EVALUATING IMPROVEMENT ACROSS REHABILITATION IN PERIPHERAL ARTERY DISEASE PATIENTS: A COMPARISON BETWEEN THE 6 MINUTE WALK TEST AND MAXIMAL TREADMILL GRADED EXERCISE TEST

A Manuscript Style Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Clinical Exercise Physiology

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College of Science and Health
Clinical Exercise Physiology

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EVALUATING IMPROVEMENT ACROSS REHABILITATION IN PERIPHERAL ARTERY DISEASE PATIENTS: A COMPARISON BETWEEN THE 6 MINUTE WALK TEST AND MAXIMAL TREADMILL GRADED EXERCISE TEST

By Charles Schauer

We recommend acceptance of this thesis in partial fulfillment of the candidate's requirements for the degree of Master of Science in Clinical Exercise Physiology

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Perforated artery disease (PAD) is a debilitating disease that increases mortality and negatively affects quality of life. The primary non-invasive therapeutic step after diagnosis is supervised exercise therapy (SET). A commonly used tool to measure outcomes in PAD patients is a symptom limited maximal graded exercise test (GXT) performed on a treadmill. A possible alternative to the GXT is the 6-minute walk test (6MWT). Patients with diagnosed PAD completed a symptom-limited maximal treadmill GXT and 6MWT pre and post SET. Primary outcome measures for the tests included GXT total walking time and 6MWT total distance. Four patients (3 male, 1 female) completed the study. No statistically significant difference was observed for the treadmill GXT or 6MWT from pre to posttest (p >0.05). Percent change from pre to post for the treadmill GXT and 6MWT were compared against one another. No significant difference was found between the percent change on the two tests (p>0.05). There was a moderate correlation between the treadmill GXT and 6MWT (r = 0.73). The GXT and 6MWT showed similar trends in improvement from pre to post SET. The present study supports the use of either the treadmill GXT or 6MWT to assess outcomes in PAD patients.
ACKNOWLEDGEMENTS

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I would like to sincerely thank my thesis advisor Dr. Carl Foster. Your help and input throughout the study and writing process has been imperative to its completion. Dr. John Porcari thank you for efforts and help with contract approval at the different sites during the study. Your efforts have not gone unnoticed. I would also like to thank Kim Radtke for being on my thesis committee.
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INTRODUCTION

Peripheral artery disease (PAD) affects millions of people and its incidence is expected to rise with an aging population (Aboyans et al., 2012; Bronas et al., 2009; Foley, Armstrong, & Waldo, 2016; McDermott et al., 2014). Peripheral artery disease is linked with increased mortality and morbidity due to its presence being indicative of systemic atherosclerotic disease (Bronas et al., 2009; Foley et al., 2016). The disease process is initially caused by endothelial injury and dysfunction leading to plaque growth in the peripheral arteries (Muir, 2009). Just as coronary artery disease is caused by endothelial damage and dysfunction leading to plaque growth in the coronary arteries, this ultimately leads to the development of atherosclerotic plaque and to narrowing of blood vessels due to plaque accumulation within the peripheral arteries (American Association of Cardiovascular & Pulmonary Rehabilitation (AACVPR), 2013; Gardner, Montgomery, & Parker, 2012; Gardner, Skinner, Cantwell, & Smith, 1991a; Gommans et al., 2016; Treat-Jacobson, Henly, Bronas, Leon, & Henly, 2011). Narrowing of peripheral arteries increases resistance to blood flow, resulting in skeletal muscle ischemia particularly during exertion. The primary symptom as a result of skeletal muscle ischemia is claudication, which typically presents in the form of pain and/or cramping in the calf muscles (AACVPR, 2013; Gardner et al., 2012; Gommans et al., 2016; Montgomery, & Gardner, 1998; McDermott et al., 2014; Muir, 2009). Though claudication is the most commonly associated symptom with PAD, most patients (upwards of 40%) are asymptomatic (Alahdab et al., 2015; Foley et al., 2016; McDermott et
Claudication is intermittent and is typically brought on by increased metabolic demand within the muscles of the lower extremities and resolves with rest (AACVPR, 2013; Nicolaï et al., 2009). Those who are asymptomatic may still have reduced function, decreased quality of life (QOL), and higher cardiovascular mortality compared to those without claudication (Alahdab et al., 2015; McDermott et al., 2014). The pain associated with increased activity is often limiting (forcing the termination of activity) and negatively impacts an individual’s ability to perform activities of daily living and reduces their quality of life (Gardner, Skinner, Vaughan, Bryant, & Smith, 1992; McDermott et al. 2014; Montgomery, & Gardner, 1998; Treat-Jacobson et al., 2011).

The ankle brachial index (ABI) is the standard laboratory tool used to diagnose PAD and determine the severity of disease (Gardner, & Afaq, 2008; Gardner et al., 1991a; Riebe, Ehrman, Liguori, & Magal, 2018). The ABI is a noninvasive method for measuring the flow restriction due to systemic atherosclerosis. An ABI measurement of \( \leq 0.90 \) or a decrease with exertion of \( >0.15 \) is diagnostic for PAD (Aboyans et al., 2012; Foley et al., 2016; Gardner, Waldstein, Montegomery, & Zhao, 2016; Gommans et al., 2016; Riebe et al., 2018). ABI sensitivity is between 94% and 97% and increases if used in combination with an exercise test (Foley et al., 2016). Symptoms usually start to present at an ABI measurement of \( <0.8 \) (Gardner & Afaq, 2008).

