%)	20.5	25.6	.591
Hematocrit (%)	43 ± 4	41 ± 5	.115
Glucose (mg/dL)	115 ± 36	105 ± 15	.869
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	.874
Total cholesterol (mg/dL)	195 ± 42	202 ± 41	.429
LDL (mg/dL)	123 ± 29	126 ± 35	.672
HDL (mg/dL)	42 ± 12	45 ± 12	.106
Triglyceride (mg/dL)	192 ± 143	165 ± 73	.708
C Reactive protein (mg/dL)	3.8 ± 2.6	2.8 ± 1.8	.092
TIMI frame count			
cLAD	36 ± 17	21 ± 6	< .001
LCX	36 ± 12	22 ± 6	< .001
RCA	38 ± 14	20 ± 6	< .001
Mean	37 ± 11	21 ± 5	< .001
MTWA (positivity, n, %)	23 (59)	11 (28.2)	.006

cLAD, corrected left anterior descending artery; HDL, high density lipoprotein; LCX, left circumflex artery; LDL, low density lipoprotein; MTWA, microvolt T-wave alternans RCA, right coronary artery.

with changes of myofibrillar degenerative foci and lipofuscin deposits at the electron microscopic level.<sup>19</sup> Luminal narrowing was attributed to endothelial swelling and degeneration. Mangieri et al. established that these findings in SCF patients by showing small-vessel thickening with associated luminal narrowing, dilated interstitial spaces filled with granular fibrillar material, decreased intracellular glycogen, distorted mitochondrial cristae, and patchy myofibrillar disarray at the electron microscopic level.<sup>20</sup> As a result of these findings, it was claimed that fibromuscular hyperplasia and medial hypertrophy with a consequent decrease in luminal diameter lead to functional obstruction, ischemia, and SCF. In addition, clinical series and individual case reports have shown that CSF may be associated with typical angina, infarction, ischemia, and even sudden cardiac death.<sup>5,6,21,22</sup>



**Figure 1.** Correlation between the RCA TIMI frame count and microvolt T-wave alternans.

**Table 2.** Relationship between MTWA and laboratory, clinical parameters

	Spearman correlation analysis	
	r	p
Age	0.086	0.455
Sex	-0.013	0.908
Smokers	0.043	0.706
Diabetes mellitus	0.126	0.276
Hypertension	0.010	0.930
Hematocrit	0.220	0.053
Glucose	0.055	0.635
Creatinine	-0.058	0.615
Total cholesterol	-0.056	0.627
LDL	-0.053	0.645
Triglyceride	-0.200	0.080
C Reactive protein	-0.027	0.815
TIMI frame count		
cLAD	0.091	0.426
LCX	0.137	0.233
RCA	0.368	0.001
Mean	0.271	0.016

cLAD, corrected left anterior descending artery; LCX, left circumferential artery; LDL, low density lipoprotein; RCA, right coronary artery.

For example, Yaymaci et al. have documented the presence of myocardial ischemia in 83.4% of patients with

positive scintigraphic findings.<sup>23</sup> Furthermore, some authors have reported exercise-induced ST-segment depression in patients with slow coronary flow without obstructive coronary artery disease.<sup>4</sup> One TIMI-III study reported that nearly 4% of patients who presented with unstable angina had no or insignificant coronary artery disease.<sup>24</sup>

MTWA is a well-established risk factor related to long-term susceptibility to ventricular tachyarrhythmia and sudden cardiac death.<sup>25</sup> Positive MTWA has also been reported in acute coronary syndrome with chest pain and ST-T changes and ischemic and non-ischemic cardiomyopathy in human and animal models.<sup>26,27</sup> Various studies in animals during coronary artery occlusion and in humans during angioplasty have demonstrated that myocardial ischemia can increase MTWA magnitude.<sup>28</sup> In these experimental studies, in which the heart rate was kept constant, it was found that myocardial ischemia provokes increases in MTWA magnitude in parallel with increased susceptibility to ischemia-induced ventricular fibrillation.<sup>29</sup> This increase in MTWA was accompanied by parallel changes in T-wave complexity and heterogeneity.<sup>30</sup> Although the ionic bases for these changes have not been well understood, it has been thought that calcium metabolism and conduction disorders are influenced by ischemia. In addition, the involvement of calcium metabolism was proposed by the observation that calcium channel blockage reversed ischemia-induced MTWA in anesthetized canines.<sup>31</sup> Potassium channels also seem to be involved in MTWA during ischemia through potassium-ATP channel activation.<sup>32</sup> Therefore, one possible mechanism for positive MTWA may be microvascular ischemia in these patients.

