Characterization of the Peripheral Artery Disease (PAD) Symptom Experience

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Dedication

"Correction does much, but encouragement does more."
Johann Wolfgang von Goethe

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Abstract

Background: Claudication is the most commonly recognized symptom of PAD. It is classically described as an *aching, cramping, painful,* or *tired* feeling in the buttock or leg muscles. However, classic claudication is only reported in 7.5% to 33% of patients with PAD. Symptoms beyond classic claudication have been reported and suspected as being part of the symptom experience, but have not been validated as directly relating to changes in calf tissue oxygenation during exercise and subsequent recovery.

Objective: The purpose of this study was to characterize the symptom experience of individuals diagnosed with PAD. Specific aims were to: (a) understand the symptom experience of individuals with PAD through in-depth qualitative interviews, and (b) simultaneously evaluate calf tissue oxygenation and self-reported symptoms experienced during treadmill exercise and throughout recovery.

Method: Adults experiencing lower extremity symptoms during exercise due to underlying PAD were asked to participate. They were asked to: (a) complete a semi-structured interview to report their symptoms and describe their symptom experience in detail; (b) use a numeric rating scale (NRS) (0 to 5) to rate their symptoms during exercise and recovery; (c) provide descriptions of their symptom(s) during exercise and recovery; and (d) wear a near-infrared spectroscopy device to obtain information on tissue oxygenation during the exercise and recovery phases. Data were analyzed using content analysis, exploration of individual graphical trajectories, grouping trajectories, and multilevel modeling to examine the relationship between self-reported symptoms and calf tissue oxygenation.

Results: A total of 40 participants were enrolled in this study. Participants were predominately Caucasian males. The average age of participants was 67.55 years (*SD*

9.18). Six themes emerged from 27 participant interviews: symptom descriptors, maintaining equilibrium, temporal fluctuations, the role of exercise, the perceived impact on QOL, and disease presence and treatment. During interviews, participants provided 24 symptom descriptors in 10 lower extremity locations. During treadmill exercise, participants provided 22 symptom descriptors in eight lower extremity locations. Under static and dynamic conditions, classic and 'atypical' descriptors were used to describe discomfort in typical and 'atypical' lower extremity locations. During three successive bouts of treadmill exercise, the largest drop in calf tissue oxygenation occurred between the start of exercise and the onset of symptom(s). During recovery, calf tissue re-saturation occurred steadily between maximum discomfort (i.e., a rating of 5 out of 5) and full symptom recovery. Individual changes in tissue oxygenation were related to total exercise time, baseline calf tissue oxygenation, exercise and recovery ratings, disease severity, and body-mass index.

Conclusions: This study provides a preliminary understanding of the relationship between subjective symptom reporting and calf tissue oxygenation with a variety of PAD risk factors and individual characteristics. Continued research is necessary to validate 'atypical' participant symptom reporting and broaden the currently accepted PAD symptom locations and descriptors. Despite the under-reporting of 'atypical' symptoms compared to classic claudication, they do exist and they are no less important for the early detection, diagnosis, and treatment of PAD to minimize the impact of this painful, debilitating, and deadly disease.

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List of Abbreviations

ABI	ankle-brachial index
AIC	Akaike's information criteria
BIC	Bayesian information criteria
BMI	body mass index
BP	blood pressure
CLI	critical limb ischemia
DM	diabetes mellitus
ECQ	Edinburgh Claudication Questionnaire
EXERT	exercise training to reduce claudication: arm ergometry versus treadmill walking
HHb	deoxygenated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HMb	deoxygenated myoglobin
HR	heart rate
IC	intermittent claudication
ICC	intraclass correlation coefficient
IRB	institutional review board
MLM	multilevel modeling
mm	millimeters
mmHg	millimeters of mercury
mph	miles per hour
NIRS	near-infrared spectroscopy
nm	nanometers
NRS	numeric rating scale
OA	osteoarthritis
O_2Hb	oxygenated hemoglobin
O_2Mb	oxygenated myoglobin
PAD	peripheral artery disease
PI	principal investigator
QOL	quality of life
SDCQ	San Diego Claudication Questionnaire
SpO_2	peripheral saturation of oxygen
StO_2	tissue oxygen saturation
tHb	total hemoglobin
tMb	total myoglobin
TSI	tissue saturation index
WHO	World Health Organization
μM	micromoles

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Chapter 1: Introduction

Background

Peripheral artery disease (PAD) is a progressive atherosclerotic occlusive disease affecting more than 8 million Americans, a number expected to rise sharply due to an aging population (Allison et al., 2007; Ostchega, Paulose-Ram, Dillon, Gu, & Hughes, 2007; Selvin & Erlinger, 2004). Early detection of PAD is crucial for timely treatment and prevention of amputation, heart attack, stroke, and death (Criqui, 2001b; Criqui, Ninomiya, Wingard, Ji, & Fronek, 2008; Diehm et al., 2009). In PAD, arterial blood flow to the lower extremities is reduced, leading to exertional skeletal muscle ischemia that results in significant discomfort (e.g., claudication) while walking even short distances. Claudication is the most commonly recognized symptom of PAD. It typically commences shortly after walking begins and resolves only when the activity ceases and is classically described as an *aching*, *cramping*, *painful* or *tired* feeling in the calves (Rose, 1962).

Although claudication is considered the classic and hallmark symptom of PAD, only 7.5% (T. C. Collins, Petersen, Suarez-Almazor, & Ashton, 2003) to 33% (Criqui et al., 1996; McDermott et al., 1999; Wang et al., 2005) of individuals report classic claudication as being part of their symptom experience. Symptom reporting may differ based on disease severity, disease location, age, or the presence of certain comorbid conditions. Women may also have different PAD symptoms, since PAD symptom definitions were based on male experiences and were established at a time when ischemic atherosclerotic diseases were thought to primarily affect men. When individuals report symptoms that are not consistent with classic claudication, provider suspicion of disease presence is not triggered; therefore individuals may not receive the necessary diagnostic

testing and subsequent treatment for this chronic, debilitating disease.

Since many patients with PAD do not experience classic claudication, heavy reliance on this symptom for screening and detection can result in mis- or under-diagnosis of the disease; thus significant comorbidities and mortality may increase (Criqui, Fronek, Klauber, Barrett-Connor, & Gabriel, 1985; McDermott, Mehta, & Greenland, 1999; McDermott et al., 2001; Weitz et al., 1996). Indeed, age- and gender-specific PAD symptoms beyond those of classic claudication are suspected, but unconfirmed (Stoffers, Rinkens, Kester, Kaiser, & Knottnerus, 1996). Further, the relationship between subjective symptom reporting and the objective measurement of lower extremity tissue oxygenation during exercise is unknown. Therefore, combining both perspectives has the potential to provide a more comprehensive understanding of the PAD symptom experience which is essential to increase disease detection, diagnosis, and subsequent treatment.

Study Objectives

The purpose of this study was: (1) to obtain a comprehensive understanding of the PAD symptom experience beyond classic claudication, including symptom location, sensation, and duration; and (2) to evaluate the relationship between the symptoms experienced and physiologic changes in calf tissue oxygenation during treadmill exercise and throughout recovery. The objectives of this project were to elicit a comprehensive description of PAD symptoms, attain related physiologic data, and obtain a preliminary understanding of the relationship between subjective and objective symptom reporting. The central premise of this study was that exploring the relationship between subjective and objective symptom data was a necessary first step toward increasing provider

understanding and use of a more comprehensive set of diagnostic PAD symptom descriptors. This study leads to a long term goal of developing and refining age- and gender-specific PAD screening tools to improve and increase lifesaving detection, diagnosis, and treatment. During this investigation, the following specific aims were pursued:

Aim 1: Understand the symptom experience of older and younger men and women with PAD through in-depth qualitative interviews. Research Question: *How do older and younger male and female patients describe the PAD symptom experience?*

Aim 2: Simultaneously evaluate calf tissue oxygenation and the self-reported symptoms experienced by older and younger men and women with PAD during treadmill exercise and throughout recovery. Research Question: *What is the relationship between calf tissue oxygenation and the onset and progression of symptoms*?

Chapter 2: Literature Review

Current Understanding of Peripheral Artery Disease (PAD)

PAD is a progressive atherosclerotic occlusive disease that causes insufficient blood flow to the lower extremities and can result in debilitating, activity-induced pain, even while walking short distances. Estimates vary widely, but it is currently estimated that between 8 and 12 million Americans are afflicted with PAD (Allison et al., 2007; Hirsch et al., 2001; Hirsch, Hiatt, & PARTNERS Steering, 2001). The prevalence of the disease has been shown to increase with age, particularly in individuals aged 60 years and older (Ostchega et al., 2007; Selvin & Erlinger, 2004). Therefore, as the population ages, PAD will become increasingly prevalent. Despite the high prevalence of PAD, it remains largely underdiagnosed and undertreated (Becker, McClenny, Kovacs, Raabe, & Katzen, 2002; Hirsch et al., 2001). Evidence suggests the underutilization of inexpensive and widely available diagnostic screening tools (Ferreira & Macedo, 2010), guideline-recommended treatments (Mukherjee & Cho, 2009), and lifestyle modifications (Mukherjee & Cho, 2009). Early detection of PAD is crucial for timely treatment and prevention of amputation, heart attack, stroke, and death (Caro, Migliaccio-Walle, Ishak, & Proskorovsky, 2005; Criqui et al., 1992; Criqui et al., 2008; Diehm et al., 2009). Individuals with PAD have 4 to 5 times the risk of dying of a cardiovascular event compared to those without PAD, which translates into a mortality risk that is 2 to 3 times higher (Bhatt et al., 2006; Newman et al., 1999).

Risk factors. Risk factors associated with PAD are similar to those for coronary artery disease and include age >50 years (Criqui et al., 1985; Vogt, McKenna, Anderson, Wolfson, & Kuller, 1993), cigarette smoking (Drexel et al., 1996; Kannel, 1996a;

Krupski, 1991; Newman et al., 1993), diabetes mellitus (DM) (Murabito, D'Agostino, Silbershatz, & Wilson, 1997; Newman et al., 1993), hypertension (Drexel et al., 1996; Murabito et al., 1997; Newman et al., 1993), elevated lipid levels (Drexel et al., 1996; Hiatt, Hoag, & Hamman, 1995; Mowat et al., 1997; Murabito et al., 1997), and elevated homocysteine levels (Hoogeveen et al., 1998; Taylor, Moneta, Sexton, Schuff, & Porter, 1999). PAD is associated with a decreased quality of life (QOL) (Khaira, Hanger, & Shearman, 1996; Pell, 1995) and functional limitations (Dolan, Liu, Criqui, et al., 2002; McDermott, Greenland, Liu, et al.; 2001), and is a strong predictor of future cardiovascular morbidity and mortality (Criqui, Langer, Fronek, & Feigelson, 1991; Criqui et al., 2008; Leng et al., 1996). Individuals with PAD suffer a 5-fold increased relative risk of a heart attack and a 2- to 3-fold greater risk of stroke and total mortality than those without PAD (Criqui et al., 1992). PAD patients have higher rates of cardiovascular ischemic morbidity and mortality than those with coronary artery disease or cerebrovascular disease (Steg et al., 2007), and greater 5-year mortality rates than those with breast cancer and many other malignancies (Criqui, 2001a; McKenna, Wolfson, & Kuller, 1991). Associations between PAD and cardiovascular mortality are independent of demographic characteristics, risk factors, or other comorbid conditions (Newman, Tyrrell, & Kuller, 1997; Resnick et al., 2004). Given the significant morbidity and mortality associated with PAD, there is an obvious need to increase diagnosis and provide timely treatment in an attempt to minimize the significant risks previously discussed.

Diagnosis. Claudication is the symptom that health care professionals most often associate with PAD, which triggers confirmatory diagnostic testing (Olson & Treat-

Jacobson, 2004). Classic intermittent claudication (IC), originally defined in the Rose Questionnaire (Rose, 1962), is exertional calf *aching*, *cramping*, *pain*, or *fatigue* that causes the patient to stop walking, resolves within 10 minutes of rest, does not resolve while the patient is walking, and does not begin at rest (Kannel, 1996b; Murabito et al., 1997; Rose, 1962). Although claudication is considered the hallmark symptom of PAD, up to 50% of patients do not report claudication (Hirsch et al., 2001; McDermott, Mehta, & Greenland, 1999), particularly those with comorbid conditions such as neuropathy, arthritis, and spinal stenosis (Dolan et al., 2002; McDermott, Mehta, & Greenland, 1999; McDermott et al., 2001).

The most commonly performed assessment to confirm disease presence is the ankle-brachial index (ABI). The ABI is a simple, rapid, (on average requiring less than 15 minutes to complete), accurate, inexpensive, and non-invasive method to identify (Dolan et al., 2002; McDermott, Mehta, & Greenland, 1999; McDermott et al., 2001) and monitor PAD (Ferreira & Macedo, 2010). The ABI is a ratio of Doppler-recorded systolic blood pressure (BP) in the lower and upper extremities (Bernstein & Fronek, 1982). Under normal conditions, the systolic pressure at the ankle should be equal to or greater than the systolic pressure of the upper arm. In PAD, systolic pressure decreases at sites distal to areas of arterial narrowing. An ABI ≤ 0.90 is diagnostic of PAD (Aboyans et al., 2012; Albert et al., 2013; Coutinho, Rooke, & Kullo, 2011; Tendera et al., 2011). Values between 0.91 and 0.99 are considered borderline abnormal, whereas normal values fall between 1.00 and 1.40. Individuals with an ABI >1.40 are thought to have non-compressible arteries secondary to calcification and should have a toe-brachial index performed. A low ABI at rest (≤ 0.90) provides significant evaluative and

prognostic information on cardiovascular risk (Norgren et al., 2007). The presence of a low ABI more than doubles the risk of coronary heart disease and stroke, and more than quadruples the risk of cardiovascular death (Doobay & Anand, 2005). Several studies have also shown that a high ABI at rest (>1.40) is associated with poorer outcomes in the general population (Aboyans et al., 2008; Collaboration et al., 2008; O'Hare, Katz, Shlipak, Cushman, & Newman, 2006; Resnick et al., 2004; Suominen, Rantanen, Venermo, Saarinen, & Salenius, 2008), as well as patients with a diagnosis of coronary artery disease (Aboyans et al., 2005). Current guidelines from the American College of Cardiology/American Heart Association recommend utilizing a resting ABI to establish PAD diagnosis in patients with suspected PAD (e.g., exertional leg symptoms), with non-healing wounds, and in those aged ≥70 years or ≥50 years with a history of smoking or DM (Hirsch et al., 2006).

Current Understanding of PAD Symptoms

The presentation and progression of PAD is varied. Some individuals remain asymptomatic despite disease progression, while others consistently experience discomfort upon exertion that subsides when physical activity ceases. Critical limb ischemia (CLI) is the most severe form of PAD. Individuals with CLI typically experience severe leg pain, even while resting, that usually occurs in the feet or toes. However, for some individuals with CLI, the first sign of the disease is the presence of tissue loss (Matzke & Lapantalo, 2001). In patients with CLI, blood flow to the lower extremities is severely reduced, resulting in chronic non-healing wounds and tissue necrosis that if left untreated can lead to amputation.

Symptom assessment. Symptom assessment often involves a combination

approach: an oral report of symptoms to a provider and written completion of a PAD symptom questionnaire by a patient. During exercise, the onset and progression of PAD symptoms can be numerically assessed using a numeric rating scale (NRS). However, the vast majority of patients with PAD descriptively report their symptoms on a questionnaire (i.e., using words to describe the symptom location and sensation), in a static condition (e.g., during an office visit).

Numeric rating scale (NRS). The NRS attempts to capture an individual's perception of a PAD symptom on a scale from 0 to 5 (see Figure 1). A rating of 0 represents *no discomfort*, whereas a rating of 5 is the *maximum ischemia-related discomfort* experienced. This scale is most commonly used as a symptom assessment technique in PAD exercise studies and is considered valid and reliable for use in this patient population (Hiatt, Wolfel, Meier, & Regensteiner, 1994; Treat-Jacobson, Bronas, & Leon, 2009; Treat-Jacobson, Henly, Bronas, Leon, & Henly, 2011).

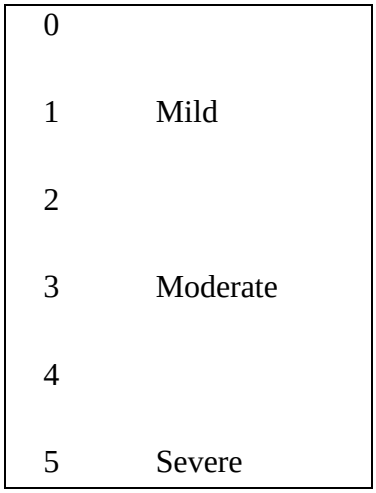

Figure 1. The numeric rating scale (NRS) used to describe ischemia-related discomfort during treadmill exercise and subsequent recovery.

Symptom questionnaires. A more common form of reporting PAD symptoms is on a questionnaire. Table 1 summarizes the evolution of claudication questionnaires,

including symptom categories and their associated characteristics that most frequently appear in the literature. The Rose Questionnaire (Rose, 1962) was the first PAD symptom questionnaire developed. It attempted to standardize the one and only symptom thought to be indicative of PAD at the time, claudication. Originally, the Rose Questionnaire was developed for use in epidemiologic studies to determine prevalence rates and it was subsequently adopted by the World Health Organization (WHO) in 1968 (Rose & Blackburn, 1968). In 1977, minor changes were made to the wording of the questionnaire to make it suitable for self-administration; claudication criteria remained unchanged (Rose, McCartney, & Reid, 1977). Results of the initial study revealed 91.9% sensitivity and 100% specificity in 37 patients with undoubted claudication (most verified by arteriograms) and 18 patients with other types of exertional leg pain (mainly sciatica, osteoarthritis (OA), and calf cramps) (Rose, 1962). The WHO/Rose Questionnaire failed to identify three participants with undoubted claudication, but correctly ruled out all of the participants reporting leg pain unrelated to claudication.

Later studies with larger sample sizes, using physician diagnosis as a comparison (usually based on an ABI), resulted in a sensitivity and specificity as low as 8.6% (Newman et al., 2001) and 91% (Leng & Fowkes, 1992), respectively. The low sensitivity in later studies may be explained by failure of the WHO/Rose Questionnaire to identify participants reporting symptoms in an 'atypical' location (e.g., buttock) or in multiple locations, as having claudication. Further, a lower specificity may be explained when participants surveyed present with other types of non-ischemic leg pain and are classified as having claudication.

Table 1

Evolution of Claudication Questionnaires

Questionnaire	Year Created/ Revised	Symptom Category	Symptom Characteristics
Rose	1962	Intermittent claudication (Rose IC)	• Exertional calf pain
WHO/Rose	1968		
		Grade 1 *Grade 2*	*Walking uphill or hurrying* *Walking at ordinary pace on the level*
			• Never starts at rest (standing or sitting) • Never disappears while walking • Causes patient to slow down or stop • Usually disappears within 10 minutes or less
	1985	Possible IC	• Exertional calf pain • Never starts at rest • Otherwise not fully concordant with Rose IC criteria
	1991	Probable IC	• Exertional calf pain • One WHO/Rose criteria not fulfilled
ECQ	1992	Definite IC (Rose IC)	• Fully concordant with Rose IC criteria
		Grade 1 *Grade 2*	*Walking uphill or hurrying* *Walking at an ordinary pace on the level*
		Atypical IC	• Pain in thigh or buttock in the absence of calf pain, otherwise concordant with Rose IC criteria
SDCQ	1996	Rose IC	• Fully concordant with Rose IC criteria

Table 1 – *Continued*.

	Non-Rose exercise calf pain	• Exertional calf pain; at least one Rose IC criteria not fulfilled
	Non-calf exercise leg pain	• Pain in either leg excluding calf (can be quadriceps or buttock); does not begin at rest
	Leg pain on exertion and at rest	• Exertional leg pain that starts at rest
	No pain	• Reports no pain in calf, quadriceps, or buttock

Note. WHO=World Health Organization; IC=intermittent claudication; ECQ=Edinburgh Claudication Questionnaire; SDCQ=San Diego Claudication Questionnaire.

The low sensitivity and reduced specificity of the WHO/Rose Questionnaire led to the development of the Edinburgh Claudication Questionnaire (ECQ) in 1992 (Leng & Fowkes, 1992). The revised questionnaire included a response for non-ambulatory patients and a lower extremity body diagram for patients to indicate leg symptoms in multiple locations. The body diagram allowed for positive claudication classification to be separated into definite claudication and 'atypical' claudication depending on involvement (or lack thereof) of the calf. Initial testing of the ECQ revealed 91.3% sensitivity and 99.3% specificity in comparison to the diagnosis of claudication made by a physician (Leng & Fowkes, 1992). The study population consisted of 50 new patients attending a peripheral vascular clinic with leg pain, aged over 55 years and 300 patients aged over 55 years visiting their general practitioner with any complaint (Leng & Fowkes, 1992).

A new questionnaire, the San Diego Claudication Questionnaire (SDCQ) (Criqui

et al., 1996), was developed in 1996. The SDCQ was a revised and expanded version of the WHO/Rose Questionnaire. It included buttock and thigh pain, which was also a component of the ECQ, but unlike the ECQ, the SDCQ inquired specifically whether symptoms were present in the right, left, or both legs. The complete results of a structured review of claudication questionnaires has been published by the principal investigator (PI) (Schorr & Treat-Jacobson, 2013). Of all the articles included in the structured review, the SDCQ was the most frequently used claudication questionnaire. Interestingly, all of the studies that utilized the SDCQ were conducted in the United States, whereas studies conducted abroad used the WHO/Rose and the ECQ.

Claudication questionnaires have undergone several revisions over time, but sensitivity remains low and specificity is variable. All three questionnaires are seemingly insensitive to PAD detection compared to ABI as a gold standard for diagnosis. This indicates the need for further questionnaire refinement to increase the sensitivity and correctly identify patients with disease, but with symptoms differing in location and/or sensation compared to those exhibiting classic claudication.

Symptom definitions. A relatively strict definition of claudication (the 'typical' PAD symptom) has persisted over time. As previously described, in its original form (Rose, 1962), classic claudication, is exertional pain restricted to one or both calves that causes a patient to slow down or stop walking, resolves within 10 minutes of standing still, does not resolve while the patient is walking, and does not begin at rest. While the introduction of the ECQ allowed for the presence of symptoms elsewhere in the lower extremities, pain still had to be present in one or both calves to be classified as definite claudication (Criqui et al., 1985; Fowkes et al., 1991; Leng & Fowkes, 1992).

The creation of the SDCQ allowed for the presence of more specific symptom categories beyond classic claudication, and the assessment of leg-specific symptoms (right versus left) (Criqui et al., 1996). The SDCQ consists of five possible symptom categories per leg: Rose claudication, non-Rose exercise calf pain, previously referred to as 'possible IC' (Criqui et al., 1985) and 'probable IC' (Fowkes et al., 1991), non-calf exercise leg pain, pain at rest, and no pain (Criqui et al., 1996).

Symptom report. Despite the evolution of such questionnaires, patients reporting pain in the hamstrings, feet, shins, joints, or radiating pain in the absence of calf pain would still not classify as 'symptomatic,' and subsequently would not be suspected of having PAD. Furthermore, although the number of symptom categories has increased on questionnaires, none allow for the reporting of symptom descriptors such as *tingling, numbness, burning, throbbing,* or *shooting* that have been reported by patients with PAD as being part of the symptom experience (Ruger et al., 2008; Tomczyk & Treat-Jacobson, 2009; Treat-Jacobson et al., 2002).

Typical symptoms. The symptom most frequently recognized as the hallmark sign of arterial insufficiency is claudication. Claudication comes from the Latin word *claudicare,* meaning to limp. But, the use of this term is misleading, as patients who experience symptoms other than classic claudication are still shown to be functionally limited (McDermott et al., 2004; McDermott et al., 2010) and report a decreased QOL (Treat-Jacobson et al., 2002). Aside from confusion about the meaning of claudication, using classic claudication as the gold standard for PAD symptom recognition results in significant under-diagnosis of the disease. Over the last 10 to 15 years, the reported prevalence of classic claudication in patients with symptomatic PAD has been highly

variable, ranging from 7.5% (Collins et al., 2003) to 33% (Criqui et al., 1996; McDermott et al., 1999; Wang et al., 2005). Higher prevalence has been reported in smaller populations (43.8%) (Makowsky et al., 2011) and specific populations including only individuals complaining of leg pain (78.8%) (Makdisse et al., 2007), or excluding individuals who have non-compressible arteries, CLI, or a history of revascularization (43.6%) (Van Zitteren et al., 2012). Overall, research indicates that there are specific characteristics of individuals who are more likely to report classic claudication. Reporting appears to increase as age increases (Criqui et al., 1985; Fowkes et al., 1991; Leng et al., 1996; Stoffers, Rinkens et al., 1996; Wang et al., 2005), and be more prevalent among men (Leng et al., 1996; Stoffers, Rinkens et al., 1996; Wang et al., 2005), and in individuals with DM (Wang et al., 2005), hypertension (Ogren, Hedblad, Engstrom, & Janzon, 2003), a previous diagnosis of PAD (Criqui et al., 1996; Hirsch et al., 2001), or a more severe form of the disease (Criqui et al., 1996; Stoffers, Rinkens et al., 1996; Wang et al., 2005). Disease location may also influence the reporting of classic claudication, with higher prevalence among those with distal lesions (Van Zitteren et al., 2012) or large vessel PAD (Criqui et al., 1985).

The highest reported prevalence of classic claudication is 100% (Gardner, Montgomery, & Afaq, 2007; Gardner et al., 2012; McDermott et al., 2001). The most recent study conducted by Gardner et al. (2012) included 114 participants with symptomatic PAD recruited from vascular and primary care clinic referrals. Prior to exercise testing, participants fell into the following three symptom categories: leg pain on exertion and rest (40.3%), 'atypical' leg pain (27.2%), and classic claudication (32.5%). However, during a graded treadmill test, all of the participants reported symptoms

consistent with classic claudication.

In 2007, Gardner and colleagues (Gardner et al., 2007) reported similar findings. Their study included 715 participants who self-reported exertional leg pain consistent with one of the first four categories on the SDCQ. Initial classic claudication prevalence was 56.8%. As with the 2012 study, during treadmill testing, all of the study participants experienced exertional leg pain that was consistent with classic claudication (i.e., participants stopped walking due to calf pain that resolved with subsequent rest). McDermott and colleagues (2001) reported similar findings with a group of 57 patients who initially self-reported no symptoms, but over half of whom became symptomatic during a 6-minute walking test. These results raise important questions that have not been previously explored: *Are the patients classified in the literature as 'asymptomatic' truly not experiencing symptoms, or are they slowing their walking pace or limiting ambulation to prevent the onset and/or progression of leg symptoms which could be revealed under controlled exercise testing?* The issue of under-reporting versus true symptom prevalence deserves further attention.

'Atypical' symptoms. When Rose (1962) developed the first claudication questionnaire in 1962, the characteristics of PAD were thought to be well-delineated, which made it suitable for diagnosis in epidemiologic surveys. However, over the last five decades, researchers have discovered a more diverse presentation of PAD symptoms. With classic claudication consistently being reported by less than one-third of patients with PAD, claudication questionnaires have been forced to evolve in order to capture the broad array of symptom experiences (Criqui et al., 1996; Leng & Fowkes, 1992). However, revised claudication questionnaires are still not sufficient, as patients are

reporting symptom locations and/or symptom descriptors that are not detected by these questionnaires. Until a more comprehensive tool exists, it is essential for clinicians to recognize that patients with underlying PAD are reporting 'atypical' symptoms more frequently than classic claudication (Collins et al., 2003; Hirsch et al., 2001; Kownator et al., 2009; Lacroix et al., 2008; McDermott et al., 1999; McDermott, Mehta, & Greenland, 1999; McDermott et al., 2011; Newman et al., 2001), and to adapt their assessment techniques accordingly.

In the literature reviewed, the prevalence of 'atypical' symptoms was difficult to ascertain compared to classic claudication, despite its increased frequency. The main reasons were the use of a variety of definitions for 'atypical' symptoms and inconsistent use of symptom categories from study to study. In its simplest form, 'atypical' symptoms included any lower extremity symptom that was not consistent with classic claudication (Criqui et al., 1996; Hirsch et al., 2001), and increased in complexity to include all lower extremity symptoms not located in the calf (Leng & Fowkes, 1992), exercise calf pain not present at rest, but otherwise not fully concordant with the Rose criteria ('possible IC') (Criqui et al., 1985; Sprynger, Fassotte, & Verhaeghe, 2007), calf pain, but one Rose criteria not fulfilled ('probable IC') (Fowkes et al., 1991), 'atypical' pain on exertion (non-Rose walk- through pain and non-Rose stop because of pain), and pain on exertion and rest (Gardner et al., 2007; McDermott et al., 2001). 'Atypical' pain was used to refer to 'walk-through pain' and/or pain that was not consistently relieved within 10 minutes of rest (Ogren et al., 2003). However, prolonged symptom recovery was also grouped together with pain at rest into a 'no pain' category (Manzano et al., 2009). Pain that presented at rest and on exertion was often referred to as 'leg pain on exertion and rest'

(Gardner et al., 2007; Gardner et al., 2012; McDermott et al., 2001; McDermott et al., 2011; Wang et al., 2005), but was also referred to as 'pain at rest' (Criqui et al., 1996; McDermott et al., 1999; McDermott, Mehta, & Greenland, 1999; Mourad et al., 2009), 'rest pain'(Lacroix et al., 2008; Siddiqi, Paracha, & Hammad, 2010), or 'symptoms at rest'(Van Zitteren et al., 2012). Some studies subdivided the 'no symptoms with exertion' category into active and inactive participants, resulting in a total of six leg categories (Collins, Petersen, & Suarez-Almazor, 2005; McDermott et al., 2001), whereas Collins and colleagues (2003), condensed the five symptom categories of the SDCQ into three: no pain, 'atypical' leg pain, (pain at rest, non-calf exercise pain, and non-Rose exercise calf pain), and Rose claudication. Others followed the original five symptom categories established by the SDCQ (Wang et al., 2005) or used a general category of 'leg symptoms'(Kownator et al., 2009), or 'symptomatic' that included lower extremity revascularization, amputation secondary to PAD, or report of claudication regardless of ABI (Missault, Krygier, Lukito, Mary-Rabine, & OPERA Investigators Study, 2007). The use of either category, 'leg symptoms' or 'symptomatic,' limits the understanding of symptom presentation by classifying symptomatic patients as asymptomatic and vice versa.

Potential symptom confounders. It has been demonstrated that older adults are more likely to become afflicted with PAD (He et al., 2006; Murabito et al., 1997) . Older age also makes it more likely that patients with PAD are afflicted with other age-related conditions that could cause or contribute to lower extremity symptoms. Consideration should also be given to PAD severity and its influence on the symptom experience. While several researchers have recognized the potential influence of comorbid conditions

on symptom presentation (Dolan et al., 2002; He et al., 2006; McDermott, Mehta, & Greenland, 1999; McDermott et al., 2001; Newman et al., 2001; Ogren, Hedblad, Engstrom, & Janzon, 2005; Ruger et al., 2008; Weinberg, Simovic, Isner, & Ropper, 2001), the topic has not been thoroughly researched or reported in the literature. Findings from McDermott and colleagues (McDermott et al., 2001) revealed an increased prevalence of DM, neuropathy, and spinal stenosis in patients who reported pain on exertion and rest. Similarly, Newman et al. (2001) discovered a higher prevalence of arthritis and depression in patients reporting exertional leg pain other than classic claudication. Findings from Bernstein and colleagues (Bernstein, Esterhai, Staska, Reinhardt, & Mitchell, 2008) revealed a low prevalence of classic claudication (2%) among patients with PAD, half of whom were also diagnosed with degenerative joint disease. Insulin resistance without a diagnosis of DM has also been identified as a factor influencing claudication prevalence (Pande et al., 2011). Further support for the effect of comorbid conditions came from a study conducted by Weinberg and colleagues (Weinberg et al., 2001), indicating that regional neuropathy is commonly associated with chronic ischemia and CLI.

The neuropathic component of ischemic pain has been examined more closely by researchers and the current understanding is that the character of ischemic pain changes from nociceptive pain in patients with classic claudication to predominately neuropathic pain in patients with CLI (Ruger et al., 2008). Despite the large numbers of patients diagnosed with PAD and reporting neuropathy, the understanding of the role that ischemia plays in neuropathic pain remains limited. Overall, these preliminary results suggest that there are differences in the symptoms reported and/or differences in the

character of the symptom in the presence of certain comorbid conditions or in those with severe PAD (i.e., CLI). This provides additional evidence that using classic claudication as the defining symptom of PAD is insufficient to capture the breadth of symptoms experienced, particularly in this patient population.

Similarly, differential diagnoses have been described in PAD literature in an attempt to clear the blurring of symptom reporting that occurs in the presence of multiple comorbidities, but it has not been extensively studied (Abul-Khoudoud, 2006; Almahameed, 2006; Jang, Jonathan & Halperin, 2005; Jeon, Han, Chung, & Hyun, 2012; Lyden & Joseph, 2006; Meru, Mittra, Thyagarajan, & Chugh, 2006; Weitz et al., 1996). An understanding of physiology can allow a clinician to locate the site of arterial occlusion based on the location of the symptom(s). For example, pain or discomfort in the calf, ankle, or foot could indicate an obstruction/occlusion in the popliteal or superficial femoral arteries (Almahameed, 2006). Symptoms located primarily in the calf or thigh could indicate femoral arteries or their branches, whereas, symptoms in the buttock, hip, and thigh indicate higher disease in the aorta or iliac artery.

The location of symptoms can serve as a guide, but they do not guarantee the presence or location of a lesion with 100% certainty. Symptoms of a patient with claudication may overlap with symptomatology of other conditions, particularly neurological and musculoskeletal diseases (Abul-Khoudoud, 2006). Take for instance a patient reporting calf pain. The pain could indicate claudication secondary to a femoral artery occlusion or it could indicate a venous occlusion, chronic compartment syndrome, nerve root compression, or a Baker's cyst (a tight bursting pain/dull ache that worsens on standing and resolves with leg elevation) (Abul-Khoudoud, 2006; Dizon-Townson,

Nelson, Jang, Varner, & Ward, 1997; Jang & Halperin, 2005; Meru et al., 2006). The presence of any of these conditions could lead a provider to suspect claudication, which could be ruled out if the symptom was relieved by a change in position. Symptoms in the hip, thigh, or buttock could be related to hip arthritis (Abul-Khoudoud, 2006; Meru et al., 2006). However, arthritis is usually a more persistent pain compared to the intermittent nature of claudication and typically associated with symptoms in other joints (Abul-Khoudoud, 2006; Meru et al., 2006). Spinal cord compression should also be considered, particularly when a patient is reporting a history of back pain, with symptoms that worsen upon standing, but are relieved by positional changes (Meru et al., 2006). Patients reporting foot symptoms could have an inflammatory condition such as arthritis or Buerger's disease (Abul-Khoudoud, 2006; Weitz et al., 1996). Current clinician recommendations are to conduct a thorough physical exam and symptom assessment that includes the location, duration, and intensity (Lyden & Joseph, 2006). If PAD is suspected based on patient symptom report or a patient's risk factor profile, a confirmatory ABI should be performed.

Summary of Symptom Reporting

Claudication questionnaires have been used extensively to assess the presence of claudication and subsequently to detect the presence of PAD. Although often highly specific, they remain insensitive for the detection and diagnosis of PAD. Additionally, the inconsistent use of one standardized questionnaire, combined with variations in sample characteristics, definition of PAD, diagnostic methods, and definition of claudication and 'atypical' symptoms make comparisons across studies difficult, if not impossible. Although appearing more frequently, the non-specific nature of 'atypical'

symptoms further complicates clear symptom categorization and necessitates classification of 'atypical' symptoms as being caused by ischemia or caused by comorbid conditions unrelated to ischemia. Furthermore, age and gender differences may affect the reporting of classic claudication and 'atypical' symptoms on PAD questionnaires. However, the largest confounder of PAD symptom report may be the presence of comorbidities, particularly those that affect mobility, as physical limitations may preclude manifestation of PAD symptoms and delay necessary diagnosis and treatment. As the role of comorbid conditions becomes more clearly defined, follow-up questions can be added to existing questionnaires to eliminate false positives and to capture participants who were originally considered false negatives.

Additional research is needed to increase the understanding of the role of age, gender, race, and comorbid conditions on the symptom experience of patients with PAD. The next logical step is to validate subjective symptom report with objective physiologic measures that detect ischemia during exercise in an attempt to broaden the current understanding of PAD symptom presentation. Lastly, better understanding and differentiation of symptom locations and descriptors that are not consistent with classic claudication or 'atypical' symptoms caused by ischemia, but rather caused by a comorbid condition that is unrelated to ischemia, is essential to further enhance understanding of the symptom experience.

Treadmill Exercise Testing

Individuals with PAD experience discomfort during exercise primarily due to the presence of ischemia in the calf, thigh, or buttocks (Holm & Bylund-Fellenius, 1981; Zatina, Berkowitz, Gross, Maris, & Chance, 1986). Subsequently, these exercise-induced

ischemic symptoms limit an individual's ability to exercise and affect oxygen consumption during exercise testing (Hiatt, Nawaz, & Brass, 1987; Hiatt, Wolfel, Regensteiner, & Brass, 1992). Thus, treadmill exercise testing is frequently utilized in clinical and research settings to assess changes in functional capacity following therapeutic interventions or to evaluate PAD disease severity and/or progression.

Treadmill testing mainly focuses on the distance at which discomfort begins (i.e., initial claudication distance) and the distance at which discomfort becomes so severe that it causes an individual to stop walking (i.e., maximal walking distance). Since walking exercise is the primary recommended non-surgical treatment for those suffering from PAD, many research studies focus on changes in the aforementioned outcomes (e.g., initial claudication distance and maximal walking distance) based on individuals participating in supervised exercise programs. Additionally, treadmill walking is considered a more controlled way to elucidate claudication symptoms compared to free-living conditions. In fact, in some circumstances, up to 100% of individuals with PAD reported classic claudication under controlled exercise testing (Gardner et al., 2007; Gardner et al., 2012; McDermott et al., 2001), while less than 60% had reported classic claudication symptoms in everyday living prior to exercise testing (i.e., participants had not stopped walking due to calf pain that resolved with subsequent rest). In light of these research findings, one proposed hypothesis is that patients with PAD who do not report any claudication symptoms or those who do not report symptoms consistent with classic claudication are not walking fast enough and/or far enough to provoke these symptoms during everyday activities.

Two standard treadmill protocols are primarily used for people with PAD: graded

and constant-load. During a graded treadmill exercise test, individuals start walking at 2 miles per hour (mph), at a 0% grade for two (Gardner, Skinner, Cantwell, & Smith, 1991) to three (Hiatt, Nawaz, Regensteiner, & Hossack, 1988) minutes. If walking continues, the grade is increased by 2% every 2 minutes (Gardner et al., 1991) or 3.5% every three minutes (Hiatt et al., 1988), while the speed is held constant until maximum claudication pain is reached. Compared to the variable workload of a graded test, a constant-load treadmill exercise test consists of a single stage, which maintains workload throughout exercise testing. Constant-load testing speed and grade range from 1.5 to 2 mph and 8% to 12% grade, respectively. While a constant-load test may be easier to administer, it makes comparing results with a graded test difficult if not impossible. Additionally, since a wide variety of PAD disease severity exists, it is difficult to justify using a single stage test for all individuals with PAD. Regardless of the protocol followed, treadmill exercise tests generally focus on individual speed, distance, and in some cases, self-reported exertion and/or symptom reporting on a numeric scale.

Simultaneous Evaluation of PAD Symptoms and Calf Tissue Oxygenation

Previous PAD studies have combined qualitative and quantitative patient data to determine that individuals with PAD suffer from both disease-specific functional limitations (e.g., claudication), and more broadly from health-related abnormalities that negatively affect QOL (Hirsch, Halverson et al., 2001). Additionally, functional impairment may lead to increased prevalence of depressive symptoms that have been observed in patients with PAD (Arseven, Guralnik, O'Brien, Liu, & McDermott, 2001). However, mixed methods PAD research has been limited since most of the available methods or techniques utilized to objectively assess the presence or severity of PAD are

performed mainly in static conditions (Manfredini et al., 2009). Otherwise, dynamic evaluations, such as functional treadmill exercise tests, have been restricted to speed, distance, and self-reported exertion and/or symptom rating on a numeric scale. Simultaneously collecting subjective symptom reporting (i.e., symptom location and description) and objective data during dynamic exercise has the potential to provide new symptom locations and/or descriptors that are necessary to consistently and accurately detect PAD, thus expanding the currently accepted definition of 'claudication.' These additional descriptors could be incorporated into existing PAD questionnaires, which could enhance the sensitivity of these questionnaires, potentially leading to improved detection and treatment of PAD.

The role of near-infrared spectroscopy (NIRS). A recently developed device, near-infrared spectroscopy (NIRS), allows for simple, non-invasive, objective study of muscle metabolism at rest and under dynamic and post-exercise conditions (Belardinelli, Barstow, Porszasz, & Wasserman, 1995; Ferrari, Mottola, & Quaresima, 2004; Mancini et al., 1994). NIRS monitors the key pathophysiological determinant of PAD, oxygen delivery to the tissues themselves, as measured by tissue oxygen saturation (StO_2). It is designed to allow for an objective assessment of muscle blood flow and oxygenation level, enabling assessment of the mismatch between oxygen demand and delivery to tissues. Thus far, NIRS has demonstrated moderate-to-high test-retest reliability (Miranda, Figoni, & Castellano, 2010; Miranda et al., 2012) and the degree of muscle deoxygenation in the legs correlates well with PAD severity (Manfredini et al., 2009).

Unlike the ABI, NIRS has the ability to indirectly measure blood flow. While Doppler ultrasound has similar capabilities (Bernink, Lubbers, Barendsen, & van den

Berg, 1982), previous reports have demonstrated that femoral artery flow is not sufficiently reliable to assess tissue ischemia (Lewis, Psaila, Morgan, Davies, & Woodcock, 1990; Vardi & Nini, 2008). Magnetic resonance angiography has been applied to evaluate PAD (Zatina et al., 1986), but clinical use is limited by high costs and lack of availability (Vardi & Nini, 2008). NIRS on the other hand, has been shown to be an inexpensive, non-invasive, accurate, stable, and sensitive tool to study the interactions between oxygen delivery and utilization in human skeletal muscle (Wariar, Gaffke, Haller, & Bertocci, 2000). Parameters measured with NIRS can establish PAD presence, severity, and response to treatment, and correlate well with ABI (Ferrari et al., 2004; Manfredini et al., 2009; Vardi & Nini, 2008).

How NIRS works. The electromagnetic spectrum is displayed in Figure 2. It illustrates the range of all possible frequencies and wavelengths of electromagnetic radiation. Regions of the spectrum are divided based on different interactions of electromagnetic radiation with matter. For example, low-frequency, long radio waves enable the use of everyday devices such as televisions and mobile phones. Whereas, higher-frequency, shorter waves are utilized in health care to perform x-rays and magnetic resonance imaging. NIRS uses infrared light, specifically near-infrared wavelengths to provide information on changes in tissue oxygenation. Higher-frequency, shorter-waves of visible light and ultraviolet light are almost completely absorbed by the skin, but near-infrared penetrates much deeper into biological tissues (Van Beekvelt, 2002).

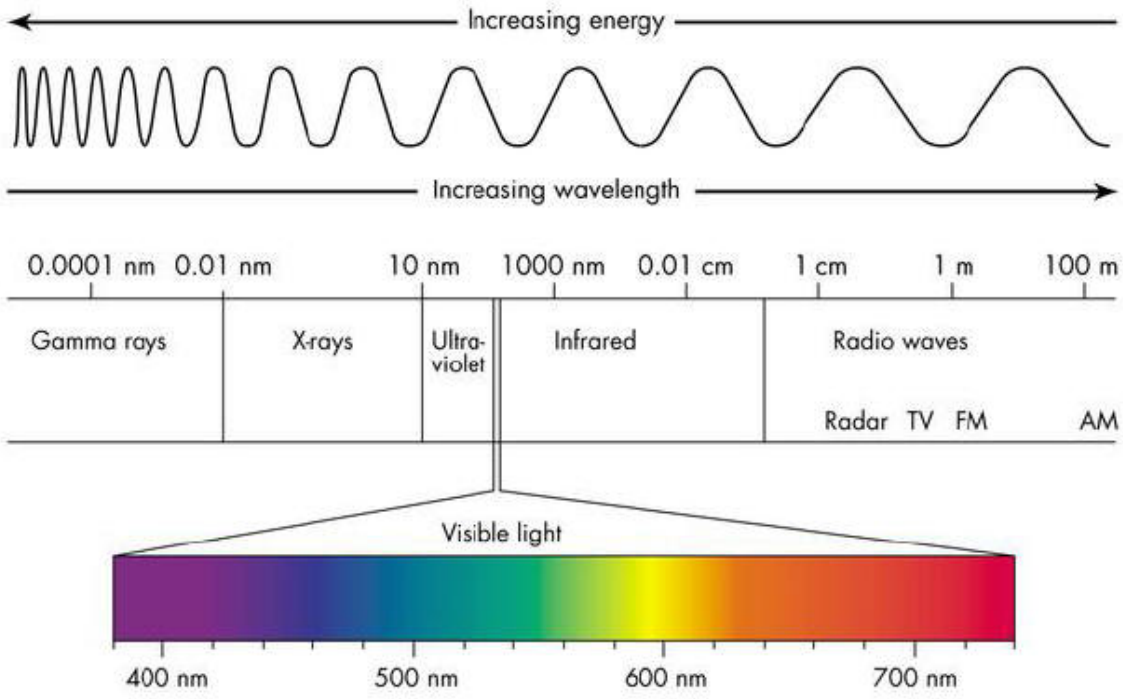

Figure 2. The Electromagnetic Spectrum. Adapted from http://lumenistics.com/what-is-full-spectrum-lighting.