The primary non-invasive therapeutic step after diagnosis is Supervised Exercise Therapy (SET) (Gardner & Afaq, 2008). Supervised exercise therapy and walking are the primary conservative treatment methods for treatment of PAD (Gommans et al., 2016; Treat-Jacobson et al. 2011). Supervised exercise therapy has been shown to be more effective than revascularization via stent and standard medical care (medication and
home walking) alone (Murphy et al., 2012). Supervised exercise therapy, in combination with medication, yields the greatest improvements in walking distance compared to SET or medication in isolation (Gardner & Afaq, 2008). Supervised exercise therapy in patients with PAD dates back to 1966 when the first randomized controlled trial showed that exercise training improved treadmill walking tolerance (Regensteiner, Gardner, & Hiatt, 1997). Supervised exercise therapy for PAD has been recognized by the American College of Cardiology and American Heart Association based on class IA evidence (highest level of evidence) (AACVPR, 2013; Burns, Rohrich, & Chung, 2011; Gardner et al., 2012). Supervised exercise therapy has been shown to be effective for decreasing pain associated with intermittent claudication (IC) and increasing QOL (Foley et al., 2016; Gommans et al., 2016). In May of 2017, the Centers for Medicare & Medicaid Services started to reimburse SET for symptomatic PAD patients (Centers for Medicare & Medicaid Services, n.d.). The most frequently used exercise modality in SET is treadmill walking (AACVPR, 2013; Regensteiner et al., 1997). Patients walk until they have claudication pain, then stop and rest until the pain dissipates. Once the pain is completely gone, the patient starts walking again until they again reach claudication pain (Bronas et al., 2009; Durstine et al., 2016; Regensteiner et al., 1997). The most improvement in increased walking duration and reduction of IC pain is seen within the first two months of SET (Gardner et al., 2012).

The standard tool used to assess PAD outcomes is a maximal treadmill graded exercise test (GXT) (Durstine et al., 2016; Gardner & Afaq, 2008; Gommans et al., 2016; McDermott et al., 2008; Montgomery, & Gardner, 1998; Nicolaï et al., 2009; Treat-Jacobson et al., 2011). A GXT, compared to a single stage test, is used because it has
been shown to be more reliable at eliciting symptoms and fatigue (Gardner et al., 1991a; Hiatt et al., 2014). There are two commonly used treadmill GXT protocols for PAD, the Gardner-Skinner and the Hiatt protocols (Gardner et al., 1991a; Gardner et al., 1992; Hiatt et al., 1988; Hiatt, Rogers, & Brass, 2014). Both use a constant increase in grade between stages but the percent increase in grade between tests is different; the Gardner-Skinner protocol uses a 2% increase in grade every stage; whereas, the Hiatt uses 3.5% increase in grade. The Gardner Skinner protocol uses 2-minute stages whereas the Hiatt protocol uses 3-minute stages (AACVPR, 2013; McDermott et al., 2014; Nicolaï et al., 2009). The Gardiner-Skinner protocol uses a constant speed of 2 miles per hour (mph) throughout the test (AACVPR, 2013; McDermott et al., 2014; Nicolaï et al., 2009). The Hiatt protocol starts at 2 mph for stage one and increase to 3 mph and stays constant throughout the remainder of the test (Hiatt et al., 1988). Handrail support during the treadmill GXT is discouraged and is only allowed for balance (Gardner et al., 1991b; Hiatt et al., 2014; Regensteiner et al., 1997). Handrail support has been shown to reduce the metabolic demand of walking, to delay onset of claudication pain, and to affect hemodynamic measurements (Gardner et al., 1991b; Gardner et al., 1992; Regensteiner et al., 1997).

The six-minute walk test (6MWT) is widely used as a means of assessing clinical outcomes after treatment in other populations such as chronic obstructive pulmonary disease and congestive heart failure (Bellet, Adams, & Morris, 2012; Cahan et al., 1999; Ng et al., 2012). The 6MWT evaluates severity of IC, functional, and aerobic capacity (Gardner et al., 2018). Additionally, the 6MWT is able to predict all-cause mortality and loss of mobility (McDermott et al., 2014). Six-minute walk distance has been shown to
have a direct relationship with PAD severity (Gardner & Afaq, 2008). McDermott et al. (2014) and Perera, Mody, Woodman, & Studenski (2006) have defined a small meaningful change as 20 meters and large change as 50 meters.

Cahan et al. (1999) has reported that the 6MWT is a reliable means of assessing functional impairment in IC patients. Furthermore, the study demonstrated that 6-minute walk distance is associated with ABI measurements and distance to onset of claudication using the treadmill (Cahan et al., 1999). Chen et al. (2017) agreed that the 6MWT is reliable in evaluating walking endurance within the PAD population. The 6MWT has class IIb evidence for its use as an objective assessment of functional limitation related to IC and outcome evaluation after SET (Burns, 2011; Chen et al., 2017). Bellet et al. (2012) noted that the 6MWT has strong evidence of responsiveness to changes in clinical status. There is moderate evidence for reliability of the 6MWT. A learning effect of 2% to 8% in repeated 6MWTs is known to exist (Bellet et al., 2012). However, Bellet et al. (2012) used subjects with a diagnosis of coronary artery disease (CAD). Though PAD and CAD have the same underlying disease process there are notable differences in how the diseases present themselves symptomatically. For example, CAD patients can experience angina (chest discomfort) with exertion; whereas, PAD patients typically experience claudication with exertion. More recently, McDermott et al. (2014) suggested that a learning effect does not exist with repeated testing 6MWT with PAD patients. Treadmill performance also has a learning effect (McDermott et al., 2014). This can be problematic when using the treadmill as the primary modality in SET because the patient is being trained to the outcome measure and determining whether an improvement was due to a training effect or not can be hard to discern (McDermott et al., 2014). The
treadmill also does not represent walking in daily life. In older adults, treadmill walking elicited higher heart rates (HR) than corridor walking at the same speeds (McDermott et al., 2014). The 6MWT has been shown to more closely represent daily activity compared to treadmill testing (Fokkenrood et al., 2015; Gardner et al., 2018; McDermott et al., 2008; McDermott et al., 2014; Nicolaï et al., 2009). Conversely Hiatt et al. (2014) states that the 6MWT has minor utility in the clinical setting. In a study with heart disease patients the 6MWT showed poor replicability (Hiatt et al., 2014).

Peripheral arterial disease affects the older adult population and negatively affects quality of life. A primary therapy for PAD should include SET, and additionally addresses education, risk factor modification, and regular exercise, whereby the primary modality is walking. The 6MWT may be a potential test to use in place of the standard max treadmill GXT for assessing clinical outcomes in PAD patients after SET. The purpose of this study was to determine if the 6MWT can be used to assess PAD patient outcomes after SET in place of the treadmill GXT. Based on current research we hypothesized that the 6MWT is a viable alternative to treadmill GXT in assessing outcome in the PAD population.
METHODS

Subjects

Patients with a diagnosis of symptomatic PAD were recruited within the first week of starting phase II SET. Patient demographic information was recorded and included cardiovascular risk factors (smoking, obesity, diabetes, hypertension, hyperlipidemia, age, family history, and sedentary lifestyle), gender, and medications. The methods of this study were reviewed and approved by the University of Wisconsin Institutional Review Board (IRB) prior to conducting the study. The study was also reviewed and approved by the IRB at Gundersen Health Systems. Written informed consent to perform both the symptom limited max treadmill GXT and 6MWT pre and post SET was provided by each patient prior to testing.

