Original Article

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A Novel Algorithm with Sublingual Nitroglycerin to Diagnose the Patients with Borderline Peripheral Artery Disease

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Objectives: To improve the diagnosis of borderline peripheral artery disease (PAD) with resting ankle-brachial index (ABI) between 0.9 – 1.0 for those unable to do exercise ABI testing is challenging. The aim of this study is to develop an algorithm with NTG (nitroglycerine, sublingually) for the borderline PAD.

Methods: Among the 180 limbs suspicious for PAD, 29 limbs had the resting ABI between 0.9 – 1.0. The values of ABI and brachial-ankle pulse wave velocity (baPWV) at rest and 3-minute after NTG sublingually were analyzed. MRA imaging was performed to confirm the diagnosis of PAD in all limbs.

Results: In a total of 29 limbs, 24 limbs were found with PAD by MRA. After sublingual NTG, ABI dropped to < 0.9 in 12/29 limbs which confirmed to be PAD. The relative change of baPWV with NTG (ΔbaPWV) < -350 cm/s was found in 11 PAD limbs among the rest 17 limbs with only one PAD left undiagnosed finally. The sensitivity, specificity, positive and false predictive values of the algorithm can be achieved up to 100%, 83.3%, 95.8% and 100 %, respectively.

Conclusions: For the borderline PAD, this user-friendly algorithm developed by coupling with post-NTG ABI and ΔbaPWV provides an easy method to diagnose PAD.

Key words: peripheral artery disease (PAD), ankle-brachial index (ABI), brachial-ankle pulse wave velocity (baPWV), nitroglycerine

Introduction

Ankle-brachial index (ABI) is one of the noninvasive methods acceptable for diagnosing patients with peripheral artery disease (PAD). The value of ABI between 1.0 and 1.3 reflects normal functioning peripheral artery.[1,2] In contrast, the incidence of significant PAD increases since ABI value falls below 1.0.[3,4] It is known that ABI value less than 0.9 is considered abnormal with 95% in sensitivity for angiographically-verified peripheral artery stenosis.[5,6] However, the gap of borderline PAD with resting ABI between 0.9 – 1.0 leaves the diagnosis of PAD uncertain and frequently

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requires further much more expensive imaging modalities to clarify, especially in those patients unable to do exercise ABI. In addition, the rate of all-cause mortality in patients with PAD rises significantly when the ABI is ≤ 1.0 instead of ≤ 0.9.[7] Therefore, a simple algorithm to identify patients with PAD whose ABI test values fall between 0.9 – 1.0 with PAD is an unmet need in order to prevent their future major cardiovascular events (MACEs) through early optimal medical intervention.

Previous studies suggested that exercise tests can enhance the diagnostic sensitivity by 31% of ABI in symptomatic PAD patients with resting ABI value between 0.9 – 1.0.[2,8] Nevertheless, this exercise-provocative method fails to apply in those who are unable to run (especially for the elderly), bedridden status, stroke, arthritis or amputated limbs, etc. For these patients, they need some much more expensive and not use-friendly alternative imaging approaches such as magnetic resonance angiography (MRA), computed tomography angiography (CTA) or invasive contrast angiography to determine the diagnosis. Those expensive imaging modalities are not always be available in ordinary clinical practice. In addition, the echo-doppler analysis for PAD can only be performed by some experienced physicians and it is time-consuming. Therefore, to create another easy, inexpensive and less invasive algorithm to identify PAD in those borderline PAD with resting ABI between 0.9 – 1.0 is really an important issue. The fundamental mechanism for exercise-provocative method to diagnose the borderline PAD is that NO makes normal vessel much more dilated during exercise due to the endothelium-derived vasodilatation but it does not happen in the stenotic ones.[9,10] Similarly, our idea is that nitroglycerine (NTG) can also have the NO-like effect on vessels. Therefore, we hypothesized that sublingual NTG might change the test values of ABI and brachial-ankle pulse wave velocity (baPWV) via its vasodilating effect, similar to exercise-provocative ABI test, to help us developing an algorithm for patients with borderline PAD. In this study, the diagnosis of PAD was validated by MRA imaging.