The near-infrared spectroscopy device used in this research, Artinis Medical Systems B.V., PortaMon™, generates near-infrared light at two wavelengths, 760 nanometers (nm) and 850 nm, from three light emitting diodes (inter-optode distances of 30, 35, and 40 mm between the receiver and each of the three diodes). The PortaMon™ provides continuous wave NIRS by converting the changes in optical density using a modification of the Lambert-Beer Law and spatially resolved spectroscopy (Van Beekvelt, Van Engelen, Wevers, & Colier, 2002). Figure 3 illustrates how the NIRS device works. Near-infrared light penetrates the skin, subcutaneous fat layer, and muscle, and is either absorbed or scattered within the tissue. The transmission of infrared light depends upon three properties: reflection, scattering, and absorption (Jobsis, 1977). The light scattering can occur in any direction, but the light detected by the receiving optode

is thought to be curvilinear (Cui, Kumar, & Chance, 1991). The receiving optode processes the color of the light that is reflected back and provides output related to tissue saturation. A particular color arises when a molecule absorbs certain wavelengths of light and transmits or reflects others.

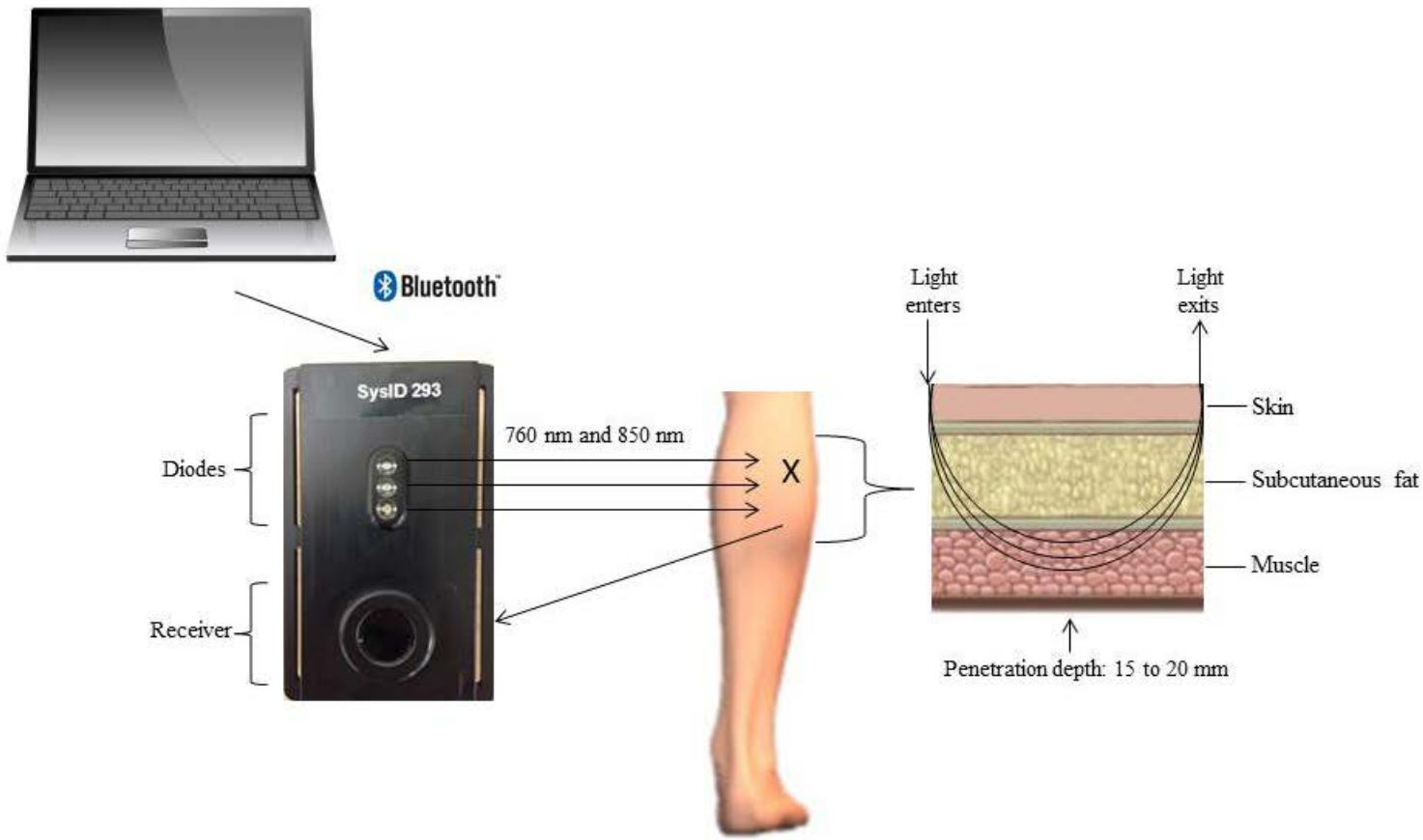

Figure 3. Measuring tissue oxygenation with the Artinis, PortaMon™ near-infrared spectroscopy (NIRS) device. Near-infrared light is transported into the tissue by three diodes, each emitting two wavelengths of light (760 and 850 nanometers (nm)), at inter-optode distances of 30, 35, and 40 millimeters (mm). Penetration depth is limited to half the inter-optode distance (i.e., 15 to 20 mm). The receiver processes the light reflected back and sends information about tissue oxygenation to a laptop computer via Bluetooth™ technology.

A chromophore is the part of a molecule that is responsible for its color (Heller & McNaught, 2009). The chromophores that absorb near-infrared light in muscle tissue are mainly hemoglobin and myoglobin, and to a lesser extent cytochrome-c oxidase (Van Beekvelt, 2002). Hemoglobin and myoglobin are both iron- and oxygen-binding proteins. Hemoglobin transports oxygen in the blood, has the ability to carry four molecules of oxygen, and has a low affinity to oxygen (i.e., affinity gradually increases as oxygen concentration increases). Myoglobin stores oxygen in the muscle, can only carry one oxygen molecule, and has a high affinity to oxygen, even in very low oxygen concentrations. Cytochrome-c oxidase is a key enzyme in aerobic metabolism. It is found in human mitochondria and converts one oxygen molecule into two molecules of water (Bairoch, 2000). Concentrations of cytochrome-c oxidase are relatively low in muscle tissue, compared to hemoglobin and myoglobin (Van Beekvelt, 2002). As a result, changes in cytochrome-c oxidase are lost within the larger and more obvious changes of hemoglobin and myoglobin. Thus, cytochrome-c oxidase did not constitute a significant contribution to this study or to any research that utilizes NIRS technology.

Hemoglobin and myoglobin have identical spectral characteristics; therefore NIRS cannot distinguish between the two. However, hemoglobin and myoglobin can be divided into two major forms: oxyhemoglobin(O_2Hb) / oxymyoglobin(O_2Mb) and deoxyhemoglobin(HHb) / deoxymyoglobin(HMb). Each form has different absorption spectra, so using more than one wavelength (the PortaMon™ uses two) allows for differentiation of oxygenated and deoxygenated forms of hemoglobin and myoglobin, which ultimately provides information about tissue oxygenation (Van Beekvelt, 2002).

The information NIRS provides. NIRS provides information about local tissue

oxygen saturation (StO_2) during dynamic and static states. In clinical settings, a more familiar and commonly used device that measures oxygen saturation is a pulse oximeter. Regardless of the location of the sensor (e.g., fingertip or earlobe), it provides information about peripheral saturation of oxygen (SpO_2). While both devices provide continuous and immediate information about oxygen saturation in a non-invasive way, there are a few distinct differences. Pulse oximetry is a *systemic* measure of the oxygen saturation of arterial blood, whereas NIRS is a *local* measure of oxygen saturation; in the tissues where the device is located (e.g., calf tissue oxygenation). Additionally, pulse oximeters utilize light-emitting diode technology, sending a combination of visible light (specifically red light) and IR wavelengths into the tissue (Ferrari et al., 2004), but NIRS relies solely on near-infrared wavelengths. NIRS measures will fluctuate based on changes in the local conditions of oxygen supply and consumption in the tissues; pulse oximetry will not. Lastly, pulse oximetry requires a pulsatile flow, whereas NIRS does not.

There are four main measures reported by NIRS: local tissue saturation index (TSI), oxygenated hemo/myoglobin (O_2Hb/O_2Mb), deoxygenated hemo/myoglobin (HHb/HMb), and total hemo/myoglobin (tHb/tMb). TSI is expressed as a percentage based on time and reflects the average oxygen saturation of underlying muscle tissue. O_2Hb/O_2Mb, HHb/HMb, and tHb/tMb are reported as change from baseline, as measured in micromoles (μM). In circumstances of total arterial occlusion, *THb/TMb* can be used as a measure of tissue blood volume. In this paper, the hemoglobin abbreviations O_2Hb, HHb, and tHb are used to simplify the text. Note that when these abbreviations are used, it is implicitly implied that myoglobin is also being discussed.

Experimental arterial occlusion. Inflating a BP cuff to 80 millimeters of mercury (mmHg) above systolic pressure, blocks both venous outflow and arterial inflow, effectively eliminating systemic circulatory changes in the limb. Without sufficient oxygenated blood, muscle metabolism will depend directly on the oxygen available in the local capillaries and muscle cells. In this situation, NIRS illustrates a decrease in O_2Hb, a concurrent increase in HHb, while tHb remains constant (see Figure 4). With the release of arterial occlusion, a hyperemic response is often observed. This is due to a rapid increase in blood volume, which supplies fresh O_2Hb and quickly eliminates HHb. Using this method, it is possible to calculate oxygen consumption, re-oxygenation rate, and the half-recovery times of the signals during this type of controlled condition.

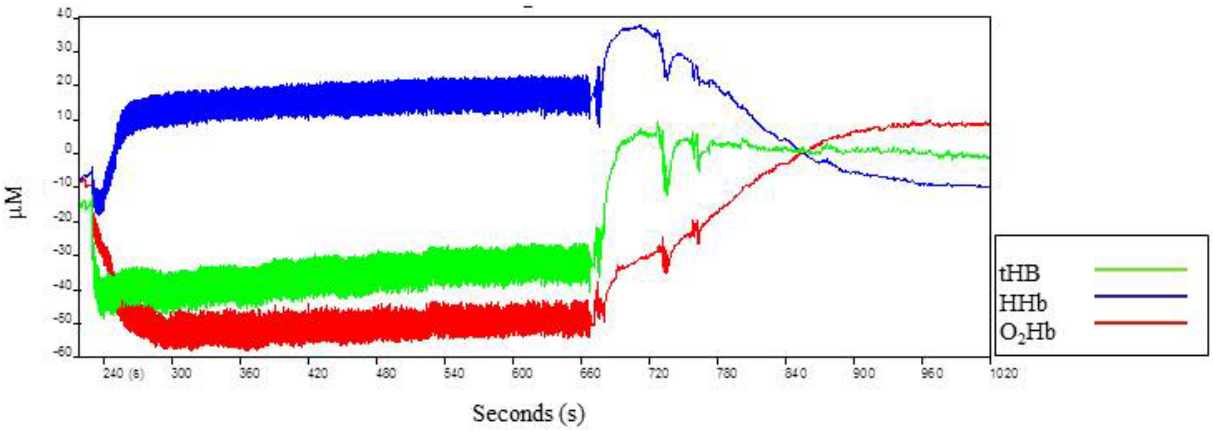

Figure 4. During arterial occlusion, NIRS displays a decrease in oxygenated hemoglobin (O_2Hb) and a concurrent increase in deoxygenated hemoglobin (HHb), while total hemoglobin (tHb) remains constant. During reperfusion, O_2Hb and tHb increase, while HHb decreases.

Arterial insufficiency in patients with PAD during exercise. The ability of NIRS to monitor changes in tissue oxygenation non-invasively and directly in the muscle makes it a powerful tool for studying PAD related ischemic changes. In this population, NIRS technology can be used during exercise to objectively assess the degree to which the

oxygenated blood supply is being restricted in the calf muscle as a result of arterial narrowing and/or blockage (i.e., ischemia). This can be compared with subjective symptom report to provide a more comprehensive description of the PAD symptom experience.

Conceptual Framework

This study was guided by current literature related to PAD symptom experiences, PAD pathophysiology, and an understanding that variables such as demographic characteristics and comorbid conditions may confound the PAD symptom experience. Figure 5 presents the conceptual framework that guided this investigation and illustrates how a symptom can be classified as ischemic or non-ischemic in three phases: at rest, during exercise, and during recovery. Individuals with PAD have arterial insufficiency. During exercise, arterial blood flow to the lower extremities cannot meet the oxygen demand of working muscles, leading to skeletal muscle ischemia and causing classic claudication and other lesser recognized symptoms. At rest, prior to exercise, or shortly after activity ceases, blood flow is sufficient to prevent or relieve ischemic symptoms. However, some individuals report 'atypical' symptoms during exertion or report discomfort that continues beyond the typical recovery time (McDermott, Mehta, & Greenland, 1999; Olson & Treat-Jacobson, 2004). It is unknown to what extent symptoms that fall outside the classic definition of claudication are 'atypical' presentations of ischemia-dependent symptoms versus ischemia-independent symptoms arising from other chronic conditions.

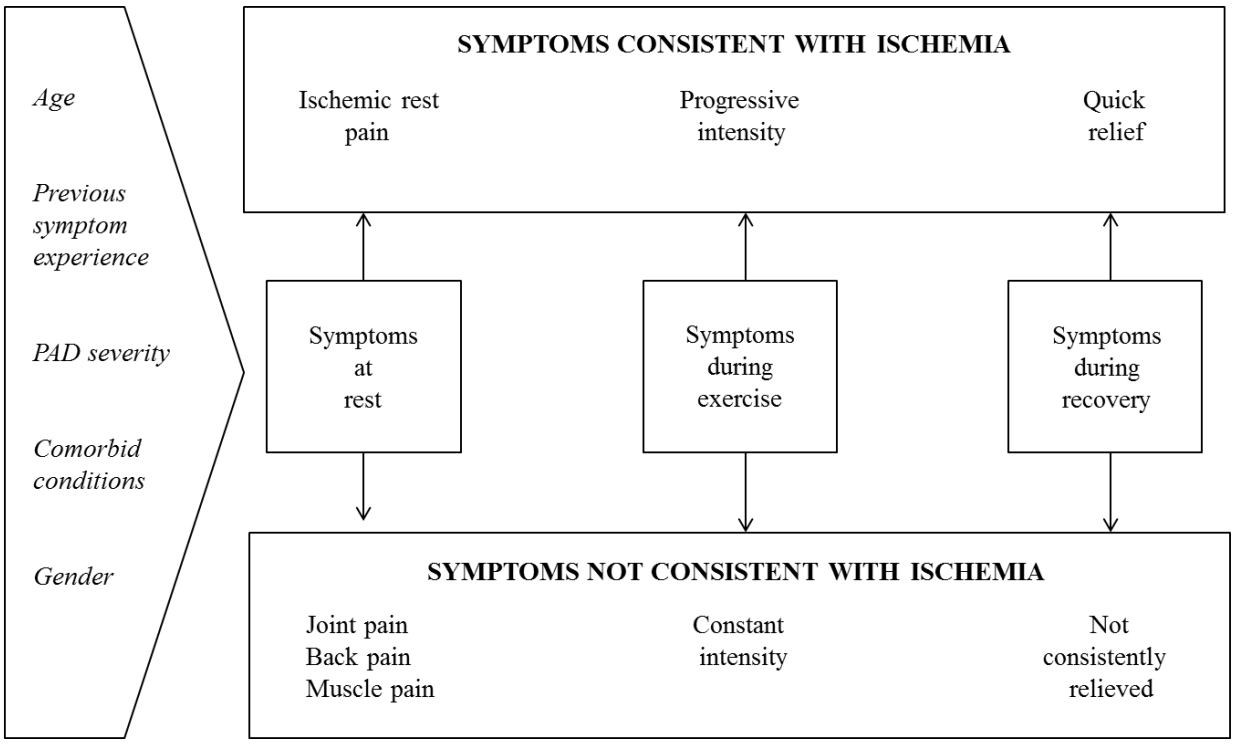

Figure 5. The conceptual framework for the study illustrates how a symptom can be classified as ischemic or non-ischemic in three phases: at rest, during exercise, and during recovery.

To determine which symptoms are related to ischemic changes in skeletal muscle it is necessary to simultaneously measure subjective PAD symptom reporting and objective lower extremity tissue oxygenation during dynamic exercise. Verbal report of symptoms (e.g., location, severity, and sensation) is uncomplicated and can be used to subjectively assess the PAD symptom experience. As previously discussed, recently developed techniques, such as NIRS, allow for non-invasive measurement of objective changes in calf tissue oxygenation during exercise in individuals with PAD (e.g., treadmill walking) (Dolan et al., 2002; McDermott, Mehta, & Greenland, 1999; McDermott et al., 2001). The physiologic data obtained with NIRS can be compared to the subjective symptoms reported to determine the relationship. Both typical and

‘atypical’ symptoms that begin after the onset of ischemia, increase in intensity as ischemia worsens, and are relieved as ischemia improves, can be distinguished from symptoms that do not consistently change with ischemia. This will confirm the exclusion of symptoms not related to ischemia and provide support for broadening the definition of claudication to include ‘atypical’ ischemia–dependent symptoms.

Chapter 3: Research Method

Design

This was a descriptive, exploratory, longitudinal study designed to comprehensively examine the symptom experience of older and younger men and women with PAD. A mixed methods approach, combining qualitative and quantitative techniques, was utilized to fully capture the subjective and objective components of the PAD symptom experience. The subjective components consisted of verbal symptom report of PAD symptoms at rest and during exercise, while physiologic data related to tissue oxygenation during exercise and recovery constituted the objective component. Gaining a more comprehensive understanding of the PAD symptom experience is a necessary first step towards improving the timeliness and accuracy of diagnosis and leading to implementation of the proper treatment to minimize the progression and complications associated with this debilitating disease.

Specific Aims

The specific aims of this study were to:

1. Understand the symptom experience of older and younger men and women with PAD through in-depth qualitative interviews.
2. Simultaneously evaluate calf tissue oxygenation and the self-reported symptoms experienced by older and younger men and women with PAD during treadmill exercise and throughout recovery.

Parent Study: Exercise Training to Reduce Claudication (EXERT)

All study participants were recruited from the **EX**ercise Training to Reduce Claudication: Arm **ER**gometry versus Treadmill Walking (EXERT) study. This study is

funded by the National Heart, Lung, and Blood Institute (NHLB) (R01 HL 090854-03, PI: Dr. Diane Treat-Jacobson), and examines the efficacy of two forms of supervised exercise compared to the usual care provided by a physician for the treatment of PAD. Specially, the EXERT study compares aerobic arm exercise and treadmill walking, to determine which, if any, form of supervised exercise reduces the symptoms of claudication and improves the walking ability in patients with PAD. Study procedures include a screening visit, baseline testing (cardiac exercise stress test, confirmatory ABI, etc.), supervised exercise training three times per week or a weekly control visit, and follow-up testing at six week increments, until 24 weeks of study participation has been completed.

Pre-Testing

Prior to full scale introduction of the main study, two small studies were planned and carried out with the goal of positively informing the recruitment, design, procedures, and measurements of the main study. Qualitative and quantitative components were assessed on separate occasions.

External qualitative pilot study. A formal and independent preliminary trial of the qualitative component of the study was conducted with four volunteers diagnosed with PAD and experiencing exercise-limiting symptoms. The main goals of the pilot study were to determine: 1) the feasibility of recruiting and consenting participants, 2) the integrity of the qualitative study protocol, and 3) the comprehensiveness and appropriateness of the semi-structured interview (see Appendix A) and the PAD symptom questionnaire (see Appendix B). The primary research question was 'How do individuals with PAD describe the symptom experience?'

Design. The pilot study was a naturalistic study, in which the researcher observed and recorded the participants' descriptions of the PAD symptom experience while interfering with participants as little as possible. To date, no studies have attempted to extract symptom descriptors through a combination of a semi-structured interview and completion of a PAD symptom questionnaire, and the recent research demonstrated a need for a more thorough description of PAD symptoms.

A semi-structured, face-to-face, descriptive interview was selected to explore the attitudes, beliefs, and perceptions of individuals diagnosed with PAD. Data obtained from interviews were particularly well-suited to answer the research question of interest since interviews allowed for a detailed account of the PAD symptom experience in a participant's own words. Each interview question was designed to be clear, open-ended, sensitive, neutral, and targeted towards the participants' PAD symptom experience, with a particular focus on symptoms during exercise.

The PAD symptom questionnaire allowed for a visual representation of the patients' symptom location and description; it also served to verify congruence with symptom information that was provided during the interview. It was designed to be a comprehensive assessment of all the symptoms a participant experienced during exercise and rest, related or unrelated to PAD. The questionnaire utilized a body diagram and color coding to differentiate the location and sensation of each symptom, and to follow its course from rest to onset and time to relief. The primary goal was for participants to first describe all of their symptoms in detail, and then target symptoms they believed to be directly related to their PAD.

Sample. The population of interest was adults with a diagnosis of PAD who were

experiencing exercise-limiting symptoms. Inclusion criteria were: (a) adults (18+ years), (b) people with a diagnosis of PAD, (c) PAD symptoms while exercising, and (d) able to read, write, and speak the English language. Exclusion criteria: (a) children under the age of 18. Participants were not included or excluded based on race, gender, or ethnicity.

Ethical considerations. In accordance with the regulations of the 1996 Health Insurance Portability and Accountability Act (HIPAA), and as stipulated by the University of Minnesota Institutional Review Board (IRB), the PI was not allowed to make the initial contact with potential participants. The EXERT Study Research Coordinator obtained permission from interested individuals at the initial EXERT study screening visit to be contacted about this study.

If an individual agreed to be contacted, the PI was provided with the potential participant's contact information. Individuals were then contacted by the PI via telephone and provided with more information about the study, prior to asking about their willingness to participate. For individuals who expressed an interest in participation, a time was arranged for the investigator and the individual to meet and proceed as appropriate. An information sheet for research was utilized to ensure participants were fully aware of the risks and benefits, as well as the burdens of participation (see Appendix C). If after being provided with more information regarding the study, individuals did not wish to participate, no further action was taken by the PI. The individuals' information was then shredded to protect confidentiality.

The participants who agreed to participate were each assigned a code name. Code names were used on all questionnaires, field notes, and audio tapes. Participant names with code names were only accessible by the PI and stored in a locked filing cabinet

separate from the data with code names.

Personal preconceptions. Since the PI had previously worked with PAD patients in the screening, exercise training, and research testing capacity as a graduate assistant on the EXERT study, personal preconceptions existed. The PI had worked with individuals with known PAD who had provided PAD symptom descriptors that were not consistent with the commonly recognized and hallmark symptom of PAD, classic claudication. Therefore, the researcher had a preconceived notion that other valid PAD symptom descriptors beyond what was currently being utilized in practice might exist. Furthermore, the PI had witnessed an apparent disassociation in the symptom experience of men versus women. For both aforementioned reasons, the PI decided to undertake this qualitative pilot study to explore this area in a more detailed and scientific manner. Despite the PI's preconceptions, every attempt was made during data collection and analysis to set aside these preconceived notions to see what naturally emerged from the data.

Data collection procedures. After obtaining IRB approval from the University of Minnesota (see Appendix D), participant recruitment began. A total of four participants were recruited through purposive sampling. All of the study meetings and activities took place on the second floor of the Delaware Clinical Research Unit in room 250, located on the University of Minnesota, Minneapolis campus. To reduce burden, meetings were scheduled to take place immediately following supervised exercise training for the EXERT study. The PI met with each participant one time to complete a semi-structured interview and the PAD symptom questionnaire (see Appendices A and B). A printed copy of the questionnaire and the information sheet for research were provided prior to

the beginning of the visit.

All participant responses during the interview and throughout the completion of the PAD symptom questionnaire were audio-recorded. Each interview lasted on average, 30 to 45 minutes. Two recorders, a primary and a backup, were started prior to the interview taking place, but after participants viewed the information sheet for research and agreed to participate. Both recorders were placed to the side of the table in an attempt to reduce measurement reactivity. However, all participants were informed of the audio recording verbally and in writing prior to enrolling in the study.

Data analysis. Conventional content analysis procedures were used to analyze the descriptive data gathered during participant interviews (Hsieh & Shannon, 2005; Van Manen, 1990). Initially, the recording unit of analysis was defined by the researcher as single words used by the study participants to describe the PAD symptom experience (i.e., symptom descriptors). However, as the analysis began, coding for thematic units (Henri, 2012; Van Manen, 1990), also referred to as dynamic units, seemed more appropriate to recognize each individual's PAD symptom experience, as well as to uncover a comprehensive group of thematic units in order to understand the phenomenon of interest as a whole. Data were coded for the existence of any descriptors of the PAD symptom experience, as opposed to using frequency to determine the validity of a select few descriptors. This was done largely because of a limited sample size (n=4). Additional details related to the content analysis of data are detailed in the data analysis section under aim one of the main study.

Results. The final sample consisted of four participants afflicted with PAD, two males and two females, aged 48 to 79 years. The following themes were extracted from

the participant transcripts: *ache, heavy, weak, Charley horse, cramp, sharp, tight, numb*, shin involvement, quick dissipation, limiting/adjusting, need for frequent sitting, progressive, indescribable, unilateral symptoms, and asymptomatic.

***Impact on main study*.** The pilot study enabled preliminary testing of the feasibility of recruiting and consenting participants for the main study. Based on the results of the pilot, the questions on the semi-structured interview form and the PAD symptom questionnaire remained unchanged. Both measurements appeared to be comprehensive and appropriate for answering the research question. However, due to the difficulty participants experienced in independently identifying accurate symptom locations and following a consistent color coding system on the questionnaire, it was decided that the researcher would complete the questionnaire in the main study on the behalf of each participant. This would enhance consistency in reporting and allow for more clear comparisons amongst responses in the main study. It is important to note that the focus of the pilot was on testing the administration of the questionnaire, as opposed to testing its validity and reliability. Based on the pilot study results, no other qualitative protocol changes were deemed necessary.

Initially, a purely qualitative study design was selected and this external qualitative pilot study was conducted based on this design. However, results from the pilot study confirmed the results of recently published research citing the existence of PAD symptom descriptors beyond those currently recognized in clinical practice (McDermott, Mehta, & Greenland, 1999; Tomczyk & Treat-Jacobson, 2009; Treat-Jacobson et al., 2002). Despite the recognition of 'atypical' ischemia-dependent symptoms in the literature, it appeared that relying solely on subjective participant PAD

symptom report, while excluding objective physiologic measurement of calf tissue oxygenation, would fail to validate any ischemia-dependent symptoms reported, thus still limiting the current understanding of the PAD symptom experience. After further consideration, a decision was made to incorporate subjective and objective elements into the design to comprehensively examine the PAD symptom experience.

NIRS feasibility. Although the information provided by the NIRS feasibility evaluation was just as important as the external qualitative pilot study and it was designed with similar goals in mind, it was a much less formal evaluation. The primary goals of the NIRS feasibility evaluation were to: 1) assess recently developed quantitative study procedures, specifically those focused on NIRS measurement and data acquisition following the testing protocol, and 2) refine the application and securing of the NIRS device on individual calf muscles, as well as accurately operate the NIRS device to ensure effective and adequate data collection during static and dynamic states.

Over a two day period, five young, healthy male and female students volunteered to participate in the feasibility evaluation. The evaluation began by covering the NIRS device with a thin and transparent layer of clear plastic wrap and placing the device over the largest part of the right gastrocnemius muscle (i.e., calf) of the first participant (based on the calf circumference obtained with a tape measure while resting in a seated position). The device was secured with 3M™ Coban™ self-adherent wrap, and resting baseline values were obtained (i.e., O_2Hb, HHb, tHb, TSI, and seated BP). Next, a large adult BP cuff was placed around the upper portion of the right leg. Participants were then asked to begin walking at a slow pace on the treadmill (generally, 2.0 mph, 0% grade). During treadmill walking, arterial occlusion was simulated by inflating the upper leg BP

cuff to 80 mmHg above the systolic arm pressure value obtained at rest. Participants were asked to numerically rate their discomfort on the NRS (Figure 1) and to provide descriptions of the symptom(s) location and sensation. Treadmill speed and grade were increased as tolerated, on an individual basis, in order for each participant to reach maximal discomfort (i.e., 5 out of 5 on the NRS). Testing was stopped when an individual reported a rating of 5 on the NRS. NIRS measurement continued until each participant reached full recovery (i.e., a rating of 0 out of 5 on the NRS).

All five participants reported symptoms consistent with exercise-induced ischemia (e.g., *cramp*, *heavy*, *tired*), that worsened as exercise continued and eventually required cessation of physical activity to achieve symptom relief. The results observed were expected to be similar to those of individuals with PAD who were invited to participate in the main study. No major changes to the main study protocol occurred based on the feasibility evaluation. However, to increase the accuracy and completeness of descriptive symptom reporting and the timing of NRS ratings, it was decided that the treadmill tests for all of the participants in the main study would be audio-recorded. Although this evaluation didn't necessitate major changes in the main study protocol, this evaluation increased the PI's familiarity with the NIRS device to obtain values, mark events, and export data, as well as providing exposure to the complexity of simultaneously recording participant data and ensuring safety during treadmill exercise.

Study Population

Setting. Study participants were recruited from the previously described EXERT study. EXERT study staff described this research study to current and future EXERT participants. If a participant expressed interest in this study, the EXERT study staff had

the individual complete a study interest form that provided the PI with basic contact information. This information was then given to the PI, at which time the individual was contacted and a more detailed study explanation was provided.

Additionally, a recruitment letter that was approved by the University of Minnesota IRB was sent to all previous EXERT study participants (see Appendices E and F). This letter provided individuals with a brief overview of the proposed study and introduced them to potential participation in a non-coercive manner.

Sample size. Given the exploratory nature of the study, some measures and their associations had not been previously studied. Therefore, there were no reliable data on which to base a power analysis. The data from this study will allow for these estimates and enable conduction of a proper power analysis in future studies. For the exercise testing study component, 40 participants was determined to be a feasible number to recruit in the time allotted, and a sufficient number of participants to get estimates of effects and a sense of the variability within measurements and between subjects. Sample size guidelines for qualitative research were used to provide an estimate of an appropriate sample size for the interview component of the study (Guba & Lincoln, 1994).

Sample. It was anticipated that 20 participants would complete the semi-structured qualitative interview with the anticipation that data saturation would be achieved with this number. The other 20 participants were to complete an abbreviated symptom interview in an effort to improve symptom reporting during exercise testing. Any English speaking individual aged 21 years or older, with an ABI ≤ 0.90, reporting exercise-limiting claudication or ischemia-related symptoms, and deemed safe to exercise was considered as a potential participant and screened for eligibility. See Table 2 for the

full list of study inclusion and exclusion criteria.

Table 2

Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• ≥ 21 years of age • English speaking • Exercise limiting claudication • ABI of ≤ 0.90 • Ability to provide informed consent • Cleared for exercise via exercise or pharmacological stress test within one year of study enrollment	• Uncontrolled hypertension (>200 SBP mmHg and/or DBP >100 mmHg) • Vascular surgery/procedure within three months of study enrollment • Exercise capacity limited by health problems other than claudication (e.g. angina, severe arthritis, or extreme dyspnea on exertion)

Note. ABI=ankle-brachial index; SBP=systolic blood pressure; mmHg=millimeters of mercury; DBP=diastolic blood pressure.

Variables and Measurements

Demographic and medical information. Data obtained from the medical record for this study included primary medical diagnosis, comorbid conditions, previous procedures and outcomes related to exercise and PAD, previous ABI values, cardiac stress test results, and medications. Additional data, including age, gender, education, ethnicity, and employment were collected with a standard demographic form (see Appendix G). During the consenting visit, participant medications were carefully reviewed to ensure that participants were not taking any medications that would be affected by exercise (Appendix H).

Ankle-brachial index (ABI). The ABI, a ratio between the ankle and arm systolic BP, was utilized to confirm the presence of PAD and to determine disease severity at the time of study enrollment. An ABI ≤ 0.90 is diagnostic of PAD (Aboyans et al., 2012; Albert et al., 2013; Coutinho et al., 2011; Tendera et al., 2011). Participants rested quietly in a supine position for 10 minutes prior to the PI obtaining the ABI

according to standard procedures (see Appendix I) (Grenon, Gagnon, & Hsiang, 2009; Leng et al., 1996; Stoffers et al., 1996).

Treadmill familiarization. This was completed prior to exercise testing to ensure participant safety and adequate understanding of treadmill exercise testing procedures, and to determine the appropriate speed and grade for exercise testing. The speed during treadmill familiarization began at 1.5 mph at a 0% grade. Both speed and grade were adjusted as necessary to induce ischemia-related discomfort within 3 minutes of treadmill walking (see Appendix J).

Treadmill test. The starting speed and grade for treadmill testing was individualized and determined by the results of the treadmill familiarization. Speed and grade progression was also individualized to prevent high functioning patients from stopping the test due to symptoms other than claudication and to prevent provoking discomfort too early in more severely limited participants, which would have potentially condensed symptom reporting and prevented the collection of meaningful data. The expected starting speed and grade for most participants was 2 mph and 0% grade, with an increase in the grade to 2% at two minutes. Thereafter, grade was increased by 1% every two minutes, maintaining a speed of 2 mph. If participants continued walking, the speed was increased to 2.5 mph at 16 minutes.

Subjective symptom reporting. To gain a better understanding of individual perceptions of PAD symptoms, participants were asked to report symptoms during static (i.e., seated interview) and dynamic (i.e., treadmill walking) conditions.

Semi-structured interview. Prior to exercise testing, participants were prompted to describe all of the symptoms they experience at rest and with exercise, related or

unrelated to PAD (see Appendix A for the interview guide). Interviews were recorded and conducted using methods established during the PI's pilot study. Field notes were be taken by the PI as necessary, but kept to a minimum to avoid participant distraction.

There was a potential risk that participants would experience emotional distress or anxiety while discussing the symptom experience during the interview. To minimize this potential risk, prior to the interview, participants were reminded that their participation was voluntary and they could withdraw at any time for any reason without suffering any adverse consequences.

To minimize response burden, only questions directly related to the study aims were utilized during participant interviews. Additionally, within the timeframe between participant consenting and exercise testing, exact timing of interviews was left up to the discretion of the individual participant. This allowed the participant to complete the interview and exercise tests when they were least burdensome and according to individual stamina.

Symptom descriptors. During the interview, each participant provided a comprehensive description of the symptom(s) they experienced during exercise. Participants were encouraged to provide the location, sensation, and estimated duration of each symptom reported. Additionally, symptoms were described on the PAD symptom questionnaire (Appendix B). Again, descriptions included location, sensation, and duration, for symptoms thought to be related to PAD, as well as those thought to be unassociated with the disease.

Numeric rating scale (NRS). Participant symptom rating was measured at the onset of symptoms and throughout symptom progression during exercise, as well as

during recovery, using the NRS (Figure 1). On this scale, a rating of 0 corresponds to *no discomfort*; whereas a rating of 5 is the *maximum ischemia-related discomfort* experienced.

Objective measurement of calf tissue oxygenation. Calf tissue oxygenation was objectively measured via near-infrared spectroscopy (NIRS). As mentioned previously, the PortaMon™ NIRS device provided baseline and continuous-wave measurement of tissue oxygenation in the exercising calf muscle to determine the degree of calf tissue ischemia during exercise and recovery. The device was placed, secured, and operated using methods established during the NIRS feasibility evaluation. Instead of placing the device on the right leg, as was done with the healthy participants in the feasibility evaluation, the device was placed on the calf muscle of the more symptomatic leg as reported by each study participant, regardless of disease severity (which was determined by the confirmatory ABI). If participants reported equal symptom severity in both legs, the device was placed on the leg with the higher disease severity (i.e., lower ABI). Equilibration, as well as baseline and continuous measurements were obtained following methods consistent with previous PAD NIRS studies (Gardner et al., 2009; Hamaoka, McCully, Quaresima, Yamamoto, & Chance, 2007; Manfredini et al., 2009; Van Beekvelt, Colier, Wevers, & Van Engelen, 2001) and the PI's previously conducted feasibility evaluation.

Safety measures. Exercise testing carries a small risk (1 in 10,000) of heart attack or death. Potential risks to participants included exercise related risks such as a change in BP, heart rate (HR), and/or rhythm. Other potential risks included physical discomfort from inflation of the BP cuff, disclosure of protected health information, and

response burden. The likelihood of potential risks was believed to be minimal and the following procedures were in place to decrease the potential risks that have been described.

Blood pressure (BP). BP was taken pre- and post-exercise, while seated and standing, as a safety measure before, during, and after exercise. During the evaluation of BP function, if a participant felt that the discomfort from the inflation of the BP cuff was more than they could tolerate, they were instructed to inform the researcher and their study participation would be terminated for safety reasons.

Heart rate (HR). A Polar™ HR monitor strap was placed across the participants' chest and a baseline HR was obtained. Participants were informed of their maximal HR based on the stress test results provided during study enrollment. HR was monitored continuously during exercise and recovery. If HR exceeded 85% of the maximum HR achieved during cardiac or pharmacological stress testing, the treadmill speed and grade were to be reduced. If HR remained elevated, the exercise test would be stopped.

Blood glucose. Any individual with a confirmed diagnosis of DM, type 1 or 2, received blood glucose testing before and after exercise (obtained via glucometer). If blood sugar levels were low, participants were provided with an appropriate snack and testing continued until the participants blood glucose returned to a normal level to ensure their safety after completing the study visit.

Procedure

After obtaining informed consent and HIPAA authorization (see Appendices K and L), data were collected from each participant's medical record. Participants then completed the treadmill familiarization. Next, participants verified their medical record,

filled out the demographic form, and completed the semi-structured interview. Following the completion of these procedures, the 10 minute rest period for the baseline ABI was initiated. After 10 minutes of rest, the ABI was obtained, recorded, and reported to the participant. The Polar™ HR monitor was placed around the participant's chest and the baseline HR was obtained. Next, the NIRS device was covered with a thin and transparent layer of clear plastic wrap to protect it from perspiration and placed on the inner aspect of the appropriate calf muscle at the area of largest circumference (consistent with the pilot study, the largest circumference was determined prior to testing with a tape measure while the participant rested in a seated position with both feet flat on the floor). The device was secured with 3M™ Coban™ self-adherent wrap and paired via Bluetooth with the study dedicated laptop computer. The participant was asked to remain in a seated position while baseline values (e.g., O_2Hb, HHb, tHb, TSI, HR, and seated BP) were obtained. During this time, a repeated explanation of study procedures was provided and participants were offered another opportunity to ask any study related questions prior to the start of exercise testing.

Each treadmill test was started at the speed and grade that was determined during the treadmill familiarization. Participants were asked to descriptively (e.g., left calf ache) and numerically (on the NRS) report the onset of symptoms (e.g., 1 out of 5) and the progression of symptom intensity, at whole integers on the NRS, until the maximum discomfort level was achieved (i.e., 5 out of 5 on the NRS). Symptom report was recorded on a data collection form (see Appendix M), as well as audio-recorded for the purposes of data verification. After reaching a rating of 5 on the NRS, the treadmill speed and grade were reduced slowly until the participant was able to safely stop walking

on the treadmill. At that point, they were assisted off of the treadmill and into a seated, resting position in a chair.

At the beginning of the recovery period, post-exercise BP and HR were obtained and recorded on the data collection form. Throughout recovery, subjective (e.g., symptom descriptions and ratings on the NRS) and objective (e.g., NIRS measures) data collection continued. Full recovery was reached when participants reported a rating of 0 on the NRS, and HR and BP returned to or fell below baseline values.

Two additional exercise tests were performed during the same session, following the same procedures as the first test. During the second and third exercise tests, participants again reported the onset and acceleration of symptoms, in addition to providing verbal descriptors of their symptoms throughout exercise. To ensure safety, continuous HR monitoring and periodic BP monitoring continued throughout the remainder of the study visit.

Ethical Considerations

Protection against potential risks. Because of the risks associated with exercise testing, several procedures were in place to minimize the risks to study participants. These procedures are described in the safety measures section.

Data management and security. Consistent with the external qualitative pilot study, numeric codes were used on all data collection forms and de-identification was ensured. Participant names with numeric codes were kept in a locked cabinet separate from the data with numeric codes and remains only accessible by the PI. All study data were kept in a secured locked file cabinet in the PI's office. Electronic databases were password protected and stored on a secure desktop computer. A codebook was

developed and revised for all of the study procedures and variables. The PI was solely responsible for the storage, entry, auditing, and analysis of all data.

Data Analysis

Data were collected during semi-structured interviews, and during the resting, exercise, and recovery phases of three consecutive treadmill tests with adequate rest periods in between. The data were analyzed using content analysis, descriptive statistics, graphing individual growth trajectories, and multi-level modeling (MLM). Lastly, the data were evaluated as a whole to provide a more comprehensive understanding of the PAD symptom experience. SPSS version 21 was used for descriptive statistics, SigmaPlot version 10.0 was used to graph individual growth trajectories, and R version 2.15.2 was used for estimating exercise and recovery models over time.

Aim 1: Content analysis of the PAD symptom experience. The semi-structured interview transcripts were analyzed using qualitative content analysis, which is the interpretation of data through the systematic identification of patterns or themes (Hsieh & Shannon, 2005). This coding method provides simplification and organization of large amounts of text (Holsti, 1969) in order to discover meaningful patterns that are descriptive of a particular phenomenon (Auerbach & Silverstein, 2003; Van Manen, 1990). The analysis procedures followed were consistent with conventional content analysis guidelines (Hsieh & Shannon, 2005; Van Manen, 1990), and were identical to those utilized when analyzing the transcripts of the previously mentioned external qualitative pilot study. The recording unit of analysis was dynamic units, also referred to as thematic units (Henri, 2012; Van Manen, 1990). Consistent with the analysis of the pilot study data, all descriptions of the PAD symptom experience were coded, regardless

of their frequency.

Transcripts were generated from the audio taped interviews. Each transcript was reviewed three times for verification of authenticity and to capture any emotional content in the recording that was not evident in the written transcripts. Transcript review was followed by preliminary analysis. This consisted of reading through every transcript once to understand each interview in its entirety, writing memos throughout as necessary to note emerging themes. The primary goal of the preliminary analysis was to get a sense of the whole and understand the essential features of each interview (Sandelowski, 1995).

Next, the emerging codes were listed and additional memos were taken throughout the duration of analysis. Connections between the codes were identified, and codes were clustered together as necessary to capture the essence of the PAD symptom experience. The final result was multiple categories that reflected topics appearing in all of the data. Verbatim quotes representative of each theme were extracted from the transcripts, as appropriate. The content of each category was analyzed to ensure that there were no subcategories that could be merged into a higher category. Lastly, descriptive statistics were calculated as appropriate to analyze the data for the consistency of symptom descriptors amongst age group and gender.

Reliability. According to Lederman (1991), there are three types of reliability relevant to content analysis: stability, reproducibility, and accuracy. Stability and reproducibility were addressed through the use of two human coders with experience in qualitative research methods. The first coder was the PI and the second coder was Dr. Cynthia Peden-McAlpine, an expert in qualitative research methodology who reviewed the transcripts and verified the codes. Intercoder reliability was further increased by

providing the second coder with the PI's content analysis steps with ambiguous words being clearly and consistently defined throughout, in addition to providing memos and field notes that detailed reactions, biases, and thought processes throughout data collection and analysis.

Accuracy was assessed by test coding pieces of text extracted from the transcripts. This aspect of rigor is reached when the investigator can provide a full range of lived experiences and fully capture the phenomenon. The PI used memoing, as well as written and spoken data while performing content analysis to gain a comprehensive understanding of the PAD symptom experience. Another method that increased data accuracy was human coding, as opposed to relying on a computer to identify, code, and cluster the emerging themes. Computer content analysis may be superior to human coding in large projects or in coding that focuses on analyzing specific words or verbatim phrases (Popping, 2000). However, in this research, computer coding would not have provided specific detail on how final codes were decided upon, as well as specify the steps involved in the process; which gives further support to human coding and recording memos.

Validity. Validity of the content analysis was assessed through confirmability and transferability, also referred to as generalizability.

Aim Two: Modeling the PAD symptom experience. Multilevel modeling (MLM) was used to determine: 1) how TSI changed from baseline to onset, during the progression of symptoms, and during recovery, and, 2) whether characteristics such as gender, age, and disease severity were related to particular patterns of change in TSI over time. The first component is descriptive and characterizes each individual's pattern of

change over time (Singer & Willett, 2003). This question was addressed through graphing individual growth trajectories to examine how TSI changed over time. The second question is relational and examines the associations between predictors and patterns of change (Singer & Willett, 2003). The second question was addressed by examining groups of smoothed individual growth trajectories for similarities and differences and utilizing MLM to estimate the associations between predictors and particular individual patterns of change during the exercise and recovery phases.