Procedures

Supervised exercise therapy for the study included 24 sessions. Each patient attended SET a minimum of two times per week with most attending three times each week during the study (approximately 2 months). Each session was 30 to 60 minutes in length and the primary exercise modality was treadmill walking. Treadmill walking consisted of repeated bouts of intermittent walking; whereby, the patient walked to maximal claudication, then passively recovered (sitting in chair) until the pain subsided (Bronas et al., 2009; Durstine et al., 2016; Regensteiner et al., 1997). Intensity (speed and grade) of treadmill walking was individualized to each patient.
Each patient performed a symptom limited max treadmill GXT using the Gardner-Skinner or modified Gardner-Skinner protocol and a 6MWT pre and post SET. The order of these tests was randomized for each patient. The tests (treadmill GXT and 6MWT) were conducted by a trained exercise physiologist. During each test a rating of perceived claudication (RPC) scale from zero to four was used to assess the severity of claudication pain (AACVPR, 2013; Riebe, et al., 2018). Zero represents no claudication pain. One represents noticeable pain (onset of claudication). Two represents moderate claudication pain. Three represents intense claudication pain but the patient can continue. Four represents severe pain and cannot continue (max claudication). Patients were given at least two but no more than seven days between tests (GXT and 6MWT) both pre and post SET. Measurements and test procedures were the same for each test (GXT and 6MWT) pre and post SET period.

Prior to the max treadmill GXT, the test administrator explained the study and test procedures. Additionally, the test administrator obtained a resting HR using a 12-lead electrocardiogram (ECG) (used for all HR measures for the GXT) and resting blood pressure (BP) using a sphygmomanometer and stethoscope (used for all BP measurements for the GXT). An ECG was used instead of a HR monitor because PAD patients most likely have underlying CAD (Hiatt, Rogers, & Brass, 2014). As a result, the ECG was used for safety of the patient and to monitor any significant findings before, during, and after the test. The Gardner-Skinner or modified Gardner-Skinner protocol was used for the GXT. For the standard Gardner-Skinner test, treadmill speed started at 2 mph and remained at 2 mph for the entire test. A modified Gardner-Skinner protocol was used for low level individuals. The modified protocol started at 1.5 mph and remained at
1.5 mph for the entire test. Stages for both protocols were 2 minutes in length, the grade started at 0% and increased every stage by 2%. Patients walked until they reached max claudication pain (rating of four on the RPC scale). During the GXT, the test administrator informed the patient prior to the start of a new stage. Measurements that were obtained during the symptom limited max treadmill GXT included BP, HR, total time walked, and RPC (using a zero to four scale). Blood pressure was taken 1-minute into each stage. Heart rate and RPC were measured at the end of each stage. The test ended once the patient reached a RPC score of four and could no longer continue. Immediately after the GXT, the patient sat in a chair at which point HR and BP were measured. Then the patient rested for 5 minutes. After 5 minutes, HR and BP were measured again and, in the absence of contraindication, the test was concluded.

If the 6MWT was the patient’s first initial test, the test administrator explained the study and test procedures. Additionally, the test administrator read the standardized instructions for the 6MWT to the patient found in the American Thoracic Society guidelines (American Thoracic Society (ATS), 2002). Afterwards the test administrator obtained a resting HR using a radiotelemetric HR monitor (Polar Electro Oy, Port Washington, NY) or a pulse oximeter (used for all HR measures for the 6MWT). In addition, BP was measured at rest using a sphygmomanometer and a stethoscope (used for all BP measures for the 6MWT). A set of standardized guidelines for administering the 6MWT were followed which included no warmup prior to testing and no vigorous exercise within 2 hours of testing. The patient was to use their normal walking aid(s) during the test (e.g. cane or walker). The test administrator did not walk in front or beside the patient so as to not encourage pacing, and a 100-foot hallway was used (AACVPR,
Ng et al. (2012) has shown that turning direction when the patient reaches the end of the hallway does not impact HR or ratings of perceived exertion. After the rest period, the patient stood up and the test began once the patient started walking. During the 6MWT did not talk to the patient except for standardized prompts that were read from every minute and the last 15 seconds of the test to provide the patient with the time remaining and standardized encouragement. Additionally, the patient was allowed to stop and rest during the test, but the time still continued. Measurements that were obtained during the 6MWT included HR, obtained at every minute during the test and RPC (using a zero to four scale) were the patient told the test administrator when their RPC status changed. In addition, the test administrator recorded the time for every 100-foot interval. If at any time during the 6MWT the patient decided to stop and rest, the time when they stopped and started walking again was recorded. Immediately after the 6MWT, the patient sat in a chair and HR and BP were measured. Then the patient rested for 5 minutes. After 5 minutes, HR and BP were measured again, and the test concluded.

**Statistical Analysis**

Descriptive statistics were used to describe the patient populations age. Percent change from pre to post testing for the treadmill GXT and 6MWT were compared using a paired t-test. Correlative statistics were used to determine whether percent change between tests were similar. Significance (p) was set at the .05 level.
RESULTS

A total of eight patients enrolled in the study. Four of the eight completed the entire study. Results only include patients who completed the entire study. Of the patients that completed the study, there were three males and one female. Average age was 68 years old. Patient 1’s risk factors where hypertension (HTN), hyperlipidemia (HLD), diabetes, obesity, and age. Patient 2’s risk factors where HTN, HLD, diabetes, and age. Patient 3’s risk factors where HTN, HLD, family history, and age. Patient 4’s risk factors where HTN, HLD, diabetes, obesity, smoker, and age. All patients in the study exhibited a normal blood pressure and HR response to exercise.

