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Clot Strength is Negatively Associated with Ambulatory Function in Patients with Peripheral Artery Disease and Intermittent Claudication

Karin Mauer^a, Andrew W. Gardner^a, Tarun W. Dasari^b, Julie A. Stoner^c, Steve M. Blevins^d, Polly S. Montgomery^a, Jorge F. Saucedo^{e,*}, and J. Emilio Exaire^{b,*}

Karin Mauer: karin-mauer-1@ouhsc.edu; Andrew W. Gardner: andrew-gardner@ouhsc.edu; Tarun W. Dasari: tarun-dasari@ouhsc.edu; Julie A. Stoner: julie-stoner@ouhsc.edu; Steve M. Blevins: steve-blevins@ouhsc.edu; Polly S. Montgomery: polly-montgomery@ouhsc.edu; Jorge F. Saucedo: jsaucedo@northshore.org

^aDepartment of Geriatric Medicine, University of Oklahoma Health Sciences Center (OUHSC), Oklahoma City, OK

^bDepartment of Cardiology, University of Oklahoma Health Sciences Center (OUHSC), Oklahoma City, OK

^cDepartment of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center (OUHSC), Oklahoma City, OK

^dGeneral Internal Medicine Section, University of Oklahoma Health Sciences Center (OUHSC), Oklahoma City, OK

^eDepartment of Cardiology, North Shore University Health System, Evanston, IL, USA

Abstract

Peripheral artery disease (PAD) is associated with exercise impairment and greater thrombotic risk. We investigated if clot formation and platelet aggregation assessed by thromboelastography and light-transmission aggregometry correlate with the severity of symptomatic PAD assessed by ambulatory function measures. We studied 40 symptomatic PAD patients in whom severity of disease was assessed using ankle brachial index, peak walking time, claudication onset time, peak

Corresponding author: J. Emilio Exaire, MD. Department of Cardiology, University of Oklahoma Health Sciences Center, 920 Stanton L. Young Blvd Room WP3010 Oklahoma City, OK 73104. Telephone (405) 271-4742 ext. 44744, fax (405) 271-2619, jose-exaire@ouhsc.edu.

*Equal contribution as senior author

Authorship Contributions: **KM**; 1) Contributions to conception and design, acquisition of data, analysis and interpretation of data; 2) drafting the article and revising it critically for important intellectual content; 3) final approval of the version to be published.

AWG; 1) Contributions to conception and design, acquisition of data, analysis and interpretation of data; 2) revising the article critically for important intellectual content; 3) final approval of the version to be published.

TWD; 1) Analysis and interpretation of data; 2) drafting the article; 3) final approval of the version to be published.

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SMB; 1) Acquisition of data; 2) revising the article critically for important intellectual content; 3) final approval of the version to be published.

PSM; 1) Acquisition of data; 2) revising the article critically for important intellectual content; 3) final approval of the version to be published.

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oxygen uptake, daily ambulatory activity and walking impairment questionnaire (WIQ) scores. Clot strength correlated negatively with peak oxygen uptake, peak walking time and WIQ distance and stair-climbing scores. Time to clot formation did not correlate with exercise parameters. Platelet aggregation was negatively correlated with WIQ distance score, and was positively correlated with peak walking time and peak oxygen uptake. In conclusion, clot strength and platelet aggregation correlated with objective and self-perceived ambulatory measures. PAD patients with more severe walking impairment may be likely to form stronger clots.