Individual graphical trajectories. Individual patterns of change were explored by graphing the trajectories of TSI and discomfort ratings throughout the exercise and recovery phases of three consecutive treadmill tests for each participant. These graphs enabled the selection of a functional form by assessing the intra-individual variation in the outcome variable (i.e., TSI) over time. Graphs were smoothed via loess and comparisons were made between groups, with a particular focus on age and gender.

Multilevel model for change. Building a multi-level model allowed for examining the associations between predictors and patterns of change. Specifically, MLM characterized change within individuals (level-1) and between individuals (level-2) over time. Each participant completed three treadmill tests, which created multiple waves of data (i.e., repeated measures). Repeated measures increased the flexibility for MLM with less restrictive assumptions compared to two wave studies (Singer & Willett, 2003).

Data were organized in a person-level data set and structured hierarchically; repeated observations were nested within individuals. The outcome variable was TSI, expressed as a percentage and recorded continuously over time. Individual level

predictors included baseline TSI, exercise time, recovery time, exercise rating, recovery rating, disease severity as measured by ABI, age, body mass index (BMI), gender, race, smoking status, and the presence of comorbid conditions such as DM and neuropathy.

Unconditional means model. The unconditional means model (equations 2 through 4), tested two null hypotheses: (1) no change over time (i.e., within-person variation), and (2) no variation between participants (i.e., between-person variation). In other words, this model tested whether there was sufficient variation in the outcome variable, TSI, to warrant further analyses. If TSI did not change significantly over time within individuals and variation in TSI did not significantly vary from individual to individual, no further analysis would be necessary. However, it was expected that there would be sufficient variation, at least between-person variation, thus a more complex model (introducing predictors) would be required to explain the intra- and inter-individual change in TSI over time.

Level-1 model:

$$Y_{ij} = \pi_{0i} + \varepsilon_{ij} \qquad [2]$$

Level-2 model:

$$\pi_{0i} = \gamma_{00} + \zeta_{0i} \qquad [3]$$

Y_{ij} = tissue saturation index (TSI) for participant *i* at time *j*

π_{0i} = true initial status of individual *i* when time *j* = 0

ε_{ij} = level-1 (within-person) residual for individual *i* at time *j*, assuming $\varepsilon_{ij} \sim N(0, \sigma^2/\varepsilon)$

γ_{00} = grand mean TSI across individuals and occasions

ζ_{0i} = person specific mean for individual *i* at time *j* = 0, assuming ζ0i ~ N (0, σ^2/0)

N = normal distribution

σ^2/ ε = within-person variance

σ^2/0 = between-person variance

The composite model:

$$Y_{ij} = \gamma_{00} + \zeta_{0i} + \varepsilon i_j \quad [4]$$

Unconditional growth model. The unconditional growth model (equations 5 through 8), introduced the predictor, *TIME*, into the level-1 sub-model. Variation in this model was partitioned across individuals and time. This model estimated how much variation in TSI was attributable to linear *TIME*. However, it was expected that sufficient variation would remain after accounting for *TIME*, meaning that a conditional growth model that includes time-invariant level-2 predictors would be warranted. This model served as a baseline model for change over time.

Level-1 model:

$$Y_{ij} = \pi_{0i} + \pi_{1i} TIME_{ij} + \varepsilon_{ij} \quad [5]$$

Level-2 model:

$$\pi_{0i} = \gamma_{00} + \zeta_{0i} \quad [6]$$

$$\pi_{1i} = \gamma_{10} + \zeta_{1i} \quad [7]$$

Y_{ij} = tissue saturation index (TSI) for participant *i* at time *j*

π_{0i} = true initial status of individual *i* when time *j* = 0

π_{1i} $TIME_{ij}$ = true rate of change per unit of TIME (second) for individual *i*

ε_{ij} = portion of individuals *i's* TSI unexplained on occasion *j*, assuming ε_{ij} ~ N (0, σ^2/ε)

γ_{00} = population average initial status when time *j* = 0

ζ_{0i} = level-2 residuals for individual *i* at time *j* = 0, assuming ζ0i ~ N (0, σ^2/0)

γ_{10} = population average true rate of change

ζ_{1i} = level-2 residuals of individual *i* from the average rate of change

N = normal distribution

σ^2/ε = within-person variance

σ^2/0 = between-person variance

The combined equation is:

$$Y_{ij} = \gamma_{00} + \gamma_{10}\, TIME_{ij} + [\zeta_{0i} + \zeta_{1i}\, TIME_{ij} + \varepsilon_{ij}] \qquad [8]$$

Conditional growth model. The conditional growth model introduced level-2 predictors that had the potential to explain some of the variation in TSI over time. With MLM, two types of effects can be modeled, fixed effects and variance components (also referred to as random effects). The following equation [9] illustrates the full mixed model for the change in TSI during *exercise* based on multiple individual-level predictors:

$$\begin{aligned} Y_{ije} = {} & \gamma_{00} + \gamma_{01}\text{ExerciseTime}_{ij} + \gamma_{02}\text{BaselineTSI}_{ij} + \\ & \gamma_{03}\text{ExerciseRating}_{j} + \gamma_{04}\text{ABI}_{j} + \gamma_{05}\text{Age}_{i} + \\ & \gamma_{06}\text{BMI}_{j} + \gamma_{07}\text{Diabetes}_{j} + \gamma_{08}\text{Gender}_{j} + \end{aligned} \qquad [9]$$

$$\gamma_{09}\text{Neuropathy}_j + \gamma_{010}\text{Race}_j + \gamma_{011}\text{SmokingStatus}_j +$$

$$[\zeta_{0i} + \zeta_{1i}\, TIME_{ij} + \varepsilon_{ij}]$$

Y_{ije} = tissue saturation index (TSI) for participant *i* at time *j* during exercise *e*

γ_{00} = population average initial status when time *j* = 0

$\gamma_{01}\text{ExerciseTime}_{ij}$ = individual intercept based on exercise time of individual *i* at time *j*

$\gamma_{02}\text{BaselineTSI}_{ij}$ = individual intercept based on baseline TSI of individual *i* at time *j*

$\gamma_{03}\text{ExerciseRating}_j$ = mean intercept for group based on exercise rating

$\gamma_{04}\text{ABI}_j$ = mean intercept for group based on ABI category

$\gamma_{05}\text{Age}_i$ = individual intercept based on the age of individual *i*

$\gamma_{06}\text{BMI}_j$ = mean intercept for group based on BMI category

$\gamma_{07}\text{Diabetes}_j$ = mean intercept for group based on diagnosis of diabetes

$\gamma_{08}\text{Gender}_j$ = mean intercept for group based on gender

$\gamma_{09}\text{Neuropathy}_j$ = mean intercept for group based on diagnosis of neuropathy

$\gamma_{010}\text{Race}_j$ = mean intercept for group based on race

$\gamma_{011}\text{SmokingStatus}_j$ = mean intercept for group based on smoking status

ζ_{0i} = level-2 residuals for individual *i* at time *j* = 0, assuming $\zeta 0i \sim N(0, \sigma^2/0)$

ζ_{1i} = level-2 residuals of individual *i* from the average rate of change

ε_{ij} = portion of individuals *i's* TSI unexplained on occasion *j*, assuming $\varepsilon_{ij} \sim N(0, \sigma^2/\varepsilon)$

The following equation [10] illustrates the full mixed model for the change in TSI during

recovery based on multiple individual-level predictors:

$$Y_{ijr} = \gamma_{00} + \gamma_{01}\text{RecoveryTime}_{ij} + \gamma_{02}\text{BaselineTSI}_{ij} + \quad [10]$$
$$\gamma_{03}\text{RecoveryRating}_j + \gamma_{04}\text{ABI}_j + \gamma_{05}\text{Age}_i +$$
$$\gamma_{06}\text{BMI}_j + \gamma_{07}\text{Diabetes}_j + \gamma_{08}\text{Gender}_j +$$
$$\gamma_{09}\text{Neuropathy}_j + \gamma_{010}\text{Race}_j + \gamma_{011}\text{SmokingStatus}_j +$$
$$[\zeta_{0i} + \zeta_{1i}\, TIME_{ij} + \varepsilon_{ij}]$$

Y_{ijr} = tissue saturation index (TSI) for participant *i* at time *j* during recovery *r*

γ_{00} = population average initial status when time *j* = 0

$\gamma_{01}\text{RecoveryTime}_{ij}$ = individual intercept based on recovery time of individual *i* at time *j*

$\gamma_{02}\text{BaselineTSI}_{ij}$ = individual intercept based on baseline TSI of individual *i* at time *j*

$\gamma_{03}\text{RecoveryRating}_j$ = mean intercept for group based on recovery rating

$\gamma_{04}\text{ABI}_j$ = mean intercept for group based on ABI category

$\gamma_{05}\text{Age}_i$ = individual intercept based on the age of individual *i*

$\gamma_{06}\text{BMI}_j$ = mean intercept for group based on BMI category

$\gamma_{07}\text{Diabetes}_j$ = mean intercept for group based on diagnosis of diabetes

$\gamma_{08}\text{Gender}_j$ = mean intercept for group based on gender

$\gamma_{09}\text{Neuropathy}_j$ = mean intercept for group based on diagnosis of neuropathy

$\gamma_{010}\text{Race}_j$ = mean intercept for group based on race

$\gamma_{011}\text{SmokingStatus}_j$ = mean intercept for group based on smoking status

ζ_{0i} = level-2 residuals for individual *i* at time *j* = 0, assuming ζ0i ~ N (0, σ^2/0)

ζ_{1i} = level-2 residuals of individual *i* from the average rate of change

ε_{ij} = portion of individuals *i's* TSI unexplained on occasion *j*, assuming ε_{ij} ~ N (0, σ^2/ε)

Model selection criteria. Statistical significance for the final results of all analyses was considered at $p<.05$. Since no overall fit index has been developed for use with general multilevel models, two commonly used 'penalized' model selection criteria served as the foundation for model selection: Akaike's information criterion (AIC) and Bayesian information criterion (BIC). Ideally, the final model would be favored by both criteria. However, if the AIC and BIC disagree, more consideration was given to the model favored by BIC in an attempt to balance good fit with parsimony (i.e., selecting a model with fewer parameters to estimate, therefore more degrees of freedom for error). Other model selection criteria included residual analysis and ease of interpretability.

Mixed methods research. This research combined qualitative and quantitative data (i.e., mixed methods) in an attempt to comprehensively examine the symptom experience of individuals with PAD. This approach is also referred to as methodological triangulation, in which more than one method is used to gather data with a goal of providing a more detailed and balanced picture of a situation (Altricher, Feldman, Posch, & Somekh, 2007) or to more fully explain the richness and complexity of human behavior (Cohen, Manion, & Morrison, 2011). Integration of methods occurred at the data collection and data analysis phases.

Semi-structured interviews conducted prior to treadmill exercise, allowed

participants to describe their PAD symptom experience in detail. Subsequent treadmill testing enabled subjective reporting of the PAD symptom experience through numeric ratings (using the NRS to rate the level of discomfort) and symptom descriptions (using words to describe the location and sensation of discomfort). The evaluation of calf tissue oxygenation via NIRS during treadmill testing allowed for an objective evaluation of the PAD symptom experience. Obtaining data from both perspectives (subjective and objective) of the PAD symptom experience and determining the level of congruence was thought to be a principle step towards improving the detection, diagnosis, and treatment of this painful and life-limiting disease.

Chapter 4: Results

Sample

A purposive sample of 40 participants was recruited from the EXERT study and enrolled in this study over an eight month period (August 11, 2011 through March 2, 2012). The sample consisted of adults who were experiencing lower extremity symptoms during exercise due to underlying PAD.

General summary. Based on the positive feedback received during the pilot study, the investigator attempted to conduct an interview and complete a symptom questionnaire with each participant who enrolled in the study. Although there was no attrition during the study, two male participants were unable to conduct the symptom interview due to time constraints on the day of their study visit. Both of these participants declined to come back for another study visit to complete the interview. Thus, interviews were conducted with 38 out of 40 participants who enrolled in the study (95%). Following the content analysis procedures previously outlined, data saturation was reached after analyzing 27 out of 38 interviews.

All of the study participants walked to a five out of five on the NRS during three consecutive treadmill tests with the exception of one male participant. This participant was limited by shortness of breath on the day of his study visit, thought to be related to deconditioning from a recent hospital stay. It is important to note that although this participant only reached a four out of five on the NRS during exercise, his symptoms did progress in intensity during exercise, were not present at rest (i.e., prior to exercise), and were relieved within the typical recovery time. Therefore, all of his information was

included in the final analysis. The missing NRS ratings and corresponding TSI values were considered to be missing at random.

Throughout the entire course of the study, there were no unanticipated or adverse events. At the participant's request, each interview took place on the same day as exercise testing, with the exception of two individuals (one male and one female) who were interviewed during their participation in the pilot study, prior to implementation of the full study. During the interviews, no participant exhibited anxiety or distress that required stopping the interview. Likewise, none of the exercise tests were terminated due to abnormal circumstances outlined in the method section (e.g., elevated BP, HR, or angina).

Demographics. Characteristics of the 40 participants appear in Table 3. The average age of participants was 67.55 years (*SD* 9.18). Participants were predominately Caucasian males (80%). Thirty percent of participants were aged 65 years and older, retired, and living with a spouse or partner at the time of study participation. Overall, it was a highly educated group, with over three quarters of the participants completing some college or graduate school.

Medical variables. Table 4 summarizes participant baseline disease status (i.e., ABI), BMI category, smoking status, medical diagnoses, and commonly used medications and supplements at the time of study enrollment. The average ABI indicated mild disease severity (*M*=0.81, *SD*=0.27). However, a mode ABI between 0.50 and 0.69 indicated that the largest percentage of participants had a moderate level of disease. The average BMI was 28.25 (*SD*=4.78), which falls into the overweight category. The majority of participants were overweight or obese with a history of smoking.

Medical diagnoses included risk factors for PAD (e.g., hypertension and hyperlipidemia), and comorbid conditions thought to confound the PAD symptom experience (e.g., neuropathy, OA, and spinal stenosis). Not surprisingly, the most frequently diagnosed medical conditions among participants were hypertension and hyperlipidemia, both of which are risk factors for the development of PAD. The majority of study participants were taking medications to control these conditions, with nearly 83% (*n*=33) taking a cholesterol-lowering medication and an anti-platelet agent, and 70% (*n*=28) taking a cholesterol-lowering medication, an anti-platelet agent, and an anti-hypertensive medication. Supplements were frequently used in this sample, with half of the participants taking a multivitamin and nearly one-third taking fish oil.

Table 3

Characteristics of the Study Sample (N=40)

Characteristic	Category	*n*	(%)
Age	49 – 64 years	17	(42.5)
	65 – 83 years	23	(57.5)
Gender	Male	35	(87.5)
	Female	5	(12.5)
Ethnicity	Caucasian	36	(90.0)
	African American	2	(5.0)
	Native American	2	(5.0)
Education	High school diploma	9	(22.5)
	Some college	16	(40.0)
	College degree	10	(25.0)
	Graduate school	5	(12.5)
Employment	Full time	5	(12.5)
	Homemaker	1	(2.5)
	Part time	8	(20.0)
	Retired	26	(65.0)
Marital Status	Married/Living with partner	23	(57.5)
	Divorced	9	(22.5)
	Widowed	2	(5.0)
	Single	6	(15.0)

Table 4

Summary of Study Sample Medical Variables (N=40)

Variable	Category	*n*	(%)
ABI[a]	Non-compressible (>1.40)	1	(2.5)
	Normal (1.00-1.40)	9	(22.5)
	Borderline abnormal (0.91-0.99)	5	(12.5)
	Mild disease (0.70-0.90)	6	(15.0)
	Moderate disease (0.50-0.69)	15	(37.5)
	Severe disease (≤ 0.49)	4	(10.0)
BMI[b]	Underweight (<18.50)	1	(2.5)
	Normal weight (18.50-24.99)	10	(25.0)
	Overweight (25.00-29.99)	18	(45.0)
	Obese (≥ 30.00)	11	(27.5)
Smoking status	History	7	(75.0)
	Current	30	(17.5)
	Never smoked	3	(7.5)
Diagnoses	Hypertension	37	(92.5)
	Hyperlipidemia	36	(90.0)
	Osteoarthritis	12	(30.0)
	Diabetes		
	Type 1	2	(5.0)
	Type 2	8	(20.0)
	Neuropathy	3	(20.0)
	Rhythm disturbance	7	(17.5)
	Cancer history	4	(10.0)
	Depression	4	(10.0)
	Metabolic syndrome	3	(7.5)
	Anemia history	2	(5.0)
	Rheumatoid arthritis	2	(5.0)
	Spinal stenosis	1	(2.5)
Medications	Anti-hypertensive	35	(87.5)
	Anti-platelet	34	(85.0)
	Cholesterol-lowering	36	(90.0)
Supplements	Multivitamin	20	(50.0)
	Fish oil	12	(30.0)
	Iron	2	(5.0)

Note. ABI=ankle-brachial index; BMI=body mass index.

[a] Categorization based on "Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement from the American Heart Association," by V. Aboyans, M. Criqui, P. Abraham, M. Allison, M. Creager, … & D. Treat-Jacobson, 2012, *Circulation*, *126*(24), pp. 2890-2909.

[b] Categorization based on World Health Organization classification.

Summary of treadmill exercise and recovery phases. Treadmill exercise testing protocols varied based on individualized treadmill familiarizations. The majority of participants (*n*=31, 78%) started walking at 2 mph and 0% grade. A summary of the treadmill speed and grade, as well as the performance during the exercise and recovery phases is presented in Table 5. On average, participants walked 6 minutes and 44 seconds, and required 6 minutes and 4 seconds to fully recover from exercise-induced ischemic symptoms.

Table 5

Summary of Treadmill Exercise Performance and Recovery

Variable	*M*	(*SD*)	*Mdn*	Minimum	Maximum
Starting Speed (mph)	1.99	(0.26)	2.00	1.00	3.00
Starting Grade (%)	0.58	(1.92)	0.00	0.00	9.00
Maximum Speed (mph)	2.15	(0.43)	2.00	1.00	4.00
Maximum Grade (%)	7.54	(3.96)	8.50	0.00	14.00
Exercise Time (s)	644.26	(288.57)	619.00	117.00	1740.00
Recovery Time (s)	364.49	(250.15)	297.50	51.00	1401.00

Note. mph=miles per hour; s=seconds.

Aim 1: Description of the PAD Symptom Experience

Description provided during interviews. Information obtained from the semi-structured interviews provided a foundational understanding of the PAD symptom experience. The interviews not only allowed participants to share their symptom experiences, but it allowed them to formulate the vocabulary they subsequently used to describe their symptom experience during treadmill walking. Following the content analysis procedure previously described, six themes emerged from 27 participant interviews: symptom descriptors, maintaining equilibrium, temporal fluctuations, the role of exercise, the perceived impact on QOL, and disease presence and treatment.

Theme 1: Symptom descriptors. Twenty-four symptom descriptors in 10 lower limb locations were provided during the semi-structured interviews (Tables 6 and 7). The average number of descriptors provided during the interviews was 3.41 (*SD*=1.72, Range=1-8), whereas the average number of locations provided was slightly less (*M*=2.96, *SD*=1.26, Range=1-7). Some individuals used the same word (e.g., *ache*) to describe symptoms that were present in multiple locations, while others had distinct vocabulary for each lower extremity location (e.g., *aching calf* and *burning buttock*). Even when symptoms were restricted to one location, participants used different vocabulary to describe their discomfort as it progressed and subsided. All of the combinations of symptom locations and descriptors reported during the interviews appear in Table 8.

Table 6

Symptom Descriptors provided during Interviews (N=27)

Ache	Hard	**Pain**	Tight
Burn	Heavy	Pressure	Tingling
Charley horse	Hurt/Tender	Prickly	**Tired**/Fatigue
Cramp	Jammed	Pulling	Twinge
Grinding/Rubbing	Knot	Sore	Warm
Gripping	Numb	Stiff	Weak

Note. Descriptors in bold are those commonly associated with classic claudication.

Table 7

Symptom Locations provided during Interviews (N=27)

Ankle	**Calf**	Groin	Hip	**Quadriceps**
Buttock	Foot	Hamstring	Knees	Shin

Note. Locations in bold are those commonly associated with classic claudication.

Table 8

Symptom Location and Descriptor Combinations Provided during Interviews (N=27)

Location	*n* (%)	Descriptor	*n*	(%)
Calf	25 (92.6)	Tight	10	(40.0)
		Ache	8	(32.0)
		Pain	8	(32.0)
		Cramp	5	(20.0)
		Sore	5	(20.0)
		Charley horse	4	(16.0)
		Tired/Fatigue	2	(8.0)
		Weak	2	(8.0)
		Burn	1	(4.0)
		Hard	1	(4.0)
		Heavy	1	(4.0)
		Knot	1	(4.0)
		Pressure	1	(4.0)
Hip	10 (37.0)	Ache	5	(50.0)
		Grinding/Rubbing	3	(30.0)
		Pain	2	(20.0)
		Gripping	1	(10.0)
		Heavy	1	(10.0)
		Hurt/Tender	1	(10.0)
		Pulling	1	(10.0)
		Stiff	1	(10.0)
		Tight	1	(10.0)
Foot	9 (33.3)	Numb (foot & heel)	4	(44.4)
		Tingling (foot & toes)	3	(33.3)
		Pain (heel & toes)	2	(22.2)
		Burn	1	(11.1)
		Jammed (toes)	1	(11.1)
		Pressure	1	(11.1)
		Prickly	1	(11.1)
		Sore (heel)	1	(11.1)
		Warm	1	(11.1)
Buttock	8 (29.6)	Ache	4	(50.0)
		Pain	2	(25.0)
		Burn	1	(12.5)
		Gripping	1	(12.5)
		Heavy	1	(12.5)
		Tired	1	(12.5)
Hamstring	6 (22.2)	Ache	3	(50.0)
		Burn	1	(16.7)
		Gripping	1	(16.7)
		Hurt/Tender	1	(16.7)

Table 8 – *Continued*.

		Tingling	1	(16.7)
		Tired/Fatigue	1	(16.7)
		Twinge	1	(16.7)
		Weak	1	(16.7)
Shin	6 (22.2)	Sore/Tender	3	(50.0)
		Burn	2	(33.3)
		Pain	2	(33.3)
		Cramp	1	(16.7)
		Tight	1	(16.7)
Quadriceps	6 (22.2)	Ache	2	(33.3)
		Pain	2	(33.3)
		Charley horse	1	(16.7)
		Numb	1	(16.7)
		Sore	1	(16.7)
		Tired/Fatigue	1	(16.7)
Knees	3 (11.1)	Ache	2	(66.7)
		Pain	1	(33.3)
		Stiff	1	(33.3)
		Weak	1	(33.3)
Ankle	2 (7.4)	Sore	1	(50.0)
		Tight	1	(50.0)
Groin	1 (3.7)	Pain	1	(100.0)

Note. Twenty-four symptom descriptors in 10 lower extremity locations provided during 27 interviews for a total of 64 location-descriptor combinations.

Gender. The most common symptom location reported by men was the calf. Table 9 provides the frequencies for each of the 12 calf descriptors provided by 21 men during the interviews. Conversely, the most commonly reported symptom location for women was the hip, followed closely by the calf. Although all of the women interviewed reported hip discomfort as being part of the symptom experience, no two individuals used the same word to describe it. The seven hip descriptors provided by women during the interviews can be found in Table 10. The frequencies of the six calf descriptors are provided in Table 11. As noted in Table 12, females reported symptoms in more locations compared to males, but both genders provided a similar number of symptom descriptors (Table 13).

Table 9

Frequency of Calf Descriptors provided by Men during Interviews (N=21)

Descriptor	*n*	(%)
Pain	8	(38.1)
Tight	8	(38.1)
Ache	7	(33.3)
Sore	5	(23.8)
Cramp	4	(19.0)
Charley horse	3	(14.3)
Tired/Fatigue	2	(9.5)
Burn	1	(4.8)
Heavy	1	(4.8)
Knot	1	(4.8)
Pressure	1	(4.8)
Weak	1	(4.8)

Note. Of the 22 male interviews included in the content analysis, 21 men described calf symptoms. Fourteen men provided more than one calf descriptor, so percentages do not add up to 100%.

Table 10

Frequency of Hip Descriptors provided by Women during Interviews (N=5)

Descriptor	*n*	(%)
Ache	1	(20.0)
Grind	1	(20.0)
Gripping	1	(20.0)
Hurt	1	(20.0)
Pain	1	(20.0)
Stiff	1	(20.0)
Tight	1	(20.0)

Note. All five women interviewed described hip symptoms. None of the women reported the same symptom descriptor and two women provided two descriptors, so percentages do not add up to 100%.

Table 11

Frequency of Calf Descriptors provided by Women during Interviews (N=4)

Descriptor	*n*	(%)
Tight	2	(50.0)
Ache	1	(25.0)
Charley horse	1	(25.0)
Cramp	1	(25.0)
Hard	1	(25.0)
Weak	1	(25.0)

Note. Of the five female interviews included in the content analysis, four women described calf symptoms. Two women provided more than one symptom descriptor, so percentages do not add up to 100%.

Table 12

Summary of Interview Symptom Locations by Gender

Category	*n*	*M*	(*SD*)	Minimum	Maximum
Male	22	2.73	(1.03)	1	4
Female	5	4.00	(1.73)	3	7

Table 13

Summary of Interview Symptom Descriptors by Gender

Category	*n*	*M*	(*SD*)	Minimum	Maximum
Male	22	3.23	(1.48)	1	6
Female	5	4.20	(2.59)	1	8

Age. The younger age group (<65 years old) comprised seven males and one female, whereas four females and fifteen males were included in the older age group (≥ 65 years old). The calf was the most frequently reported symptom location among younger and older participants during the interviews. Tables 14 and 15 summarize the descriptors provided by each age group. On average, older individuals provided one symptom location more than younger participants (Table 16), while the number of

symptom descriptors provided by individuals in each age group appeared to be similar (Table 17).

Table 14

Frequency of Calf Descriptors provided by Participants < 65 Years Old during Interviews (N=7)

Descriptor	*n*	(%)
Pain	4	(57.1)
Tight	3	(42.9)
Ache	2	(28.6)
Charley horse	2	(28.6)
Sore	2	(28.6)
Weak	1	(14.3)

Note. Of the eight younger participant interviews included in the content analysis, seven described calf symptoms. Five younger participants provided more than one symptom descriptor, so percentages do not add up to 100%.

Table 15

Frequency of Calf Descriptors provided by Participants ≥ 65 Years Old during Interviews (N=18)

Descriptor	*N*	(%)
Tight	7	(38.9)
Ache	6	(33.3)
Cramp	5	(27.8)
Pain	4	(22.2)
Sore	3	(16.7)
Charley horse	2	(11.1)
Tired/Fatigue	2	(11.1)
Burn	1	(5.6)
Hard	1	(5.6)
Heavy	1	(5.6)
Knot	1	(5.6)
Pressure	1	(5.6)
Weak	1	(5.6)

Note. Of the 19 younger participant interviews included in the content analysis, 18 described calf symptoms. Eleven older participants provided more than one symptom descriptor, so percentages do not add up to 100%.

Table 16

Summary of Interview Symptom Locations by Age

Category	*n*	*M*	(*SD*)	Minimum	Maximum
< 65 years old	8	2.25	(1.04)	1	4
≥ 65 years old	19	3.26	(1.24)	2	7

Table 17

Summary of Interview Symptom Descriptors by Age

Category	*n*	*M*	(*SD*)	Minimum	Maximum
< 65 years old	8	2.88	(0.83)	2	4
≥ 65 years old	19	3.63	(1.89)	1	8

Overall. Irrespective of gender and age, a subset of participants reported symptoms that were consistent with the descriptors associated with classic claudication (e.g., *aching*, *cramping*, *painful*, and *tired*). Participants provided the following 'classic' descriptions during interviews:

"I get a cramping in the left calf."

"My legs get tired. I can feel it in my thighs."

"I get a strong pain in the right buttock, it's a painful throbbing."

"I start having pain in my calf. And the further I go, it keeps going up my leg."

"Originally, it's a feeling of tiredness, but then it develops into a pain."

Other participants provided symptom descriptors in 'atypical' locations, symptom descriptors that differed by location, and symptom descriptors that extended beyond the *aching*, *cramping*, *painful*, and *tired* description of the classic and most commonly recognized symptom, claudication.

"My feet get kind of tingly…like they're sleeping."

"My legs start to hurt and my calves will get real hard."

"It's like a knot, and it's in my calf. If I'm walking up the stairs, it goes to my shin, and that's a burning sensation."

"My left calf and heel get sore. Even after a couple hours, it feels like I've already put a full day on it."

Additionally, symptom descriptors varied based on the intensity and duration of exercise, as well as the treadmill grade.

"I have to walk really far to get it to go to the shin. It's kind of dull, unless I push it, then it gets to be a sharper pain as I go on."

"The faster or the steeper on that thing [treadmill] I go, the quicker it comes on."

Theme 2: Maintaining equilibrium. Participants described different tactics that enabled them to prevent symptoms from occurring or to maintain symptoms at a tolerable level once they had begun. This theme consisted of three sub-categories, all with a common element of control: controlling the pace, controlling the environment, and controlling the elements of recovery.

Control the pace. Participants described deliberately controlling the pace of their walking to prevent or delay the onset of ischemic symptoms and/or prevent further symptom progression.

"I don't walk at a pace that's enough [to bring about symptoms]."

"I regulate my pace so that it doesn't bother me."

"I compensate for the pain by slowing down."

"It depends completely on how hard I walk. If I walk very slowly, I can go many, many blocks, more than a dozen, or so. If I walk aggressively, I can start to feel something in maybe two blocks."

"[My husband] will walk with me, but then we have to hold hands so he doesn't get ahead."

Control the environment. Maintaining equilibrium for some individuals involved asking walking companions to slow down or simply catching up with them later. For others, this meant avoiding situations in which they knew they would have to walk faster or further than they were comfortable doing.

"I walk at a pace where I'm not holding anybody up, or I just tell them 'I'll catch up.'"

"We try not to have to keep up to somebody. My wife has rheumatoid arthritis, so she is limited too. We went to Alaska a couple of years ago with our neighbors, and they are younger people, a little younger than we are. We just let them go where they wanted to go, and we went where we wanted to, because it was just too difficult to keep up all the time."

"I'll drive a block and a half over to the Y. I can't get there without taking a time-

out on the way."

"Like going to the Mall of America. I usually decline to join in that because it's just too much walking. It's going to be way too much walking. [It's] the same with Walt Disney World."

"Any hiking or anything like that, I just don't attempt to do."

"I usually shy away from places where I won't be able to sit down and rest."

Many individuals identified self-imposed limits and activities that were avoided because of having PAD. However, several individuals described being able to walk through the discomfort in certain situations.

"Sometimes I can walk through it, and then other times I have to stop and rest."

"I just tend to ignore the pain. I just keep going and attempt to push through it. I'm used to the pain, so I don't stop."

"I don't baby it, I just keep on going."

Control the elements of recovery. The last element of control involved manipulating the recovery position and utilizing specific techniques participants believed to aid in recovery. Some described achieving complete symptom relief from stopping the activity and simply standing still. However, the vast majority of participants preferred to recover in a seated position.

"I prefer to sit down, but if I stand it will eventually go away. It goes away faster

if I'm sitting."

"I sit and lean against a wall and take all the pressure off my leg."

"I can stand during all of this stuff. It's not that type of pain or anything. I just casually walk around a little bit and it will go away."

"I'll massage the shin, trying to get the blood flow back up to snuff."

"I'll massage my leg, and it gets warmer."

"I just wiggle [my leg] around for a couple of minutes."

"If I stretch it out and kind of move the muscle around, then I can recover quicker."

Theme 3: Temporal fluctuations. Participants described the influence of time on the symptom experience and described day to day fluctuations in their symptoms. This included fluctuations based on exercise duration and the amount of time spent in recovery.

"Every day is a little different."

"It's really odd, because some days I have it worse than others. Lately, I'm not having it as bad, but it seems like I always have some in my calves---it varies. Sometimes I can only walk five minutes, sometimes eight. I notice [the variation], especially when I'm on the treadmill"

"Even the time of day will change a lot for me, or if I've exercised a lot."

"It changes not only day to day, but hour to hour. I'm not really sure what controls it, but some days I just feel much better than other days."

"I have a longer recovery if I've pushed harder."

"In some cases, you have to be at a 5, and you have to keep going before you can stop. In those cases, it can take 5, 6, or 7 minutes to really recover."

Participants also reported fluctuations in symptoms based on the walking surface or incline, as well as the influence of various medical conditions and medications.

"The harder [the surface] the worse [the pain]…the softer the better."

"You have more resistance with hard pavement. You have more absorption with a softer grass or something like that. The treadmill seems to be in the middle of all that. Most of my walking around the home is on tar, so I'm stuck with that. I can't walk on people's lawns…"

"I think the tile is really hard to walk on. Carpet seems good and the treadmill is good. But, hard, ceramic floor; it seems like it bothers you more."

"I could walk as much as 14 minutes at one time, but I was 'cheating' because the platform was flat. So when they lifted it to 0.6%, then the best I could do was three to four minutes."

"I normally walk either on the treadmill or on asphalt. I try to avoid concrete or grass, for that matter, because of the unevenness of it."

"It's bad when you're working on a ladder where you're almost on your toes. The forward part of your foot is on a tread, which is tensing the calf muscle."

"My hemoglobin makes a big difference in how my legs feel."

"I have sore legs when [my blood] sugars are high."

"If [my blood sugar is] a little over 250, the legs ache."

Participants described a blurring of symptoms that made it difficult to decipher the cause of their discomfort at certain points in time. Some felt that the symptoms they were experiencing during exercise were a direct result of PAD, for some they thought the symptoms were a result of another medical condition, and for others, it was thought to be a combination of both.

"For me it's hard to distinguish. Is it the PAD totally or is it the medication? As soon as they took me off of the Effexor is when I saw a major improvement in my leg symptoms."

"The number one thing I can't do is walking and running, and this may be partly related to the multiple sclerosis."

"I can't run. That's PAD and knee related, at the same time. It hurts a lot. I have weak ankles too."

"It's easier to go up than down [stairs], and I'm wondering if that isn't the neuropathy."

"Sometimes I have to sit down to recover. I'm not sure if it's because of the buttock pain or if it's the neuropathy in my feet. I have a hard time distinguishing there. If my feet are doing okay, then I think I stand and wait."

"It feels like I don't have a lot of movement in the hip. You know, it's real tight, but that may be because of the bursitis too."

Theme 4: The role of exercise. Participants described the effects of repetitive

exercise on the symptom experience, in addition to the cumulative effects.

"Yesterday I probably overdid it a little, and this morning I had to stop much more than I normally do."

"The further I walk, the worse the pain and the more frequently I will have to stop."

"It seems if I continue walking again, I won't be able to walk as far. The distance decreases."

"One thing I have noticed is that if I've walked hard enough to develop pain and then have it go away, I don't have to go as far to have it come back. It will start coming back sooner than the first time."

Some individuals also reported experiencing a post-exercise pain spike after stopping activity.

"After I get off of the treadmill and I come to sit down, I've got maybe 5 to 15 seconds, then I'll just hit a streak of it, it just goes up."

"When I stop walking and sit down, it will be even more severe. More severe after I stop walking than when I was doing the actual walking."

A separate, but related sub-category in the role of exercise theme was the progress that individuals perceived they were making because of their commitment to an ongoing exercise program.

"I've made progress [on the treadmill], but it doesn't always correlate to walking on

the ground."

"I work through the pain. Now I can go quite a ways."

"In the beginning, it was about two minutes [of recovery time] after seven or eight minutes of walking. Now I can walk up to 15 minutes, but then I need about four minutes of recovery. If I only go seven or eight minutes, then two minutes [of recovery] is fine."

"I kept working at it, walking around Normandale Lake, which has lots of inclines. At first, I would have to take frequent breaks, but I kept working at it to where I was finally able to go around without having to stop."

"The more exercise I do, the better off I feel."

Theme 5: The perceived impact on quality of life (QOL). Having a diagnosis of PAD and living with the disease on a daily basis impacted participants in different ways. For some, the biggest impact was personal. Having PAD negatively affected their self-esteem and their outlook on life. For others, the impact of the disease on their QOL was relative to their advanced age or to a medical condition that they perceived as being more severe (e.g., cancer). Despite the perceived personal and relative impact on QOL, most individuals had defined limits in place and spoke fondly of their "old life" and described a variety of activities they used to enjoy.

"When I swim, I don't feel a thing. It's only when I'm walking that prevents me from having a normal life. Walking, which is very important to my wife, she loves to walk and I hate to walk."

"I get angry, at myself, I guess, because I don't like being restricted. I used to walk for miles and miles."

"It's definitely affected walking and anything that associated with walking more than a block or two. And I'm embarrassed, so I don't tell anybody, and then I just say, 'No, I can't do that. No, I'm not up to that,' and I don't say why."

"My brother asked us to go to Italy again, and we're not. They walk around faster than we do, so it's just not fair to keep them kind of slowed down."

"I can't go for a walk or go on a picnic and take a hike, and I used to like doing that stuff. I'm embarrassed that I don't have the energy or the ability to do it and I don't want to hold them back."

"Well, considering my age, I don't do as much running, or that kind of behavior. I was pretty active working with kids as a teacher for 40 years. I was able to move around pretty much as I wished, but I'm slower now and I just don't do as much. I must be getting older."

"I will go [grocery shopping], but not often. I usually send my husband, and I didn't even think about that. It's kind of unconscious that you just don't do things anymore. I used to be very, very active, and I can see that I've just slowed down, but I figure that's the age."

"I love to dance. I can't do that. Bending down, housework, I don't do a lot of that just because it hurts so much to bend down. I can't go on picnics and walks and stuff with my grandkids like I normally would in the summer because I can't walk that far, and I can't walk that fast."

"I have to stop and think about when I was diagnosed with PAD and what kind of

symptoms I was having. That wasn't the number one thing in my life because I've been dealing with cancer since 1991."

"I think it has limited me from doing 85 to 90% of things. Fishing, I can't do that, not the way that I would like to do it. Basically just going places and walking. It limits my range of operation, I'd put it that way."

"I had to give up my job as a fireman because of PAD. I knew I couldn't keep doing what I was doing. The more intense it was, I had to stop. And I thought, this could be trouble if I were on a scene or something, so I quit."

"I can't run, just run because it felt good. I can't do it anymore. I can't go hill climbing or anything…or hiking is something I would like to do."

"The last 2 years, my husband has gone to the fair alone because he doesn't want to have to meet me every half hour somewhere if I'm sitting around. And so with walking at the fair, I don't really enjoy that anymore."

"I think it's just a matter of becoming limited in what you're going to do. You just don't move around as much as you used to. And that's basically the whole extent of what it's done to me.

Theme 6: Disease presence and treatment. Participants described their awareness of the disease and subsequent treatment to prevent further disease progression to varying degrees. Some individuals provided accurate physiological descriptions of the disease and appropriate lifestyle modifications in hopes of preventing disease progression and avoiding an increased chance of having a heart attack or stroke. While others expressed having knowledge of what they needed to do or should be doing, but

acknowledged that they were unable or unwilling to change their behavior (e.g., quitting smoking). Some individuals were able to articulate the symptoms they experienced better than others. A few individuals struggled to describe their symptoms beyond "pain" or "hurt." However, most of the individuals interviewed were able to provide very specific symptom descriptors that appeared to fully encompass the symptoms experienced by all 40 participants during treadmill walking.

"It's like a cramp. The legs are hollering because they're not getting sufficient oxygen."

"I'll stop and lean on the fence for a minute just because the legs are talking to me."

"I always visualize a closure of a path that there's not enough blood circulating and then the body is signaling starvation."

"The doctor said 'If you keep smoking, you're going to have to redo [the surgery]' so I started wearing support hose. But being a blockhead, I decided not to give up smoking yet."

"The doctor kept saying, 'Quit smoking, quit smoking,' which I never did, so the stents re-occluded."

"I saw an ad in the paper for PAD, and I thought, well, I don't even know what PAD is. Why don't I do that? Maybe I'll find out more about what PAD is. I had been diagnosed with it, but I was just stunned that it hurt so badly. I kept trying to walk, but everybody had to rest with me. I didn't know that was part of PAD."

Description provided during treadmill exercise. Interestingly, the majority of the symptom descriptors provided during interviews and all of the symptom locations reported during interviews (a static state) were also reporting during treadmill walking (a dynamic state) (see Tables 18 and 19). Based on this evidence, the symptom descriptors and locations provided by the individuals included in the content analysis (*n*=27) appear to be representative of the whole group (*n*=40), since there weren't any symptom descriptors or locations provided during treadmill walking that weren't originally described by the 27 participants interviewed. The average number of descriptors provided during exercise was three (*SD*=1.75), whereas the average number of locations provided during treadmill walking was slightly less (*M*=2.50, *SD*=1.32). Similar to the interview results, some individuals used only one word to describe symptoms in multiple locations, while others used a different word for each lower extremity location that was affected during exercise. Table 20 summarizes all of the location and descriptor combinations provided by all 40 participants during treadmill exercise.

Table 18

Symptom Descriptors provided during Exercise (N=40)

Ache	Knot	Sore	*Gripping*
Burn	Numb	Tight	*Hard*
Charley horse	**Pain**	Tingling	*Hurt/Tender*
Cramp	Pressure	**Tired**/Fatigue	*Jammed*
Grinding/Rubbing	Prickly	Twinge	*Stiff*
Heavy	Pulling	Warmth	*Weak*

Note. Descriptors in bold are those commonly associated with classic claudication. Italics denotes symptom descriptors that were only described during the interviews (*n*=27) and not reported during subsequent treadmill walking by any of the 40 study participants.

Table 19

Symptom Locations provided during Exercise (N=40)

Ankle	**Calf**	Groin	Hip	**Quadriceps**
Buttock	Foot	Hamstring	Knees	Shin

Note. Locations in bold are those commonly associated with classic claudication.

Table 20

Symptom Location and Descriptor Combinations provided during Exercise (N=40)

Location	*n* (%)	Descriptor	*n*	(%)
Calf	39 (97.5)	Ache	19	(48.7)
		Tight	18	(46.2)
		Cramp	11	(28.2)
		Pain	9	(23.1)
		Tired/Fatigue	8	(20.5)
		Burn	5	(12.8)
		Sore	5	(12.8)
		Heavy	3	(7.7)
		Knot	3	(7.7)
		Tingling	3	(7.7)
		Charley horse	2	(5.1)
		Pressure	2	(5.1)
		Warm	2	(5.1)
		Discomfort	1	(2.6)
		Sensitive	1	(2.6)
		Stretch	1	(2.6)
Hamstring†	15 (37.5)	Ache	5	(33.3)
		Burn	3	(20.0)
		Tight	3	(20.0)
		Tired/Fatigue	3	(20.0)
		Sore	2	(13.3)
		Pain	1	(6.7)
		Pull	1	(6.7)
Buttock	10 (25.0)	Ache	3	(30.0)
		Pain	3	(30.0)
		Burn	2	(20.0)
		Tight	2	(20.0)
		Sore	1	(10.0)
		Twinge	1	(10.0)
		Warm	1	(10.0)

Table 20 – *Continued*.

Foot‡	8 (20.0)	Sore (foot & heel)	2	(25.0)
		Burn	1	(12.5)
		Cramp (toes)	1	(12.5)
		Pain (heel)	1	(12.5)
		Pressure (toes)	1	(12.5)
		Numb (toes)	1	(12.5)
		Prickly	1	(12.5)
		Tingling	1	(12.5)
		Wet	1	(12.5)
Hip	8 (20.0)	Ache	6	(75.0)
		Warm	2	(25.0)
		Burn	1	(12.5)
		Grind	1	(12.5)
		Pain	1	(12.5)
		Pull	1	(12.5)
		Sore	1	(12.5)
		Tight	1	(12.5)
Quadriceps	7 (17.5)	Tired/Fatigue	3	(42.9)
		Tight	2	(28.6)
		Pain	2	(28.6)
		Ache	1	(14.3)
		Sore	1	(14.3)
		Tingling	1	(14.3)
		Warm	1	(14.3)
Shin††	6 (15.0)	Burn	3	(50.0)
		Ache	1	(16.7)
		Discomfort	1	(16.7)
Knees	5 (12.5)	Ache	3	(60.0)
		Burn	1	(20.0)
		Sore	1	(20.0)
		Tight	1	(20.0)
		Warm	1	(20.0)

Note. Twenty-two descriptors in eight locations provided by 40 participants during exercise for a total of 62 location-descriptor combinations.

† One male participant reported discomfort in the hamstring, but did not report a descriptor.

‡ Location only reported by men.

†† One male participant reported discomfort in the shin, but did not report a descriptor.

Gender. For males, the most common symptom location reported at any point during treadmill exercise was the calf (*n*=34, 97%). For 68% of those males (*n*=23), the calf was the limiting location for all three treadmill tests. For an additional 9% (*n*=3) of male participants reporting calf discomfort, the calf was the limiting symptom location for at least one treadmill test. Table 21 summarizes the 16 calf symptom descriptors provided by males during treadmill exercise. Table 22 provides a breakdown of the exercise limiting symptom location for all 40 men in the study. Other exercise limiting locations included the hamstring, buttock, foot, quadriceps, hip, and shin.