No statistically significant difference was observed for the treadmill GXT or 6MWT from pre to posttest (p >.05) (Table 1). No significant difference was found between the change on the two tests (p >.05) (Table 1). No significant difference was found between percent change from pre to post for the treadmill GXT and 6MWT (p >.05) (Table 1). There was a moderate correlation between the treadmill GXT and 6MWT (r = 0.73).

Table 1. Treadmill GXT and 6MWT primary outcomes

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<th>Post-test</th>
<th>% change pre to post</th>
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<td>GXT total time (minutes:seconds)</td>
<td>6:50 ± 0.591</td>
<td>10:41 ± 3:382</td>
<td>57 ± 50.1</td>
</tr>
<tr>
<td>6MWT total distance (feet)</td>
<td>1150 ± 241.8</td>
<td>1222 ± 276.2</td>
<td>8 ± 5.9</td>
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Values represent mean (SD) and percentages.
Treadmill time between initial and final where compared. It was found that patient one, three and four improved, while patient two declined (Figure 1 and Figure 3). During the final treadmill test patient one, three, and four were able to walk the same or further at any given RPC relative to their initial treadmill test. Patient two decreased in their ability to walk at all RPC’s relative to their initial treadmill test.

![Figure 1. GXT total time pre and post SET](image)

During the 6MWT, all patients were able to walk further during their final test compared to their initial (Figure 2 and Figure 3). Patient one had the greatest increase in walking distance from initial to final compared to patient two, three, and four, 150 feet (ft.), 49 ft., 18 ft., and 70 ft., respectively. Patient one took one less stop during their 6MWT, going from two stops to one. Patient two took one less stop during their 6MWT.
going from one to zero. Patient three and four’s number of stops during the 6MWT stayed the same from initial to final, at zero stops during the test.

Figure 2. 6MWT total distance traveled pre and post SET

Figure 3. Change in 6MWT distance versus change in GXT time

\[ r = 0.73 \]
DISCUSSION

The primary purpose of the study was to determine whether the 6MWT can be used in place of treadmill GXT to assess PAD patient outcomes after SET. To determine this, percent change from pre to post for both tests were compared. If both tests showed similar improvements across SET, then it could be assumed that either test could be used to assess outcomes in PAD patients. On the other hand, if the tests did not show similar improvement this would mean that one test may be more sensitive to changes from an intervention than the other. Additionally, it may also mean that the validity of one test in PAD patients is superior to the other.

Results showed that percent change from pre to post for the GXT and 6MWT were not significantly different. However, when looking at average increase from pre to post there was a notable difference between tests. The GXT was 58% compared to 6% for the 6MWT. This finding is similar to Hiatt, Rogers, and Brass (2014) where after an exercise intervention the resultant increase was 52% for the GXT and 6.4% for the 6MWT. This suggest that the GXT has a greater sensitivity to change in PAD patients (Hiatt, Rogers, & Brass, 2014). Additionally, treadmill validity in PAD patients for assessing functional capacity and QOL is well documented whereas the 6MWT is not (Hiatt, Rogers, & Brass, 2014).

Results from the present study showed a moderate correlation between the treadmill GXT and 6MWT ($r = 0.73$). This shows that both tests showed a trend in
improvement across SET. However the degree of improvement between tests was not similar, 58% for the GXT versus 6% 6MWT. The present studies correlation was higher than another study showing a weak correlation between the two tests (Hiatt, Rogers, & Brass, 2014). The moderate correlation and the different percent change from pre to post SET between the two tests suggests that one test may be better than the other.

Significant differences from pre to post testing were not observed in either the treadmill GXT or 6MWT. There was a trend in improvement that was noticed for patients 1, 3 and 4 in the GXT and for all patients in the 6MWT. If the SET length was increased from 24 sessions to 36 or 48 session, statistical significance might have been observed. The only patient who did not improve from pre-SET to post was patient 2 and their treadmill GXT time. Alternatively, patient 2 did improve on the GXT.

Only half of the total patients enrolled in the study completed. This shows that adherence to SET for PAD patients is poor. One potential reason for this is the structure of SET. The most effective method for SET is intervals where the patient walks on a treadmill until they reach near maximal or maximal claudication pain and then rest. These bouts of walking and rest are repeated (Bronas et al., 2009; Durstine et al., 2016; Regensteiner et al., 1997). Walking to near maximal or maximal claudication pain is challenging and unpleasant for patients. As a consequence, this could impact adherence to SET. Additionally, if patients do participate in SET they may not push themselves as hard which could impact how much they improve. One method to help with adherence and to ensure patients are pushing themselves hard enough is encouraging the patient throughout SET. Other factors that could have contributed to the low adherence is economic stress or the need to return to work.
CONCLUSION

The present study supports the use of the symptom limited maximal treadmill GXT but not the 6MWT to assess outcomes in PAD patients. The treadmill GXT was more sensitive to changes in improvement and as a result is better able to detect changes in improvement compared to the 6MWT. There are key differences between the tests that should be noted. The treadmill GXT is a maximal test whereas the 6MWT is submaximal. The treadmill GXT may not be as representative of daily walking tolerance as the 6MWT. Studies have suggested that both tests may have a learning effect (Bellet et al., 2012; McDermott et al., 2014).
LIMITATIONS

There are limitations to the present study. First the study size only included four patients and was conducted at only one site. The design of the study was multi-center. However, difficulty in patient referral for SET and administrative complications between institutions presented significant barriers to recruiting subjects. Supervised exercise therapy length was relatively short. Though most improvement occurs within the first two months, there is improvement seen up to four months (Gardner et al., 2012). A learning effect for both tests has been noted (Bellet et al., 2012; McDermott et al., 2014). With the 6MWT, the patient only completed one test initially. To rule out a learning effect two or three tests could have helped to eliminate a potential learning effect with both tests. Additionally, the treadmill GXT, the post test could have been impacted by a learning effect because during SET the primary modality of exercise was treadmill walking. As a result, the patient was trained to the test outcome and could have affect the degree of improved.