Keywords

Peripheral artery disease; clot strength; ambulatory function

Introduction

Peripheral artery disease (PAD) affects approximately 8 million Americans.¹ Patients with PAD have significant ambulatory limitations associated with intermittent claudication, and higher cardiovascular morbidity and mortality.¹⁻³

Platelet reactivity and clotting play a pivotal role in the genesis of arterial thrombotic events. Hence anti-platelet agents are considered an important therapeutic option in reducing adverse vascular outcomes in high risk patients.⁴⁻⁷ Several studies have reported increased platelet reactivity in patients with moderate to severe symptomatic PAD compared with healthy controls and platelet function appears to correlate with disease severity indicated by lower ankle brachial index (ABI) and worse symptoms.⁸⁻¹⁸ None of these studies correlated platelet aggregation with actual quantified measures of exercise performance and walking impairment. Although it has been shown that elderly patients with PAD form denser and poorly lysable fibrin clots when compared to healthy controls¹⁹, it is unknown if clot formation parameters correlate with the degree of exercise performance capacity in symptomatic PAD patients. We therefore sought to study this association in PAD patients with intermittent claudication.

Methods

Subjects

This analysis included 40 symptomatic patients with lower extremity PAD from a cohort of patients enrolled in a prospective, randomized, controlled clinical trial that compared a home-based exercise program with a supervised exercise program and its impact on exercise performance at the General Clinical Research Center at the University of Oklahoma Health Sciences Center from September 2004 to April 2007.²⁰ Patients who had intermittent claudication secondary to vascular insufficiency were included if they had a history of any type of exertional leg pain, ambulation during a graded treadmill test was limited by leg pain consistent with intermittent claudication, and an ABI ≥ 0.90 at rest or an ABI ≥ 0.73 after exercise. Patients were excluded for the following conditions: 1) absence of PAD (ABI ≥ 0.90 at rest and ABI ≥ 0.73 after exercise), 2) inability to obtain an ABI measure because of non-compressible vessels, 3) asymptomatic PAD determined from the medical history and

verified during the graded treadmill test, 4) use of cilostazol and pentoxifylline initiated within 3 months before investigation, because these drugs may improve the patient's ambulatory function²¹, 5) exercise tolerance limited by factors other than leg pain, and 6) active cancer, renal disease or liver disease.

The local institutional review board approved the study and only those that signed a written informed consent were included. Baseline demographic and clinical characteristics were collected on each patient in addition to a detailed physical examination.

Ambulatory and exercise performance assessment

Objective and self-reported measures of ambulatory and exercise performance were obtained at baseline before beginning an exercise program.

Self-reported physical activity level was assessed with the Baltimore Activity Scale for Intermittent Claudication (BASIC) questionnaire.²² Self-reported ambulatory ability was assessed using the Walking Impairment Questionnaire (WIQ) that evaluates the ability to walk at various speeds and distances and to climb stairs.²³ ABI was determined by obtaining the ankle and brachial systolic blood pressures.²⁰

Patients with intermittent claudication performed a progressive, graded treadmill protocol (2 mph, 0% grade with 2% increase every 2 min) until maximal claudication pain occurred. The claudication onset time (COT), the peak walking time (PWT) and peak oxygen uptake were obtained. COT was defined as the walking time at which the patient first experienced pain, and PWT was defined as the time at which ambulation could not continue because of maximal pain.²⁰ Peak oxygen uptake was measured as previously described²⁴, the ischemic window was expressed as an area under the curve of the resting ankle systolic BP and its recovery from a maximal graded treadmill test. Daily Ambulatory Activity (steps/day) was measured with a step activity monitor (StepWatch3™, OrthoInnovations, Inc., Oklahoma City, OK) during 7 consecutive days at baseline. None of the exercise interventions were included in the monitoring period. The monitor, attached to the right ankle above the lateral malleolus with elastic Velcro straps, continuously recorded the number of strides taken on a minute-to-minute basis.²⁰

Measures of clot formation and platelet aggregation

Whole blood samples were obtained at baseline. Clot formation parameters were measured by Thrombelastography (TEG). Within 2 h of drawing, citrated whole blood was activated with kaolin, calcium citrate was added to obtain the thrombin-induced clot. The TEG Hemostasis System (Haemonetics Corporation, Braintree, MA, USA) provided quantitative measurements of the physical properties of the clot, such as the clot strength (MA) and the time to clot formation (R). Both parameters were compared with a normal range of values provided by the test manufacturer, which is based on the lot of kaolin used to initiate the reaction (upper limit for MA is 69 or 71 mm, and lower limit for R is 2 or 5 min, based on the batch of kaolin reagent used for each patient).