Table 21

Frequency of Calf Symptom Descriptors provided by Men at any point during Treadmill Exercise (N=34)

Descriptor	*n*	(%)
Ache	18	(52.9)
Tight	15	(44.1)
Cramp	10	(29.4)
Pain	8	(23.5)
Tired/Fatigue	7	(20.6)
Sore	5	(14.7)
Burn	4	(11.8)
Knot	3	(8.8)
Charley horse	2	(5.9)
Heavy	2	(5.9)
Pressure	2	(5.9)
Tingling	2	(5.9)
Warm	2	(5.9)
Discomfort	1	(2.9)
Sensitive	1	(2.9)
Stretching	1	(2.9)

Note. All but one male reported calf symptoms; twenty-three provided more than one calf descriptor, so percentages do not add up to 100%.

Table 22

Exercise Limiting Symptom Locations for Males

Location	3 Exercise Tests (%)	2 Exercise Tests (%)	1 Exercise Test (%)
Calf	65.7%	4.0%	1%
Quadriceps	8.6%	---	1%
Hip	5.7%	---	1%
Buttock	3.0%	---	1%
Foot	3.0%	---	---
Hamstring	3.0%	---	---
Heel	3.0%	---	---

Note. Percentages are based on *N*=105 since each of the 35 male participants completed three treadmill exercise tests.

The calf was also the most frequently reported symptom location among female study participants (*n*=5, 100%). Two female participants were limited by the calf for all three treadmill tests (40%), while two more were limited by the calf during at least one treadmill test (40%). Although all five women experienced symptoms in the calf during exercise, the only descriptor reported by more than one individual was "tight." Table 23 lists the seven calf symptom descriptors provided by women during exercise. All of the locations that limited women during treadmill walking are listed in Table 24. Compared to men, none of the female participants were limited during exercise by symptoms in the shin, heel, foot, or buttock. However, both genders reported a similar number of symptom locations and symptom descriptors during treadmill exercise (see Tables 25 and 26).

Table 23

Frequency of Calf Symptom Descriptors provided by Women at any point during Treadmill Exercise (N=5)

Descriptor	*n*	(%)
Tight	3	(60.0)
Ache	1	(20.0)
Burn	1	(20.0)
Cramp	1	(20.0)
Pain	1	(20.0)
Tingling	1	(20.0)
Tired/Fatigue	1	(20.0)

Note. All five women reported calf symptoms; three provided more than one calf descriptor, so percentages do not add up to 100%.

Table 24

Exercise Limiting Symptom Locations for Females

Location	3 Exercise Tests (%)	2 Exercise Tests (%)	1 Exercise Test (%)
Calf	40.0%	13.3%	6.7%
Hamstring	20.0%	---	---
Hip	---	13.3%	---
Quadriceps	---	---	6.7%

Note. Percentages are based on *N*=15 since each of the five female participants completed three treadmill exercise tests.

Table 25

Summary of Exercise Symptom Locations by Gender

Category	*N*	*M*	(*SD*)	Minimum	Maximum
Male	35	2.37	(1.26)	1	6
Female	5	3.40	(1.52)	1	5

Table 26

Summary of Exercise Symptom Descriptors by Gender

Category	*n*	*M*	(*SD*)	Minimum	Maximum
Male	35	3.06	(1.83)	1	8
Female	5	2.60	(1.14)	1	4

Age. Despite the differences reported during interviews, the calf was the most frequently reported symptom location among younger and older study participants during exercise. A complete list of the calf symptom descriptors reported by each age group during exercise appears in Tables 27 and 28. Moreover, the calf was the most common exercise limiting symptom location among both age groups. Tables 29 and 30 provide a complete list of exercise limiting symptom locations for participants in each age group.

Table 27

Frequency of Calf Descriptors provided by Participants < 65 Years Old at any point during Treadmill Exercise (N=16)

Descriptor	*n*	(%)
Tight	8	(50.0)
Ache	7	(43.8)
Tired/Fatigue	5	(31.3)
Cramp	4	(25.0)
Pain	4	(25.0)
Sore	3	(18.8)
Burn	2	(12.5)
Knot	2	(12.5)
Charley horse	1	(6.3)
Discomfort	1	(6.3)
Heavy	1	(6.3)
Pressure	1	(6.3)
Stretching	1	(6.3)
Tingling	1	(6.3)

Note. All but one younger participant reported calf symptoms: eleven provided more than one calf descriptor, so percentages do not add up to 100%.

Table 28

Frequency of Calf Descriptors provided by Participants ≥ 65 Years Old at any point during Treadmill Exercise (N=23)

Descriptor	*n*	(%)
Ache	12	(52.2)
Tight	10	(43.5)
Cramp	7	(30.4)
Pain	5	(21.7)
Burn	3	(13.0)
Tired/Fatigue	3	(13.0)
Heavy	2	(8.7)
Sore	2	(8.7)
Tingling	2	(8.7)
Warm	2	(8.7)
Charley horse	1	(4.3)
Knot	1	(4.3)
Pressure	1	(4.3)
Sensitive	1	(4.3)

Note. All older participants reported calf symptoms; fifteen provided more than one calf descriptor, so percentages do not add up to 100%.

Table 29

Exercise Limiting Symptom Locations for Participants < 65 Years Old

Location	3 Exercise Tests (%)	2 Exercise Tests (%)	1 Exercise Test (%)
Calf	58.8%	3.9%	---
Quadriceps	17.6%	---	---
Buttock	5.9%	---	---
Foot	5.9%	---	---
Heel	5.9%	---	---
Hamstring	---	---	2.0%

Note. Percentages are based on *N*=51 since each of the 17 participants under the age of 65 years completed three treadmill exercise tests.

Table 30

Exercise Limiting Symptom Locations for Participants ≥ 65 Years Old

Location	3 Exercise Tests (%)	2 Exercise Tests (%)	1 Exercise Test (%)
Calf	65.2%	5.8%	2.9%
Hip	8.7%	2.9%	1.4%
Hamstring	8.7%	---	---
Buttock	---	---	1.4%
Quadriceps	---	---	1.4%
Shin	---	---	1.4%

Note. Percentages are based on *N*=69 since each of the 23 participants aged 65 years and older completed three treadmill exercise tests; percentages do not add up to 100% due to rounding.

As illustrated in Tables 31 and 32, there were no apparent differences in the number of symptom locations or symptom descriptors provided by younger versus older participants.

Table 31

Summary of Exercise Symptom Locations by Age

Category	*N*	*M*	(*SD*)	Minimum	Maximum
< 65 years old	17	2.12	(1.05)	1	4
≥ 65 years old	23	2.78	(1.44)	1	6

Table 32

Summary of Exercise Symptom Descriptors by Age

Category	*N*	*M*	(*SD*)	Minimum	Maximum
< 65 years old	17	3.00	(1.90)	1	8
≥ 65 years old	23	3.00	(1.68)	1	8

Aim 2: Modeling the PAD Symptom Experience

The information obtained from the semi-structured interviews informed and

guided treadmill exercise data collection. Subjective data in the form of NRS scores, symptom descriptors, and symptom locations were combined with objective data obtained from the NIRS (i.e., TSI values) to provide a comprehensive understanding of the PAD symptom experience. Individual change trajectories were explored to get a preliminary understanding of the data before proceeding with general multilevel modeling of the repeated measures. The loess method for smoothing was used for all of the individual and group trajectories.

Overview of the dataset. Three treadmill tests were conducted with each of the 40 participants for a total of 1,264 observations during 120 treadmill tests. The number of observations varied based on exercise and recovery times, as well as the number of NRS ratings provided during each phase. More than half (60%) of the observations occurred during exercise (*n*=762), with the remaining 502 observations occurring during recovery. Each observation had a TSI value and a corresponding numeric symptom rating based on the NRS**.** Table 33 provides a summary of observations based on the exercise and recovery phases. The average number of observations per participant during exercise was slightly less than the average number reported during the recovery phase.

Table 33

Summary of Observations: Total Number and Average per Individual throughout Treadmill Exercise Testing and Recovery

Category	*N*	*M*	(*SD*)	Minimum	Maximum
Exercise Observations	762	19.05	(3.08)	12	30
Recovery Observations	502	12.48	(2.67)	7	16

Note. Each observation had a tissue saturation index value and a corresponding numeric symptom rating based on the numeric rating scale.

TSI values. Calf muscle tissue oxygenation, as measured by TSI values obtained via NIRS, was recorded prior to the start of each test, and throughout the exercise and recovery phases. A summary of the TSI values obtained during all three phases is presented in Table 34. As expected, the average TSI of participants at baseline was higher than the average TSI during both the exercise and recovery phases. Figure 6 illustrates that baseline TSI values followed a relatively normal distribution (*M*=62.24, *Mdn*=62.32), whereas TSI values throughout exercise and at peak exercise (i.e., NRS=5) exhibited a slightly negatively skewed distribution as shown in Figure 7 and 8 (*M*=49.72, *Mdn*=52.57, and *M*=46.74, *Mdn*=49.25, respectively). Figures 9 and 10 illustrate similarly skewed distributions of TSI values obtained throughout the recovery phase (*M*=58.13, *Mdn*=61.92), as well as when participants reported full recovery (i.e., NRS=0; *M*=63.73, *Mdn*=66.93). However, since the skewing of the exercise and recovery TSI values was minimal, the mean was the primary measure of central tendency reported.

Table 34

Summary of Tissue Saturation Index (TSI) values

Variable	*n*	*M*	(*SD*)	Minimum	Maximum
Baseline TSI (%)	120	62.24	(8.24)	30.46	77.95
Overall exercise TSI (%)	762	49.72	(14.62)	0.00	77.95
Peak exercise TSI (%)	120	46.74	(13.62)	0.00	64.42
Overall recovery TSI (%)	499	58.13	(16.51)	0.00	88.49
Full recovery TSI (%)	120	63.73	(12.36)	16.84	81.48

Note. Values for baseline TSI, peak exercise TSI, and full recovery TSI were recorded once during each of the 120 treadmill tests.

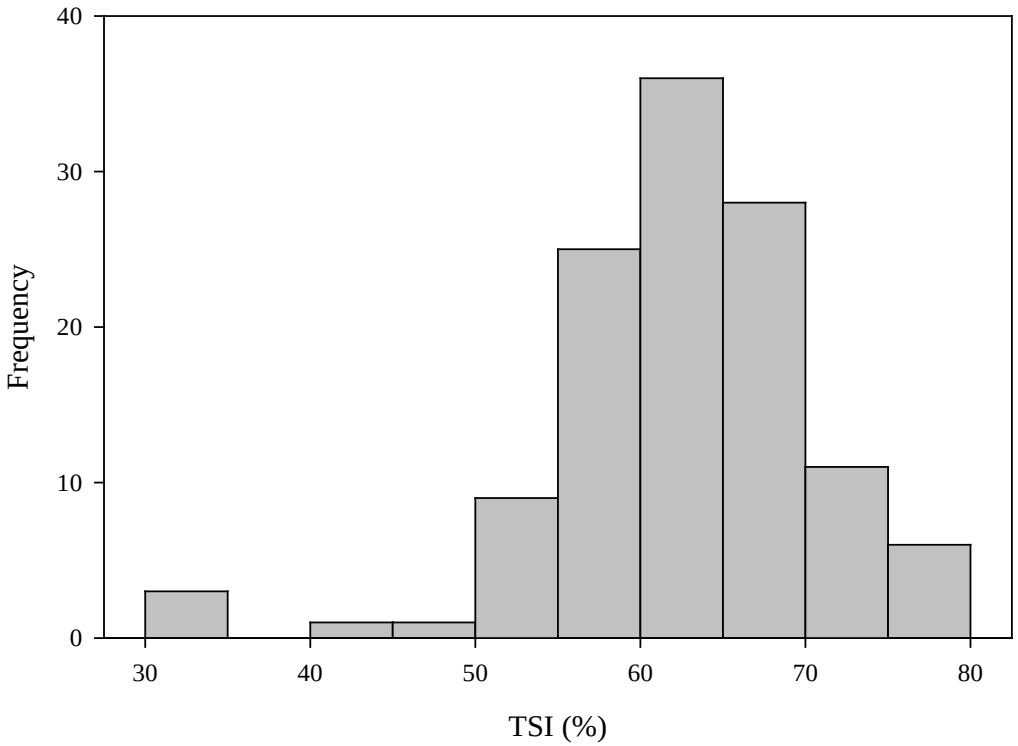

Figure 6. Histogram of baseline tissue saturation index (TSI) values.

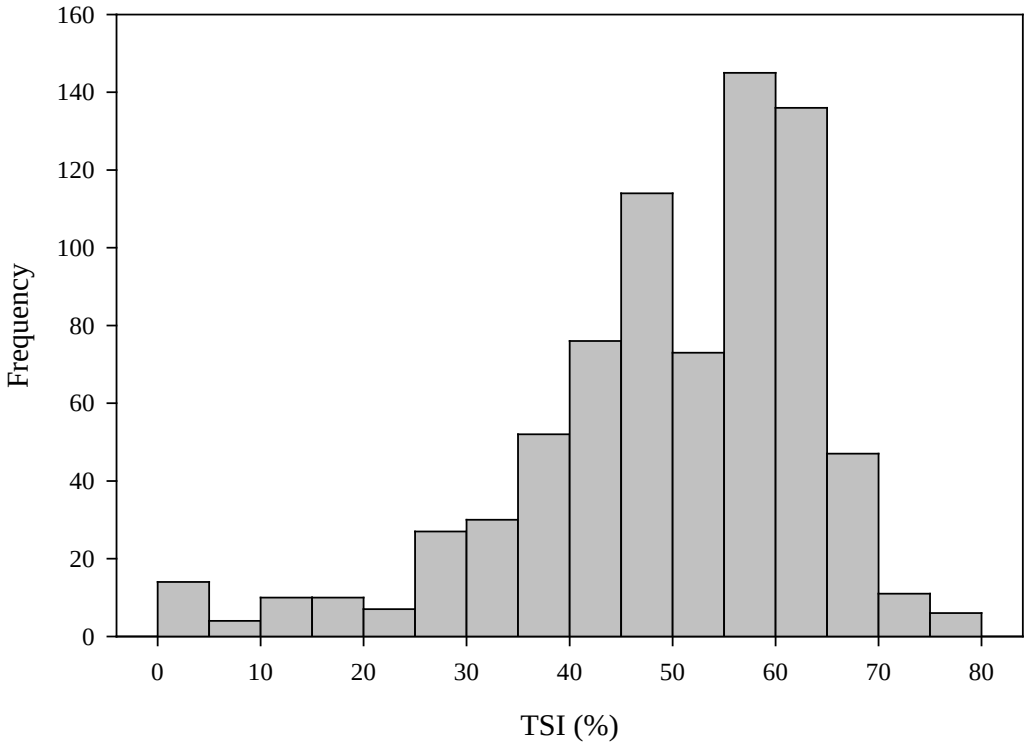

Figure 7. Histogram of tissue saturation index (TSI) values during exercise.

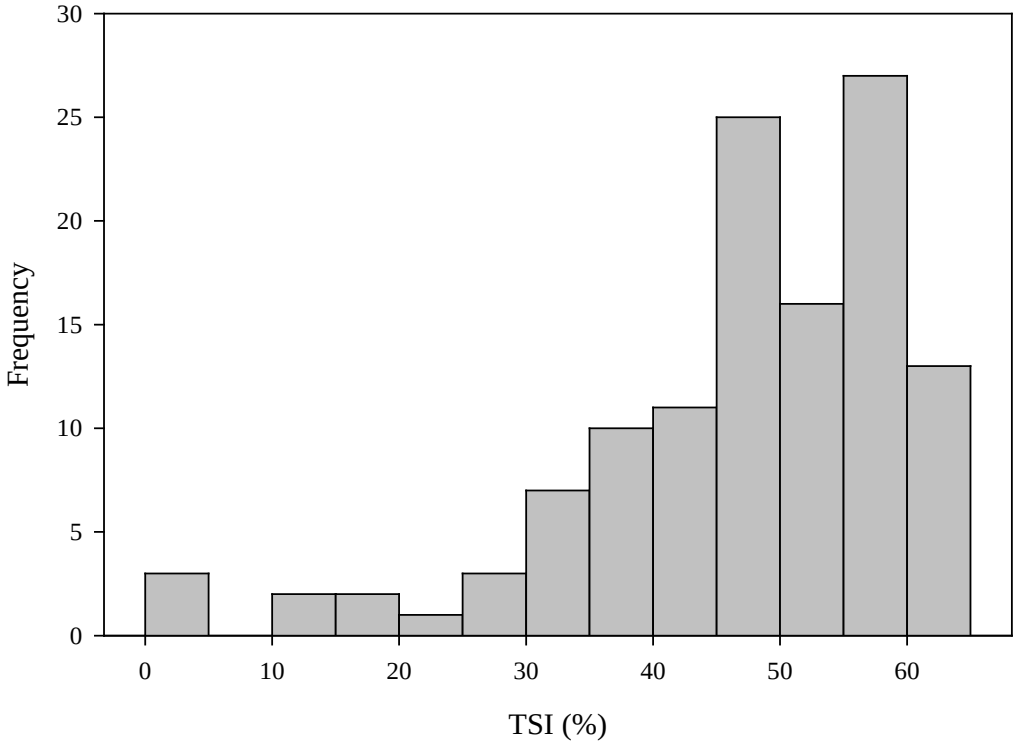

Figure 8. Histogram of tissue saturation index (TSI) values at peak exercise (NRS=5).

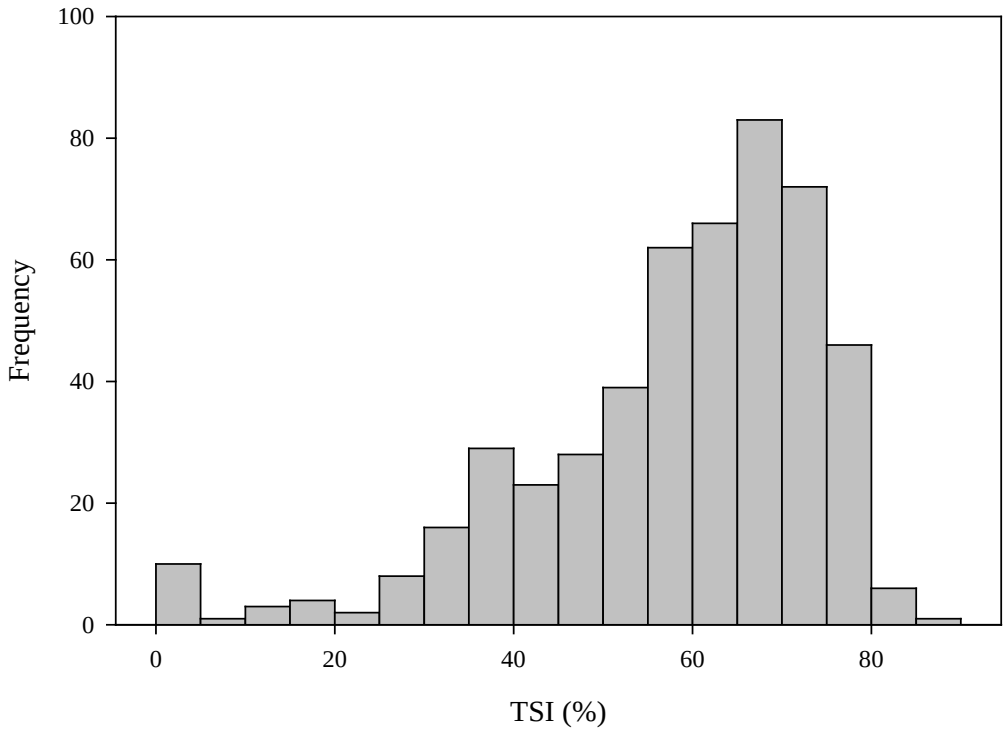

Figure 9. Histogram of tissue saturation index (TSI) values during recovery.

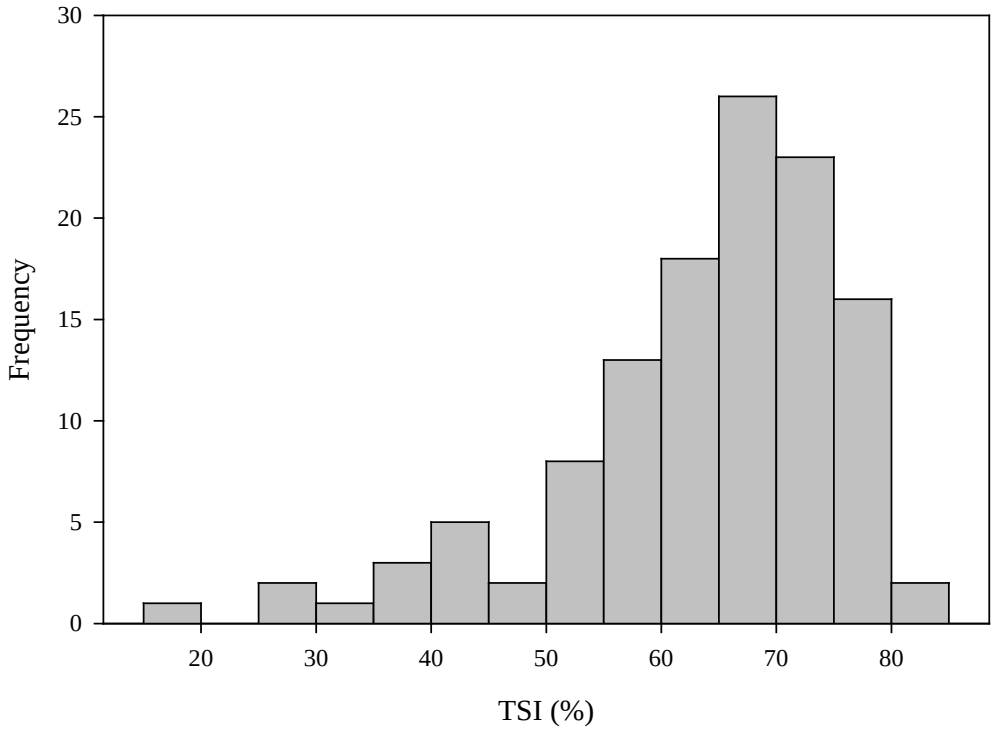

Figure 10. Histogram of tissue saturation index (TSI) values at full recovery (NRS=0).

NRS ratings. The NRS ratings provided during exercise and recovery are summarized in Tables 35 and 36. The total number of NRS ratings during exercise equaled 723, which didn't match the total number of exercise observations reported in Table 34 (*n*=762). This inequity arose from circumstances in which participants reported discomfort in a location other than the primary and exercise limiting location or when participants reported an NRS rating in another location, but did not provide a NRS rating for the primary, exercise limiting location. This situation occurred 39 times during exercise. Likewise, the 498 NRS ratings reported during recovery didn't equal the total number of recovery observations (*n*=502). This discrepancy occurred due to individuals not reporting a NRS rating for the exercise limiting symptom location when they provided a NRS rating for another symptom location. This situation occurred four times during recovery.

Table 35

Summary of Numeric Rating Scale (NRS) Ratings Reported during Exercise

NRS Rating	Frequency
0	120
1	114
2	110
3	129
4	133
5	117

Note. If every individual had reported all six NRS ratings on each treadmill test, the frequency for each NRS rating would have been 120.

Table 36

Summary of Numeric Rating Scale (NRS) Ratings Reported during Recovery

NRS Rating	Frequency
5+[a]	3
5	12
4	65
3	100
2	87
1	101
0	130

Note. If every individual had reported all six NRS ratings during each recovery period, the frequency for each NRS rating would have been 120. The frequency of a NRS rating of zero exceeded 120 due to circumstances in which the exercise limiting symptom location had fully recovered, but another symptom location had not.
[a] A rating of 5+ reflects a post-exercise spike in pain.

Combining TSI values and NRS ratings. One of the unique aspects of this study was the comparison between subjective symptom reporting and objective changes in calf tissue oxygenation during exercise and throughout recovery. Figure 11 illustrates that the most rapid decline in TSI values during exercise took place between the start of exercise and the onset of discomfort (i.e., between NRS 0 out of 5 and 1 out of 5). Overall, the decline in TSI values between the onset of discomfort and peak discomfort (i.e., NRS 5 out of 5) was relatively minimal. A different relationship was observed during recovery (see Figure 12). After participants stopped walking, TSI values steadily increased from the maximum discomfort (i.e., NRS 5 out of 5) and full recovery (i.e., NRS 0 out of 5).

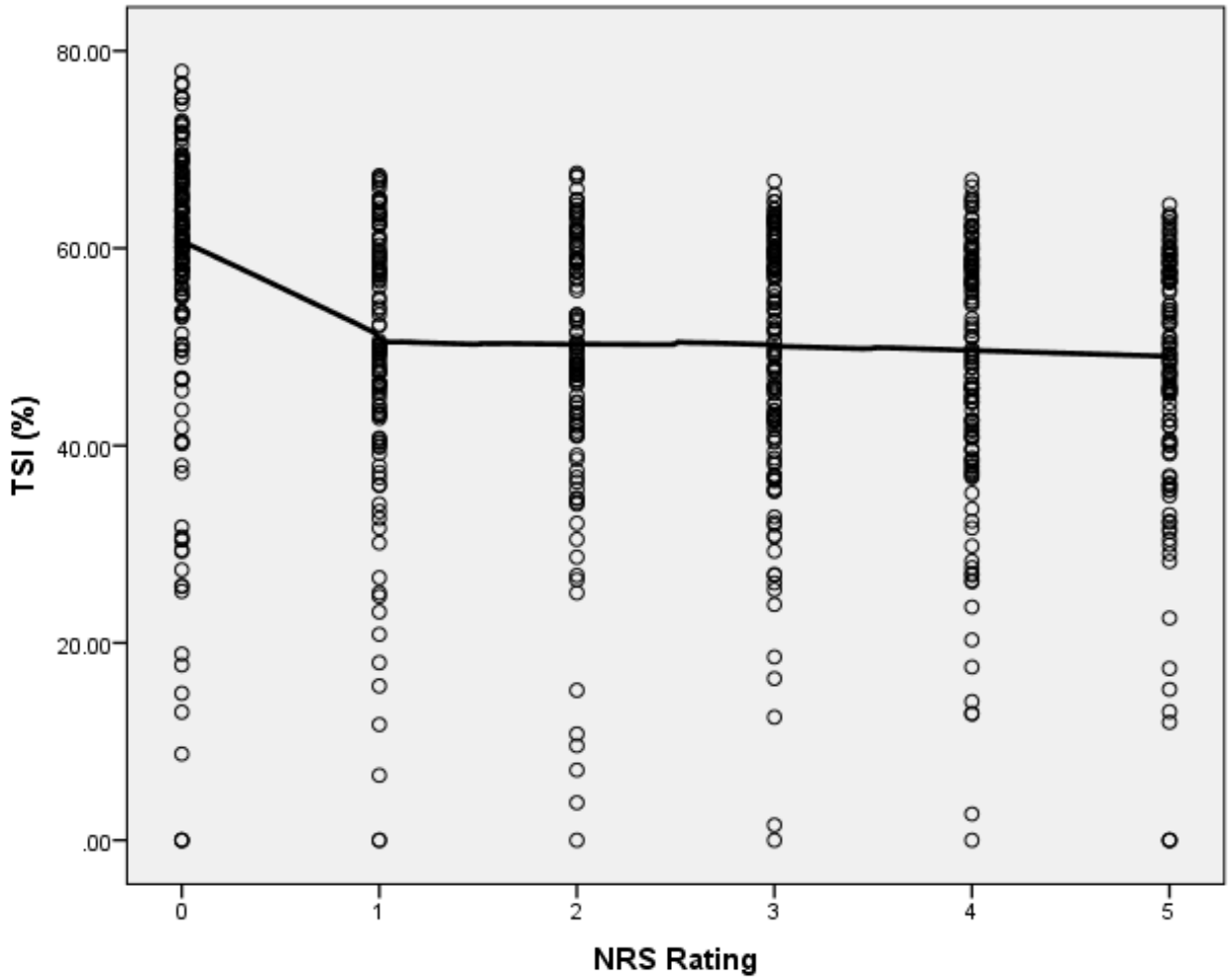

Figure 11. Tissue saturation index (TSI) values by numeric rating scale (NRS) rating during exercise.

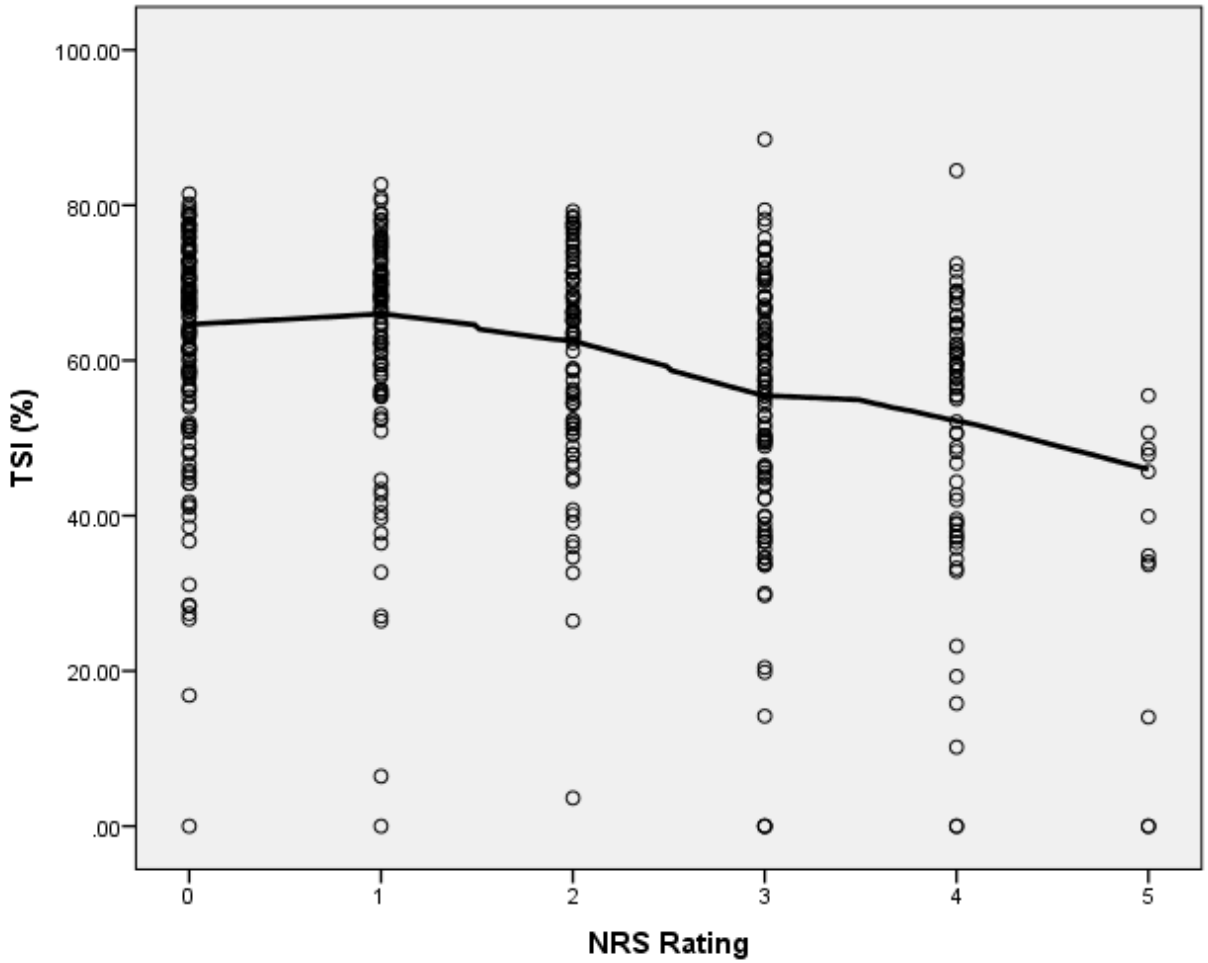

Figure 12. Tissue saturation index (TSI) values by numeric rating scale (NRS) rating during recovery. A NRS rating of 0 signifies full recovery.

Individual graphical trajectories. Although each individual trajectory during the exercise and recovery phases was unique, several common patterns were identified. Patterns were separated into the exercise and recovery phases, with distinctive groupings identified in each phase. However, a subset of individuals either walked for a short period of time or had a great deal of variability in their trajectories that precluded them from fitting into any of the identified patterns. One individual case is provided as an example for every pattern. All 40 of the participants grouped according to exercise and recovery patterns appear in Appendices N and O.

Exercise. Six patterns emerged from the individual exercise trajectories. The most common pattern (n=10) was an initial rapid decline in TSI, followed by slowly declining or relatively unchanged TSI values throughout the rest of exercise (see Figure 13). Figures 14 and 15 illustrate the next two patterns identified, which were exponentially declining (n=8) and relatively unchanged (n=8) TSI values during exercise. The fourth most common pattern (n=7), depicted in Figure 16, was a gradual decline in TSI values throughout the exercise phase. The last identifiable pattern appears in Figure 17. The two individuals in this group illustrated a nearly quadratic change in their TSI values during treadmill walking; TSI values decreased at the beginning of exercise testing, but then started increasing prior to the termination of the test.

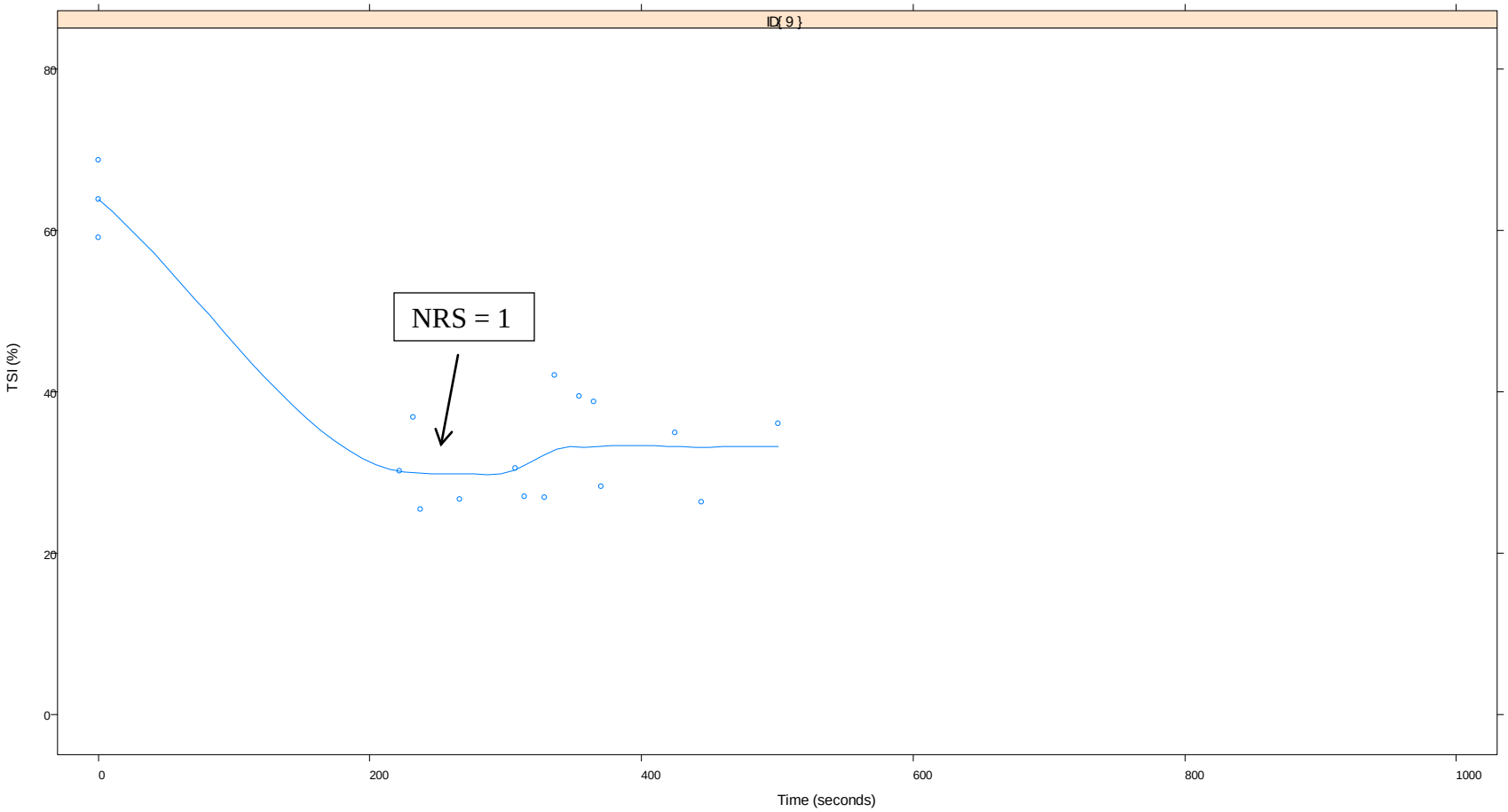

Figure 13. The exercise trajectory for participant #9. This participant exhibited an initial rapid decline in TSI values, followed by relatively unchanged TSI values throughout the rest of treadmill exercise.

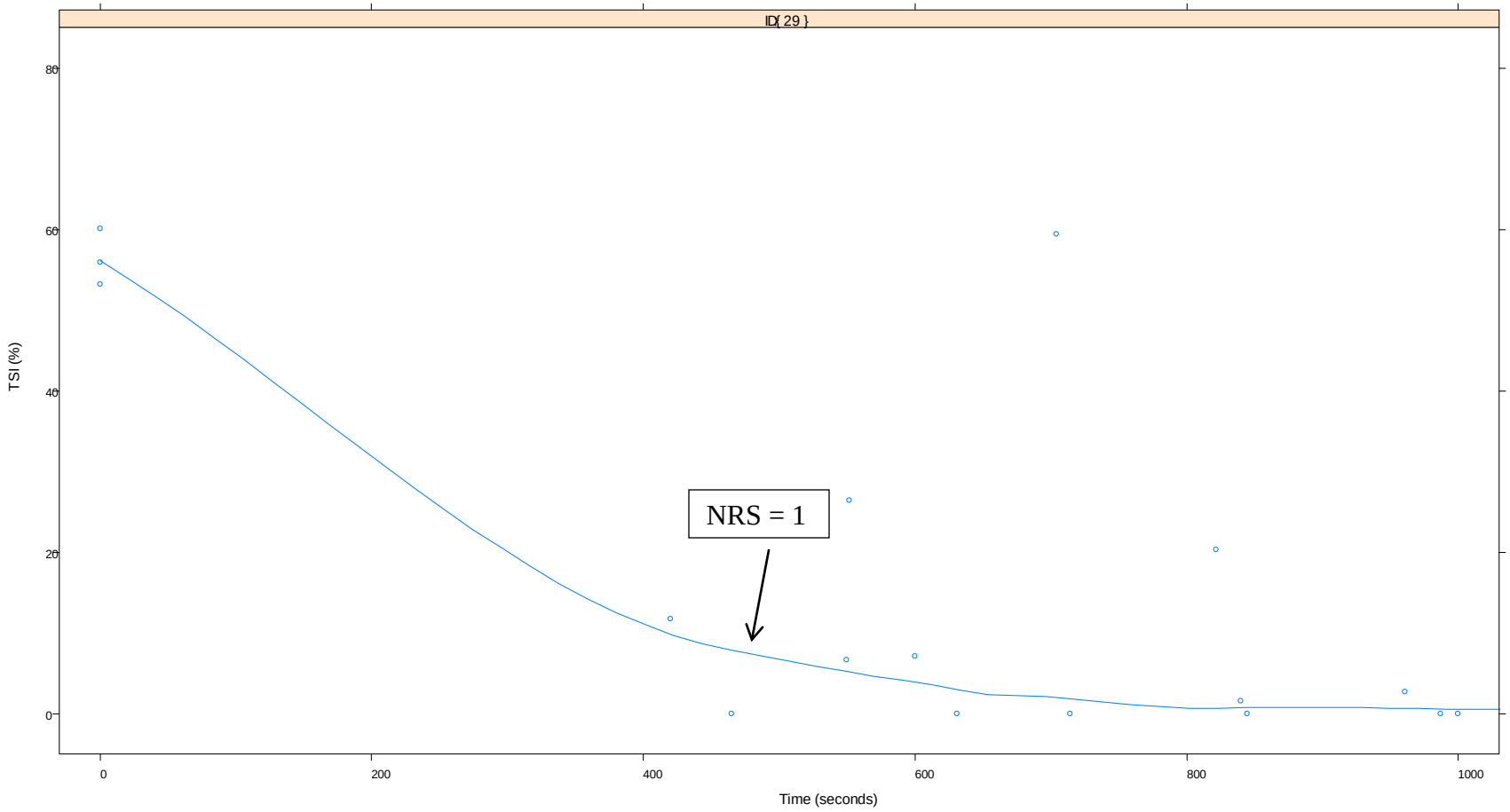

Figure 14. An exponentially declining TSI trajectory exhibited by participant #29 during exercise testing.

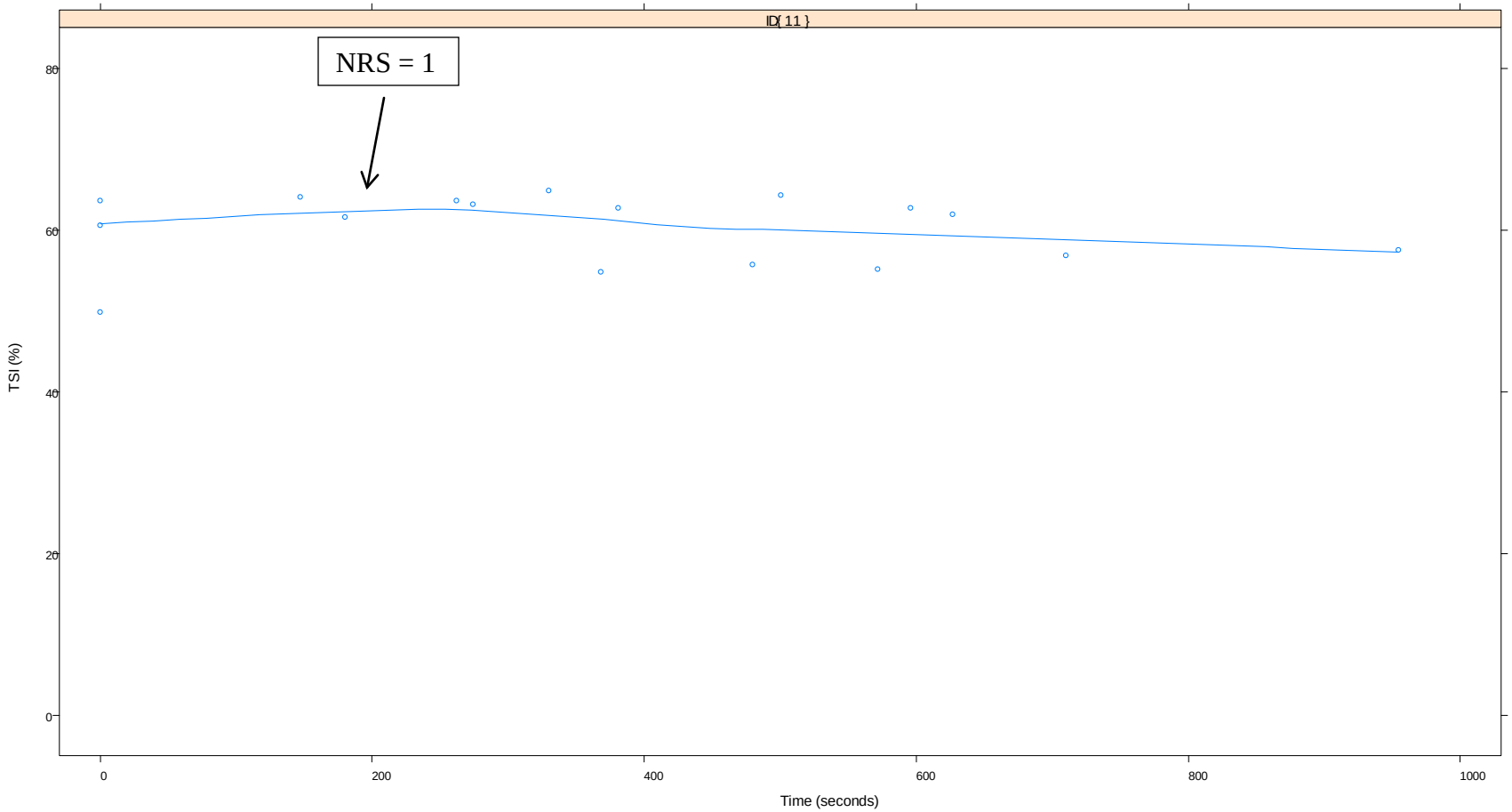

Figure 15. Participant #11 illustrated a relatively unchanged TSI trajectory during treadmill exercise.