APPENDIX A
INFORMED CONSENT
Title: Evaluating Improvement Across Rehabilitation in Peripheral Artery Disease Patients: A Comparison Between the 6 Minute Walk Test and Max Treadmill Graded Exercise Test

Principal Investigator: Brant Stevermer

You are being asked to participate in a medical research study. Your participation in this study is voluntary. This means that you may or may not choose to take part. To decide whether or not you want to be part of this research, the risks and possible benefits of the study are described below so that you can make an informed decision on whether you want to participate. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study. This form explains how your medical information will be used and who may see it. You may have a copy of this form to review or to ask advice from others.

Please read this document carefully. The study staff will answer any questions you may have. You may discuss your decision with your friends and family. This form may contain words that you do not understand. Please ask the study staff to explain the words or information that you do not understand. After reading the consent form, if you would like to participate, you will be asked to sign this form. You will be given a signed copy of your consent form to take home and keep for your records.

Background
Peripheral artery disease (PAD) is a debilitating disease that negatively affects quality of life. After diagnosis of PAD, the next step in treatment is recommendation of supervised exercise therapy (SET). Before starting SET, patients complete a baseline max treadmill graded exercise test (GXT). After completion of SET, the patient will complete the same test to assess treatment outcome. The standard tool used to measure outcomes in PAD patients is a max treadmill GXT. A possible alternative to the GXT is the use of the 6-minute walk test (6MWT).

The 6MWT is used to assess treatment outcome in different populations including chronic obstructive pulmonary disease and congestive heart failure. In addition, the 6MWT is more closely associated with daily activity and functional capacity compared to the treadmill GXT. This suggests that the 6MWT could be used as an outcome measure in PAD patients. However, no study has performed an experiment in PAD patients comparing the GXT and 6MWT to evaluate outcome after treatment.

Purpose
The purpose of this study is to determine if measurements from the 6-minute walk test correlate with the standard treadmill walking test.

What happens during the study?
The 6-minute walk test and treadmill walking test will be administered by a trained exercise physiologist. The research study will be conducted by a University of Wisconsin-La Crosse (UWL) graduate student under the direction of a UWL faculty advisor and the supervision of a Gundersen Health System exercise physiologist. Your participation in the study will consist of a 6-minute walk test and treadmill walking test (in a randomized order) within one week of starting cardiac rehabilitation and after 24 sessions (approximately 2 months) of cardiac rehabilitation. Each test will last approximately 45 to 60 minutes.

The treadmill walking test will gradually increase in difficulty as the test progresses. The increase in difficulty will continue until you feel and verbally report to the test administrator any symptoms of fatigue, shortness of breath, light headed, chest discomfort or until you reach a score of four (maximal claudication, and cannot continue) on the rating of perceived claudication scale. It is your right to discontinue the test at any point and to report any symptoms you experience immediately to the test administrator.

Prior to both treadmill walking tests you will have 10 adhesive electrodes attached to your chest for the duration of the test. Your heart rate and blood pressure will be measured by the test administrator before, during (once every 2 minutes), and after the test. Additionally, during the test you will be asked what your rating of perceived claudication is on a scale of zero to four and will answer (verbally or nonverbally) to the best of your ability.

The 6-minute walk test will require you to walk as fast and as safely as you are able to for 6 minutes. You are allowed to use usual walking aid(s) (e.g. walker or cane) during the test. You will be allowed to stop and rest at any point during the test. The test will continue until either the 6 minutes are up, when you report any symptoms, or you request to end the test.

If you agree to participate, before any information is collected, you will be asked to review and sign this informed consent document. If you are physically unable to sign this informed consent document, you may designate your legally authorized representative (LAR) to sign it for you.

**Are there any potential risks or side effects?**
Fatigue, shortness of breath, and muscle soreness are possible as a result of participating in the study. The risk for cardiac events (e.g. heart attack, ventricular fibrillation, and hospitalization) during exercise testing are very low (6 cardiac events per 10,000 tests). The test will be stopped immediately upon any complications or when you request to stop. The test administrator will be trained in CPR and trained staff will be nearby during the tests in case of an emergency. The test administrator will be knowledgeable of emergency procedures for the site location.

**Are there benefits?**
There is no guarantee that you will personally benefit from participating in this study. Taking part in this study may or may not improve your condition. The information obtained from the study will help to evaluate a test that will aid in determining the outcome of treatment for peripheral artery disease.

**Are there any costs to participate in the study?**
You are invited to participate in this study at no cost to you.
**Is there any compensation?**
You will not be compensated for your participation in the study.

**What if I am injured during the course of the study?**
If you get ill or injured while taking part in this study, your primary investigator will help get you medical treatment. However, neither Gundersen Clinic, Ltd. nor Gundersen Lutheran Medical Center, Inc. will pay for expenses incurred. The only exception is if it is proven that your injury or illness is directly caused by inappropriate medical care.

**Voluntary participation/withdrawal**
Your decision to take part in this study is voluntary. You may decide not to take part, or to stop taking part, at any time without penalty or loss of benefits to which you are otherwise entitled. Your ongoing medical care will not be affected by your decision to be in this study or to withdraw from the study. Any information obtained prior to withdrawal from the study will be included in the database for this study. If you agree to participate and later change your mind, call Brant Stevermer at 608-782-7300.

The primary investigator may stop your participation in the study without your consent for any of the following reasons:
- Failure to follow the investigator’s instructions
- A serious adverse event which may require evaluation
- If the investigator feels it is in the best interest of your health and welfare

**Will my medical information be kept private?**
Your identity and the information obtained will remain confidential to the extent of the law. However, the research team and the Human Subjects Committee/IRB may review your medical records to verify study related information and the signed consent form. The results of this study may also be published in a scientific journal or presented at a medical meeting, but you will not be identified by name.

**What if I change my mind and do not want my information used or disclosed?**
The permission to use or disclose your protected health information for this study does not have an expiration date. If you no longer want to share your protected health information, you may cancel your permission at any time by writing to the study staff at the address below:

Brant Stevermer  
1900 South Avenue  
La Crosse, WI 54601

If you cancel your permission after you have started the study, the study staff will stop collecting your health information. Although they will stop collecting new information about you, they will need to use the information they have already collected to evaluate the study results.

If you start the study and then cancel your permission, you will not be able to participate in the study at a later date.