Materials and Methods

Study population and protocol

Patients who had intermittent claudication and were suspected to have PAD clinically were enrolled. To eliminate the confounding effects, medications including prostacyclin and phosphodiesterase inhibitor were avoided. Nitroglycerine administration was also withheld before the test day. The values of ABI and baPWV were obtained by using Colin VP-1000 device (Colin Medical Technology Company, Komaki, Japan). The resting PVR values were obtained by simultaneous oscillometric blood pressure measurements using the Cuffs with 13 cm × 26 cm bladders placed over both right and left brachial arteries for the arm, and both right and left posterior tibial arteries for the leg, after bed rest for 10 minutes. For patients with resting ABI values between 0.9 – 1.0, nitroglycerin (NTG) 0.6 mg was given sublingually. After 3 minutes of sublingual NTG, the 2nd ABI and BAPWV were rechecked. According to the 2nd ABI and baPWV data, patients were subsequently divided into 2 subgroups with either ABI values between 0.9 – 1.0 or with ABI values < 0.9, respectively. Moreover, we also measured baPWV before and after NTG in each patient and the ΔbaPWV of each patient was defined as the difference between baPWV values before and after NTG. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, and all patients provided written informed consent.

MR angiography

MR angiography was performed by a 1.5 T Excite HD MR scanner (Signa Excite GE, Medical system, *Milwaukee,* wis, USA), using the fluoroscopically triggered contrast-en-

hanced 3D MR DSA method.[11] The optimized HR Gd-enhanced MRA protocol combines a high spatial resolution sequence with the use of a PV (peripheral vascular) coil applied to 3 areas (1st area-including lower aorta and pelvic vessels, 2nd area-thighs, 3rd area-lower legs). This allowed the acquisition of multiple (n = 3 – 4) consecutive coronal or coronal-oblique volumes at an anteroposterior slab thickness of 80 – 100 mm. Multiphase Gd-enhanced MRA is acquired after the intravenous injection of 0.2 mL/kg of gadodiamide at 1 mL/sec, followed by normal saline solution at 2.5 mL/sec. Subsystolic thigh compression method was applied to eliminate venous contamination. Compared with conventional angiography, previous studies have shown that MRA has sensitivity and specificity greater than 95% in the detection of significant peripheral arterial stenosis.[12] Lesions of stenosis greater than 50% or an occlusion in the entire lower extremity arterial tree are defined as PAD.[13]

Biochemistry data

Peripheral venous blood and urine samples were collected into pyrogen-free tubes in the morning after more than 8 hours' fasting overnight. Serum glucose, lipid panels, hs-CRP, immunoglobulin(Ig)s, urine microalbumin and Bence-Jones protein and routine biochemical profiles were analyzed.

Statistical analysis

Demographic and laboratory data are presented as mean ± SD. Categorical variables were compared using contingency tables (Pearson chi-square test and Fisher exact test) and continuous variables using student's t-test. Sensitivity and specificity of ABI and baPWV before and after NTG were assessed and were compared with the results of standard peripheral MRA with cumulative results of those with ABI < 0.9 after NTG given in step 1 and searching the most reliable cut-point of ΔbaPWV to increase the specificity stepwise in step 2. ROC curve is of limited use in this 2-step method. ROC curve with AUC (and its 95% confidence interval (CI)) was also evaluated in this 2-step method. 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 between patients with and without PAD are summarized in Table 1. Diabetes and hypertension were significantly more prevalent in the PAD group. The ratio of total CHOL(T)/HDL was borderline but significantly higher in the PAD group. In addition, significantly higher serum hs-CRP, BUN, IgG, uric acid levels, and proteinuria (dipstick) were found in PAD patients. No significant difference in BMI was noted; however, a significantly higher waist-hip ratio (WHR) was found in PAD patients.