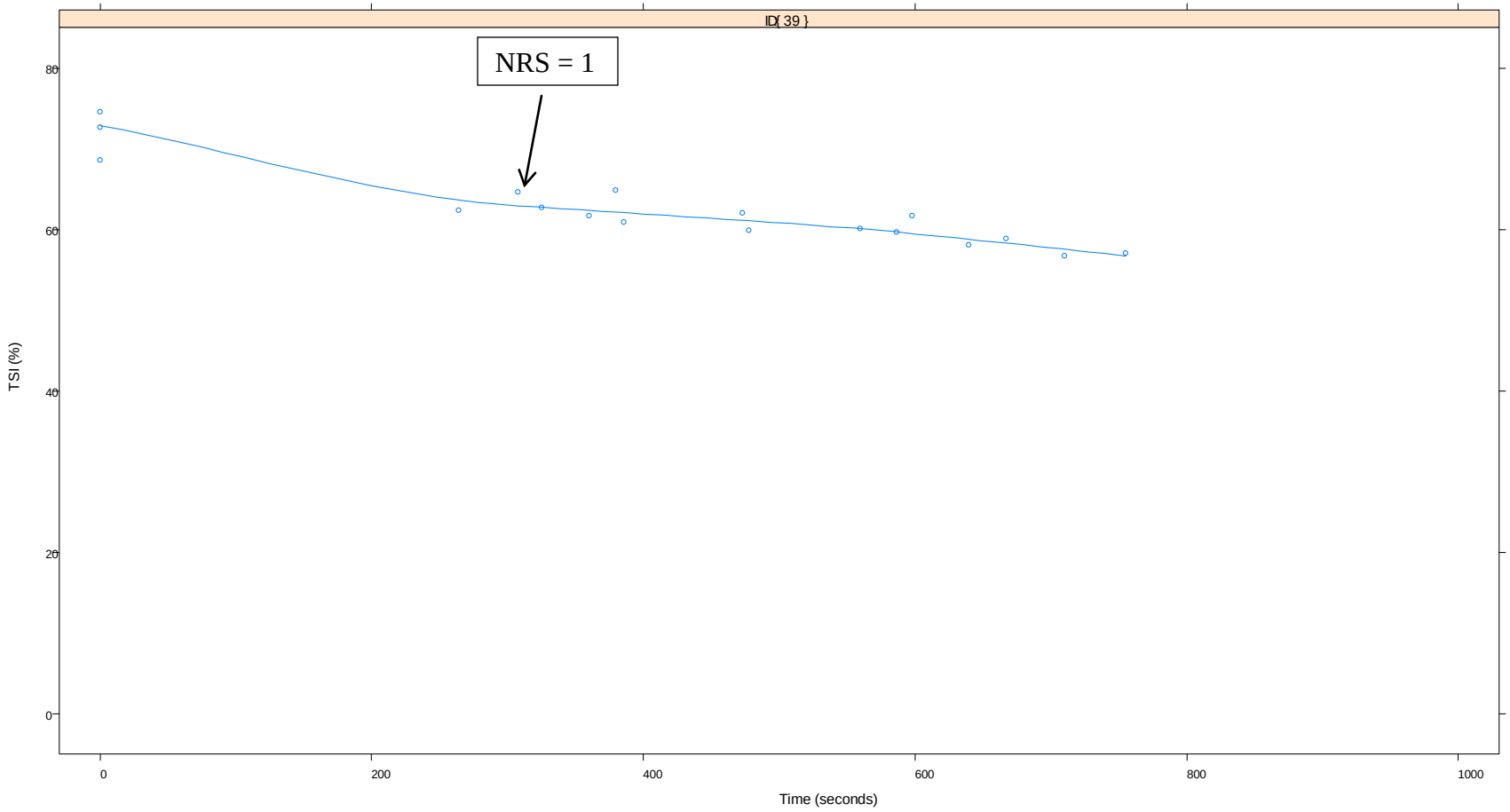

Figure 16. A gradually declining TSI trajectory was identified during exercise for participant #39.

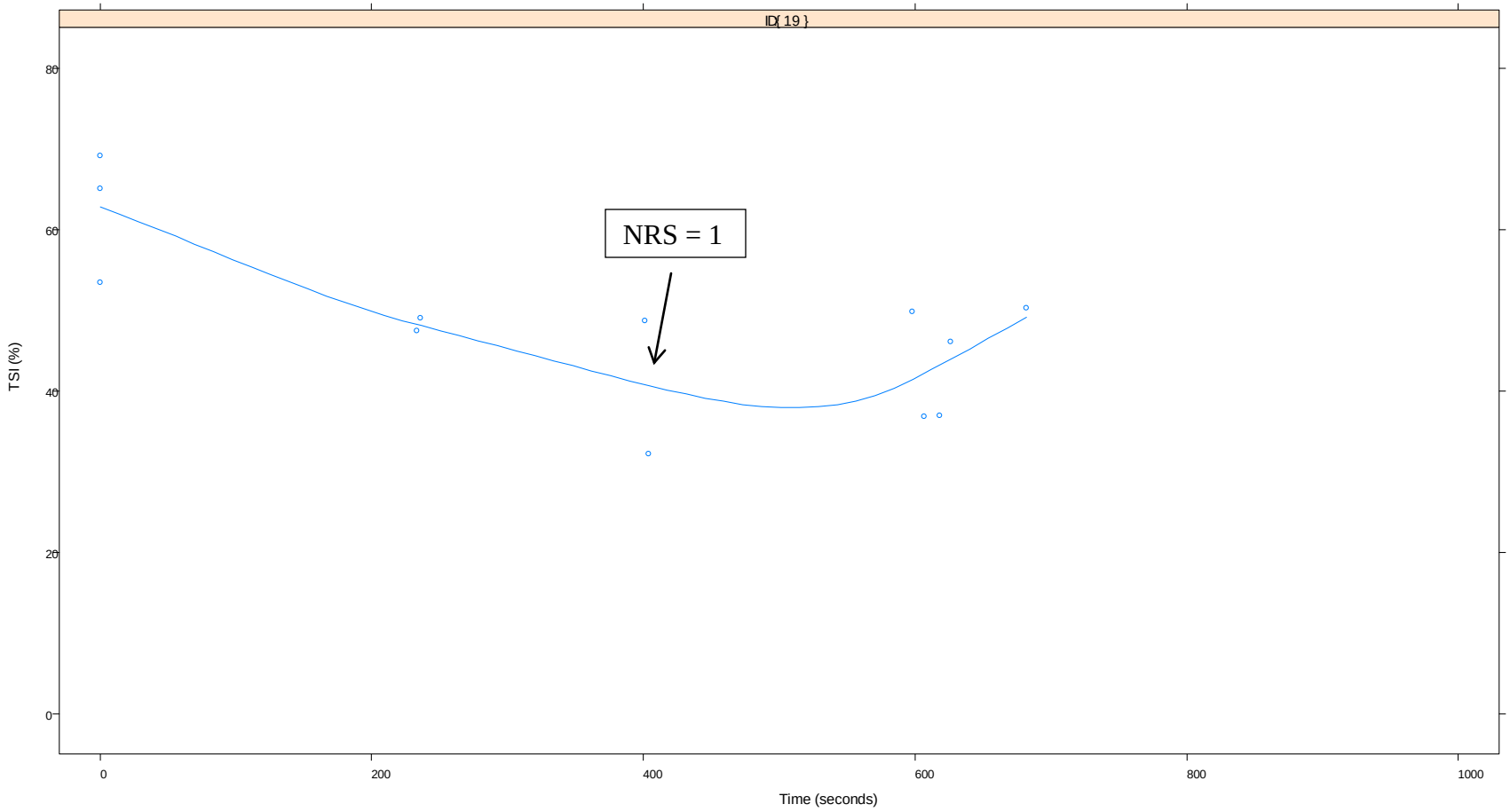

Figure 17. Participant #19 demonstrated a quadratic change in TSI values during treadmill exercise testing.

Of the five remaining individuals, three walked for less than six minutes, which complicated cross comparison with other study participants who walked longer. When the time scale for these individuals was condensed, two of the participants, #4 and #5, fell into the relatively unchanged TSI pattern, whereas participant #10 fit more closely into the gradually declining TSI group. The remaining two participants, #21 and #36, followed a cubic change in TSI values during exercise, with the latter participant experiencing a more severe decline in TSI at the beginning of exercise compared to the more prolonged decline in TSI experienced later in the exercise phase for participant #21 (see Figure 18). Appendix P provides a numeric summary of the exercise phase for each individual.

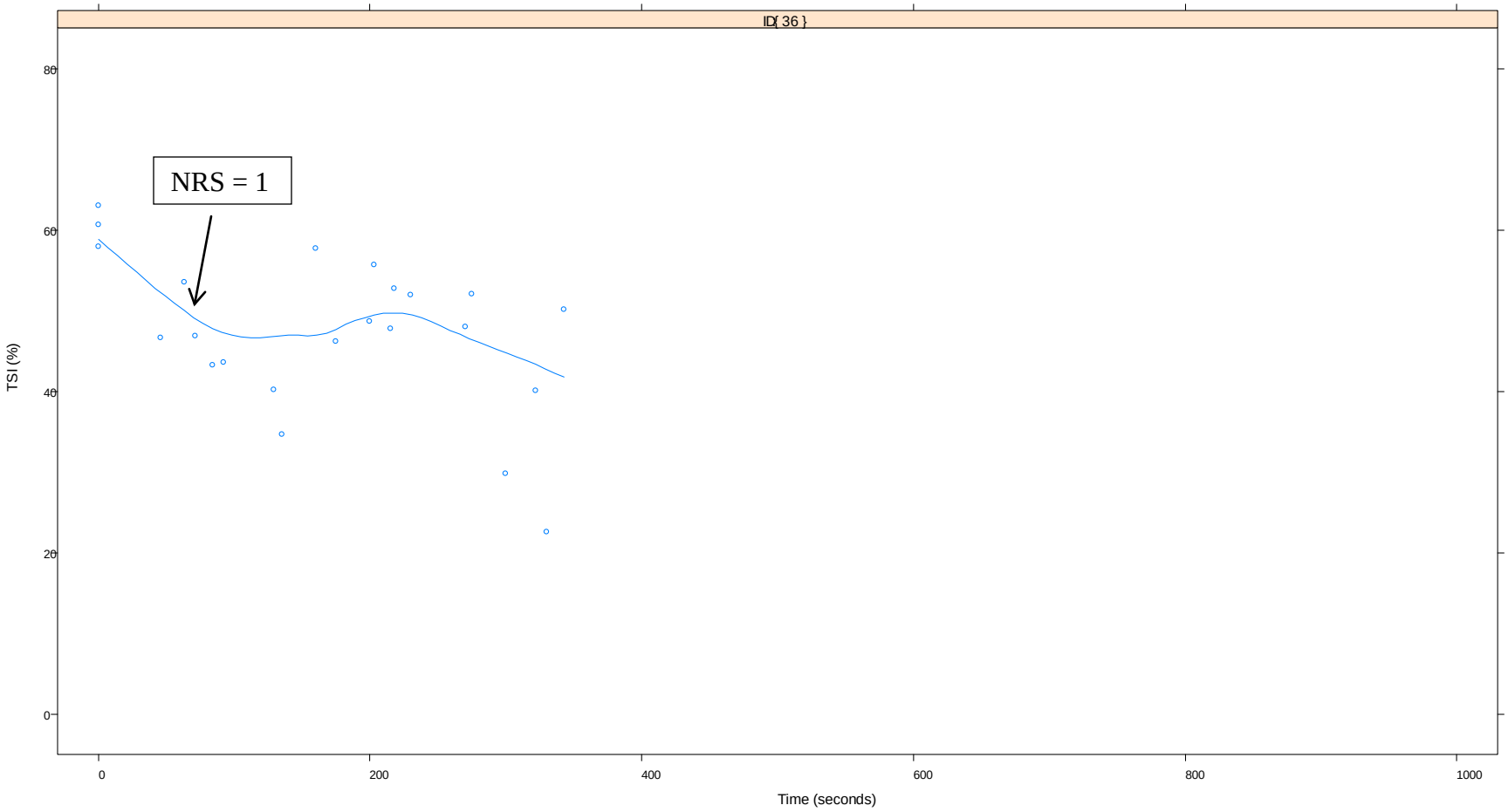

Figure 18. Individual exercise trajectories for participant #36 exhibiting a cubic change in TSI values.

Recovery. TSI recovery patterns were more diverse compared to TSI exercise patterns. Eight patterns emerged from the individual recovery trajectories. The most common pattern was a peak in TSI during recovery (*n*=11). Three individuals reached a peak TSI rapidly, followed by a gradual decline in TSI values (Figure 19), whereas the other eight participants had a slower TSI recovery, with a less pronounced peak in TSI before values started declining again (Figure 20). Figures 21 and 22 illustrate the next two recovery patterns identified, which were an exponential recovery (*n*=6) and a cubic recovery (*n*=6). The cubic recovery patterns were further broken down into a rapid initial TSI recovery (Figure 22) and a slower (i.e., flatter) TSI recovery at the beginning of the recovery phase (Figure 23).

The next most common recovery pattern (*n*=5), depicted in Figure 24, was a slightly flat TSI recovery, indicating that TSI values remained relatively unchanged throughout the recovery phase compared to the other patterns identified. The next two patterns, a linear recovery (*n*=4) and a rapid full recovery (*n*=4), are shown in Figures 25 and 26. During the initial exploratory analysis, the rapid full recovery pattern appeared to be a vertical line. However, when the x-axis was condensed, the true form emerged. The last pattern identified was a quick initial TSI recovery, similar to the rapid full recovery, but this group did not reach full recovery for some time after the initial spike in TSI, and TSI values gradually declined throughout the recovery period (*n*=3) (see Figure 27). Figure 28 illustrates the unique recovery pattern exhibited by participant #19. TSI values for this individual appeared to decline initially, then peak mid-recovery, followed by another decline and finally reaching the highest TSI at the end of the recovery phase. Numeric recovery phase summaries for each individual are listed in Appendix Q.

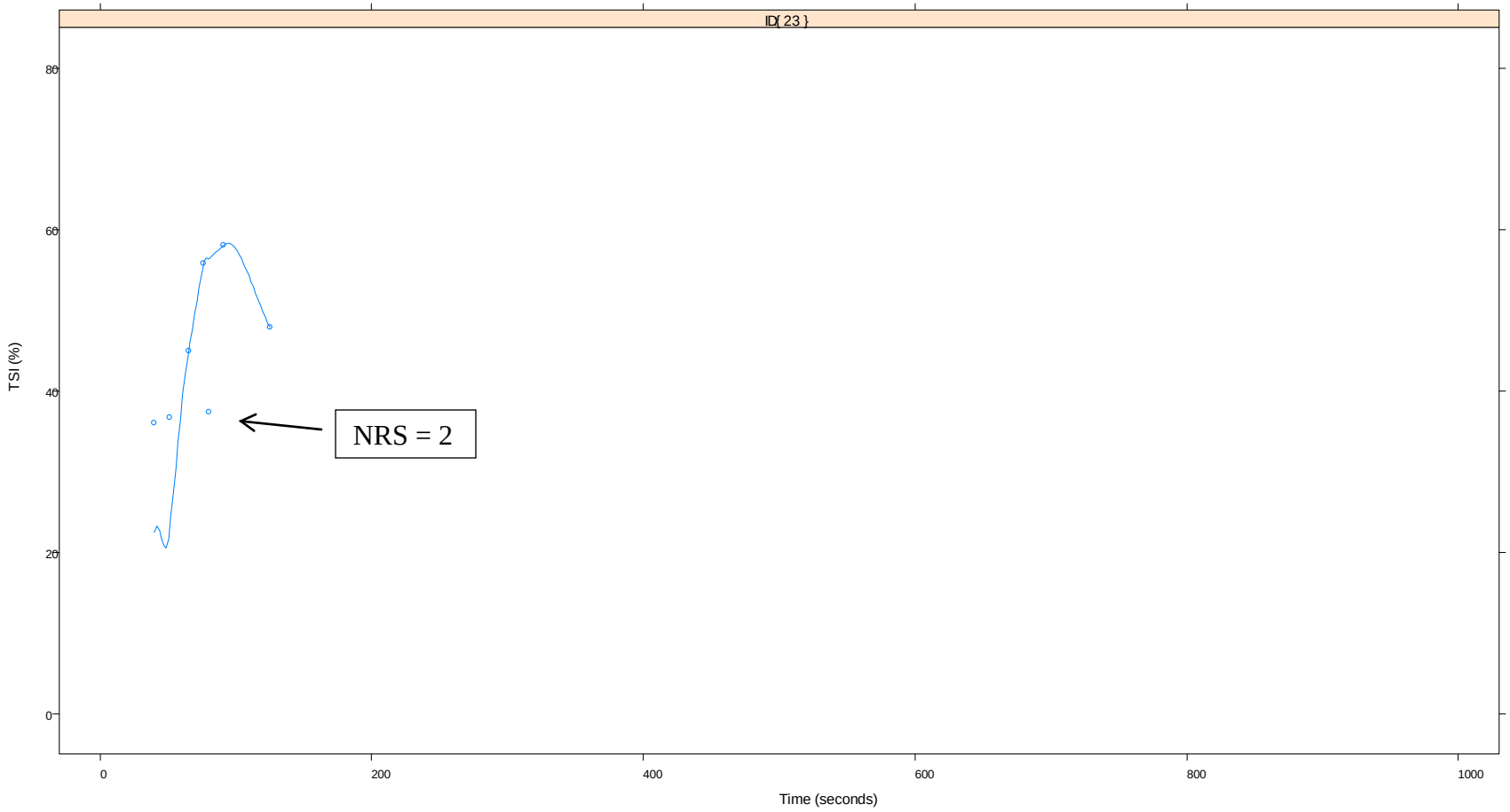

Figure 19. A rapid peak in tissue saturation index (TSI), followed by a decline exhibited by participant #23 during recovery.

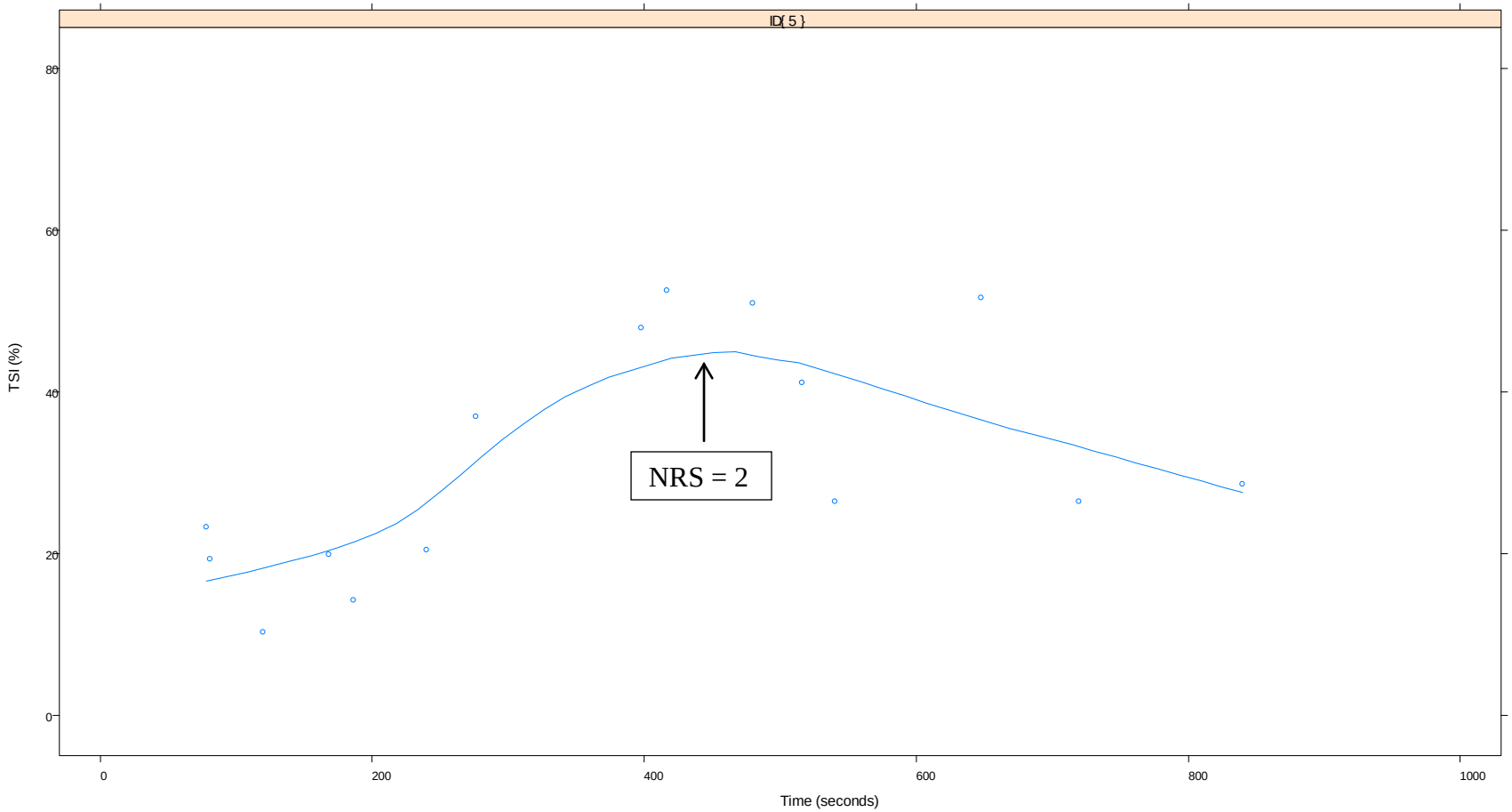

Figure 20. Participant #5 illustrated a less pronounced peak in tissue saturation index (TSI), followed by a gradual decline during recovery.

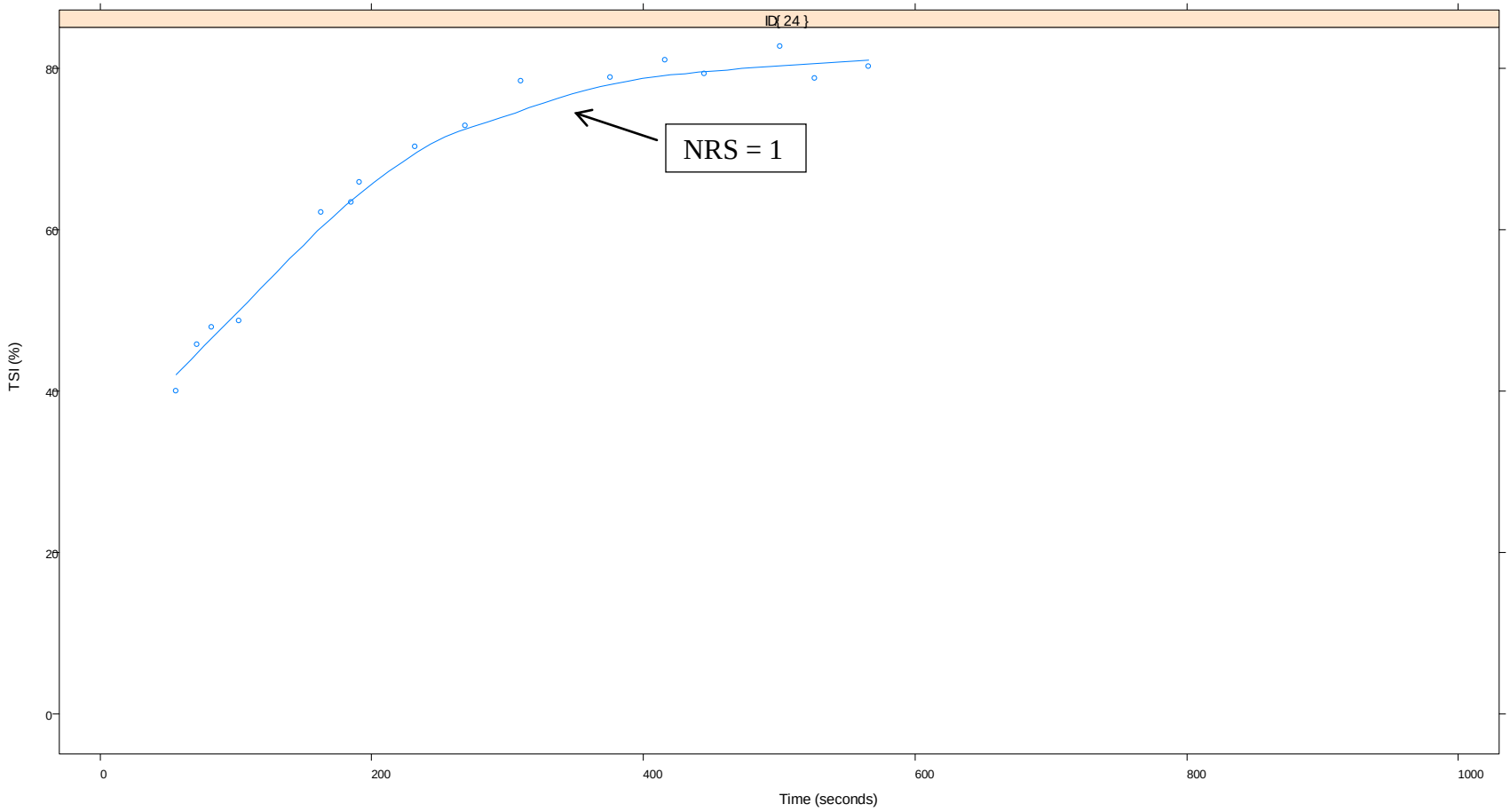

Figure 21. An exponential tissue saturation index (TSI) recovery trajectory was identified for participant #24.

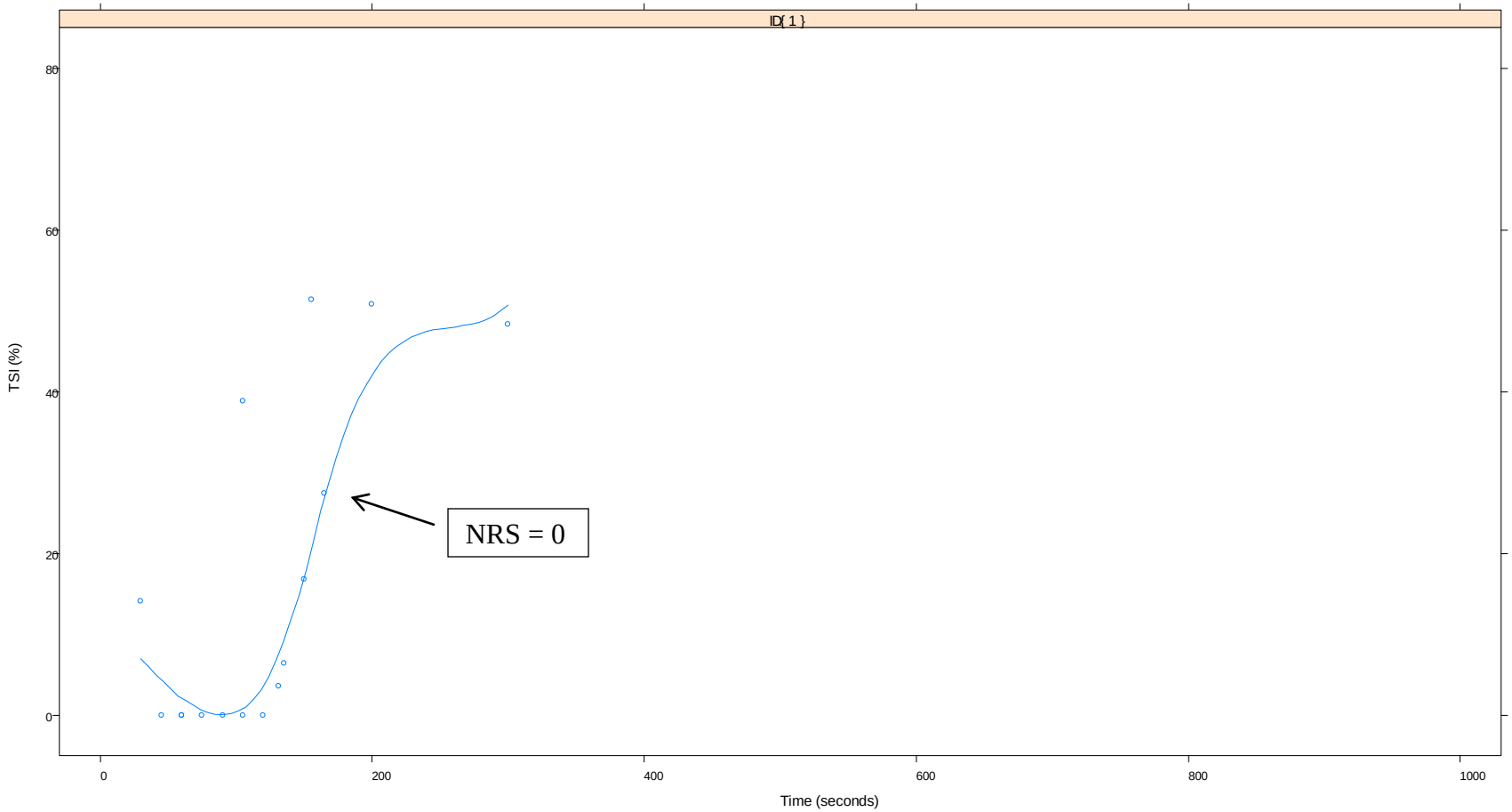

Figure 22. Participant #1 demonstrated a steep cubic tissue saturation index (TSI) trajectory during recovery.

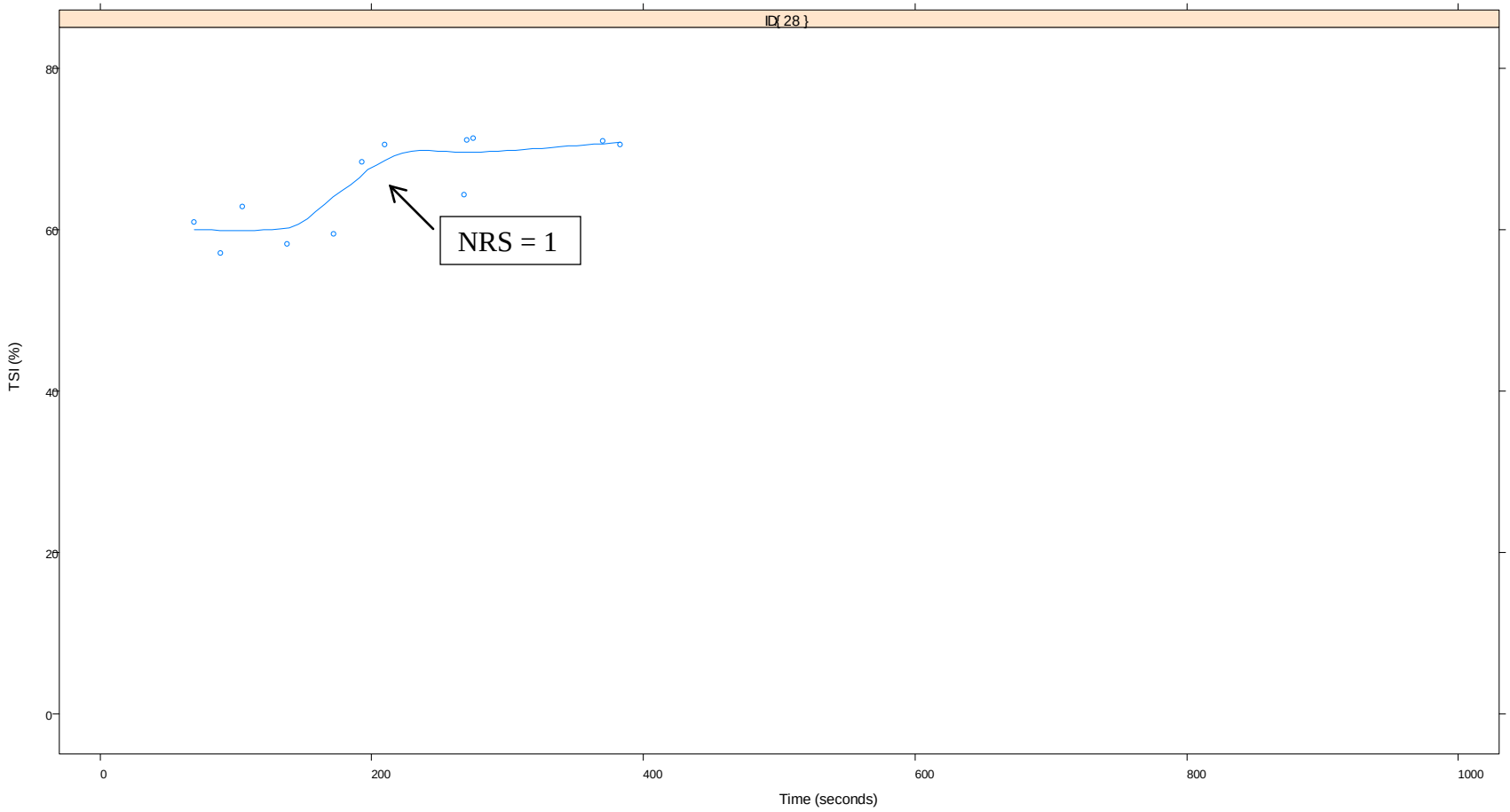

Figure 23. A less pronounced cubic tissue saturation index (TSI) recovery trajectory was exhibited by participant #28.

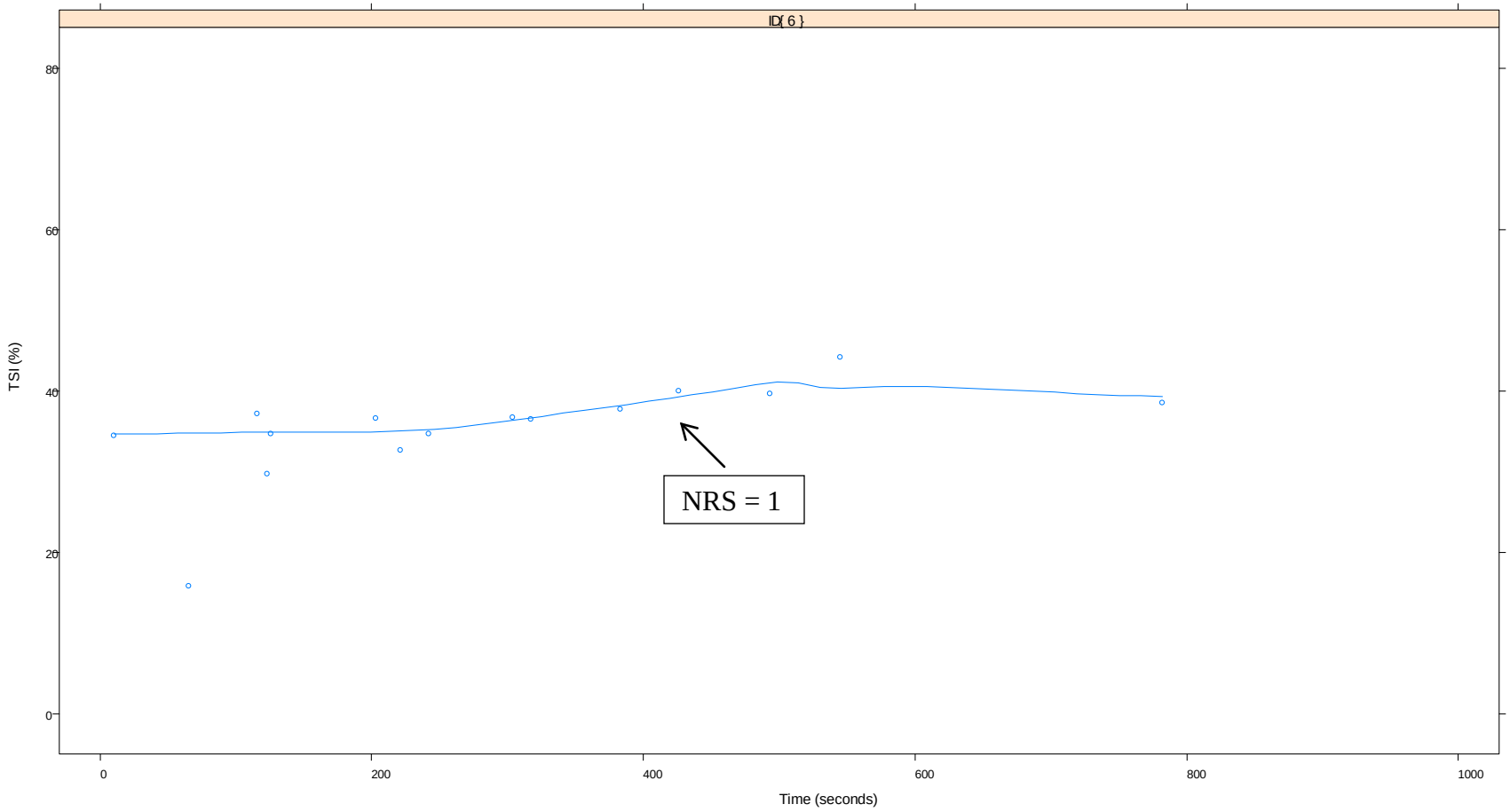

Figure 24. Participant #6 exhibited relatively unchanged tissue saturation index (TSI) values throughout the recovery phase.

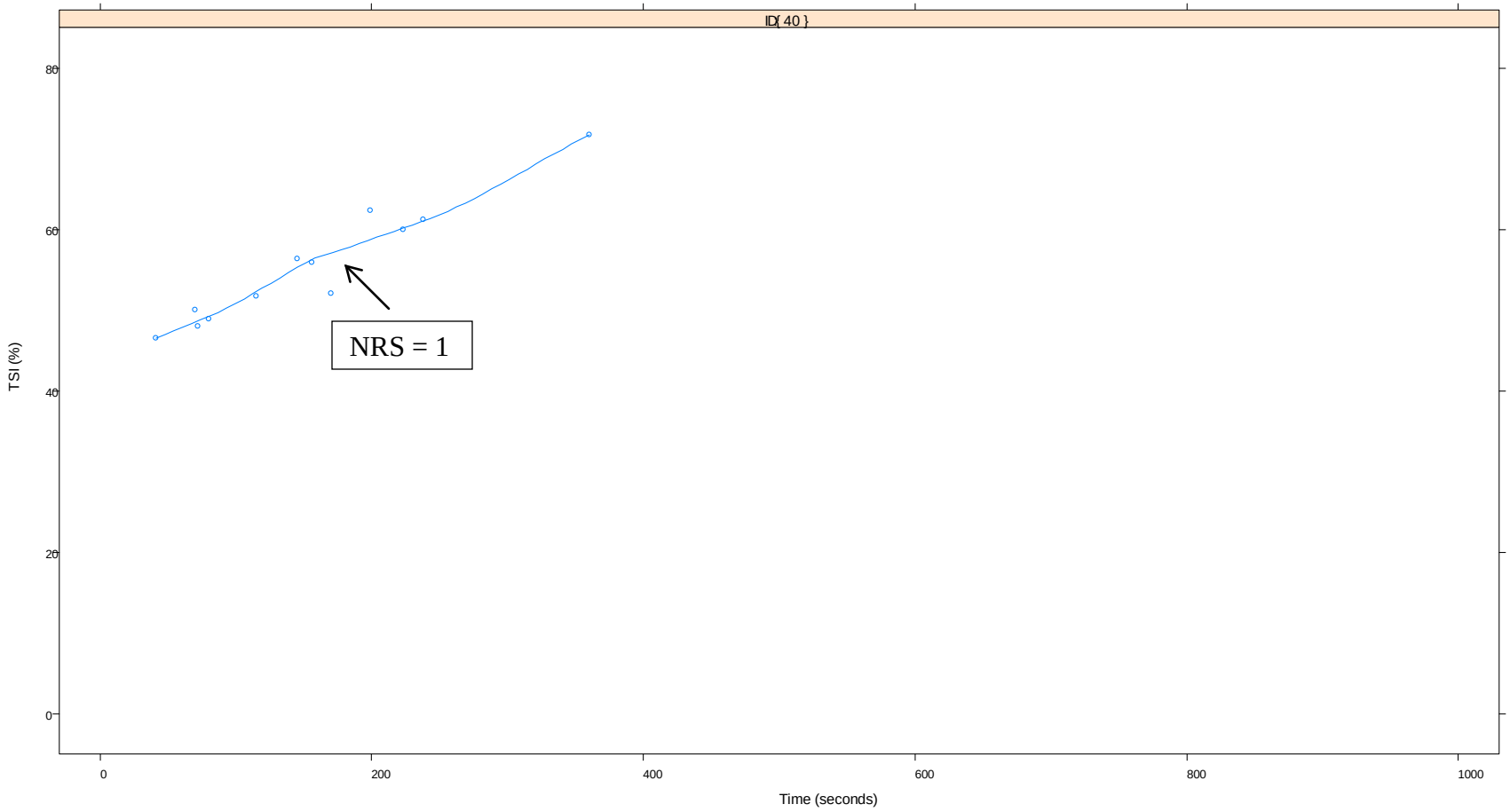

Figure 25. A linear tissue saturation index (TSI) recovery trajectory was identified for participant #40.

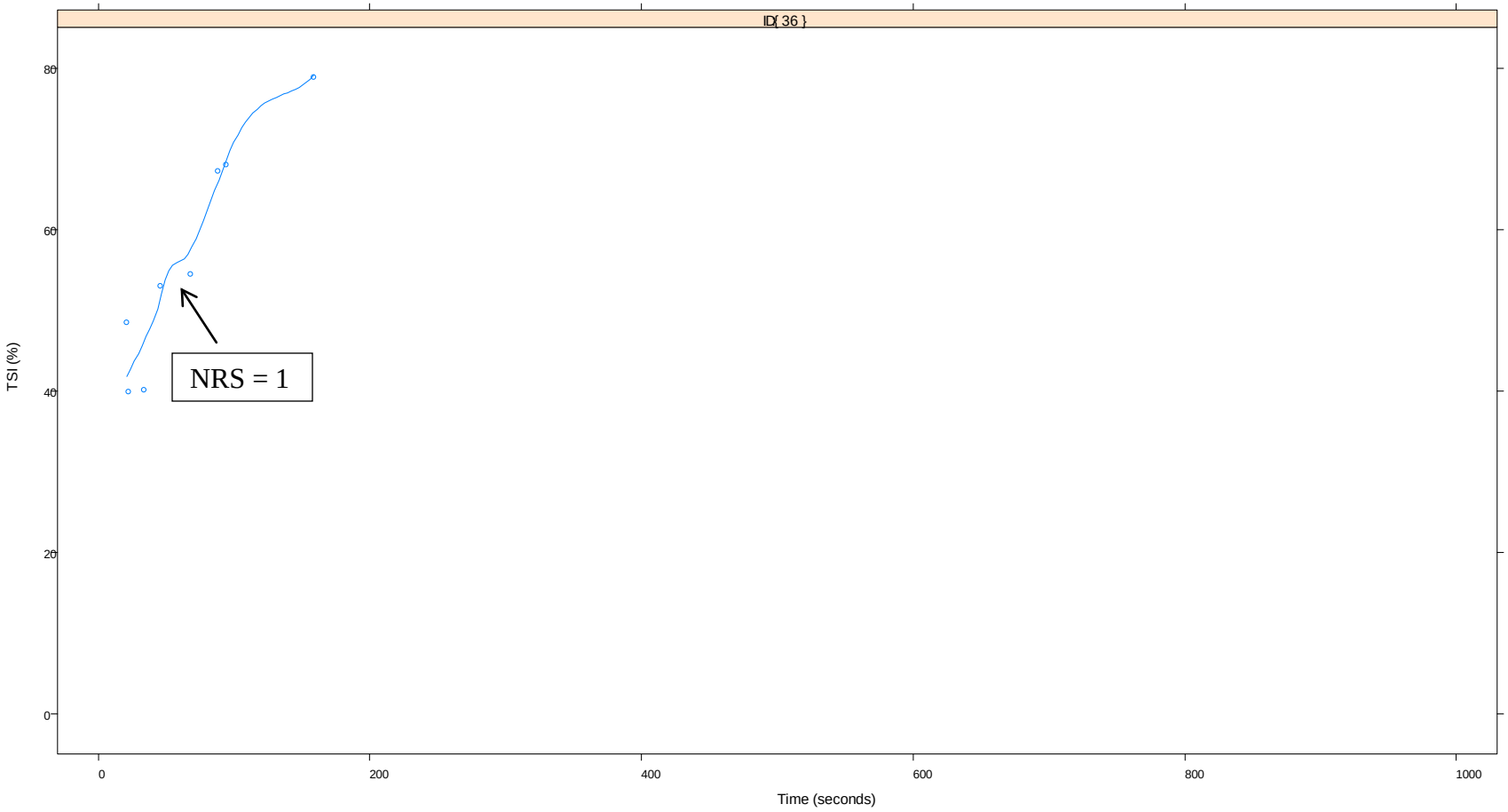

Figure 26. The individual recovery trajectory for participant #36, exhibiting a rapid and full recovery of tissue saturation index (TSI).