**Questions**
For more information regarding the research and research-related risks or injuries you are instructed to contact the Principal Investigator for this study, Brant Stevermer at 608-782-7300 or 1-800-362-9567. After 5pm or if you are not able to reach the Principal Investigator, you are to contact the Nurse Advisor at 608-775-4454 or 1-800-858-1050, please tell them that you are on a
research study and that you may need to be connected to the appropriate on call provider. For more information about my rights as a research participant, you may contact Thomas D. Harter, PhD, Chairperson of the Gundersen Clinic, Ltd. Institutional Review Board at (608) 782-7300 or 1-800-362-9567. An institutional review board (IRB) is a group of health care professionals and community members who review research studies to protect the rights and welfare of research participants.

Participant statement and authorization

If you consent, please read and then sign below.

This consent form contains important information. It will help you decide if you want to take part in this study. If you still have questions, please ask the study doctor, before signing this form.

Agreement to take part in the study

- I have read this information, or it has been read to me.
- It has been written in a language that I can read and/or understand.
- This study has been explained to me.
- All my questions about the study have been answered to my satisfaction.
- Based on this information, I volunteer to take part in this study.
- I give my permission to the study doctor to use and disclose my protected health information as described in this consent form.
- I have not waived any of my legal rights by signing this document.

You will receive a copy of this signed Participant Informed Consent Form and Authorization to Use and Disclose Medical Information.

Printed Name of Participant

Signature of Participant Date

Printed Name of Legally Authorized Representative (LAR)

Signature of Legally Authorized Representative (LAR) Date

Printed Name of Researcher Explaining Consent
The participant says the consent form is understood and the consent is willingly given. I am writing my name below as witness and I believe the patient understands what is being done and has willingly signed the consent form.

______________________________  __________________
Witness Signature                  Date
APPENDIX B
DATA COLLECTION SHEET
Patient name ____________________
Patient ID ____________________
Gender ______
Age ______
Comorbidities □ HNT □ HLD □ Diabetes □ pre-diabetic (FBG >100 and <125) □ current or former (within past 6mo) smoker, □ Age (male >45 women >55), □ history (first degree male >55 or female >65), □ Sedentary, □ obesity (BMI 18.5-25 normal, 25-29.9 OW, 30-34.9 Obese 1, 35-39.9 Obese 2, ≥40 Obese 3)

**Treadmill GXT**

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### 6MWT

![6MWT Table](image)

- □ Pre □ Post  Date of test ____________

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<tr>
<td>Recovery</td>
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### Distance vs. Time

![Distance vs. Time Table](image)

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APPENDIX C
REVIEW OF LITERATURE
Review of Literature

Peripheral artery disease (PAD) affects millions of people and is expected to increase with the aging of the population (Aboyans et al., 2012; Chen et al., 2017; Foley, Armstrong, & Waldo, 2016; Gohil et al., 2013; McDermott et al., 2014; Muir, 2009). It is estimated that the prevalence of PAD is 20% of the population over the age of 70 and increases to an estimated 50% after age 85 (Chen et al., 2017). The purpose of this paper is to review the current literature associated with PAD.

Pathology of Peripheral Artery Disease

Peripheral artery disease (PAD) is caused by the development of atherosclerotic plaque in the extremities (American Association of Cardiovascular & Pulmonary Rehabilitation (AACVPR), 2013). Atherosclerotic plaque is not only the cause of PAD but also causes coronary artery disease (CAD) and cerebrovascular disease (CVD); as a result, a diagnosis of PAD is suggestive of CAD and CVD (Durstine, Moore, & Painter, 2016; Hiatt, Rogers, & Brass, 2014). The disease process is initially caused by endothelial dysfunction in the arteries. The endothelium is the innermost layer of blood vessels. Major blood vessels associated with systemic atherosclerosis include the aorta, the carotids, the visceral arterial branches, and arteries of the lower extremities. Damage to the endothelial layer is caused by multiple factors including hypertension, hyperlipidemia, aryl hydrocarbon receptor activation (a result of cigarette smoking), oxidative stress, and inflammation (Naem et al., 2012). These factors lead to injury of the endothelial layer causing it to become permeable and allowing molecules to flow through leading to a cascade of processes that result in lesion formation, essentially as a repair process (Khurana et al. 2013; Muir, 2009).
Another factor in endothelial dysfunction is oxidative stress. Oxidative stress is the result of multiple variables which include diabetes, hypercholesterolemia, and hypertension. For example, when low density lipoproteins are oxidized they become soluble in blood plasma allowing it to pass through the endothelial layer of blood vessels. This progresses the atherosclerotic process, causing inflammation, platelet activation, and vasoconstriction within the blood vessels. Atherosclerosis leads to narrowing of blood vessels due to lesion formation and plaque buildup (Gardner, Montgomery, & Parker, 2012; Gardner, Skinner, Cantwell, & Smith, 1991a; Gommans et al., 2016; Hiatt, Rogers, & Brass, 2014; Treat-Jacobson, Henly, Bronas, Leon, & Henly, 2011). In the peripheral arteries, this causes resistance to blood flow and causes blood pressure to rise. Narrowing of peripheral arteries additionally causes skeletal muscle to become hypoxic as a result of the decreased blood flow that cannot match metabolic needs. To compensate for the reduced blood flow, collateral vessels are developed (Muir, 2009).

The primary symptom as a result of arterial stenosis and skeletal muscle hypoxia is claudication which typically presents itself in the form of pain in the calf muscles of the legs (AACVPR, 2013; Gardner et al., 2012; Gardner et al., 2018; Gommans et al., 2016; Hiatt, Rogers, & Brass, 2014; Montgomery, & Gardner, 1998). Claudication symptoms typically do not occur until occlusion of the artery is greater than 50% (Muir, 2009). Additionally, studies have reported that few (<30% or approximately 10%) patients report being symptomatic which may be attributed to collateral vessel formation (Durstine et al., 2016; Foley, Armstrong, Waldo, 2016; Khurana et al., 2013; Muir, 2009). Hiatt et al. (2014) noted that regardless of symptomatic status, PAD patients have low exercise capacity. Claudication is intermittent and is brought on by the increased
metabolic demand within skeletal muscles of the lower extremities during exercise and dissipation with rest (AACVPR, 2013; Nicolaï et al., 2009). The severity of claudication has been shown to reflect lower limb outcome and the need for amputation (AACVPR, 2013). The pain associated with activity is limiting and negatively impacts an individual’s ability to function and their quality of life (Gardner, Skinner, Vaughan, Bryant, & Smith, 1992; Gardner, Montgomery, Flinn, & Katzel, 2005; Hiatt, Nawaz, Regensteiner, & Hossack, 1988; McDermott et al. 2014; Montgomery, & Gardner, 1998; Muir, 2009; Treat-Jacobson et al., 2011).