ABI and baPWV algorithm

The diagnosing algorithm for PAD is summarized in Figure 1. Among a total of 180 limbs in suspected PAD patients in the test, 29 limbs met the criteria of ABI value between 0.9 – 1.0. The mean value of resting ABI of these 29 limbs was 0.97 ± 0.04. Significant PAD documented by MR angiography was found in 24 of 29 limbs. After NTG 0.6 mg sublingually, the ABI decreased to < 0.9 (mean value: 0.85 ± 0.04) in 12 of the 29 limbs, in which all these 12 limbs had significant PAD demonstrated by MR angiography. In another 17 limbs in which the ABI remained between 0.9 and 1.0 after NTG, there were 11 limbs with significant PAD. Accordingly, the sensitivity, positive predictive value, false predictive value and specificity of diagnosing PAD by ABI augmented after NTG use were 52.2%, 100%, 35.5% and 100%, respectively. On the other hand, the

mean values of baPWV in those with PAD and non-PAD were 2007.8 ± 404.8 cm/s and 1530.7 ± 253.3 cm/s, respectively. After sublingual NTG, the values of baPWV decreased to 1459 ± 321.0 and 1219.7 ± 216.5 cm/s respectively. After removal of the baPWV values from those patients with ABI < 0.9 after NTG given, the remaining baPWV values before and after NTG intervention were demonstrated in Figure 2. The ΔbaPWV values for patients

Table 1. The baseline characteristics of patients with PAD and Non-PAD (limb no. = 29).

	PAD (n = 24)	Non-PAD (n = 5)	*p* value
Male gender, n (%)	13 (57)	4 (67)	0.11
Age (years)	72.3 ± 13.4	63.8 ± 17.5	0.21
BMI (kg/m^2); BMI > 24 kg/m^2, n (%)	24.9 ± 5.3; 10 (43.5)	24.9 ± 6.9; 2 (33.3)	1.00; 0.62
Abnormal waist-hip ratio, n (%) (male > 0.95; female > 0.85)	11 (47.8%)	0 (0%)	< 0.001*
DM, n (%)	16 (70)	0 (0)	0.002*
Hypertension, n (%)	16 (70)	1 (17)	0.02*
Current smoking, n (%)	7 (30)	0 (0)	0.12
Dyslipidemia history, n (%)	6 (26)	0 (0)	0.16
ESRD history, n (%)	3 (13)	0 (0)	0.35
LVEF (%)	66.8 ± 13.8	68.0 ± 9.5	0.84
Blood biochemistry			
Fasting glucose (mg/dL)	123.5 ± 36.7	101.8 ± 14.7	0.07
hs-CRP (mg/L)	18.6 ± 26.4	3.4 ± 2.8	0.03*
Total cholesterol (mg/dL)	213.6 ± 57.7	171.2 ± 20.2	0.12
LDL-C (mg/dL)	123.2 ± 32.5	110.6 ± 11.7	0.16
HDL-C (mg/dL)	40.7 ± 11.3	42.8 ± 14.2	0.73
TG (mg/dL)	208.6 ± 243.1	93.2 ± 27.9	0.31
LDL-C/HDL-C	3.3 ± 1.2	2.8 ± 0.8	0.41
CHOL(T)/HDL	5.7 ± 2.2	4.2 ± 1.0	0.04*
WBC (× 103 /μL)	6.9. ± 1.8	6.0 ± 1.6	0.31
BUN (mg/dL)	27.6 ± 12.4	12.7 ± 6.9	0.02*
Creatinine (mg/dL)	2.0 ± 1.8	1.1 ± 0.1	0.25
AST	24.0 ± 10.2	26.4 ± 13.6	0.66
ALT	20.0 ± 10.2	33.2 ± 28.9	0.37
Uric acid	8.2 ± 2.0	4.6 ± 1.9	0.002*
IgG	1533.7 ± 696.3	1168.0 ± 111.0	0.03*
IgA	291.4 ± 146.0	326.3 ± 51.2	0.65
IgM	87.7 ± 43.7	116.0 ± 25.3	0.23
IgE	597.8 ± 1512.5	255.9 ± 266.9	0.63
Urine biochemistry			
Urine protein (dipstick)	14.7 ± 26.0	0 ± 0	0.03*
Urine microalbumine (mg/L)	329.4 ± 839.4	27.1 ± 43.2	0.56
Medication			
Aspirin, n (%)	15 (65.2)	2 (33.3)	0.16
Clopidogrel, n (%)	3 (13)	0 (0)	0.35
ACEI, n (%)	4 (17.4)	0 (0)	0.27
ARB, n (%)	13 (56.5)	1 (16.7)	0.08
CCB, n (%)	17 (73.9)	2 (33.3)	0.06
BB, n (%)	2 (8.7)	2 (33.3)	0.12
Statin, n (%)	2 (8.7)	1 (16.6)	0.57

Data are displayed as mean ± SD or n (%). *p < 0.05; DM: diabetes mellitus; CHOL(T): total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglyceride; LVEF: left ventricle ejection fraction; WBC: white blood cells; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine transaminase; Ig: immunoglobulin; ACEI: angiotensinogen converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; BB: beta-blocker.