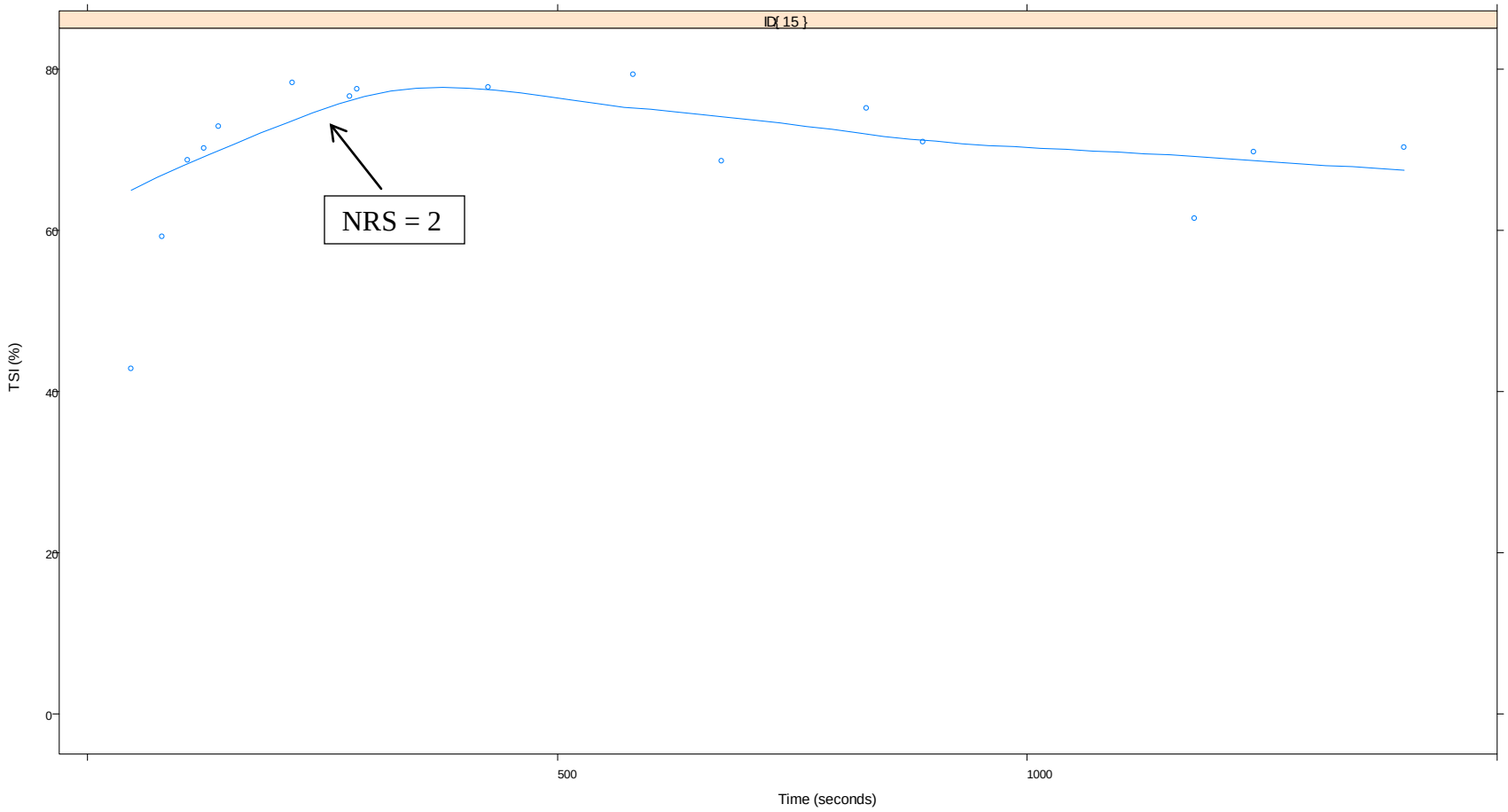

Figure 27. The recovery trajectory for participant #15. This individual exhibited a rapid initial recovery, followed by gradually declining tissue saturation index (TSI) values.

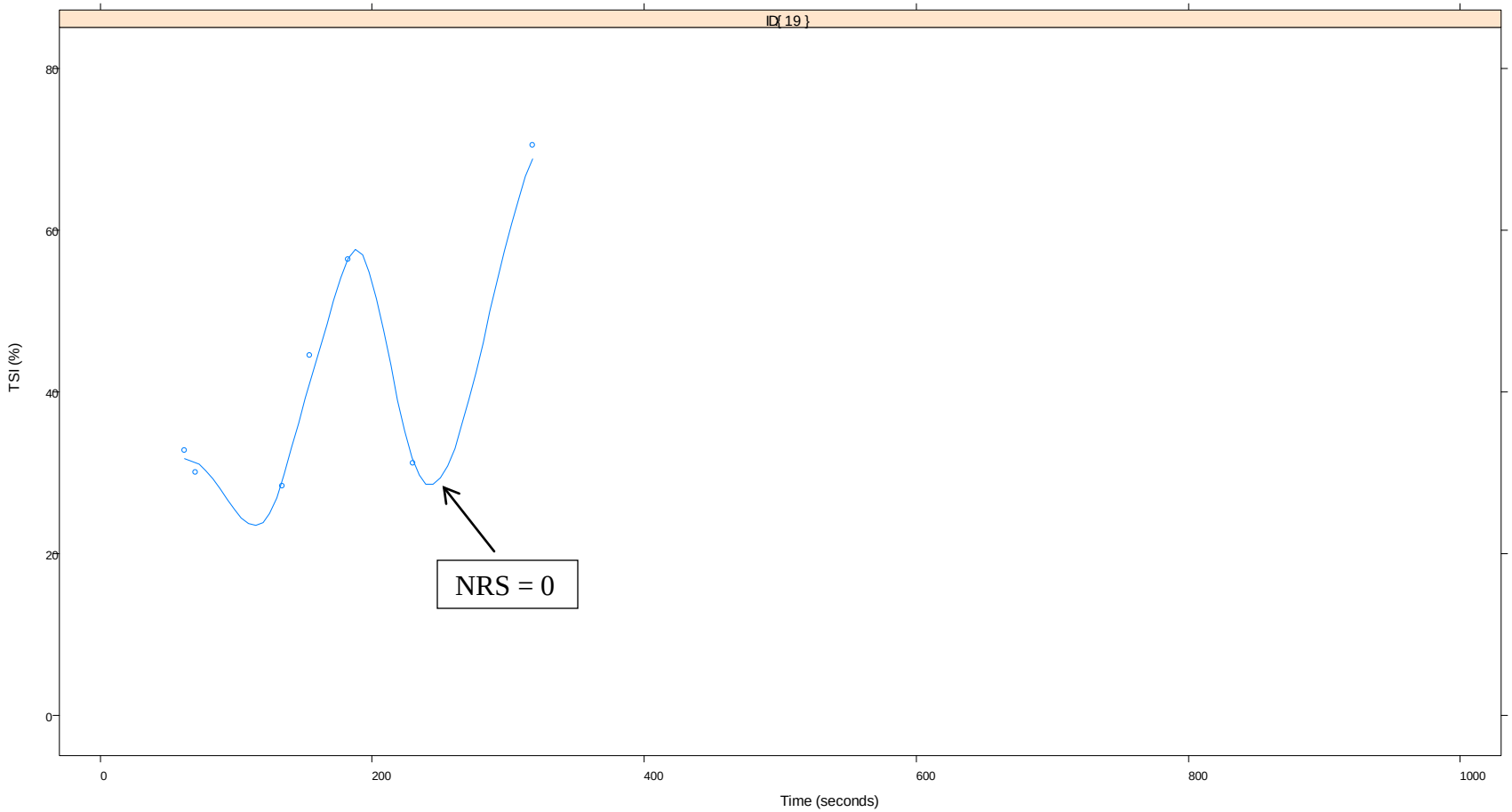

Figure 28. Participant #19 had a tissue saturation index (TSI) recovery trajectory unlike any other study participant.

Grouping graphical trajectories. Individual TSI values during exercise and recovery were grouped together and subsequently explored from multiple perspectives. Again, the exercise and recovery phases were split, mainly because of the inflection point that appeared to separate the entire trajectory into two distinct phases. The initial focus was on grouping trajectories based on each of the three exercise tests. Additional exploration included grouping trajectories based on several PAD risk factors (e.g., ABI, DM, smoking status, and age), comorbid conditions that could potentially confound the PAD symptom experience (e.g., neuropathy and OA), and other potentially influencing factors (e.g., gender, BMI, and ethnicity). Some of the more interesting group trajectories are presented. However, all of the graphical trajectories for each group during the exercise and recovery phases appear in Appendices R and S.

Exercise test. Interestingly, TSI values for the entire group remained relatively unchanged from test to test. The nearly identical loess lines depicted in Figure 29 demonstrates how similar the TSI values were in the first, and subsequent two exercise tests. Similarly, Figure 30 illustrates the stability in TSI values among the three recovery phases. The stability in TSI values during both the exercise and recovery phases indicated that individuals fully recovered between tests, and eliminated the need to control for exercise tests in multilevel modeling, which simplified the interpretation of the final model results.

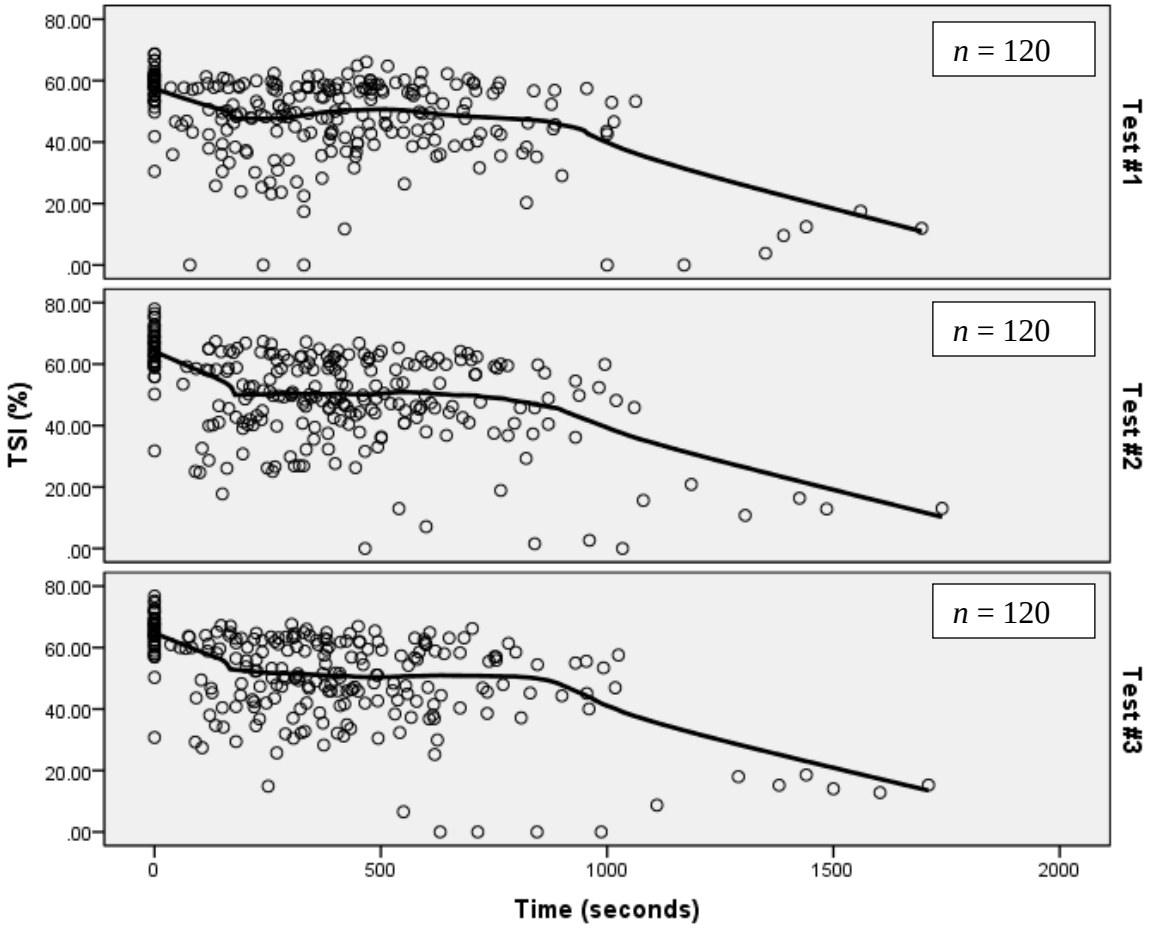

Figure 29. Stability in TSI values during exercise for each treadmill test.

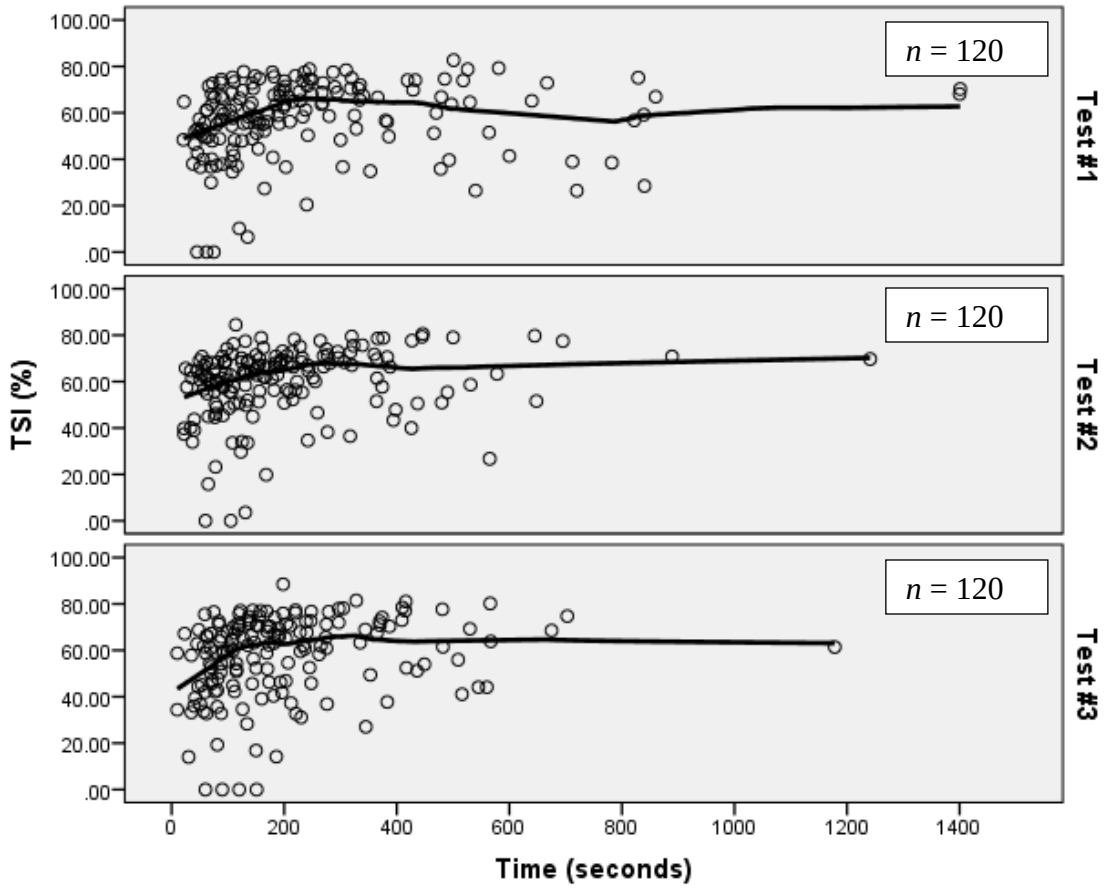

Figure 30. Stability in TSI values during recovery for each treadmill test.

PAD risk factors. Graphical trajectories based on ABI, DM, smoking status, and age were explored during the exercise and recovery phases. According to baseline ABI measurements, the majority of participants (*n*=15) were considered to have a moderate form of PAD (i.e., ABI 0.50-0.69). Those with borderline disease (i.e., ABI=0.91-0.99) or those with a normal ABI (i.e., 1.00-1.40) had trajectories that appeared relatively unchanged throughout exercise (see Figure 31). Individuals with the most severe PAD (i.e., ABI ≤ 0.49) had the most pronounced decline in TSI, followed by individuals with non-compressible arteries (i.e., ABI >1.40). Those with mild (i.e., ABI = 0.70-0.90) to moderate disease, appeared to experience an initial decline in TSI values, followed by a

steady decline throughout the rest of exercise. Figure 32 suggests that individuals with non-compressible arteries recovered the quickest, while those with mild to moderate disease experienced an initial increase in TSI, followed by a steady stabilization of TSI values throughout the duration of recovery. Individuals with normal or borderline ABI values followed similar patterns in which TSI values remained relatively unchanged throughout the recovery phase.

The presence of DM or metabolic syndrome did not appear to influence TSI values during the exercise or recovery phases. All four groups exhibited similar trajectories during exercise and recovery, except that individuals with Type 2 DM had a more pronounced dip in TSI values mid-exercise compared to the other three groups. Likewise, no apparent differences in the group trajectories based on smoking status were observed. During exercise, current smokers appeared to exercise longer and reach lower TSI values compared to non-smokers and those with a history of smoking. Longer recovery times were observed for individuals with a smoking history, and again, lower TSI values were exhibited by current smokers.

As illustrated in Figure 33, younger adults appeared to have a less steep initial decline in TSI values compared to individuals aged 65 years and older. However, the TSI values of younger participants continued to decline throughout the duration of exercise. Since younger adults, as a group, walked longer than their counterparts, it's difficult to conclude that older adults wouldn't have followed a similar pattern if they had similar exercise times. Comparable trajectories were followed during recovery (see Figure 34), with older participants having an earlier and more pronounced recovery of TSI values compared to their younger counterparts.

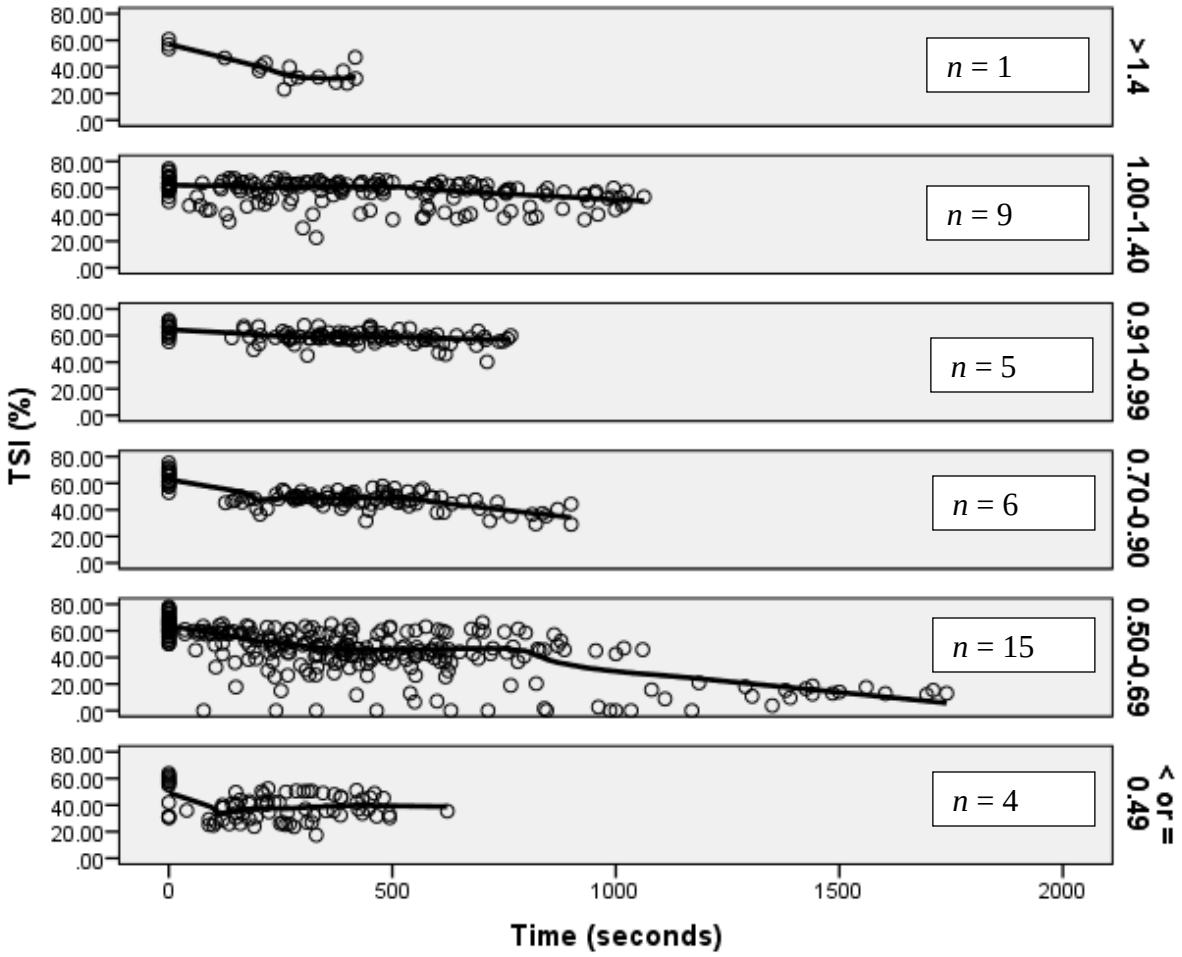

Figure 31. TSI values during exercise based on ABI category.

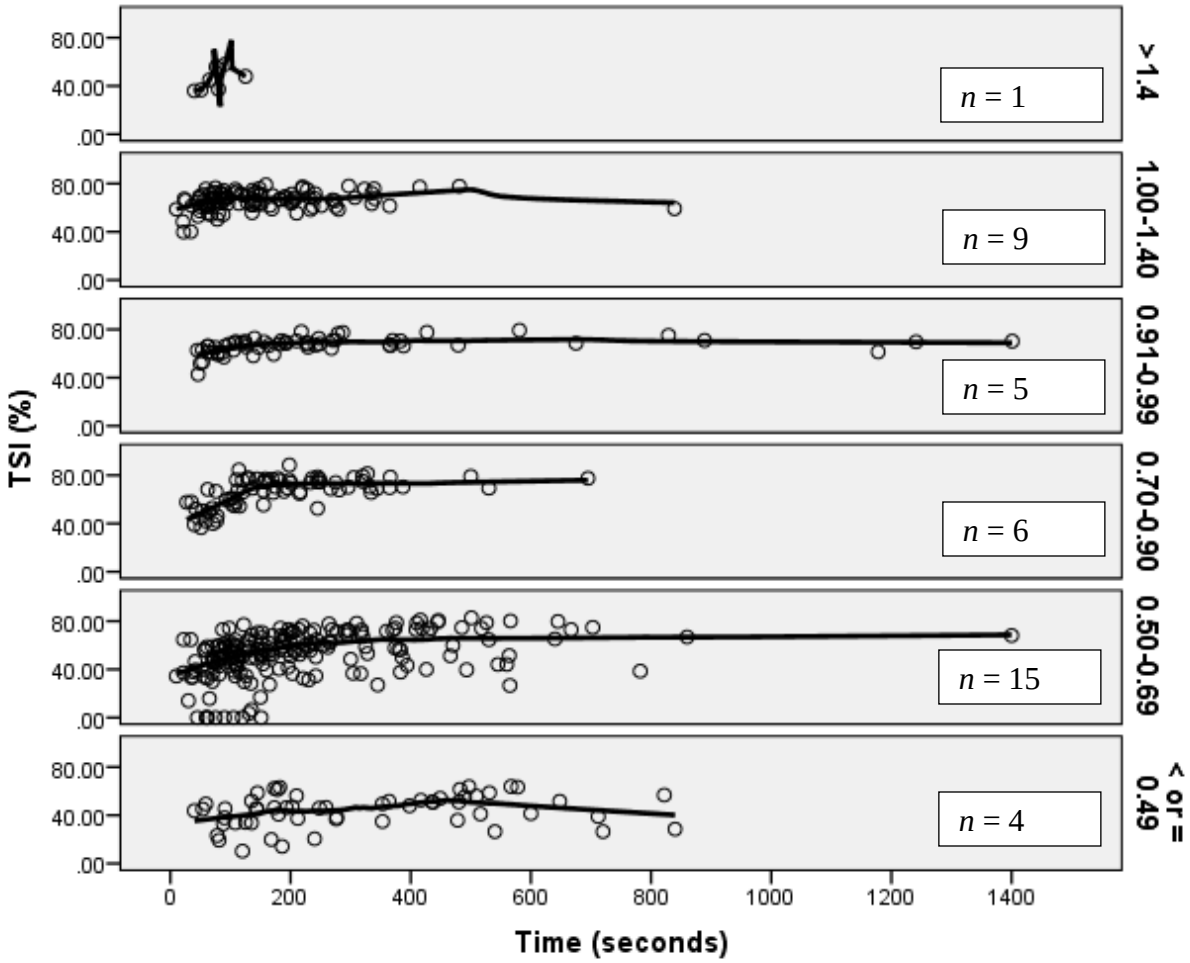

Figure 32. TSI values during recovery based on ABI category.

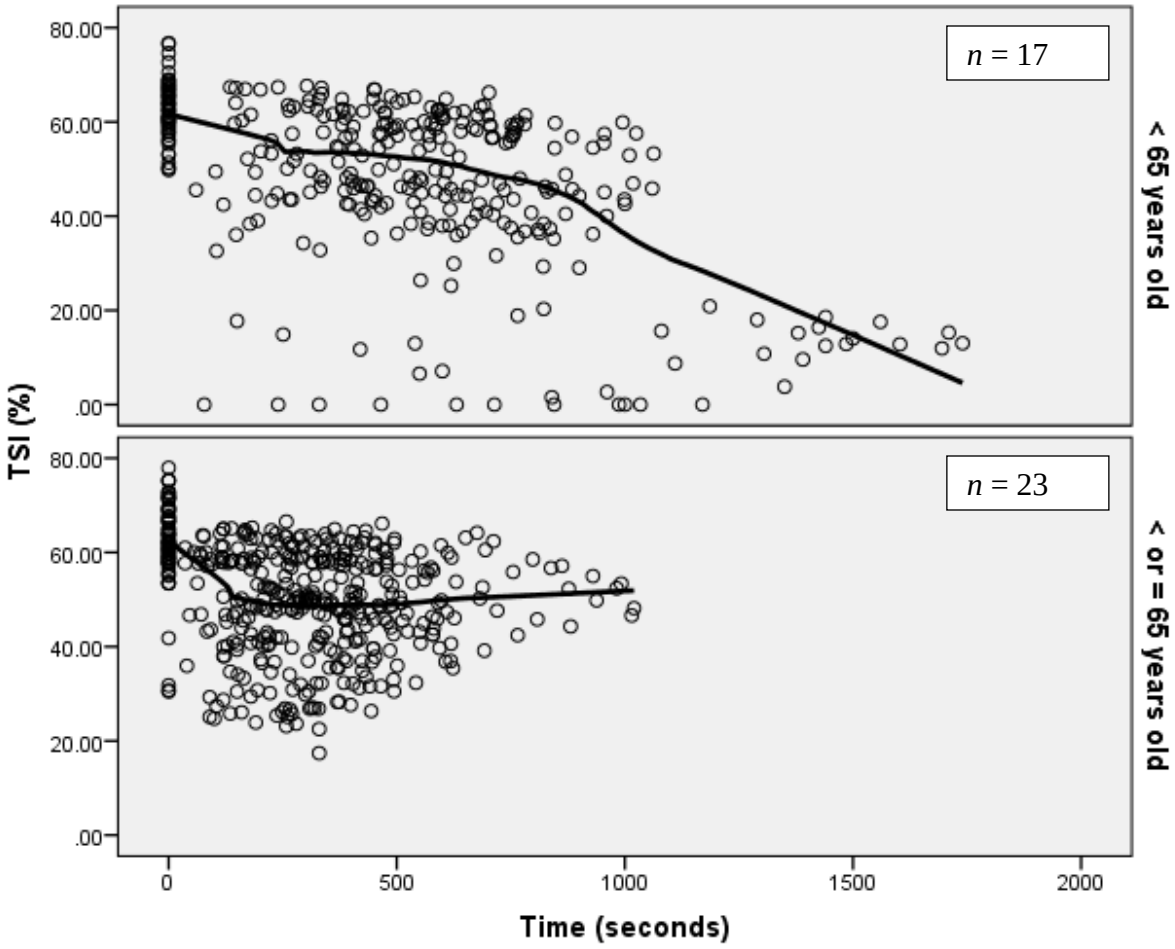

Figure 33. TSI values during exercise in younger versus older participants.

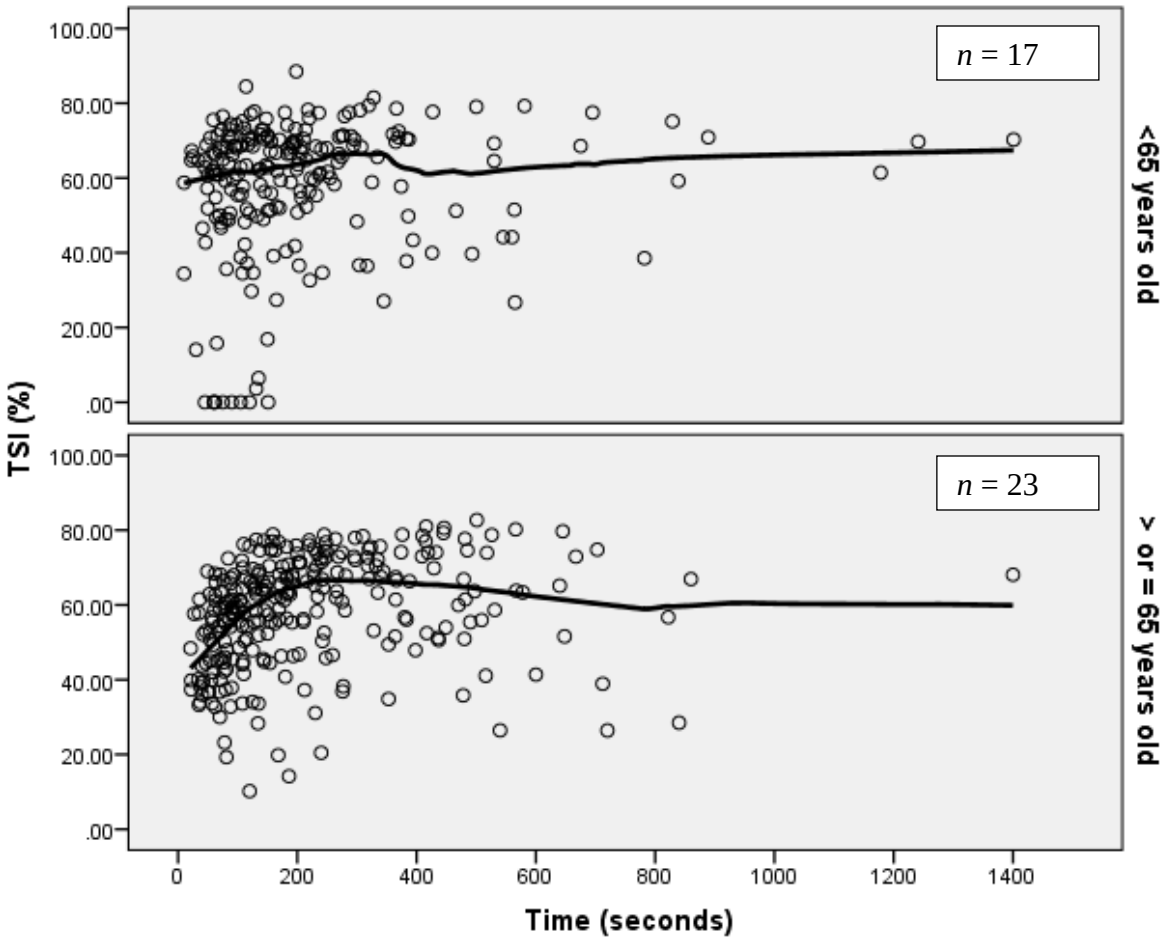

Figure 34. TSI values during recovery in younger versus older participants.

Comorbid conditions. Regardless of a diagnosis of neuropathy, individuals experienced similar exercise and recovery patterns. At the start of exercise, both groups demonstrated a comparable drop in TSI, followed by stabilization of TSI values mid-exercise, and an eventual decline in values until exercise ceased. Both groups experienced a similar recovery, but those without a diagnosis of neuropathy had a more pronounced TSI recovery at the beginning of the recovery phase. Additionally, a diagnosis of OA did not appear to affect TSI values during exercise (see Figure 35).

However, even though individuals without a diagnosis of OA walked longer and recovered quicker, they exhibited lower TSI values compared to those diagnosed with OA. Figure 36 illustrates that both groups experienced similar recovery patterns with a few individuals with OA experiencing a prolonged recovery. Similar to individuals with neuropathy, those with a diagnosis of OA had a more pronounced TSI recovery at the beginning of the recovery phase compared to individuals without OA.

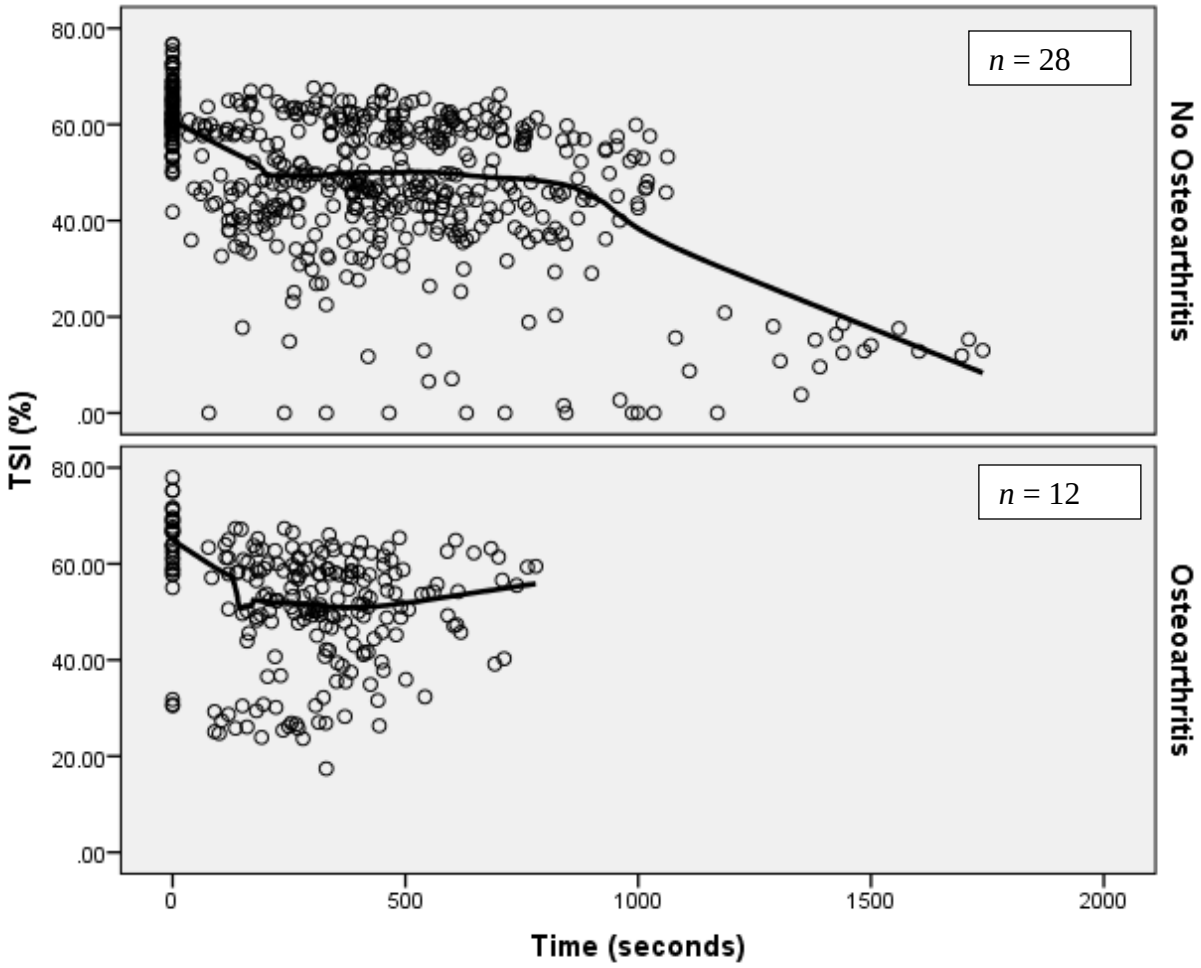

Figure 35. TSI values during exercise based on diagnosis of osteoarthritis.

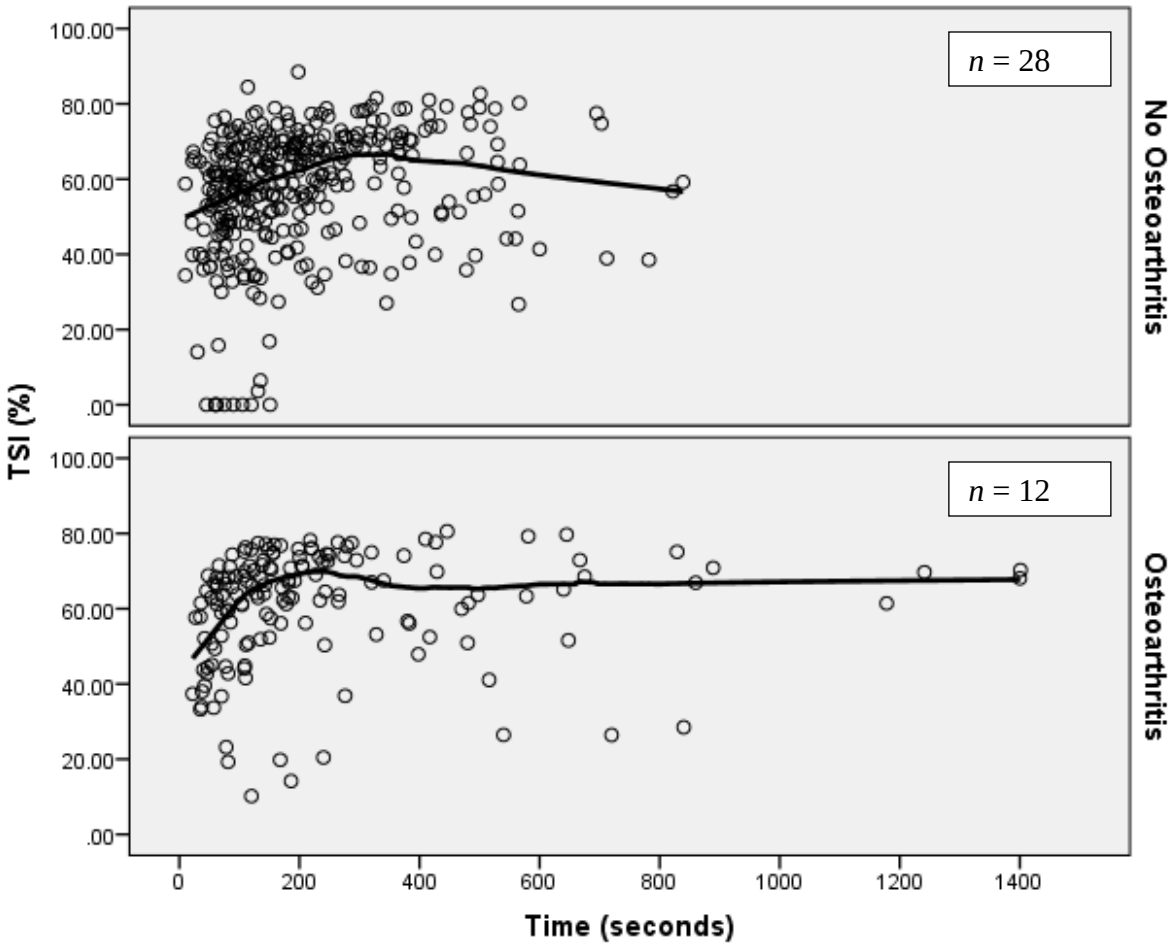

Figure 36. TSI values during recovery based on diagnosis of osteoarthritis.

Other factors. Figure 37 indicates that males walked longer and reached lower TSI values during exercise compared to females. However, only five females participated in the study. Both groups exhibited similar recovery times, but females had higher TSI values at the beginning of recovery, with a subsequent decline (see Figure 38). On the other hand, men exhibited a slower initial recovery, but were able to maintain higher TSI values throughout the rest of the recovery period.

BMI may influence TSI values during exercise and recovery, but there were a limited number of individuals that fell into each category. Viewing Figure 39,

individuals with a normal ABI appeared to walk the longest, but exhibited a similar exercise trajectory as those in the overweight group. The individuals in the obese category exhibited relatively stable TSI values during exercise and recovery (see Figure 40), with a slight dip in TSI mid-exercise. However, the average ABI in the obese category was 0.92, a borderline normal value, which may be the underlying explanation for stabilization in TSI values during both phases.

Trajectories based on ethnicity were difficult to interpret, particularly since only four individuals were not Caucasian. Based on the study sample, African Americans appeared to have relatively unchanged TSI values during exercise and recovery. Caucasians exhibited a gradual decline in TSI, whereas Native Americans had a sharp initial decline, followed by a partial increase in TSI values, and an eventual decline. During recovery, Caucasians experienced an initial TSI recovery, followed by stabilization of TSI values throughout the recovery phase. Native Americans exhibited a more gradual TSI recovery, followed by a gradual decline.

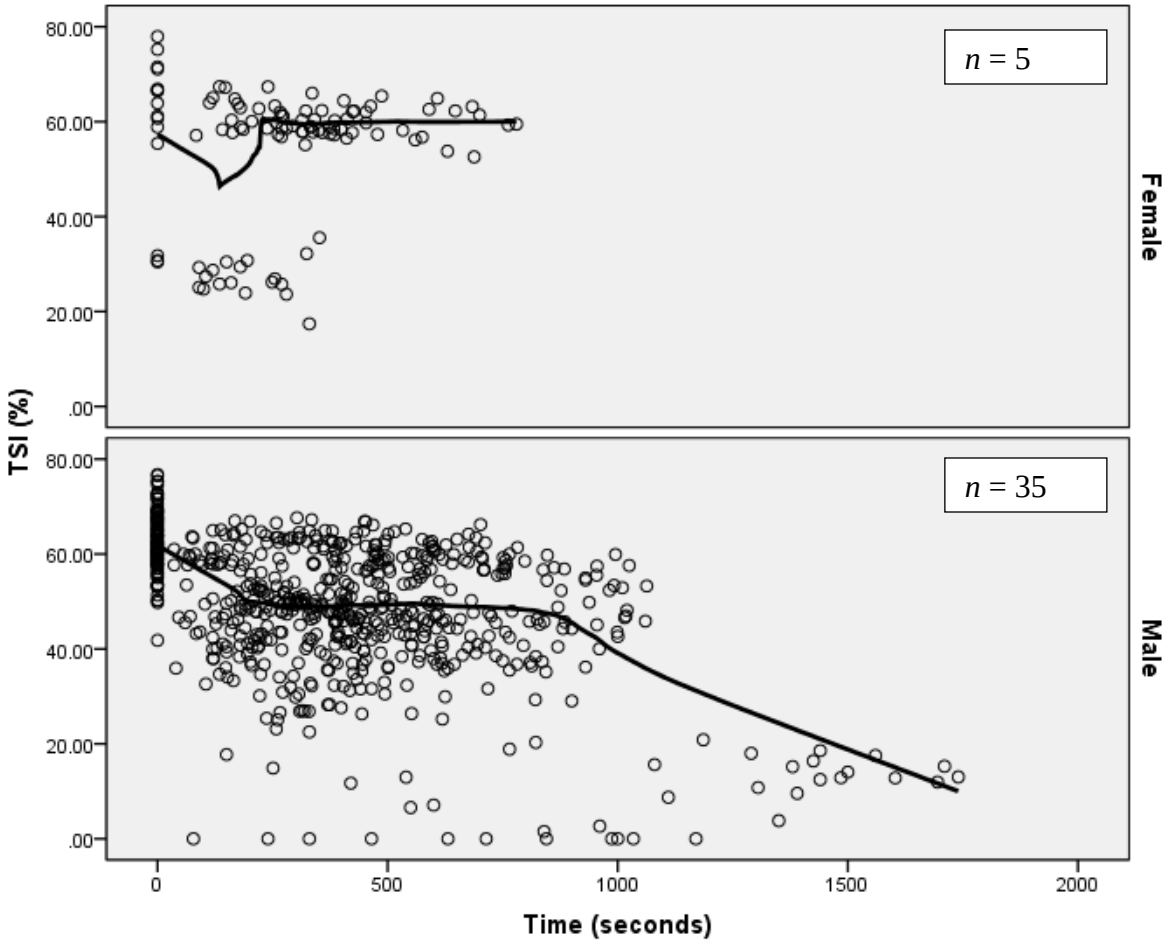

Figure 37. TSI values during exercise based on gender.