**Risk Factors**

Risk factors for PAD are directly related to atherosclerosis (Alahdab et al., 2015). The Framingham Heart study showed that aging and prevalence of PAD were related. Non-modifiable risk factors for PAD include age, male gender, and family history. Modifiable risk factors include smoking, diabetes, hypertension, sedentary lifestyle, and hyperlipidemia (Alahdab et al., 2015; Muir, 2009). Risk for cardiovascular events in PAD patients outweighs ischemic limb events (alahdab et al., 2015; Foley, Armstrong, & Waldo, 2016). Peripheral artery disease patients are at increased risk for falls as a result of impaired proprioception leading to balance deficits (Gohil et al., 2013; McDermott et al., 2014).

**Diagnosis of Peripheral Artery Disease**

The ankle brachial index (ABI) is the standard tool used to diagnose PAD and determine the severity of the disease (Gardner et al., 1991a; Riebe, Ehrman, Liguori, & Magal, 2018). The ABI is a noninvasive method for measuring systemic atherosclerosis.
Systolic blood pressure (SBP) is measured using a sphygmomanometer and a Doppler ultrasound device (Aboyans et al., 2012; Durstine et al., 2016; Muir, 2009; Gardner et al., 2018). The ABI is calculated by taking the highest SBP in the arms using the brachial artery and dividing it by the highest SBP in the ankles at the posterior tibialis and/or dorsalis pedis artery (Aboyans et al., 2012; Cahan et al., 1999; Durstine et al., 2016; Gardner et al., 2018). The patient should rest 10 to 15 minutes in the supine position prior to testing and should remain in this position during testing as this will allow for the measurements at the feet and arms to be at the same level as the heart (Aboyans et al., 2012; Durstine et al., 2016). An ABI measurement of ≤0.90 or a decrease of >0.15 over time or after exercise is positive for PAD (Aboyans et al., 2012; Foley, Armstrong, Waldo, 2016; Gardner, Waldstein, Montegomery, & Zhao, 2016; Gommans et al., 2016; Riebe et al., 2018). ABI sensitivity is between 94% and 97% and increases if used in combination with an exercise test (Foley, Armstrong, & Waldo, 2016). Ankle brachial index measurements between males and females without PAD are minor, with one study reporting average ABI measurements 0.07 lower in females compared to males (Aboyans et al., 2012). Additionally, Aboyans et al. (2012) found even less difference in ABI measurements when comparing African Americans (0.02 lower ABI), to non-Hispanic whites, both without PAD. Ankle brachial index is not only used to diagnose PAD but is a predictor of all-cause mortality and is used to evaluate risk for limb amputation (Aboyans et al., 2012). An ABI measurement of ≤0.90 puts individuals at an increased 7-year risk of amputation in patients with diabetes mellitus (a common comorbidity of PAD) (AACVPR, 2013; Aboyans et al., 2012).
**Supervised Exercise Therapy**

Exercise training in patients with PAD dates back to 1966 when the first randomized controlled trial involving PAD patients showed exercise training improved treadmill walking tolerance (Regensteiner, Gardner, & Hiatt, 1997). Supervised exercise therapy (SET) for PAD has been recognized by the American College of Cardiology and American Heart association as class IA evidence (highest level of evidence) (AACVPR, 2013; Burns, Rohrich, & Chung, 2011; Gardner et al., 2012). Additionally, SET has been shown to be an effective tool to decrease pain associated with intermittent claudication (IC) and QOL (Foley, Armstrong, & Waldo, 2016; Gommans et al., 2016). In May of 2017, the Centers for Medicare & Medicaid Services started to cover SET for patients with symptomatic PAD. Supervised exercise therapy covers 36 sessions over the course of 12 weeks and consists of exercise sessions lasting 30 to 60 minutes (Centers for Medicare & Medicaid Services, n.d.). The standard exercise modality in SET is treadmill walking, whereby patients walk until near maximal claudication pain and then stop and rest until the pain dissipates (AACVPR, 2013; Gardner, Montgomery, Flinn, & Katzel, 2005). Once pain is completely gone, the patient starts walking again until they reach claudication pain (Durstine et al., 2016; Regensteiner et al., 1997). The goal of SET is to improve functional capacity, decrease modifiable risk factors, reduce symptoms (IC), and improve walking distance (Hiatt et al., 1988; Regensteiner et al., 1997). The most improvement in reduction of IC and increased walking duration are seen within the first two months of SET (Gardner et al., 2012). There are many mechanisms in which exercise improves PAD outcome, which include increased lower extremity blood flow, increased capillaries, increased vasodilation, improved systemic circulation, reduced blood
viscosity, increase in oxidative enzymes (mitochondria), more reliance on oxidative pathways for energy, improved walking economy, and improved strength (Durstine et al., 2016; Hiatt, et al., 2014).

**Supervised Exercise Therapy Outcome Measures**

The treadmill graded exercise test (GXT) has been around since the 1970s were it was used to evaluate sedentary and active adult men and women (some with underlying heart disease) (Bruce, Kusumi, Hosmer, 1973). The GXT was also used during this time to assess patients with potential ischemic heart disease (Nicolaï et al., 2009). The standard tool used to assess PAD outcomes is a maximal treadmill GXT (Durstine et al., 2016; Gommans et al., 2016; Medermott et al., 2008; Montgomery, & Gardner, 1998; Nicolaï et al., 2009; Treat-Jacobson et al., 2011). A GXT is used because it has been shown to be more reliable compared to a single stage treadmill test (Gardner et al., 1991a; Hiatt et al., 2014). There are two commonly used treadmill GXT protocols for PAD, the Gardner-Skinner and Hiatt protocols (Gardner et al., 1991a; Gardner et al., 1992; Hiatt et al., 1988). Both use a constant incremental grade, the Gardner-Skinner protocol uses a 2% increase in grade every stage whereas the Hiatt uses 3.5%. Gardner-Skinner uses 2-minute stages whereas Hiatt uses 3-minute stages. The Gardiner-Skinner protocol uses a constant speed of 2 miles per hour (mph) throughout the test (AACVPR, 2013; McDermott et al., 2014; Nicolaï et al., 2009). The Hiatt protocol starts at 2 mph for stage one and increase to 3 mph and stays constant throughout the remainder of the test (Hiatt et al., 1988). Handrail support during the treadmill GXT is discouraged and should only be used for balance (Gardner et al., 1991b; Hiatt et al., 2014; Regensteiner et al., 1997). Handrail support has been shown to reduce the metabolic demand of walking.
delays onset of claudication pain and affects hemodynamic measurements (Gardner et al., 1991b; Gardner et al., 1992; Regensteiner et al., 1997).