Platelet aggregation was measured by Light Transmission Aggregometry (LTA). Within 3 h of drawing, the sample was centrifuged at 208 g for 10 min to obtain platelet rich plasma

(PRP) and at 1302 g for 15 min to obtain platelet-poor plasma (PPP). Platelet aggregation was measured using a Chrono-log 490-4D Aggregometer (Chrono-log Corporation, Havertown, PA, USA). PRP was stimulated with agonists that stimulate different pathways involved in platelet activation to distinguish a drug-related effect: thrombin receptor-activated peptide (TRAP) 2 and 20 $\mu\text{mol/L}$, arachidonic acid (AA) 0.5 mg/mL (1.5 $\mu\text{mol/L}$), and adenosine diphosphate (ADP) 5 and 20 $\mu\text{mol/L}$. Aggregation was expressed as the maximal percent change in light transmittance from baseline.

Statistical Analyses

A Spearman's rank correlation coefficient was used to quantify the association between measures of clot formation and platelet aggregation and PAD severity. Partial correlation coefficients were estimated after adjustment for potential confounding factors including smoking status, diabetes status, dyslipidemia and hypertension. A Wilcoxon rank sum test was used to compare the median clot formation measures between subgroups of patients defined by medication use. A two-sided 0.05 alpha level was used and a p-value ≤ 0.05 was considered significant. Given the exploratory nature of this project, no formal adjustment was made for multiple hypothesis testing among the exercise performance measures, clot formation, or platelet aggregation measures. Data were analyzed using SAS (SAS System for Windows, ver. 9.2, SAS Institute Inc., Cary, NC).

Results

Forty symptomatic PAD patients were included in this cross-sectional study. Baseline demographic and clinical characteristics are summarized in table 1.

The exercise performance characteristics are summarized in table 2. Patients in this study had considerable walking impairment typically seen in patients with claudication, as reflected by their BASIC total score, COT, PWT, peak oxygen uptake, ischemic window, WIQ scores and daily ambulatory activity.

Clot formation parameters and platelet aggregation measures are summarized in table 3. No significant differences were found in clot formation parameters, when comparing patients who were ($n=5$) and were not ($n=32$) taking warfarin for various medical conditions other than PAD, such as atrial fibrillation and valvular heart disease (data not shown). Twelve patients presented either increased clot strength or shorter time to clot formation when compared with the normal range provided by the manufacturer's controls. Ten patients (27%) had MA greater than the upper limit of normal and 2 patients (5%) had R of less than the lower limit of normal, while none of the patients had both parameters outside the established range.

The associations between measures of ambulatory function and clot formation and platelet aggregation, after adjustment for clinically significant risk factors (smoking, diabetes, dyslipidemia and hypertension), are shown in table 4. Clot strength (MA) was negatively correlated with peak oxygen uptake ($p=0.001$) and WIQ distance score ($p=0.050$), as well as WIQ stair-climbing score ($p=0.002$). Table 5 shows that these associations remained largely unchanged when only those patients who were not using warfarin and had available exercise

parameter measures (n=29) were considered (peak oxygen uptake $p=0.0002$ and WIQ stair climbing score $p=0.0069$). In addition, a negative association between MA and peak walking time was also found ($p=0.017$). Time to clot formation (R) was not significantly correlated with any of the ambulatory function measures even after excluding patients who were using warfarin as shown in tables 4 and 5.