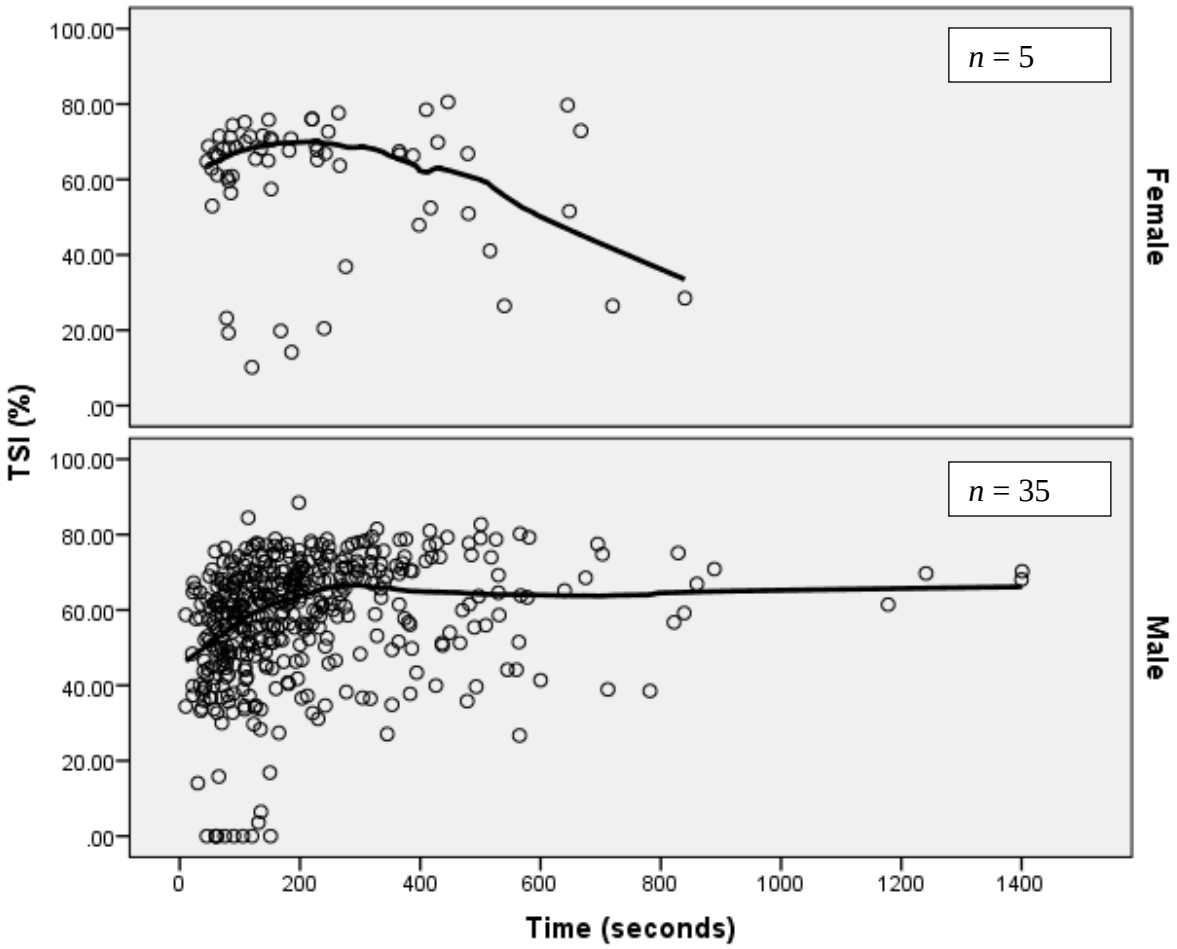

Figure 38. TSI values during recovery based on gender.

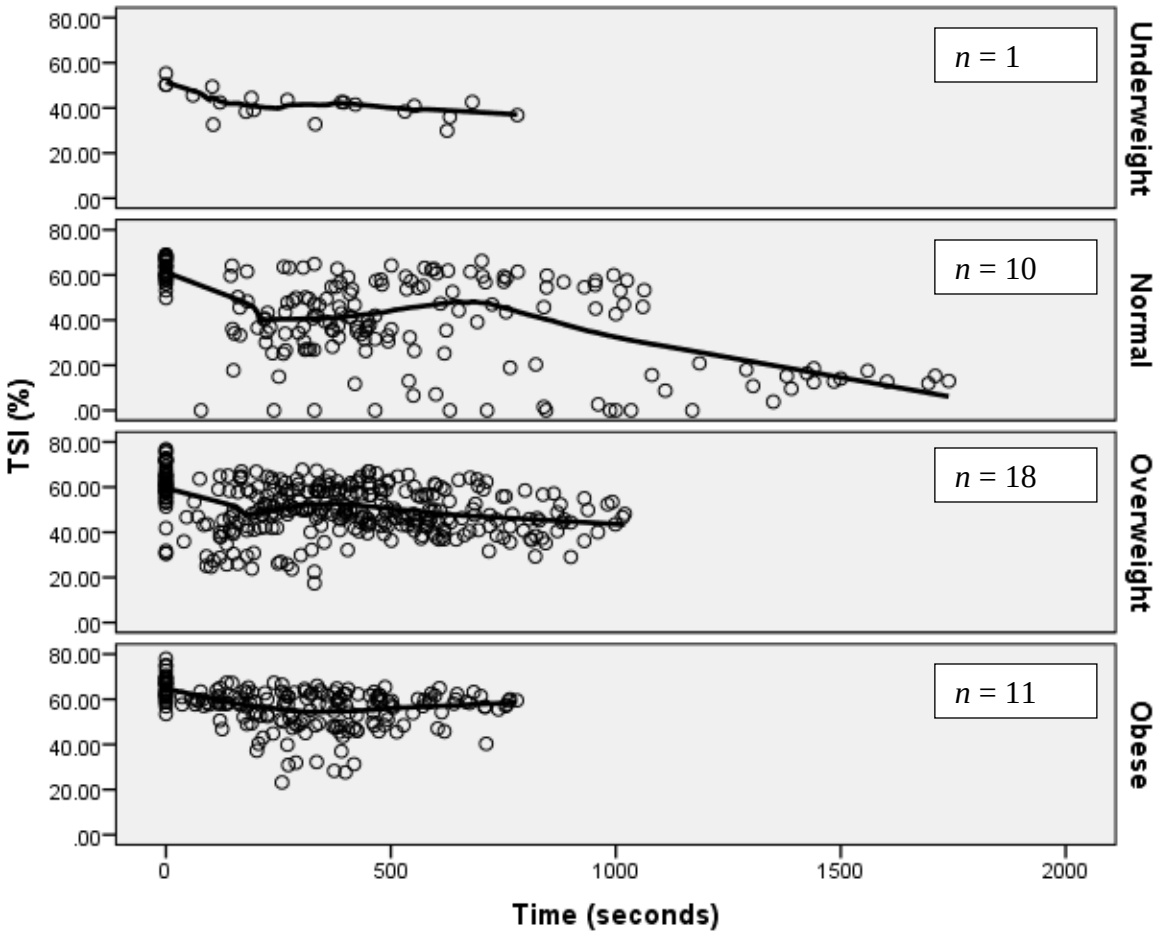

Figure 39. TSI values during exercise based on BMI category.

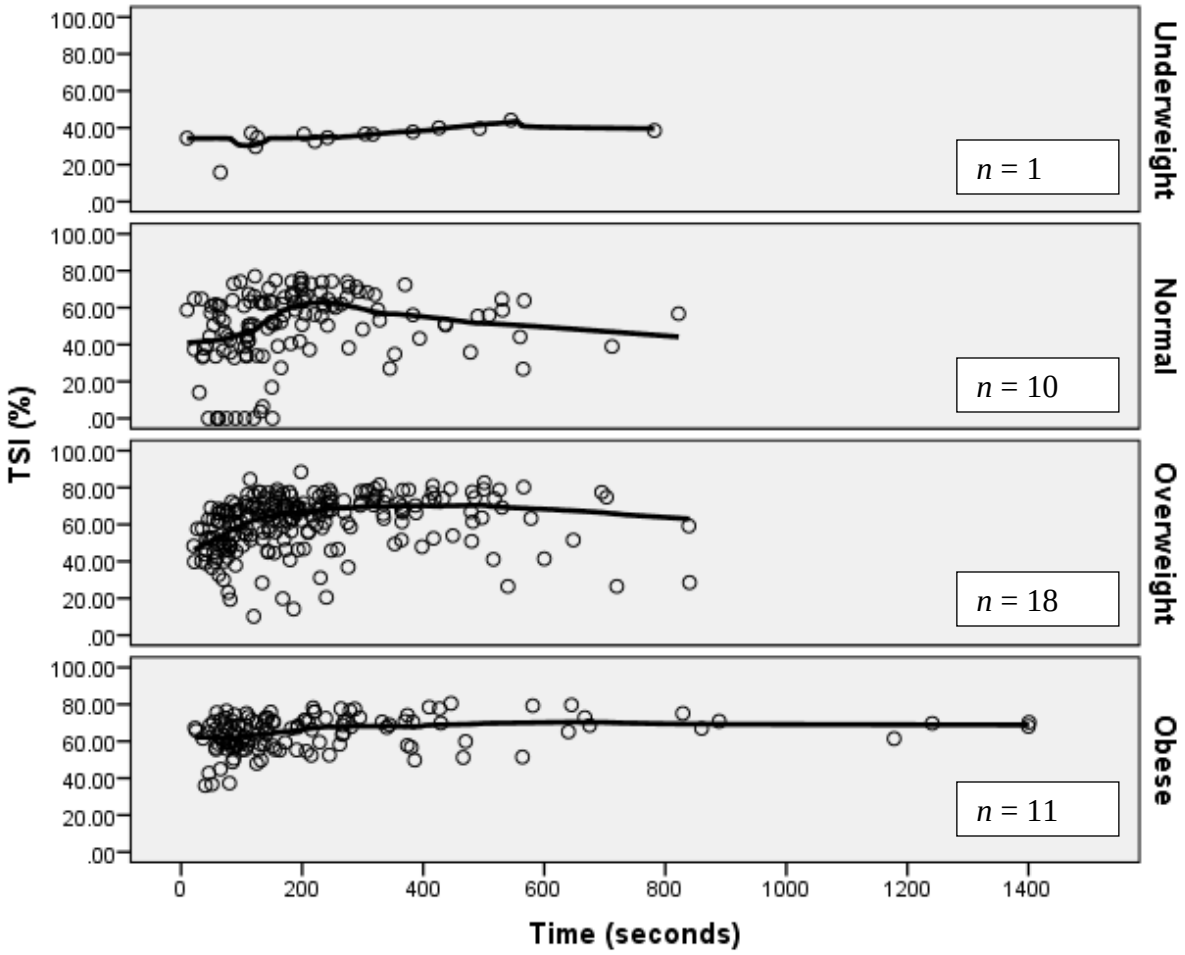

Figure 40. TSI values during recovery based on BMI category.

Multilevel modeling. In conjunction with the rest of the data analyses, multilevel modeling was divided into two phases: exercise and recovery. Based on the within-person data correlation, a compound symmetry covariance structure was selected. Restricted maximum likelihood was the estimated method utilized since it accommodated for data that was missing at random. Lastly, the residual degrees of freedom were divided into between-subject and within-subject portions.

Individual growth curves during the exercise phase for a random subset of 12 study participants were examined (see Figure 41). They appeared to have varying

intercepts, but all exhibited a negative, linear slope as exercise discomfort increased; some were more flat than others (i.e., less change, smaller slope). Similarly, graphical analysis of the recovery data for another random subset of 12 study participants (see Figure 42) revealed a positive and linear slope throughout recovery; thus a linear growth model was selected for both phases; exercise and recovery. Despite the apparent difference in slopes, including the slope as a random effect greatly increased the number of estimated parameters; and with a sample size of 40, including random slopes had the potential to overwhelm model estimation. Additionally, the slope estimates for exercise and recovery were both very small and arguably wouldn't have added a meaningful contribution to the model (e.g., a change of 0.05% TSI for every 5 minutes of exercise, and a change of 0.07% TSI for every 5 minutes of recovery). Considering that the average walking time was less than 11 minutes, and the average recovery time was roughly 6 minutes, the inclusion of random slopes during either phase was not justified.

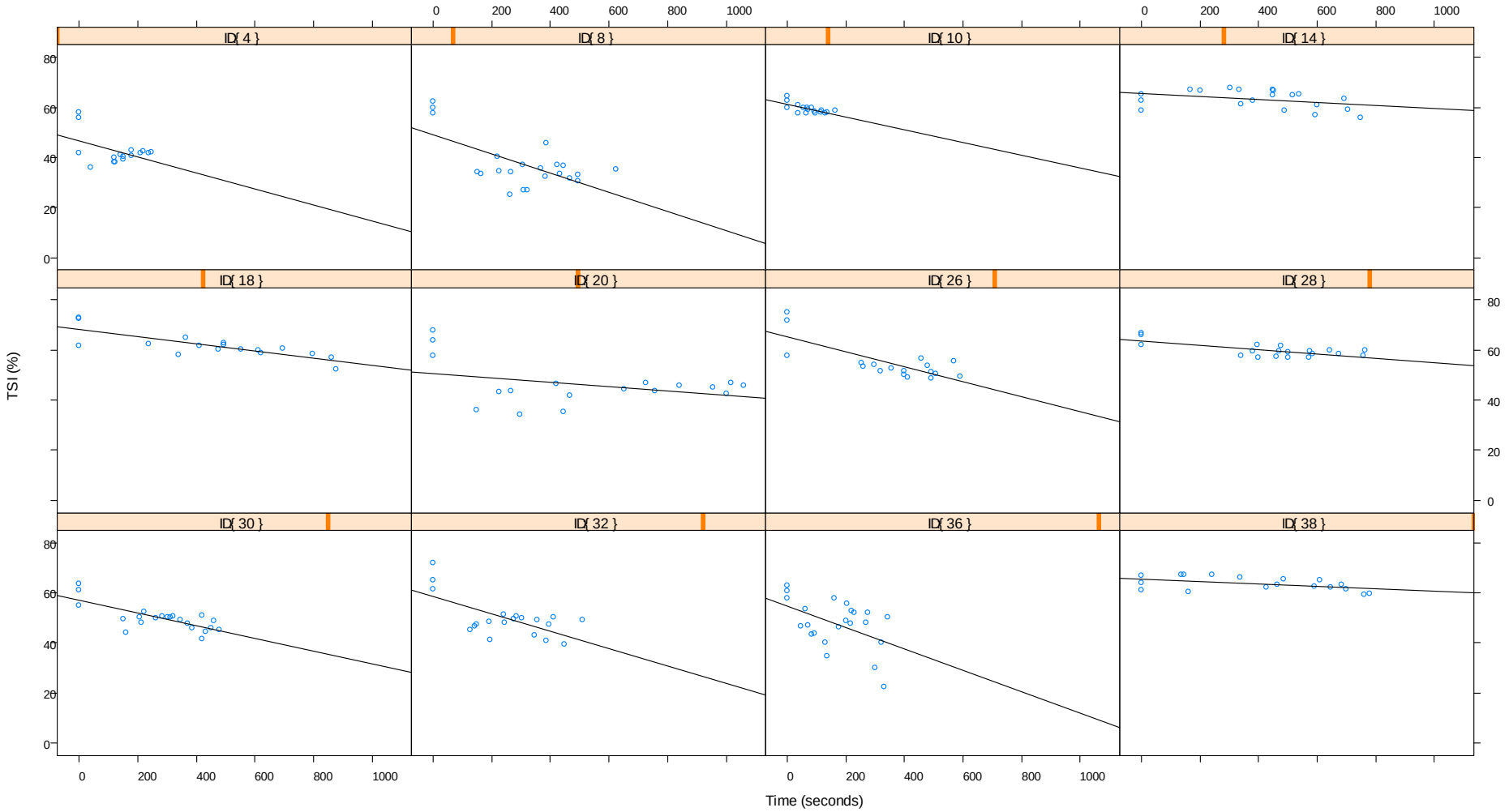

Figure 41. A random subset of 12 study participants illustrated a negative, linear slope during exercise, but varying intercepts at the start of exercise.

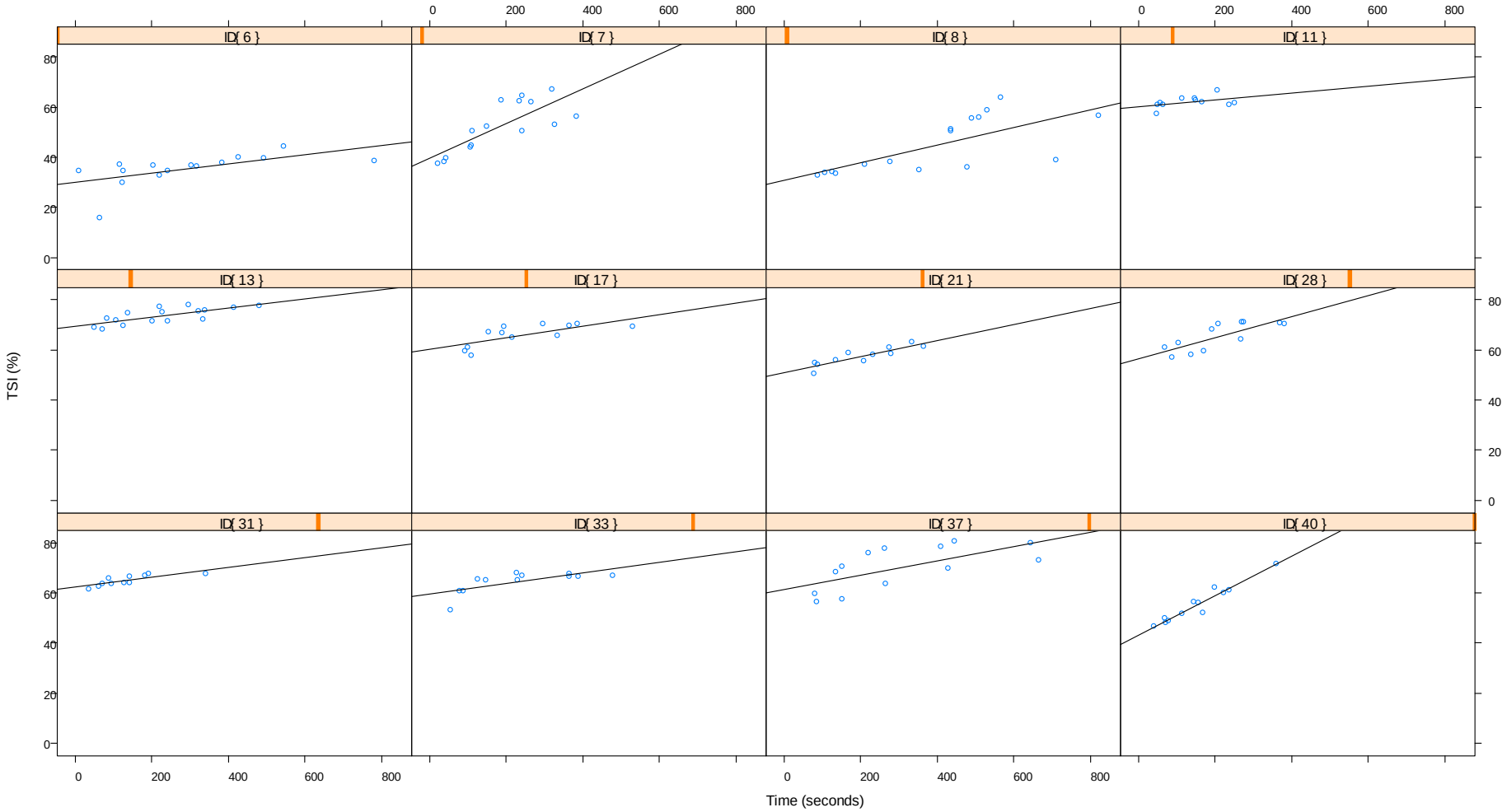

Figure 42. A random subset of 12 study participants illustrated a positive, linear slope throughout recovery, but varying intercepts at the beginning of the recovery phase.

Exercise. The first model constructed was the unconditional means model. This model partitioned the total variation in the outcome variable, TSI, in a meaningful way. The within-person variation ($\sigma^2/\varepsilon = 69.95$), was smaller than the between-person variation ($\sigma^2/_0=132.30$). To determine the relative magnitude of the variance components, the intraclass correlation coefficient (ICC) was calculated. The ICC, denoted as ρ, describes the proportion of the total outcome variation that lies "between" people (Singer & Willet, 2003). For the exercise data, 65% of the variation in TSI was attributable to individual differences ($\rho=0.65$). These results indicated that sufficient variation existed and that the analysis should continue.

The next model built was the unconditional growth model (see Table 37). This model was constructed to determine if the relationship between the predictor, time, and the outcome variable, TSI, was the same for all individuals, or if the regression coefficient varied from participant to participant. The results indicated that the relationship between time and TSI varied by participant ($p<.001$), and that 71% of the variation in TSI was attributable to additional individual differences ($\rho=0.71$). These results suggested that a "random effect" needed to be added to the model in an attempt to account for the variation that remained after including exercise time.

Linear and quadratic growth curve models were considered, as well as models centering time, models including treadmill test as a covariate, and models taking pack year smoking history into consideration. Additionally, variables were treated as continuous and categorical for consideration in the model. Interactions were tested throughout, but none were detected. The final three models (Table 37) included exercise time, baseline TSI, and exercise rating as covariates. Using BIC criteria (Table 38), the

final model for the exercise phase was selected. Compared to the full model, the final model had a 14 point decrease in BIC, which provided very strong evidence to support choosing it as the final model (Raftery, 1995). The final model included exercise time, baseline TSI, NRS exercise rating, ABI category, and BMI category as covariates. Intercepts were allowed to vary by individual, but the slope was held constant.

The final exercise model revealed a significant grand mean intercept and significant intercepts for each NRS exercise rating. Only three ABI categories were significantly predictive of TSI during exercise, which suggested that having a "normal" ABI (0.91-1.40) or an ABI that indicates mild disease (0.70-0.90), didn't influence TSI variability during exercise.

Table 37

Fixed Effects Estimates (Top), Random Parameter Estimates (Middle), and Summaries for Models of the Predictors of Tissue Saturation Index (TSI) during Exercise

Parameters	Growth Model |*p*|	Partial Model |*p*|	Full Model |*p*|	Final Model |*p*|
		Fixed effects		
Intercept	56.93 (1.79) |*|	39.66 (3.59) |*|	51.55 (16.98) |.003|	43.21 (4.73) |*|
Exercise time (minutes)	-1.08 (0.06) |*|	-0.84 (0.12) |*|	-0.84 (0.12) |*|	-0.84 (0.12) |*|
Baseline TSI	–	0.37 (0.05) |*|	0.35 (0.05) |*|	0.35 (0.05) |*|
NRS exercise rating				
Rating 0 (*baseline*)	–	0	0	0
Rating 1	–	-9.67 (0.95) |*|	-9.62 (0.95) |*|	-9.58 (0.95) |*|
Rating 2	–	-9.41 (1.06) |*|	-9.36 (1.06) |*|	-9.315 (1.06) |*|
Rating 3	–	-8.17 (1.14) |*|	-8.10 (1.15) |*|	-8.04 (1.14) |*|
Rating 4	–	-7.26 (1.28)|*|	-7.18 (1.29) |*|	-7.1027 (1.28) |*|
Rating 5	–	-6.82 (1.44)|*|	-6.72 (1.45) |*|	-6.33 (1.44) |*|
ABI category				
ABI 1.00-1.40	–	–	0	0
ABI 0.91-0.99	–	–	1.45 (5.48) |.79|	0.223 (4.29) |.96|
ABI 0.70-0.90	–	–	-6.23 (4.57) |.19|	-8.097 (4.05) |.05|
ABI 0.50-0.69	–	–	-7.23 (4.08) |.09|	8.97 (3.31) |.01|
ABI ≤ 0.49	–	–	-10.11 (7.31) |.18|	-14.97 (4.75) |.004|
ABI > 1.40	–	–	-17.89 (10.13) |.09|	-21.87 (8.29) |.01|
Age	–	–	-0.002 (0.19) |.99|	–
BMI category				
Normal	–	–	0	0
Underweight	–	–	-7.79 (13.19) |.56|	0.23 (8.07) |.98|
Overweight	–	–	4.74 (3.84) |.23|	4.00 (3.21) |.22|
Obese	–	–	9.05 (4.18) |.04|	7.07 (3.56) |.06|
Diabetes	–	–	0.12 (1.64) |.94|	–

Table 37 – *Continued*.

Gender category						
Male	–	–	0			–
Female	–	–	1.96	(4.93)	|.70|	–
Neuropathy	–	–	-3.17	(3.98)	|.43|	–
Race category						
Caucasian	–	–	0			–
African American	–	–	9.22	(9.92)	|.36|	–
Native American	–	–	-8.31	(8.52)	|.34|	–
Smoking category						
Never	–	–	0			–
Current smoker	–	–	-5.43	(8.08)	|.51|	–
History of smoking	–	–	-7.60	(5.72)	|.20|	–
		Random parameters				
Residual (within)	49.91 (7.06)	35.64 (5.97)	35.62	(5.97)		35.63 (5.97)
Intercept (between)	119.67 (10.94)	86.16 (9.28)	60.78	(7.80)		55.85 (7.47)
		Model summary				
AIC	5310	4806	4738			4760
BIC	5329	4852	4856			4842
Number of parameters	4	10	26			18

Note. Standard errors are in parentheses. NRS = numeric rating scale; ABI = ankle-brachial index; BMI = body mass index; AIC = Akaike information criterion; BIC = Bayesian information criterion. Significant at the $p<.05$ level.
* $p < .001$.

Table 38

Interpreting differences in Bayesian Information Criteria (BIC) across Models

Decrease in BIC	Level of evidence
0 to 2 points	Weak
2 to 6 points	Positive
6 to 10 points	Strong
>10 points	Very strong

Note. Criteria adapted from "Bayesian Model Selection in Social Research," by A. Raftery, 1995, *Sociological Methodology*, *25*, p. 139.

Recovery. Modeling of the recovery phase followed a similar process as the exercise phase modeling. The first model constructed was the unconditional means model. Within-person variation (σ^2/ε =89.41) was smaller than the between-person variation ($\sigma^2/_0$=170.70) and 66% of the variation in TSI was attributable to differences between individuals (ρ=.66). The next model, the unconditional growth model, illustrated that the relationship between time and TSI varied by participant during recovery (p<.001) (see Table 39). Additional models that included linear and quadratic growth curves were constructed, but a linear model was deemed the most appropriate. Similar to the modeling process outlined for the exercise phase, other model construction included treating variables as continuous and categorical, as well as the inclusion of other covariates. There was evidence to suggest an interaction between recovery time and recovery rating, as well as an interaction between baseline TSI and NRS recovery rating. Both interaction terms were included in the full and final models (see Table 39).

The final recovery model illustrated a significant grand mean intercept and significant intercepts for each NRS recovery rating (p<.001). Other significant covariates included both interactions, ABI's indicative of non-compressible arteries (ABI>1.40) and ABI's indicating the presence of moderate and severe disease (ABI 0.50-0.69 and ABI ≤

0.49). Even though none of the BMI categories were significant, BMI was included in the final model for two reasons. First, it improved the overall fit of the final model, and second, because the *p*-value of the underweight category decreased when included in the final model. BMI was explaining variation in the final model that wasn't explained by the other covariates already included the model. Comparing the BIC of the full and final models, there was a 6 point decrease. Using the modeling selection criteria that were used in the exercise model selection (Table 38), the decrease in BIC provided positive to strong evidence of choosing the final model over the full model (Table 39).

Table 39

Fixed Effects Estimates (Top), Random Parameter Estimates (Middle), and Summaries for Models of the Predictors of Tissue Saturation Index (TSI) during Recovery

Parameters	Growth Model |*p*|	Partial Model |*p*|	Full Model |*p*|	Final Model |*p*|
		Fixed Effects		
Intercept	53.79 (2.19) |*|	31.94 (5.73) |*|	32.37 (22.46) |.15|	18.89 (9.07) |.04|
Recovery time (minutes)	1.20 (0.12) |*|	0.12 (0.18) |.58|	-0.10 (0.18) |.61|	-0.06 (0.18) |.72|
Baseline TSI	–	0.10 (0.08) |.18|	-0.03 (0.10) |.76|	-0.01 (0.09) |.94|
NRS exercise rating				
Rating 5 (maximum)	–	0	0	0
Rating 4	–	12.09 (2.58) |*|	16.17 (3.10) |*|	16.10 (3.10) |*|
Rating 3	–	14.85 (2.54) |*|	22.73 (4.41) |*|	22.62 (4.41) |*|
Rating 2	–	21.22 (2.61) |*|	32.92 (6.00) |*|	32.77 (6.00) |*|
Rating 1	–	22.57 (2.61) |*|	39.10 (7.72) |*|	38.94 (7.72) |*|
Rating 0	–	24.49 (2.69) |*|	46.71 (9.54) |*|	46.52 (9.55) |*|
Time*rating	–	–	0.01 (.002) |.004|	0.01 (.002) |.003|
Baseline TSI*rating	–	–	0.061 (.03) |.03|	0.06 (.03) |.03|
ABI category				
ABI 1.00-1.40	–	–	0	0
ABI 0.91-0.99	–	–	-3.10 (7.54) |.69|	-1.44 (5.80) |.81|
ABI 0.70-0.90	–	–	5.21 (6.32) |.42|	1.89 (5.48) |.73|
ABI 0.50-0.69	–	–	-7.33 (5.65) |.21|	-9.97 (4.47) |.03|
ABI ≤ 0.49	–	–	-7.07 (10.10) |.49|	-19.14 (6.39) |.005|
ABI > 1.40	–	–	-24.14 (14.06) |.01|	-25.27 (11.29) |.03|
Age	–	–	-0.12 (0.25) |.64|	–
BMI category				
Normal	–	–	0	0
Underweight	–	–	-21.42 (18.16) |.25|	-12.79 (10.84) |.25|
Overweight	–	–	6.63 (5.28) |.22|	6.11 (4.32) |.17|
Obese	–	–	11.39 (5.72) |.06|	9.50 (4.77) |.06|

Table 39 – *Continued*.

Diabetes	–	–	1.14 (2.26) |.62|	–
Gender category				
Male	–	–	0	–
Female	–	–	2.13 (6.78) |.76|	–
Neuropathy	–	–	-0.77 (5.49) |.89|	–
Race category				
Caucasian	–	–	0	–
African American	–	–	8.80 (13.63) |.52|	–
Native American	–	–	-17.15 (11.70) |.16|	–
Smoking category				
Never	–	–	0	–
Current smoker	–	–	-11.90 (11.16) |.30|	–
History of smoking	–	–	-8.75 (7.89)|.28|	–
		Random parameters		
Residual (within)	76.39 (8.74)	58.15 (7.63)	56.85 (7.54)	56.90 (7.54)
Intercept (between)	175.37 (13.24)	161.97 (12.73)	114.12 (10.68)	100.14 (10.01)
		Model summary		
AIC	3727	3569	3498	3524
BIC	3744	3611	3614	3608
Number of parameters	4	10	28	20

Note. Standard errors are in parentheses. NRS = numeric rating scale; ABI = ankle-brachial index; BMI = body mass index; AIC = Akaike information criterion; BIC = Bayesian information criterion. Significant at the p<.05 level.
* $p < .001$.

Chapter 5: Discussion

The purpose of this study was to obtain a comprehensive understanding of the PAD symptom experience, beyond classic claudication, including symptom reporting and changes in calf tissue oxygenation during exercise and recovery. The specific aims of the study were to: (1) understand the symptom experience of younger and older men and women with PAD through in-depth qualitative interviews; and (2) simultaneously evaluate calf tissue oxygenation and the self-reported symptoms experienced by individuals with PAD during treadmill exercise and throughout recovery. This research was designed and conducted based on review of the literature, which identified a gap in regards to understanding the frequency and presentation of 'atypical' claudication. Furthermore, experiences in clinical practice suggested that 'atypical' symptoms existed and that they may be more prevalent that what was currently being recognized.

Both qualitative and quantitative methodologies were utilized to characterize the symptom experience of individuals with PAD. Semi-structured interviews included completing a PAD symptom questionnaire and providing a detailed description of the symptoms experienced at rest and during exercise (e.g., location, sensation, and duration). Individuals were given another opportunity to descriptively as well as numerically report PAD symptoms during three successive treadmill exercise tests. NIRS provided an objective measurement of calf tissue oxygenation via TSI values. Content analysis revealed six themes of the PAD symptom experience, while graphing the individual and group trajectories visually depicted the patterns of change in TSI during exercise and recovery based on particular characteristics and baseline status. Lastly, general MLM was utilized to explore the relationship between particular

characteristics, baseline values, and symptom ratings with TSI during the exercise and recovery phases. This chapter provides a summary and discussion of the results by aim, the study limitations, and the implications for future research and vascular disease practice.

Aim 1: Description of the PAD Symptom Experience

Although a variety of vocabulary and phrases were provided during interviews, responses were categorized into six main themes: symptom descriptors, maintaining equilibrium, temporal fluctuations, the role of exercise, the perceived impact on QOL, and disease presence and treatment. These six themes were closely aligned with the themes identified in a broader exploration of the PAD experience and its perceived effects on health-related QOL (Treat-Jacobson et al., 2002). Participant characteristics of the two studies were similar, but Treat-Jacobson and colleagues (2002) included a larger percentage of females and conducted open-ended interviews with participants from two geographical locations. Participants in the Treat-Jacobson et al. (2002) study provided similar descriptions of the symptom experience (e.g. *cramping, aching, burning, cramping,* and *tired/fatigue*), but provided a less exhaustive list compared to the participants in this study. Additionally, participants in the Treat-Jacobson et al. (2002) study only reported claudication in classic locations (e.g., calf, thigh, and buttock), as opposed to the broader list of locations (i.e., typical and 'atypical') provided by participants in this study. Similar to the participants in this study, individuals described the limitations in their physical and social functioning, including the loss of activities they used to enjoy. Additionally, participants expressed feelings of social isolation, and described the burden of the disease on their family. Participants addressed these

limitations by being flexible and adjusting, but also expressed a degree of uncertainty and fear as to what to expect in the future. The aspects of adjusting and uncertainly, closely aligned with the maintaining equilibrium and temporal fluctuations themes identified in this study. In these two themes, participants reported exerting control over their pace, the environment, and the elements of recovery, as well as expressing uncertainly regarding day to day fluctuations in symptom onset, severity, and progression. Individuals described their unsuccessful attempts to identify patterns in physical functioning, which led to further frustration and uncertainty. However, unlike the Treat-Jacobson et al. (2002) study, participants in this study did not express fear regarding the loss of a limb or more significantly, death as a result of the disease. This could be reflective of the more moderate disease severity of the sample in this study compared to the broad range of PAD severity in the Treat-Jacobson et al. (2002) study, which included individuals with rest pain and non-healing wounds.

Study findings also resembled the themes identified by a qualitative study conducted in 2005 that investigated the experience of living with PAD and the influence of the disease on activities of daily living (Wann-Hansson, Hallberg, Klevsgård, & Andersson, 2005). Participants described PAD as being physically, socially, and emotionally burdensome. Yet again, participants talked about the consequences of the disease and specific coping strategies designed to relieve the burden and gain control in daily life. This theme closely aligned with the maintaining equilibrium theme of this study and the adaptation theme of the Treat-Jacobson et al. (2002) study. Participants in the Wann-Hanson et al. (2005) study also talked about accepting and adapting to the burden, and discussed particular limitations in daily life because of the disease, which

again closely aligned with themes identified in both of the aforementioned studies.

Symptom descriptors provided by study participants during the interviews were consistent with the descriptors that typically indicate classic claudication (e.g., *ache, cramp, pain,* and *tired/fatigue*). The calf was the most commonly reported location of pain or discomfort, which is consistent with the classic definition of claudication. Many described the sensation as a *pain*, which is also consistent with classic claudication. However, nearly half described calf discomfort as *tight*. In fact, this was the most frequently reported descriptor among men, women, and older participants, and the second most frequently reported descriptor among younger participants. Aside from the other classic claudication descriptors reported by participants (e.g., *cramp, ache,* and *tired/fatigue*), calf discomfort was described as *sore, a Charley horse, weak, burning, hard, heavy, knotting,* and *pressure*.

During interviews, participants reported discomfort in the two other commonly recognized locations, the buttock and the quadriceps. However, participants also reported discomfort in 'atypical' locations. The second most commonly reported location during interviews was the hip, followed by the foot. Other 'atypical' locations included the hamstring, shin, knee, ankle, and groin. Again, classic descriptions in 'typical' and 'atypical' locations were provided (e.g., *ache, pain,* and *tired*), but were not exhaustive. Similar to the calf, participants described the sensation as *burning*, *tight*, *grinding*, *tingling*, *pulling*, *pressure*, *numb, prickly*, and *a twinge*. *Burning* has previously been a descriptor of the PAD symptom experience (Ruger et al., 2008; Tomczyk & Treat-Jacobson, 2009; Treat-Jacobson et al., 2002), as well as *tingling*, *numbness*, *throbbing*, and *shooting*.

Interestingly, the descriptions of lower extremity claudication that participants provided were nearly identical to the early descriptions of ischemic heart pain (i.e., angina) from the initial Rose Questionnaire (Rose, 1962). In the Rose study (1962), participants described chest pain as, *gripping*, *occasionally sharp*, *burning*, *sharp*, *shooting*, *kind of pricking*, *pins and needles*, and *like something pressure*. Even on early surveys, ischemic heart pain descriptors such as *tight, heavy, constricting, crushing, numbing,* and *burning*, with the ability to radiate to other locations were recognized as being associated with angina. Lower extremity ischemia is a similar physiological process, but it occurs in a different body location. Even without the provision of further objective evidence, these descriptions and qualities should also be more commonly accepted descriptions of ischemia occurring in the lower extremities.

Classic claudication rates reported during exercise were lower than those reported in other PAD studies (Gardner et al., 2007; Gardner et al., 2012; Leng & Fowkes, 1992; Makdisse et al., 2007; Ogren et al., 2005). Only 62.5% of study participants (23 men and two women) were limited by discomfort in the calf during all three treadmill tests. Even fewer provided a classic calf descriptor (e.g., *ache, cramp, pain,* or *tired/fatigue*) at the time that discomfort became so severe they had to stop walking (i.e., NRS rating 5 out of 5). Other calf descriptors included *tight, burn, tingling, sore, knot, Charley horse, heavy, pressure, warm, sensitive,* and *stretching*. The calf was the most common exercise limiting symptom location for both genders, as well as younger and older participants. *Ache, tight,* and *cramp* were the calf symptom descriptors most frequently reported by both age and gender groups.

Unlike the findings from Gardner and colleagues (Gardner et al., 2007; Gardner et

al., 2012), all study participants did not report symptoms consistent with classic claudication under controlled exercise testing conditions. During exercise, participants were limited by symptoms in typical locations (e.g., calf, quadriceps, and buttock), as well as 'atypical' locations (e.g., hamstring, hip, foot, and heel). Some individuals provided symptom descriptions consistent with the definition of classic claudication (e.g., *ache, cramp, pain,* and *tired/fatigue*), while others reported lesser recognized descriptors (e.g., *tight* or *burning*). These results serve as evidence to challenge the theory that all individuals with PAD will experience classic claudication under controlled exercise testing conditions. In this study, symptom onset and progression were provoked by individualized speed and grade increases during treadmill exercise, but individuals reported symptoms other than classic calf claudication that were related to ischemic changes in calf muscle tissue and limited their ability to continue exercising.

In addition to the descriptions of the PAD symptom experience that participants provided while in a static state (i.e., semi-structured interviews), they also provided this information during a dynamic state (i.e., treadmill exercise). Several similarities and differences between the two states were identified.

The symptom descriptors provided during exercise were similar to those reported during the interviews, but the frequencies of descriptors based on gender and age groups changed slightly. Again, the most commonly reported location during exercise was the calf, most frequently described as a *discomfort, ache, tight, cramp, pain,* and *tired/fatigue*. Calf discomfort was also described as *burning, sore, heavy, knotting, tingling, Charley horse, pressure, warm, sensitive* and *stretching*. *Tightness* remained the most common descriptor reported by women, but the second most common among men

and older participants during exercise. Younger participants primarily described calf discomfort as *tight* during exercise, as opposed to *pain* described during interviews. *Ache* was the most frequently reported descriptor by men and older participants, and the second most common descriptor reported by younger participants. Similar to findings from other studies (Gardner et al., 2007; Gardner et al., 2012; McDermott et al., 2001), a larger percentage of participants reported calf discomfort during exercise (*n*=39, 97.5%), compared to the 92.6% (n=25) who reported calf discomfort during the interviews.

The other symptom locations reported during exercise were consistent with those provided during interviews, with the exception of the groin and ankle. Exercise limiting locations included all three typical locations (i.e., calf, quadriceps, and buttock), but also included locations considered to be 'atypical' presentations of claudication (i.e., hamstring, hip, foot, and heel). Interestingly, although all five female participants described hip discomfort during the interview, the hip was the exercise limiting location during only two female exercise tests. On the other hand, only five men reported hip discomfort during interviews, but seven male exercise tests were stopped due to pain in this location. Another apparent gender difference was revealed when comparing the number of descriptors provided by men and women under static and dynamic conditions. On average, women provided more descriptors than men during interviews, but during exercise it was the inverse. The number of symptom locations and descriptors provided by younger and older participants during interviews was similar, with consistency in reporting under static and dynamic conditions for both groups. Similar to the findings in patients with angina, these preliminary results suggest that symptom reporting may differ by gender. However, additional research should be conducted in order to confirm these

findings to determine whether PAD screening and education should be individualized based on gender.

Aim 2: Modeling the PAD Symptom Experience

Exploration of individual trajectories revealed that TSI values during exercise and recovery were varied. However, several distinct patterns were identified during each phase. This preliminary and informal analysis indicated that the most common pattern of change in TSI during exercise was an initial rapid decline in TSI, followed by slowly declining or relatively unchanged TSI values throughout the rest of exercise. Some individuals stopped at the point of minimum TSI, while others were able to continue exercising after the minimum TSI was reached. The resiliency exhibited by some individuals was in direct contrast to those who had to stop exercising as soon as TSI declined to a specific point. It is unknown whether there a specific compensatory mechanism that some individuals have that allowed them to continue exercising despite low TSI values, or that enabled TSI values to increase above the minimum TSI obtained despite the progression of exercise intensity and duration.

Recovery patterns were similar to the patterns identified during exercise, but more numerous. The most common pattern was a peak in TSI, either during a rapid recovery, or more commonly in this sample, a slower initial recovery of TSI values. Some individual's symptoms resolved fully once peak TSI was reached, whereas others had TSI values that continued to decline even though symptom discomfort was lessening. Individual recovery patterns produced similar questions to those raised during the exercise phase. It has yet to be determined whether some individuals recover more quickly than others based on specific characteristics such as gender or age, and why some

individuals report a full recovery as soon as TSI peaks, while others don't report a full recovery until TSI starts to decline.

The most notable findings from this study are in regards to the relationship between symptom rating and TSI values during exercise and recovery. All of the symptom rating categories were significant for both the exercise and recovery models. During exercise, the most severe decline in TSI was observed between the start of exercise and the onset of pain (i.e., NRS 1 out of 5). TSI continued to decline slightly throughout the duration of exercise until the maximum discomfort was reached (i.e., NRS 5 out of 5). The recovery model told a similar story in which TSI values were at their lowest point when participants were still experiencing maximum discomfort (i.e., NRS 5 out of 5) and then steadily increased until full recovery was achieved (i.e., NRS 0 out of 5). These patterns were depicted clearly in the group trajectories during both phases.

Findings similar to these have not been reported in the literature. Researchers have collected data on perceived exertion while measuring oxygenation with NIRS, but have not collected data on symptom descriptions or provided analysis comparing tissue oxygenation to the perceived exertion data collected. Miranda and colleagues (Miranda et al., 2012) collected data on perceived exertion every minute during rest and exercise, but provided no results comparing oxygenation values to perceived exertion. Similarly, Collins et al. (2012) tracked perceived exertion during exercise, but only reported a mean rating of 5.04 at peak exercise on the Borg scale in the final presentation of study findings. To the authors' knowledge, this study is the first of its kind to analyze the relationship between subjective and objective PAD symptom reporting.

To explore the potential relationships of TSI values and specific characteristics,

individual trajectories were grouped based on several PAD risk factors, and comorbid conditions that could influence the PAD symptom experience, as well as gender and BMI. Further exploration involved model construction for the exercise and recovery phases using general MLM. Due to a relatively homogenous sample, the group trajectory patterns identified, and the exercise and recovery models constructed cannot be generalized to the PAD population. Generalizability of these findings could be strengthened by a larger, more diverse sample.

Based on the preliminary data, individuals with the lowest ABI (≤ 0.49) had the most pronounced oxygen desaturation during exercise, followed by individuals with non-compressible vessels; whereas fixed effects coefficients of the exercise model suggested the reverse. These two groups, as well as the mild and moderate disease categories were all significant terms included in the final exercise model. TSI recovery was gradual for all of the ABI groups, except those with non-compressible vessels who exhibited a slightly erratic recovery pattern. On the other hand, individuals with a borderline or a normal ABI had trajectories that remained relatively unchanged throughout the exercise and recovery phases. This was confirmed by non-significance in the recovery model. However, non-compressible, moderate, and severe disease categories were all statistically significant, indicating that differing TSI recovery patterns were present. These findings aren't surprising since individuals with borderline or normal ABI's have less arterial narrowing, which allows for a quicker restoration of blood flow once activity ceases. Furthermore, research supports the correlation of NIRS measures with disease severity (i.e., ABI) and recovery times.

Age was a non-significant predictor of TSI in both the exercise and recovery

models. Although no interaction was detected, ABI may have influenced the apparent relationship between oxygenation and age during exercise and recovery; particularly since age in healthy individuals has been shown to have no effect on saturation values (Miranda et al., 2010). Older participants appeared to have a quicker and more pronounced recovery, which could have been a result of an uneven distribution of disease severity among both age groups. If the older participants were less diseased overall, they could have exhibited quicker recovery times as a result of less arterial narrowing instead of another mechanism.