The six-minute walk test (6MWT) has been used in other populations including chronic obstructive pulmonary disease and congestive heart failure (Bellet, Adams, & Morris, 2012; Cahan et al., 1999). The 6MWT evaluates submaximal functional capacity and severity of IC (Gardner et al., 2018). The objective of the test is for the patient to walk as far as possible in a 6-minute period. The patient should rest in a chair for 10 minutes before beginning the 6MWT. During this time the test administrator should obtain a resting heart rate and blood pressure. Furthermore, a set of standardized instructions are read to the patient. There are a set of guidelines for administering the 6MWT to include no warmup prior to testing, no vigorous exercise within 2 hours of testing, patient should use their normal walking aid(s) (e.g. cane or walker) during the test, not walking in front of or beside patient so as to not encourage pacing, and a 100-foot hallway should be used. After the rest period, the test begins once the patient starts walking. During the 6MWT, the test administrator should not talk to the patient except for standard prompts that are read every minute and the last 15 seconds of the test to provide the patient with the time remaining and standardized encouragement. Additionally, the patient is allowed to stop and rest during the test, but the time still continues. The test concludes once the 6 minutes expire or the patient becomes unstable with symptoms (AACVPR, 2013; American Thoracic Society (ATS), 2002; McDermott et al., 2014).

Clinically significant outcome measurements for PAD include time to initial onset of claudication pain and maximal walking distance (Durstine et al., 2016; Gardner et al., 1992; Regensteiner et al., 1997).
(1991b; Gardner et al., 1992; Gardner et al., 2018; Nicolaï et al., 2009). Cahan et al. (1999) notes that the 6MWT is a reliable means of assessing functional impairment in IC patients. Furthermore, the study demonstrated that 6-minute walk distance is associated with ABI measurements and distance to onset of claudication using the treadmill (Cahan et al., 1999). Chen et al. (2017) agreed that the 6MWT is reliable in evaluating walking endurance with the PAD population. The 6MWT is class IIb evidence for objective assessment of functional limitation as a result of IC and outcome evaluation post SET (Burns, 2011; Chen et al., 2017). Bellet et al. (2012) observed that the 6MWT has strong evidence of responsiveness to changes in clinical status. Furthermore, there is moderate evidence for reliability with the 6MWT (Bellet et al., 2012). Additionally, there is moderate evidence that a learning effect exists in the 6MWT (2%-8% in repeated 6MWTs) (Bellet et al., 2012). It is important to note that Bellet et al. (2012) used subjects with a diagnosis of coronary artery disease (CAD). Though PAD and CAD have common disease processes there are notable differences in how the disease presents itself in the form of symptoms. More recently, a study by McDermott et al. (2014) suggests that a learning effect does not exist in the 6MWT with PAD patients. The 6MWT has also been shown to more closely represent daily activity when compared to treadmill testing (Gardner et al., 2018; McDermott et al., 2008; Nicolaï et al., 2009). Conversely, Hiatt et al. (2014) states that the 6MWT has marginal utility in the clinical setting. In a study with heart disease patients the 6MWT showed poor retest ability (Hiatt et al., 2014).

**Treatment of Peripheral Artery Disease**

Supervised exercise therapy and walking are the primary conservative treatment methods for PAD (Gommans et al., 2016; Treat-Jacobson et al. 2011). Pentoxifylline was
the only FDA approved drug for treatment of IC in PAD patients up until the late 1990s (Dawson et al., 2000; McDermott et al., 2014; Regensteiner et al., 1997). Pentoxifylline is a phosphodiesterase inhibitor and the mechanism of action is increasing deformability of red blood cells which helps to improve blood flow in the narrowed peripheral arteries (AACVPR, 2013; Durstine et al., 2016; Gardner et al., 2016; Muir, 2009). A second drug approved by the FDA for treatment of PAD is cilostazol which is also a phosphodiesterase inhibitor with an antiplatelet and vasodilation effect (Dawson et al., 2000; Durstine et al., 2016; Foley, Armstrong, & Waldo; Gardner et al., 2016; McDermott et al., 2014; Muir, 2009). Dawson et al. (2000) showed after 24 weeks that increase in maximal walking distance was greatest in the cilostazol group compared to pentoxifylline and placebo groups which were comparable to each other. McDermott et al. (2014) agrees noting that Pentoxifyline is comparable to placebo and cilostazol being superior but showing only modest improvements. Muir (2009) showed that cilostazol improved ABI measurements and walking distance in PAD patients. Another treatment method is revascularization. Though this may eliminate the occlusion within the artery and improve blood flow, it has not been associated with improvement in exercise capacity measurements (Hiatt et al., 2014).

**Conclusion**

Peripheral artery disease affects the older adult population and greatly affects quality of life. Steps to treat PAD should include SET which addresses risk factor modification and regular exercise in the form of walking. When measuring PAD outcomes in patients after SET the type of test used should be reliable, valid, and
accurate. The 6MWT maybe a potential test for assessing outcome in PAD patients after SET and may be a viable alternative to GXT.
References


Centers for Medicare & Medicaid Services. (n.d.) *Decision memo for supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD) (CAG-00449N).* Retrieved from https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=287&NcaName=Supervised+Exercise+Therapy+%28SET%29+for+Symptomatic+Peripheral+Artery+Disease+%28PAD%29&ExpandComments=y&CommentPeriod=0&bc=gAAAAAACAAAAAA%3D%3D