In addition, several associations between measures of ambulatory function and platelet aggregation were found as shown in table 4. Platelet aggregation induced by AA was negatively correlated with WIQ distance score ($p=0.050$). This negative correlation remained among patients who were not using aspirin (n=10), even though it was not statistically significant ($r = -0.80$, $p=0.054$). On the other hand, platelet response to low and high dose TRAP was positively correlated with PWT ($p=0.003$ and $p=0.018$, respectively) and peak oxygen uptake ($p=0.025$ and $p=0.042$, respectively). Platelet aggregation induced by ADP did not correlate with any of the ambulatory function measures. Since P2Y₁₂ inhibition by clopidogrel can affect ADP-induced platelet aggregation^{21, 25}, when only patients not using clopidogrel (n=22) were analyzed, platelet aggregation was not associated with any of the ambulatory function measures.

Discussion

Our primary finding was a negative correlation between clot strength and both objectively measured exercise parameters (peak oxygen uptake and peak walking time), and self-perceived ambulatory function (WIQ distance and stair-climbing scores) in PAD patients with intermittent claudication. This suggests that clot strength may be lower in patients with better ambulatory function. Further analysis of only patients that were not using warfarin confirmed our initial results, and the established associations between clot strength and specific exercise parameters appeared to be stronger. On the other hand, time to clot formation was not significantly related to any exercise parameters, suggesting that the period of latency until the initial fibrin formation is not related to the patient's walking impairment.

This is the first study to compare quantitative clot formation parameters with validated measures of ambulatory function, as opposed to ABI alone, to assess both functional limitations and disease severity in PAD patients with claudication. Of particular importance, clot strength was correlated with exercise parameters but not with ABI in patients with intermittent claudication, suggesting that clot strength is more strongly related to the functional impairment of PAD than to the vascular severity of disease.

The negative correlations between clot strength and peak oxygen uptake (a measure of whole body oxygen uptake and aerobic fitness) and peak walking time imply that the clot is stronger in PAD patients that are less fit and walk less. In addition, the negative association between the clot strength and the WIQ distance and stair-climbing scores suggests that the clot is stronger among those who have severe self-perceived ambulatory impairment. Formation of a stronger clot in patients with worse walking impairment may contribute to the greater thrombotic risk seen in those with more severe disease. However, our study did not assess adverse vascular outcomes and this remains to be investigated in larger studies.

Clot strength is a measure of platelet contribution to clot formation through platelet-fibrin bonding. Since it is well established that PAD patients have increased platelet reactivity when compared with healthy controls⁸⁻¹⁸, our secondary objective was to evaluate any associations between platelet aggregation and validated measures of walking performance in PAD patients with claudication.

We found a negative correlation between platelet aggregation induced by AA and self-perceived ambulatory function reflected by the WIQ distance score. This indicates that patients who poorly perceived their ambulatory ability to walk at various distances at a constant speed had higher platelet aggregation triggered by this agonist. Although this relationship was not seen with COT and PWT, these measures are obtained during a standardized treadmill test and may not reflect perceived ambulatory tasks that are performed throughout the course of an entire day. Aspirin can block platelet aggregation triggered by AA^{21, 25, 26}, but this association remained among those patients who did not use this drug, even though the p-value was not statistically significant probably due to the small sample size.

The finding that symptomatic PAD patients with better exercise performance and aerobic fitness (measured by PWT and peak oxygen uptake) have greater TRAP-induced platelet aggregation is contrary to what we expected. Plausible causes for such discrepancy include but are not limited to: a) concomitant use of anti-platelet agents in some but not all patients, b) non inclusion of critical limb ischemia patients who are more likely to have increased platelet aggregation, and, c) in-vitro testing which may not be reflective of in-vivo mechanisms.

Opposing results in the association between platelet aggregation induced by different agonists and walking impairment in these patients may suggest that platelet aggregation is not the sole factor associated with morbidity and poor performance in PAD patients. Other clot forming parameters may also be relevant to disease progression and there may be other pathways through which platelets contribute to clot strength that were not measured in this study and deserve further investigation.