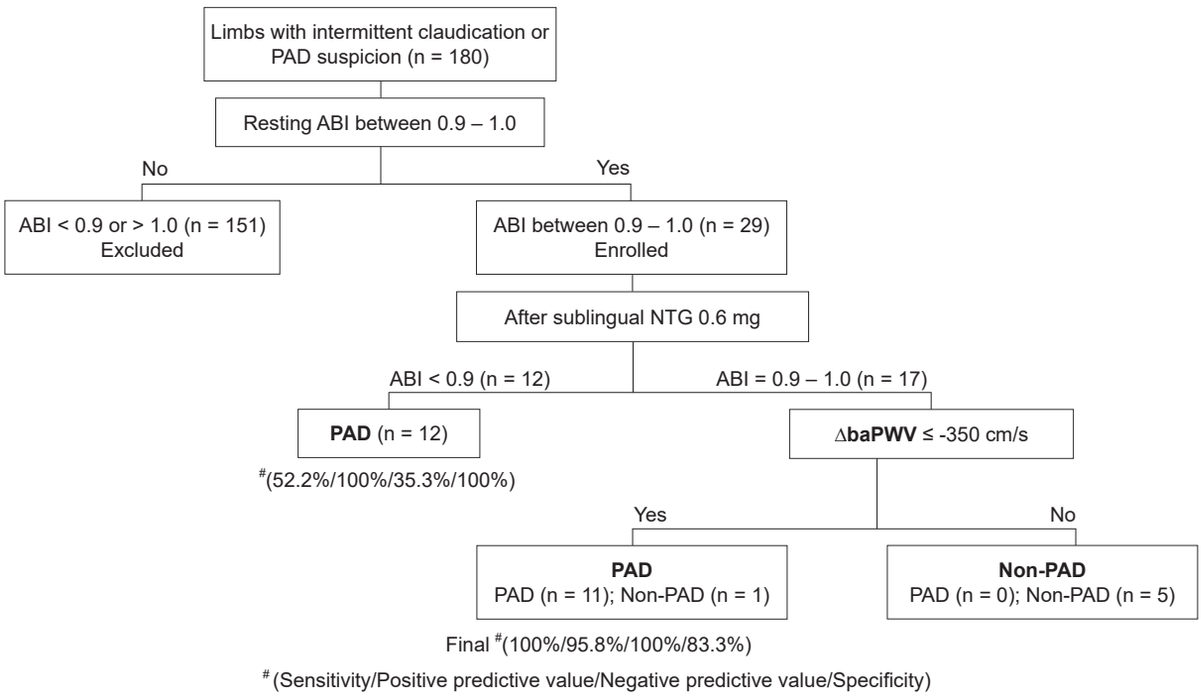


Fig. 1 Algorithm for with sublingual nitroglycerin to diagnose the patients with borderline peripheral artery disease. Algorithm for patients with PAD whose ABI fell between 0.9 – 1.0. When ABI between 0.9 – 1.0, PAD is favored (1) when 2nd PVR revealed ABI < 0.9 after NTG 0.6 mg taken subligually 3 min later; and then (2) ΔbaPWV, defined as the value of baPWV before NTG minus that after NTG, ≤ -350 cm/s. The sensitivity and specificity of the 2-step algorithm can reach up to 100% and 83.3% respectively.