Impaired coronary flow reserve, which is related to increased resting coronary microvascular tone, is another important characteristic of SCF. With increased myocardial oxygen demand, the inability to maximize coronary flow can induce persistent and recurrent chest pain in SCF patients. Previous studies have revealed that high small-vascular resistance and increased microvascular tone might cause SCF.<sup>19</sup> It is well known that coronary vascular tone is regulated by the autonomic nervous system. Coronary adrenergic hyperactivity may be the cause of reduction in coronary blood flow and angina. Higher adrenalin and noradrenalin levels and TIMI frame counts have been detected in SCF patients com-

pared to individuals with normal coronary flow.<sup>33</sup> This finding could suggest that adrenergic hyperactivity may have a role on the pathogenesis of SCF.

Heart rate is the most important factor in MTWA.<sup>34</sup> However, it is not the only determinant; autonomic neurotransmitters, independent of heart rate, can also affect MTWA magnitude.<sup>35,36</sup> Changes in autonomic nervous system activity, particularly beta-adrenergic activation and blockade, can significantly alter the magnitude of MTWA. For example, Kovach et al. demonstrated that the establishment of an anger-like state significantly increased MTWA, both with and without myocardial ischemia, in conscious animals, and that this effect was significantly decreased by acute beta-adrenergic blockade with intravenous metoprolol.<sup>37</sup> Furthermore, in humans, Kaufmann and colleagues compared the effects of increasing heart rate by pacing to ~100 beats/min to beta-adrenergic stimulation with isoproterenol to the same heart rate on MTWA test results in normal subjects, in patients with monomorphic ventricular tachycardia, and in patients with a history of sudden cardiac arrest.<sup>34</sup> The results of the combined group analysis revealed no difference in MTWA positivity between the two protocols. Thus, change in autonomic tone might be another mechanism of positive MTWA in SCF.

In our study, we found through linear regression analysis that only RCA TIMI frame count correlated with positive MTWA. This suggests that the specificity of our study, and consequently the diagnostic power, is higher. SCF carried a nearly equal moderate positive predictive value and a moderate negative predictive value. As we mentioned above, one possible mechanism for positive MTWA may be microvascular ischemia in SCF patients. Potent vagal reflex stimulated by inferior ischemia (Bezold-Jarisch reflex) has been determined under particular conditions of transmural ischemia in animal and human studies.<sup>38</sup> In humans, similar observations have been made under specific conditions of severe transmural inferior ischemia and its reperfusion, such as those that occur with myocardial infarction, vasospastic angina, or angioplasty of the right coronary artery.<sup>39,40</sup> This reflex is mainly caused by stimulation of vagal sensory nerve endings from myocardial ischemia affecting the inferoposterior wall of the left ventricle. The influence of three receptor groups (cardiac receptors with vagal and sympathetic afferents and arterial barore-

ceptors) may be changed simultaneously during myocardial ischemia. Hypotension, which often results from myocardial ischemia, causes decreases in arterial baroreceptor activity and reflex increases in efferent sympathetic nerve activity.<sup>41,42</sup> Activation of cardiac receptors with vagal afferents during myocardial ischemia causes central inhibition of efferent sympathetic nerve activity and increases in efferent parasympathetic nerve activity.<sup>43</sup> Activation of cardiac receptors with sympathetic afferents may cause reflex increases in efferent sympathetic nerve activity.<sup>44</sup> Thus, the net reflex response to coronary occlusion depends on the balance of these inputs. In SCF patients, activation of cardiac receptors with sympathetic afferents may explain MTWA. However, unknown mechanisms that have not been previously established may exist.

## STUDY LIMITATIONS

Our study is single-center focused and has a relatively small sample size, both of which limit the power of our research. In addition, our study provides no information about long-term outcomes.

## CONCLUSIONS

In conclusion, our study suggests that SCF is associated with MTWA positivity. Furthermore, we determined that only RCA TFC correlated with positive MTWA. Further prospective studies should be conducted to establish the significance of MTWA as a risk factor for ventricular arrhythmias and subsequent sudden cardiac death in patients with slow coronary artery flow.

## Conflicts of interest

This study was not financially supported. The authors have no conflicts of interest to disclose.

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