This study has inherent limitations. The associations between walking performance measures and platelet function tests from this cross-sectional design do not allow causality to be established. The present findings are also limited by the relatively small sample size, which may explain why some of the associations found are not very strong and some comparisons were not statistically significant. Results were not compared with age-matched controls, but the clot strength and time to clot formation were compared with a normal range of values provided by the test manufacturer. Correlation of walking performance measures with other tests that evaluate the coagulation cascade, such as bleeding time, may be needed to validate our findings. We recognize that many correlation coefficients were calculated, given the exploratory nature of this study, without adjustment for the inflated false positive error rate. Also, given the small sample size, no formal regression model building was performed to identify exercise performance characteristics independently associated with clot formation parameters or platelet aggregation. Therefore, our results are preliminary and further studies are needed to confirm our observations. Additionally, this study is limited to

PAD patients who have intermittent claudication, and may not be generalized to patients with less or more severe disease. The effect of exercise training on clot formation is currently being evaluated as a second phase of this study.

Conclusions

In PAD patients with intermittent claudication, clot strength and platelet aggregation correlated with objective and self-perceived ambulatory measures. PAD patients with more severe walking impairment may be likely to form stronger clots.

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Table 1
Clinical characteristics for symptomatic PAD subjects

Values are means $\pm$ standard deviations [Min, Max] and counts (percentages).

Characteristic	PAD Patients (n=40)
Age (years)	63 $\pm$ 10 [47, 82]
BMI (kg/m ²)	29 $\pm$ 6 [18, 42]
Ankle/brachial index	0.67 $\pm$ 0.19 [0.33, 1.13]
Male	23 (58%)
Caucasian	23 (58%)
Current smoking	19 (48%)
Diabetes	14 (35%)
Hypertension	34 (85%)
Dyslipidemia	33 (83%)
Obesity [BMI $\geq$ 30 kg/m ²]	13 (33%)
Aspirin	28 (70%)
Clopidogrel	13 (33%)
Coumadin	6 (15%)
Statin	28 (70%)

PAD, peripheral artery disease; %, percentage; BMI, body mass index

Table 2
Exercise performance characteristics for symptomatic PAD subjects

	n	Median [P25-P75]
BASIC Total Score	40	2 [1-5]
Claudication Onset Time (seconds)	38	118 [62 - 162]
Peak Walking Time (seconds)	38	262 [167 - 449]
Peak Oxygen Uptake (ml/kg/min)	37	12.59 [10.6 - 14.11]
Ischemic Window (min/mmHg/m)	38	-0.65 [-1.12 - -0.29]
WIQ Distance (%)	40	17 [5 - 57]
WIQ Speed (%)	40	32 [11 - 50]
WIQ Climbing (%)	40	21 [8 - 67]
Daily Ambulatory Activity (strides/day)	36	3133 [1988 - 3906]

P25, 25th percentile; P75, 75th percentile; BASIC, Baltimore Activity Scale for Intermittent Claudication; WIQ, Walking Impairment Questionnaire; %, percentage

Table 3
Clot formation and platelet aggregation measures for symptomatic PAD subjects

Clot Formation Parameter	n	Median [P25-P75]
Clot strength, MA (mm)	37	67 [63 – 71]
Time to clot formation, R (min)	37	7 [6 – 9]
Maximum platelet aggregation (%)		
TRAP 2	39	74 [66 – 82]
TRAP 20	40	81 [77 – 86]
AA 1.5	39	4 [3 – 73]
ADP 20	40	67 [58 – 78]
ADP 5	40	58 [44 – 67]

P25, 25th percentile; P75, 75th percentile; %, percentage; TRAP, thrombin receptor-activated peptide; AA, arachidonic acid; ADP, adenosine diphosphate

Table 4
Association between PAD severity and clotting measures and platelet aggregation (n=40)

Data are summarized as the partial Spearman rank correlation coefficient (r) and p-value (p). Analyses were adjusted for smoking, diabetes, dyslipidemia and hypertension.