with PAD and Non-PAD were -538.9 ± 185.8 and -311.0 ± 185.8 cm/s, respectively (both $p < 0.05$). Furthermore, to enhance the test specificity, ΔbaPWV ≤ -350 cm/s was chosen to reach the optimal values as shown in Figure 3. Among the 17 limbs with ABI between 0.9 and 1.0 after NTG, 12 limbs had ΔbaPWV ≤ -350 cm/s, in which 11 limbs had significant PAD documented by MR angiography. In contrast, in the remaining 5 limbs with ΔbaPWV ≤ -350 cm/s, no one had significant PAD. The optimal values of sensitivity, positive predictive value, false predictive value and specificity achieved by using this novel combined algorithm, using both post-NTG ABI < 0.9 and ΔbaPWV ≤ -350 cm/s, were 100%, 95.8%, 100% and 83.3%, respectively. ROC curve analysis of this 2-step algorithm for diagnosing patients of PAD showed that AUC (and its 95% CI) was 0.91 (0.00 – 1.00). Therefore, this algorithm can detect PAD with nearly 100% accuracy (97%).

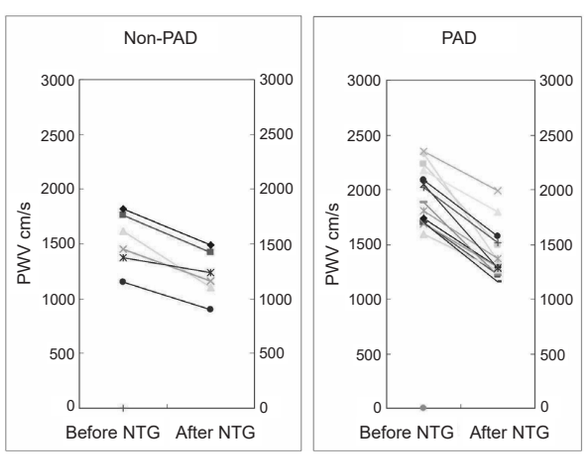
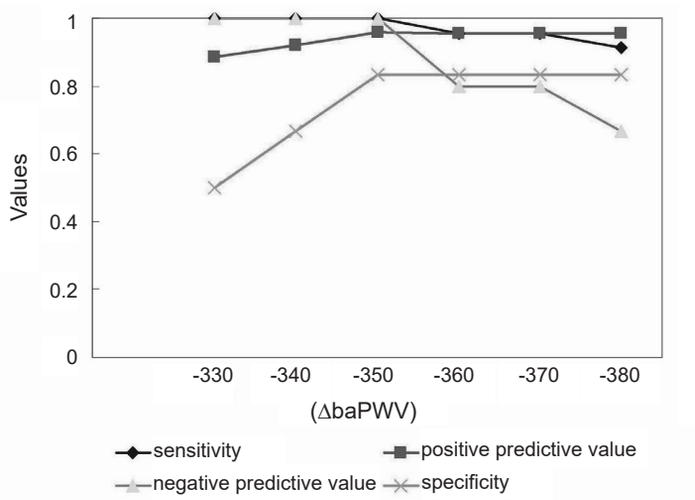


Fig. 2 The baPWV changes before and after NTG intervention between patients with PAD and with Non-PAD. The ΔbaPWV were 538.9 ± 185.8 and 311.0 ± 185.8 cm/s in patients with PAD and Non-PAD (p = 0.01).

Discussion

In this study, we found that in PAD patients with ABI values between 0.9 – 1.0, sublingual NTG can increase the diagnostic accuracy to 97% by using combination criteria



ΔbaPWV ≤ (cm/s)	-330	-340	-350	-360	-370	-380
Sensitivity (%)	100	100	100	95.7	95.7	91.3
Positive predictive value (%)	88.5	92	95.8	95.7	95.7	95.5
Negative predictive value (%)	100	100	100	80	80	66.7
Specificity (%)	50	66.7	83.3	83.3	83.3	83.3

Fig. 3 Finding the optimal value for sensitivity, specificity, positive predictive value and negative predictive value. The sensitivity and specificity both reached maximal values of 100 % and 83.3% when ΔbaPWV ≤ -350 cm/s.

of both post-NTG ABI < 0.9 and ΔbaPWV ≤ -350 cm/s, which was much better than conventional exercise testing enhancement.[8]