	Clot forming parameter or platelet aggregation measure											
	MA	R	AA 1.5	TRAP 2	TRAP 20	ADP 20	ADP 5					
Exercise parameter	r	p	r	p	r	p	r	p	r	p	r	p
ABI	0.01	0.14	0.19	0.05	0.20	0.04	-0.09	0.62				
BASIC Total Score	-0.06	0.11	-0.13	0.29	0.18	0.22	0.19					
	0.77	0.59	0.48	0.13	0.34	0.24	0.30					
Claudication Onset Time (seconds)	0.04	0.17	-0.19	-0.12	-0.01	-0.35	-0.26					
	0.85	0.40	0.31	0.54	0.97	0.052	0.16					
Peak Walking Time (seconds)	-0.29	0.09	-0.02	0.52	0.42	0.14	0.21					
	0.14	0.66	0.90	0.003	0.018	0.47	0.25					
Peak Oxygen Uptake (ml/kg/min)	-0.59	-0.03	-0.05	0.41	0.37	0.06	0.02					
	0.001	0.88	0.80	0.025	0.042	0.75	0.90					
Ischemic Window (min/mmHg/m)	0.17	-0.11	-0.08	0.31	0.18	0.27	0.32					
	0.38	0.56	0.67	0.10	0.33	0.15	0.084					
WIQ Distance Score (%)	-0.37	0.01	-0.36	0.27	0.13	-0.03	0.06					
	0.050	0.95	0.050	0.15	0.50	0.86	0.76					
WIQ Speed Score (%)	-0.27	-0.15	-0.30	0.24	0.10	-0.03	0.09					
	0.17	0.45	0.10	0.21	0.58	0.86	0.63					
WIQ Stair Climbing Score (%)	-0.56	-0.09	-0.29	0.27	0.18	0.07	0.11					
	0.002	0.66	0.12	0.15	0.34	0.69	0.54					

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	Clot forming parameter or platelet aggregation measure						
	MA	R	AA 1.5	TRAP 2	TRAP 20	ADP 20	ADP 5
Daily Ambulatory Activity (strides/day)	-0.16 0.41	-0.18 0.35	-0.22 0.24	0.22 0.25	0.33 0.068	0.04 0.83	0.06 0.76

ABI, ankle brachial index; BASIC, Baltimore Activity Scale for Intermittent Claudication; WIQ, Walking Impairment Questionnaire; %, percentage; MA, clot strength; PAD, peripheral artery disease; R, time to clot formation; AA, arachidonic acid; TRAP, thrombin receptor-activated peptide; ADP, adenosine diphosphate

Table 5
Association between PAD severity and clotting measures among patients not taking warfarin (n=29)

Data are summarized as the partial Spearman rank correlation coefficient (r) and p-value (p). Analyses were adjusted for smoking, diabetes, dyslipidemia and hypertension.

	Clot forming parameter	
	MA	R
Exercise parameter	r	r
	p	p
ABI	0.21	-0.078
	0.32	0.71
BASIC Total Score	0.0220	0.076
	0.92	0.72
Claudication Onset Time (seconds)	0.0520	0.11
	0.81	0.61
Peak Walking Time (seconds)	-0.47	0.16
	0.017	0.43
Peak Oxygen Uptake (ml/kg/min)	-0.68	-0.065
	0.0002	0.76
Ischemic Window (min/mmHg/m)	0.0320	-0.058
	0.88	0.78
WIQ Distance Score (%)	-0.33	-0.067
	0.10	0.75
WIQ Speed Score (%)	-0.27	-0.16
	0.20	0.44
WIQ Stair Climbing Score (%)	-0.53	-0.21
	0.0069	0.30
Daily Ambulatory Activity (strides/day)	-0.17	-0.21
	0.42	0.32

ABI, ankle brachial index; BASIC, Baltimore Activity Scale for Intermittent Claudication; WIQ, Walking Impairment Questionnaire; %, percentage; MA, clot strength; PAD, peripheral artery disease; R, time to clot formation