Compared with the non-PAD group, patients with PAD had significantly higher incidence of DM, hypertension and hyperuricemia. In this study and previous reports have demonstrated that DM, hypertension[14-16] and hyperuricemia[17-19] are important risk factors for PAD development. Also consistent with previous reports, the high serum level of BUN and proteinuria (dipstick) were noted in these PAD patients.[19] As the waist-hip ratio (WHR) was previously reported to be a better predictor of coronary heart disease than BMI,[20] the rate of abnormal WHR was significantly higher in patients with PAD. In addition, hs-CRP, a predictor of PAD,[14,21] is also significantly higher in patients with PAD. In this study, we demonstrated significantly higher IgG levels in PAD group patients, and some specific IgG autoantibodies against complexed beta2GPI (oxLDL/beta2GPI complexes) are reported to be pro-atherogenic.[22]

Patients with PAD are at triple the risk of all-cause mortality and at more than 6 times the risk of death from coronary heart disease as compared with those without PAD. Unfortunately, PAD is probably the most often-overlooked and the least aggressively managed atherosclerotic disease.[2] Since the CV mortality started to become elevated in PAD patients once their ABI values are less than 1.0 instead of 0.9, it is important to identify PAD patients whose ABIs are within the equivocal zone 0.9 – 1.0.[7]

ABI is normally between 1.0 and 1.3[1] due to higher systolic blood pressure presents in the lower extremities relative to the upper ones. The Colin VP-1000 is an oscillometric device that allows simultaneous blood pressure measurements at the left and right brachial and posterior tibial arteries. As to comparison of different measures to ABIs, doppler and oscillometric ABIs were similar while below 1.0.[23] In general, an ABI value less than 0.9 is strongly considered diagnostic of PAD.[1,5] However, for PAD patients with resting ABI

between 0.9 – 1.0, accurate diagnostic criteria are still lacking.

The plausible mechanism is that NTG can dilate the normal vessels but not diseased vessels which increases the differences of pressures and velocities (much higher in normal vessels and much decreased in diseased vessels) between normal and diseased ones which makes the ABI < 0.9 and/or ΔbaPWV ≤ -350 cm/s. The supportive evidences including exercise stress test enhancing the diagnostic sensitivity in PAD patients whose ABI is between 0.9 – 1.0[8] by finding ABI < 0.9 after exercise by Stein R HI *et al.* This effect was made by the endothelium-derived vasodilatation enhanced during exercise is primarily due to its improved production of NO,[9,10] which was similar to the current study with the administration of sublingual NTG.[24] In addition, the increase of leg blood flow (velocity) with NTG is presumably less in patients with PAD than in subjects without PAD.[24] The differential responses of leg and forearm blood flow to NTG will change and shift the ABI value from 0.9 – 1.0 to < 0.9 in patients with PAD. In addition, another test with similar concept is the myocardial perfusion imaging administered with coronary vasodilators done for patients with suspected coronary disease who are unable to exercise. The vasodilator creates flow heterogeneity by causing a greater blood flow in normal coronary arteries and less flow in coronary arteries with significant stenosis which, in turn, enhances the severity of transmural myocardial ischemia (also known as coronary steal).[25,26] Therefore, the baPWV is presumably to have a greater drop after NTG over a stenotic lesion as compared to a non-stenotic site. In our study, the newly developed parameter, ΔbaPWV, which represents the difference of baPWV before and after NTG, helps to differentiate those with significant PAD. Our study showed that ΔbaPWV ≤ -350 cm/s could serve as a reliable cut-point to enhance the diagnosis of PAD.

Study limitation

The number of patients in our study population was relatively small, mostly due to the fact that the prevalence of this group with equivocal resting ABI values 0.9 – 1 is low. However, the findings of ABI and ΔbaPWV were consistent. The pilot study with the integrated algorithm with post-NTG ABI value and ΔbaPWV requires a large, prospective study in the future to confirm the accuracy of these diagnostic criteria.

Conclusions

For patients with resting ABI values between 0.9 – 1.0, the integrated algorithm using both ABI and the ΔbaPWV after sublingual NTG is a good measure for diagnosing PAD in patients with borderline PAD.

Conflict of Interest

There are no conflicts of interest.

Acknowledgements

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