Similar imbalances in gender led to inconclusive results. Overall, male participants walked longer, but they exhibited lower TSI values. This directly contrasts the saturation patterns identified in healthy subjects based on gender in which women had a 15% lower baseline tissue saturation compared to men; with women maintaining lower values throughout exercise compared to males (Miranda et al., 2010). However, in the Miranda et al. study (2010), calf skinfold was 107% higher in women compared to men, and calf skin temperature of women was 3% lower. Adipose tissue thickness has been identified as a factor that influences oxygenation values (Van Beekvelt, Borghuis, Van Engelen, Wevers, & Colier, 2001), while the role of skin temperature is less understood. Since neither were measured and accounted for in this study, the lack of both measures could have compounded the difficulty to conclude the existence of true gender differences. The conclusions of group trajectories were supported by the exclusion of both groups in the final exercise and recovery models.

Group trajectories based on DM suggested that individuals with type 2 DM experienced a more pronounced tissue oxygen desaturation mid-exercise and a post-

exercise delay in oxygen saturation recovery. Individuals without a diagnosis of DM and those with type 1 DM displayed similar oxygen desaturation and re-saturation patterns. Changes in TSI during exercise and recovery were expected in individuals with either type of DM based on the physiology of the disease and on recent research findings. Arterial calcifications are more prevalent and more severe in patients with DM than in non-diabetics (Morrison & Bogan, 1929) and even in the absence of PAD (i.e., normal ABI), individuals with DM have been shown to have reduced skeletal muscle capillary blood volume expansion during exercise (plantar flexion and treadmill walking), as measured by NIRS (Mohler, Lech, Supple, Wang, & Chance, 2006). Even after combining both types of DM into one category, DM was not a significant predictor of TSI in the final model for either phase.

The non-significance of any smoking category could have resulted from the fact that the majority of participants had a history of smoking. Based on the group trajectories, current smokers appeared to have an initial oxygen desaturation during exercise that wasn't present in non-smokers or in those with a history of smoking. Similarly, less conclusive study results about the role of ethnicity and BMI could have primarily been caused by an unbalanced design. Additionally, there is some debate about ethnicity being an independent risk factor for PAD after adjusting for atherosclerotic risk factors (Collins et al., 2005). If the disease affects all ethnicities equally, perhaps similar patterns of tissue oxygenation would be observed as well. The non-significance of any of the BMI categories except obesity in the full exercise model, suggests that there is no relationship between BMI and calf tissue oxygenation during exercise. However, the categories were unbalanced and BMI was included in both final models (i.e., exercise and

recovery) because it explained variation that wasn't explained by any of the terms already included in the model. Based on these findings, it is conceivable that significant effects would be observed with a larger, more diverse sample. The apparent protective effect of obesity on calf tissue oxygenation during exercise could be due to the fact that many individuals who smoke tend to have lower BMI's than those who do not. However, this did not hold true for the seven smokers in this study, who on average had a BMI of 26.7, which falls into the overweight category.

Limitations

Study limitations included issues related to measurement, the study sample, and model selection. The NIRS device used to collect calf tissue oxygenation data could not account for factors such as collaterals, cardiac function, inotropic and chronotropic response to therapeutic agents, vessel wall stiffness, and the presence of comorbid conditions that could have influenced calf tissue oxygenation during exercise (Manfredini et al., 2009). Additionally, the subcutaneous layer can vary considerably among individuals due to differences in adipose tissue thickness, which may confound NIRS measurements (Matsushita, Homma, & Okada, 1998; Niwayama et al., 1999; Van Beekvelt et al., 2001). Calf skin temperature has also been measured in similar research conducted with healthy adults (Miranda et al., 2010). Calf adipose tissue thickness and skin temperature were not measured in this study. Furthermore, no data on ambient temperature or humidity levels in the exercise testing room were collected. However, all exercise testing took place in the same room, at roughly the same time of day for all study participants. Individualized testing protocols were selected to guide individuals through symptom progression, while attempting to avoid stopping exercise for any other reasons.

The lack of a standardized exercise testing protocol may limit the comparison of study findings with future research studies.

The sample in this study was small and relatively homogenous. In addition, all of the study participants were recruited from a single parent study in one geographical location. The lack of heterogeneity in this study could have impacted the ability to construct stronger, more accurate exercise and recovery models, which limits generalizability of the study findings to other individuals with PAD. Another limitation of the study sample is that all of the study participants were volunteer research subjects, which could have potentially introduced a response bias. Perhaps individuals with PAD that do not volunteer for research would report distinctly different PAD symptom experiences. Collecting data from individuals in a variety of geographical locations with more diverse backgrounds and a spectrum of disease severity will strengthen generalizability of study findings.

Likewise, a small and homogenous sample placed limitations on model selection. If the study sample was larger and more diverse, other functional forms (i.e., non-linear) may have been more apparent. Models based on a larger and more heterogeneous sample could have included different characteristics based on more or less statistically significant findings. However, this was an exploratory study and the primary purpose was to summarize the data of the study sample, describe individual and group trajectories, and gain an initial understanding of the relationship between symptom reporting and calf tissue oxygenation during exercise and recovery.

Implications for Research

The results of this research add further evidence to support more comprehensive

PAD assessment. Classic claudication is widely accepted and well understood. Therefore, research that supports the existence of and more clearly describes the presentation of 'atypical' claudication (e.g., location, sensation, and duration) is needed. Based on the research conducted to date, there is a particular need for research studies that include a larger number of participants, with a balanced number of individuals with respect to age, gender, ethnicity, and disease severity categories. This research would enable further exploration of the effect, if any, of PAD risk factors, baseline characteristics, and comorbid conditions on calf tissue oxygenation during exercise and recovery.

This study is foundational for future research to determine patterns of calf tissue oxygenation, their relationship to symptom reporting, and potential changes with therapeutic interventions. Future research should focus on longitudinal studies to evaluate patterns in calf tissue oxygenation throughout disease progression, pre-and post-intervention, and perhaps most importantly, pre- and post-supervised exercise programs, since this is the number one recommended treatment for individuals with PAD.

Insufficient research has been conducted to evaluate the impact of supervised exercise programs on calf tissue oxygenation during exercise and recovery; study findings are inconclusive thus far. Not surprisingly, researchers have found that exercise improved the maximal treadmill exercise time (Collins et al., 2012; Figoni et al., 2009), but the impact of a program of exercise on calf tissue oxygenation remains unclear. Collins et al. (2012) found no obvious differences in calf tissue oxygenation pre- and post-exercise program, but found a lengthened time to reach minimum calf tissue oxygenation values during exercise. Miura and colleagues (Miura, McCully, & Chance,

2003) found that exercise training reduced calf tissue saturation recovery half-time by 17% in individuals with PAD, whereas Figoni et al. (2009) found no significant improvement in recovery times after participating in a three month supervised exercise program. A recently conducted NIRS study illustrated promise for extending PAD exercise programs into the home (Manfredini et al., 2012). Manfredini et al. (2012) observed hemodynamic and functional improvements for 31 individuals that participated in a 34 week home-based exercise program at a prescribed walking pace, compared to individuals with PAD walking at a free pace and a healthy control group performing usual activities. Revisiting the parallels between heart disease and PAD, Gerovasili and colleagues (Gerovasili et al., 2009) discovered that physical exercise improved the peripheral microcirculation, as measured by NIRS, after three months of supervised cardiac rehabilitation. These results highlight the need for additional research to clarify the relationship between individual characteristics and calf tissue oxygenation, as well as the need to establish abnormal cutoff values based on specific oxygen demands for inadequate calf tissue oxygenation at rest and during exercise that could be used to detect individuals at a higher risk for developing PAD and those in the early stages of the disease.

Implications for Practice

The knowledge gained from this study has significant implications for the improvement of PAD detection and diagnosis by broadening currently accepted symptom descriptors to provide a more clear and comprehensive symptom presentation of the disease. Unlike the results published in other studies, participants were limited by symptoms in 'atypical' locations (e.g., hip, hamstring, and shin) and/or they used

uncommonly recognized vocabulary to describe the sensation (e.g., *tight*, *burning*, and *numb*). These results suggest that in clinical practice, patients may be confused by the language used by their providers to describe the locations and sensations experienced by individuals with PAD. Similarly, providers may assume that the symptoms being reported by their patients are attributable to another medical condition since they don't mirror the definition of classic claudication. In this study, participants reported 'atypical' symptoms in 'atypical' locations, but experienced similar changes in calf tissue oxygenation as those who reported symptoms consistent with classic claudication. Although they were reported less frequently than classic calf claudication, a greater emphasis should be placed on broadening the current understanding of factors related to 'atypical' symptom presentation.

The results of this study emphasize the importance of a more comprehensive assessment to detect PAD before it progresses, or even to identify individuals at-risk before the disease develops (i.e., borderline disease; ABI 0.90-0.99). For example, individuals with borderline ABI values or those in an early stage of the disease may report symptoms in 'atypical' locations and/or use vocabulary less familiar to clinicians to describe the sensations related to the disease. These 'atypical' descriptions may not trigger clinicians to perform the simple, yet necessary testing to diagnosis the disease (e.g., ABI). Clinicians should encourage patients who are already diagnosed with PAD to share their symptom experiences. This would: 1) allow clinicians to better appreciate the diversity of disease presentation, 2) enable individuals to gain insight into the disease, and 3) provide therapeutic relief through the sharing of symptom experiences since chronic disease can cause a tremendous amount of stress in one's life.

Lastly, clinicians should continue to educate patients with PAD, as well as the general public about the typical and the less commonly recognized symptoms of the disease. Education regarding pain and pain management should be ongoing, as the causes and treatments of the disease are commonly misunderstood. For example, two participants in this study were taking opioids to relieve their claudication. Claudication is caused by ischemic conditions and by definition it is intermittent in nature, thus it should not be treated with medications designed to alleviate acute and/or chronic pain. Pain education should include regular evaluation of all sources of pain and the appropriate pain management for each affected site based on the primary cause of discomfort.

Clinicians should also continue providing education regarding the role of exercise and the risks associated with worsening of the disease. Not all of the participants in this study understood the importance of regular physical activity and none expressed knowledge of the implications of disease progression. Once the relationship between individual characteristics and their effects on calf tissue oxygenation are more clearly understood, patients should be individually assessed and provided with their information about calf tissue oxygenation during exercise and recovery. This information has the potential to increase an individual's insight into the symptoms they experience and enable them to distinguish PAD symptoms from symptoms related to other comorbid conditions.

Conclusion

This study provides a unique perspective and a preliminary understanding of the relationship between subjective symptom reporting and calf tissue oxygenation with a variety of PAD risk factors and individual characteristics. At rest, during exercise, and during recovery, participants provided typical and 'atypical' symptom locations and

descriptors to describe the PAD symptom experience. During exercise, the most severe oxygen desaturation took place between the start of exercise and the initial onset of symptoms. Oxygen desaturation continued throughout exercise to a lesser extent and to varying degrees. When the recovery phase began, blood flow was restored to the lower extremities. During this phase, the majority of individuals experienced an initial re-saturation of oxygen in calf tissue, but the increase in oxygenation did not provide immediate symptom relief.

Continued research simultaneously comparing subjective symptom reporting with objective physiologic changes during exercise is necessary to validate 'atypical' participant symptom reporting and broaden the currently accepted PAD symptom locations and descriptors. Despite the under-reporting of 'atypical' symptoms compared to classic claudication, they do exist and they are no less important for the early detection, diagnosis, and treatment of PAD to minimize the impact of this painful, debilitating, and deadly disease.

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Appendix A
Peripheral Artery Disease (PAD) Semi-Structured Symptom Interview

Questions:

1. Please describe in as much detail as possible the symptoms you experience while exercising. This can include activities such as walking, gardening, shoveling, etc.

2. When does this symptom come?

3. How does it feel? What words would you use to describe it?

4. If you rest (stand still, sit or lie down) how long does it take to go away?

5. Do you experience any other pain or discomfort while exercising or resting?

6. If you got up to walk right now what would happen?

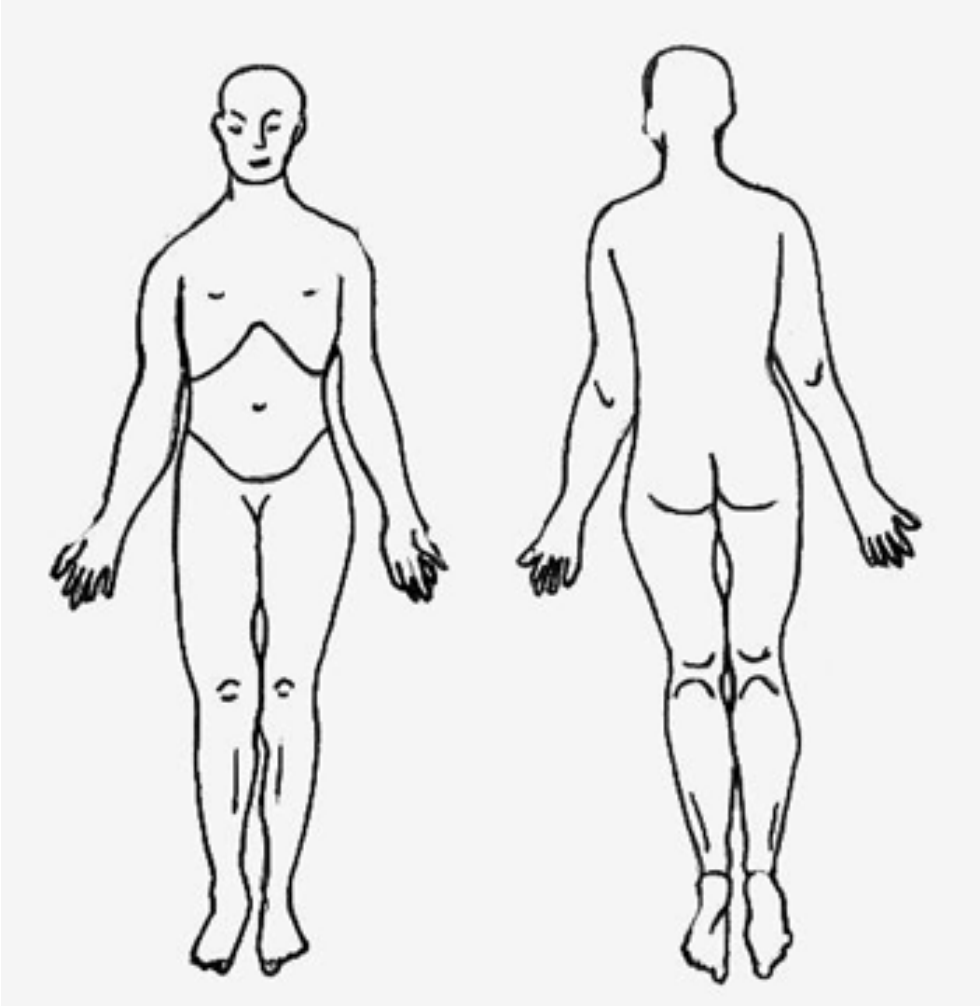
7. Does your ability to exercise change from day to day?

Sample Interviewer Prompts:
…Tell me more about that.
…Can you elaborate a little on that?

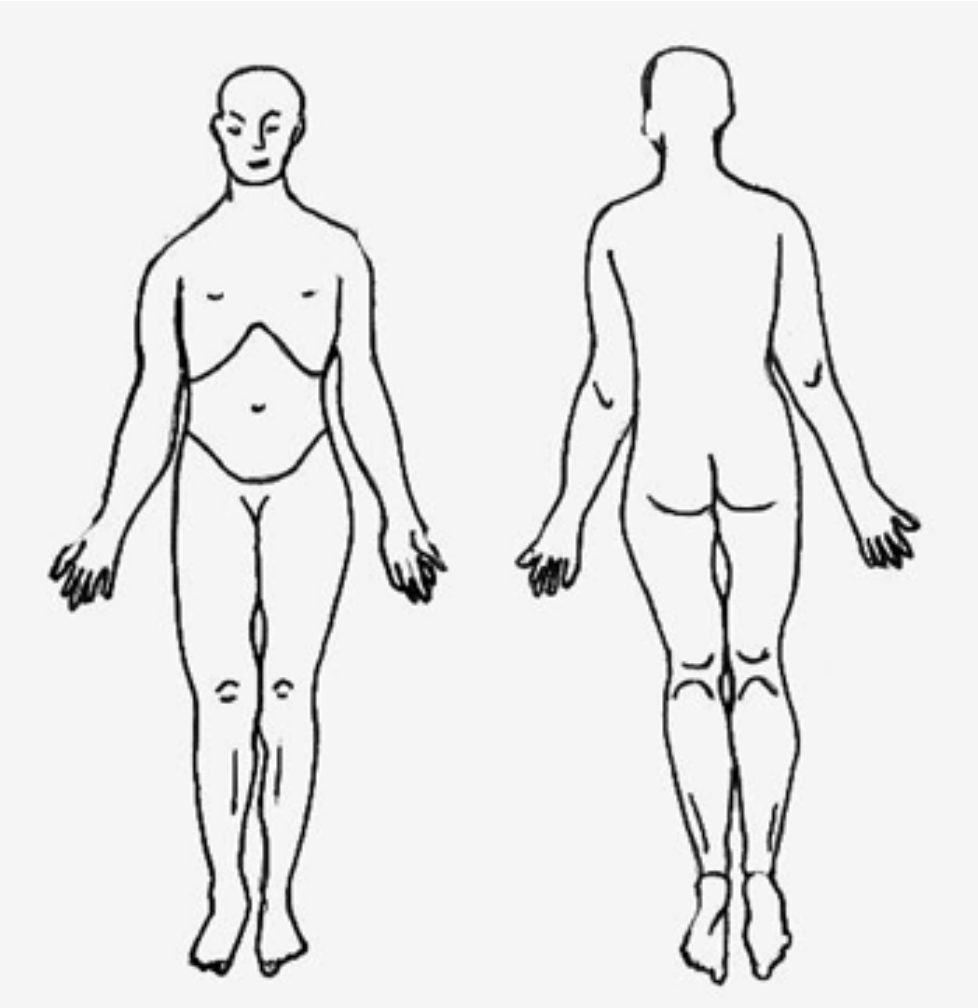
Appendix B

Peripheral Artery Disease (PAD) Symptom Questionnaire

1. On the diagram below, shade in the areas where you experience symptoms **while exercising** (walking, gardening, shoveling, etc). Use a different color for each type of pain, for example use red to shade the calf area for an *ache* and use blue to shade the foot for *numbness*.



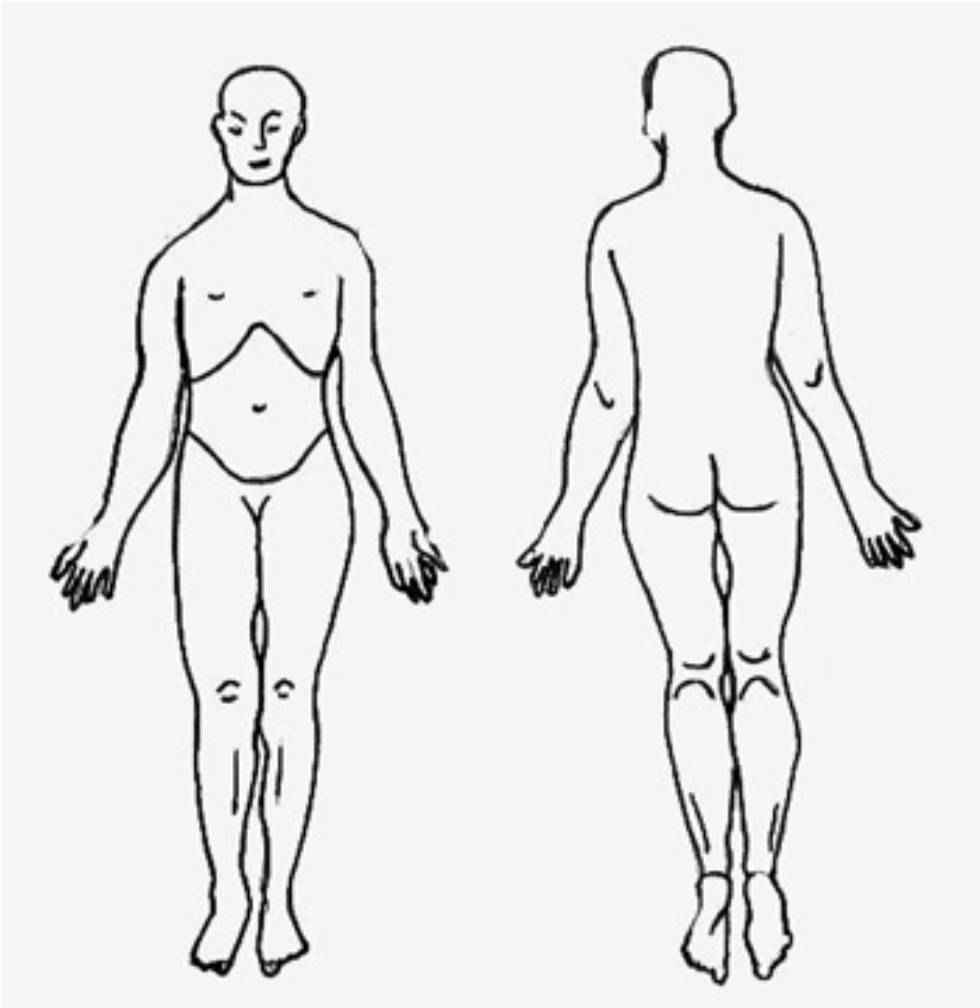
2. Following the same directions as above, shade in the areas where you continue to experience symptoms after you **stop exercising** (standing still, sitting or lying down).



3. If any or all of your symptoms go away when you rest, please write below an estimate for how long you have to rest for each symptoms to go away.

Symptom location: _____Time at rest for symptom to go away: _____minutes
Symptom location: _____Time at rest for symptom to go away: _____minutes
Symptom location: _____Time at rest for symptom to go away: _____minutes

4. Continuing to follow the initial directions, shade in the areas you experience symptoms at different times of the day, **not related to exercise**. For example, while sitting in your recliner chair you get a *shooting pain* along your thigh.



Appendix C
Information Sheet for Research
Exploring Peripheral Artery Disease (PAD) Symptoms

You are invited to be in a research study of the description of symptoms people with PAD experience while resting and with activity. You were selected as a possible participant because you have been given a diagnosis of PAD by a doctor or nurse and expressed an interest to participate in this study while attending a screening visit for the EXERT study. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by: Erica Schorr, BSBA, BSN, RN, Graduate Student of the University of Minnesota School of Nursing.

Procedures:

If you agree to be in this study, we would ask you to do the following things: Complete a brief questionnaire about your symptoms, then describe your symptoms in more detail to the principal investigator (PI), Erica Schorr, during a voice taped interview. This will take approximately 45 to 60 minutes of your time. There is a slight risk you may become emotionally upset discussing the pain you experience, however the risk is small and is minimized by you sharing only what you feel comfortable with during the interview. You will not receive any compensation for your participation.

Confidentiality:

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a subject. Research records will be stored securely and only researchers will have access to the records. Only the PI will have access to the audio recordings. They will be erased at the completion of the study or within four years, whichever occurs first.

Voluntary Nature of the Study:

Participation in this study is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University of Minnesota. If you decide to participate, you are free to no answer any question or withdraw at any time without affecting those relationships.

Contacts and Questions:

The researcher(s) conducting this study (are): Erica Schorr and Cynthia Peden-McAlpine. You may ask questions you have now. If you have questions later, **you are encouraged** to contact them at Erica Schorr 120 Dinnaken Office Building, 925 Delaware Street, Minneapolis, MN 55455, (612) 381-4449, scho0828@umn.edu. Cynthia Peden-McAlpine, 6-109 Weaver-Densford Hall, 308 Harvard Street SE, Minneapolis, MN 55455, (612) 624-0449, peden001@umn.edu.

If you have any questions or concerns regarding this study and would like to talk to someone other than the researcher(s), **you are encouraged** to contact the Research Subjects' Advocate Line, D528 Mayo, 420 Delaware St. Southeast, Minneapolis, Minnesota 55455; (612) 625-1650.

You will be given a copy of this information to keep for your records.

Appendix D
Pilot Study IRB Approval

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Human Research Protection Program
Office of the Vice President for Research

D528 Mayo Memorial Building
420 Delaware Street S.E.
MMC 820
Minneapolis, MN 55455

Office: 612-626-5654
Fax: 612-626-0061
E-mail: irb@umn.edu or ihc@umn.edu
Website: http://research.umn.edu/subjects/

March 9, 2010

Erica Schorr
120 Dinnaken Office Building
925 Delaware Street
Minneapolis, MN 55455

RE: "Exploring Peripheral Artery Disease (PAD) Symptoms"
IRB Code Number: **1002P77795**

Dear Dr. Schorr

The referenced study was reviewed by expedited review procedures and approved on March 9, 2010. If you have applied for a grant, this date is required for certification purposes as well as the Assurance of Compliance number which is FWA00000312 (Fairview Health Systems Research FWA00000325, Gillette Children's Specialty Healthcare FWA 00004003). Approval for the study will expire one year from that date. A report form will be sent out two months before the expiration date.

The IRB would like to stress that subjects who go through the consent process are considered enrolled participants and are counted toward the total number of subjects, even if they have no further participation in the study. Please keep this in mind when calculating the number of subjects you request. This study is currently approved for 4 subjects. If you desire an increase in the number of approved subjects, you will need to make a formal request to the IRB.

The code number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office.

As the Principal Investigator of this project, you are required by federal regulations to inform the IRB of any proposed changes in your research that will affect human subjects. Changes should not be initiated until written IRB approval is received. Unanticipated problems and adverse events should be reported to the IRB as they occur. Research projects are subject to continuing review and renewal. If you have any questions, call the IRB office at 612-626-5654.

On behalf of the IRB, I wish you success with your research.

We have created a short survey that will only take a couple of minutes to complete. The questions are basic, but will give us guidance on what areas are showing improvement and what areas we need to focus on:

https://umsurvey.umn.edu/index.php?sid=36122&lang=um

Sincerely,

APPROVED
03/09/10
dobrovca

Christina Dobrovolny, CIP
Research Compliance Supervisor
CD/pm
CC: Cynthia Peden-McAlpine

Appendix E
IRB Approval for the Main Study

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Human Research Protection Program
Office of the Vice President for Research

D528 Mayo Memorial Building
420 Delaware Street S.E.
MMC 820
Minneapolis, MN 55455

Office: 612-626-5654
Fax: 612-626-6861
E-mail: irb@umn.edu or ihc@umn.edu
Website: http://research.umn.edu/subjects/

March 17, 2011

Erica Schorr
120 Dinnaken Office Building
925 Delaware Street
Minneapolis, MN 55455

RE: "Characterization of the PAD Symptom Experience"
IRB Code Number: 1101M95114

Dear Dr. Schorr:

The Institutional Review Board (IRB) received your response to its stipulations. Since this information satisfies the federal criteria for approval at 45CFR46.111 and the requirements set by the IRB, final approval for the project (application date January 18, 2011) is noted in our files. Upon receipt of this letter, you may begin your research.

IRB approval of this study includes the consent form dated January 10, 2010[sic], received February 18, 2011 and recruitment materials received March 1, 2011 (letter dated March 1, 2001 [sic]).

The HIPAA Authorization received February 18, 2011 has been approved.

The IRB would like to stress that subjects who go through the consent process are considered enrolled participants and are counted toward the total number of subjects, even if they have no further participation in the study. Please keep this in mind when calculating the number of subjects you request. This study is currently approved for 80 subjects. If you desire an increase in the number of approved subjects, you will need to make a formal request to the IRB.

For your records and for grant certification purposes, the approval date for the referenced project is February 2, 2011 and the Assurance of Compliance number is FWA00000312 (Fairview Health Systems Research FWA00000325, Gillette Children's Specialty Healthcare FWA00004003). Research projects are subject to continuing review and renewal; approval will expire one year from that date. You will receive a report form two months before the expiration date. If you would like us to send certification of approval to a funding agency, please tell us the name and address of your contact person at the agency.

As Principal Investigator of this project, you are required by federal regulations to:
*Inform the IRB of any proposed changes in your research that will affect human subjects, changes should not be initiated until written IRB approval is received.
*Report to the IRB subject complaints and unanticipated problems involving risks to subjects or others as they occur.
*Inform the IRB immediately of results of inspections by any external regulatory agency (i.e. FDA).
*Respond to notices for continuing review prior to the study's expiration date.

*Cooperate with post-approval monitoring activities.

Information on the IRB process is available in the form of a guide for researchers entitled, What Every Researcher Needs to Know, found at http://www.research.umn.edu/irb/WERNK/index.cfm

The IRB wishes you success with this research. If you have questions, please call the IRB office at 612-626-5654.

Sincerely,

for

Andrew Allen
Research Compliance Supervisor
aa/ry

CC: Diane Treat-Jacobson

Appendix F
Recruitment Letter

«Month» «Day» «Year»

«Title» «FirstName» «LastName»
«Address1», «Address2»
«City», «State» «PostalCode»

Dear «Title» «LastName»:

As a previous participant in the EXERT study I thought you might like to know about a new study I am conducting at the University of Minnesota to learn more about the peripheral artery disease (PAD) symptom experience.

This study would involve completing an interview about your symptoms and walking on a treadmill to test a new device to measure the amount of oxygen in your calf muscle during exercise. The technology is near-infrared spectroscopy (NIRS) and it allows for pain free measurement to obtain this valuable information.

If you have any questions regarding this study, or would like more information about enrollment, please do not hesitate to contact me at 612-381-4449. If you would like more information about why you were contacted or how this relates to your participation in the EXERT study please contact the EXERT study coordinator, Laura Kirk at 612-626-4687. Thank you for your time and consideration.

Sincerely,

Erica Schorr, R.N.
Principle Investigator
University of Minnesota School of Nursing
(612) 381-4449
scho0828@umn.edu

Appendix G
Demographic Information Form

Visit: Consent

Sex: Male _____ Female _____

Age: _____

Date of Birth: _____

Marital Status:
- Single _____
- Married/Living with Partner _____
- Divorced _____
- Widowed _____

Race (Please check all that apply):
- American Indian or Alaskan Native _____
- Asian _____
- Black or African American _____
- Native Hawaiian or Pacific Islander _____
- White _____

Ethnicity:
- Hispanic or Latino _____
- Non-Hispanic or Non-Latino _____

Education:
- Less than High School Diploma _____
- High School Diploma _____
- Some College _____
- 4 year College Degree _____
- Graduate School _____

Employment Status:
- Full-Time Employed _____
- Part-Time Employed _____
- Homemaker _____
- Retired _____

Previous Occupation: _____

Participant Namecode _____ Visit Date ___/___/___
Participant ID _____

Appendix H
Medication List

Visit: Consent

Previous Medications

Name	Dose	Reason

Current Medications

Name	Dose	Reason

Participant Namecode _____ Visit Date ___/___/___
Participant ID _____

Appendix I
Resting ABI Measurement Form

Visit: Consent

ABI MEASUREMENT

Right Arm
Systolic pressure (mmHg)

_____

Left arm
Systolic pressure (mmHg)

_____

Right ankle
Systolic pressure (mmHg)
Posterior Tibial (PT)

_____

Dorsalis Pedis (DP)

_____

Left ankle
Systolic pressure (mmHg)
Posterior Tibial (PT)

_____

Doralis Pedis (DP)

_____

Right ABI equals ratio of:

Higher of the right ankle pressures (PT or DP). _____mmHg

DIVIDED BY =_____

Higher arm pressure (left or right arm). _____mmHg

Left ABI equals ratio of:

Higher of the left ankle pressures (PT or DP). _____mmHg

DIVIDED BY =_____

Higher arm pressure (left or right arm). _____mmHg

Rest start time _____
ABI start time_____

Participant Namecode: _____ Visit Date: ___/___/___
Participant ID _____

Appendix J
Treadmill Familiarization Form

Visit: Consent

TREADMILL and TESTING PROCEDURE FAMILIARIZATION

Prior to completing the treadmill familiarization, participants will have the opportunity to examine the discomfort scale (0-no discomfort to 5-maximal discomfort). Explain the meaning of the scale and its use during subsequent testing. Explain that he/she will be walking briefly on the treadmill and that he/she will be asked to mimic the testing procedures, verbally reporting a number between 0 and 5 to indicate their level of discomfort and providing symptom descriptors during exercise.

The treadmill familiarization should begin at a slow treadmill speed of 1.0 mph and 0% grade. Increase speed and grade until claudication discomfort is reached within 3 minutes. The walking bout should only last until the appropriate speed and grade to induce claudication is determined, but may be repeated if needed.

1. Have the participant straddle the treadmill belt and step on it once it is fully up to speed at between 1.0 and 2.0 mph. Participant should walk for a minimum of two separate bouts of walking. Additional bouts of walking may be repeated as necessary.
2. During familiarization, the participant should walk on the treadmill in as normal a manner as possible. Make sure they are using a normal stride and not doing a shortened stutter or shuffle step. They should be instructed to walk with their back straight and looking forward instead of looking down at the belt.
3. Ensure that participants walk on the treadmill with their hands resting lightly **on the handgrips at the front of the treadmill** to help with balance only.
4. Have participant walk at 1.5 mph for 3 minutes. Assess discomfort at 30 second intervals.
5. Have participant walk at 2.0 mph for 3 minutes. Again, assess discomfort at 30 second intervals.
6. If participant did not experience claudication discomfort, additional bouts may be performed until the appropriate speed and incline for treadmill testing has been determined.

(Note: Stop treadmill if participant is unsteady or reporting discomfort >1).

□ Treadmill explained

□ Discomfort scale explained

□ NIRS probe placement explained

□ Patient Verbalizes Understanding

Appendix J
Treadmill Familiarization Form

Visit: Consent

Assess gait, noting any gait instability. Describe: _____
_____

Treadmill Walking Trial:

Trial	30 Second Rating	60 Second Rating	90 Second Rating	120 Second Rating	150 Second Rating	180 Second Rating
1.5 MPH 0.0% Grade						
2.0 MPH 0.0% Grade						
_____ MPH _____ Grade						

From Treadmill Familiarization (please check one):

_____ 2.0 MPH is appropriate beginning testing speed

_____ 1.5 MPH is appropriate beginning testing speed

_____ Other (specify speed achieved and duration)

Notes from TM Familiarization: _____

_____

_____

Appendix K

CONSENT FORM

Characterization of the Peripheral Artery Disease (PAD) Symptom Experience

You are invited to be in a research study exploring the way people diagnosed with peripheral artery disease (PAD) describe the symptoms they experience. You will be asked to describe your symptoms during an interview and while walking on a treadmill. You were selected as a possible participant because a doctor or nurse has given you a diagnosis of PAD, you are a current participant in the **EX**ercise Training to Reduce Claudication: Arm **ER**gometry versus **T**readmill Walking (EXERT) study, and you expressed an interest to participate in this study to an EXERT staff member.

We ask that you read this form and ask any questions you may have before agreeing to be in the study.

Erica Schorr, RN of the University of Minnesota School of Nursing, is conducting this study. It is funded by a grant received from the Nursing Research Section at the National Institutes of Health.

Study Purpose

The purpose of this study is to gain a comprehensive understanding of the PAD symptom experience in older and younger men and women beyond classic claudication, including the quality, duration, and intensity of symptoms. We also want to know if there is a relationship between how much oxygen is getting to your leg muscles and the symptoms you are reporting. You will verbally report your symptom(s) using words to describe what you are feeling and giving each symptom a numerical rating on a scale of 0 to 5.

Study Procedures

You have been cleared to exercise by a qualified cardiovascular clinician based on the EXERT study protocol.

If you agree to participate in this study, you will meet one time with the Principle Investigator (PI) for approximately two hours. Your visit will include the following:

<u>PAD Questionnaire</u>

You will be asked to complete a two-page questionnaire with the help of the PI. This form will ask you to identify the location of all of your symptoms (while exercising, immediately after, and at rest) on a body diagram. For symptoms that go away or lessen with rest, you will be asked to give an estimate of how long it takes your symptoms to go away after stopping exercise.

Symptom Interview
You will be asked to describe all of your symptoms (related or unrelated to PAD) in more detail during a voice-recorded interview. You will be asked to describe your diagnosis of PAD, your symptoms, and how you feel they affect your life.

Ankle-Brachial Index (ABI)
The ABI is a test that compares the blood pressure in your arms to the blood pressure in your legs. During this procedure, blood pressure cuffs will be placed around your upper arms and ankles, and a small amount of gel will be placed over the artery being measured. A Doppler probe attached to a small speaker will be placed on the gel and you will hear a loud pulsing sound. The cuffs will be inflated individually until the sound is no longer heard and then slowly released. A resting ankle-brachial index (ABI) will be taken prior to walking on the treadmill and four times immediately after your first exercise test (immediately after stopping exercise, 2 minutes after stopping exercise, 5 minutes after stopping exercise, and 10 minutes after stopping exercise). These intervals could change based on how quickly the blood flow in your legs improves according to a piece of equipment called near-infrared spectroscopy (NIRS). It is a painless procedure that involves placing a small *patch* (optode) over your calf muscle. The patch will be placed at rest and will remain on your calf until all three exercise tests have been completed.

Treadmill Familiarization
You will review a discomfort scale (0-no discomfort to 5-maximal discomfort). We will explain how it will be used during testing. Next, you will walk briefly on a treadmill to imitate the testing procedures. The treadmill speed will begin at 1.5 mph and 0% incline. The speed and incline will be increased until discomfort is reached (1 out of 5) within 3 minutes. You will also describe your leg discomfort in words during exercise. The treadmill will be stopped if you are unsteady or reporting discomfort >1.

Treadmill Testing
You will be asked to walk on a treadmill three separate times, with at least 10 minutes of rest in between to allow the blood flow in your legs to return to *normal*. The treadmill will start at the speed and incline determined during your treadmill familiarization. The amount of oxygen in your leg muscles will be measured by NIRS. You will walk on the treadmill reporting a number from 0 to 5 that corresponds to your discomfort, as well as reporting words that describe your symptoms. The test will be stopped as soon as you report a discomfort level of 5 out of 5.

Risk of Study Participation

The study has the following risks:

The risks associated with this study are primarily related to exercise. For safety reasons, before study testing, you will be placed on a treadmill and asked to walk at a slow speed to determine an appropriate speed for testing.

Exercise testing carries a small risk (1 in 10,000) of heart attack or death. To minimize this risk, you will only be allowed to participate if you do not have severe heart disease. Your risk is also minimized by being cleared for exercise through your participation in the EXERT study.

We will check a resting ABI before the test. Your blood pressure will be taken before and after exercise, while seated and standing. You may experience discomfort in the leg and arm when the blood pressure cuff inflates. If you feel the discomfort is too much, please tell the researcher and the study will be stopped immediately. You heart rate will be monitored continuously with a strap placed around your chest and a watch on your wrist. If you have diabetes, a pre- and post-exercise blood sugar with be taken with a glucometer. These measures will be taken to ensure that it is safe to perform exercise on the treadmill.

Trained staff and the necessary equipment will be available should anything unusual happen while you are exercising. The treadmill will be stopped if you have shortness of breath or chest pain that makes it uncomfortable for you to continue. The treadmill will also be stopped anytime that you ask it be stopped. If you are suspected of having a cardiac event, 911 will be called immediately and the emergency protocols of the facility will be followed.

There is a slight risk that you may become emotionally upset discussing the experience of your symptoms during the interview, particularly those that cause you a great deal of pain. However, the risk is small and is minimized by you sharing only what you feel comfortable with during the interview.

Benefits to Study Participation

The benefits to study participation are:

There is no direct benefit to you for participating in this study.

This research has potential benefit for current and future patients with PAD. This study will provide information on the assessment, evaluation, and diagnosis of PAD based on age, gender, and symptoms reported.

Alternatives to Study Participation

Choosing not to participate in this study will not affect treatment for your PAD in any way. If you choose not to participate, your participation with the EXERT study will not be affected.

Study Costs/Compensation

All care provided as part of this study will be provided to you at no charge. A parking permit will be provided for your visit. There is no other compensation provided to you for participation in this study.

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment, and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the principle investigator know right away.

Confidentiality

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a study participant. Your research records will be stored securely and only study investigators and staff will have access to the records. Study records may be subject to review by the NIH and the FDA. There are also departments at the U of MN with appropriate regulatory oversight which may review your records.

Protected Health Information (PHI)
Your PHI created or received for the purpose of this study is protected under the federal regulation known as HIPPA. Please refer to the attached HIPPA authorization for details concerning the use of this information.

Voluntary Nature of the Study

Your decision whether or not to participate in this study is strictly voluntary. Your decision will not affect your current or future relations with your regular doctor or the University of Minnesota. Your decision will have no effect on your participation in the EXERT study.

If you decide to participate, you are free to withdraw at any time without affecting those relationships. The principle investigator or study staff may withdraw you from the study without your approval if you do not follow study instructions, or for any other reason(s) that they feel are appropriate.

Contacts and Questions

If you have any questions now or in the future concerning your participation in this study, you may contact Erica Schorr at 612-381-4449. You may ask any questions you have now. You have the right to ask the study staff or the principle investigator any questions concerning this study at any time.

If you have any questions or concerns regarding the study and would like to talk with someone other than the research(s), you are encouraged to contact the Fairview Research Helpline at 612- 672-7692 or toll free at 1-866-508-6961. You may also contact this office in writing or in person at Fairview University Medical Center-Riverside campus, 2200 Riverside Avenue, Minneapolis, MN 55454.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Subject_____ Date_____

Signature of Investigator_____ Date_____

You will be given a copy of this form to keep for your records.

Appendix L
HIPAA Authorization Form

HIPAA[1] AUTHORIZATION TO USE AND DISCLOSE INDIVIDUAL HEALTH INFORMATION FOR RESEARCH PURPOSES

1. Purpose. As a research participant, I authorize Erica Schorr, RN and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research project entitled "Characterization of the Peripheral Artery Disease (PAD) Symptom Experience."

2. Individual Health Information to be Used or Disclosed. My individual health information that may be used or disclosed to conduct this research includes: Demographic information, ABI results, medical history, interview transcripts, and treadmill testing descriptors and oxygenation status.

3. Parties Who May Disclose My Individual Health Information.
The researcher and the researcher's staff may obtain my individual health information from other
healthcare providers, such as laboratories, which are a part of this research, as well as healthcare providers that are not part of this research (other doctors, hospitals and/or clinics) for the purposes of carrying out this research study. I authorize these parties to disclose my individual health information to the researcher and the researcher's staff for the purposes of carrying out this research study.

4. Parties Who May Receive or Use My Individual Health Information. The individual health information disclosed by parties in item 3 and information disclosed by me during the course of the research may be received and used by Erica Schorr, RN and the researcher's staff and [list any collaborators, other clinical sites involved in the research, sponsors if applicable, outside laboratories-N/A]. [OPTIONAL: Also, if I receive compensation for participating in this study, identifying information about me may be used or disclosed as necessary to provide compensation.]

5. Right to Refuse to Sign this Authorization. I do not have to sign this Authorization. If I decide not to sign the Authorization, I may not be allowed to participate in this study or receive any research related treatment that is provided through the study. However, my decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

6. Right to Revoke. I can change my mind and withdraw this authorization at any time by sending a written notice to Erica Schorr; 5-140 Weaver-Densford Hall, 308 Harvard St SE; Minneapolis, MN 55455 to inform the researcher of my decision. If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information.

7. Potential for Re-disclosure. Once my health information is disclosed under this authorization, there is a potential that it will be re-disclosed outside this study and no longer covered by this authorization. However, the research team and the University's Institutional Review Board (the committee that reviews studies to be sure that the rights and safety of study participants are protected) are very careful to protect your privacy and limit the disclosure of identifying information about you.

7A. Also, there are other laws that may require my individual health information to be disclosed for public purposes. Examples include potential disclosures if required for mandated reporting of abuse or neglect, judicial proceedings, health oversight activities and public health measures.

8A. [Optional Item] **Suspension of Access**. I may not be allowed to review the information collected for this study, including information recorded in my medical record, until after the study is completed. When the study is over, I will have the right to access the information again.

This authorization does not have an expiration date.

I am the research participant or personal representative authorized to act on behalf of the participant.

I have read this information, and I will receive a copy of this authorization form after it is signed.

signature of research participant or research participant's personal representative	date
printed name of research participant or research participant's authority to act on behalf personal representative	description of personal representative's of the research participant

Appendix M

Introductory & Treadmill (TM) Data Collection Form

(Keep original as Source Document in participant's file)

Item #	**Data Item**	**Data Entry**
1.	Anthropometric measurements	Height _____ inches Weight _____ pounds
2.	Date of birth	Month/day/year: _____ Age _____
	E-mail address	_____
3.	Co-morbid conditions Smoke? _____ PPD _____	_____ _____ _____ _____ _____ _____ _____ _____
4.	Date of cardiac stress test	Month/day/year: _____
	Details of test EXERT Group: _____	Max heart rate _____ bmp Rest HR _____ Peak speed: _____ mph Rest BP _____ Peak incline: _____ % Peak BP_____ Onset _____ Max_____ Peak RPE _____
	ABI History	Date: Value:
	Symptoms & Location(s) Blockage(s) _____	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____
4.	Calf circumference	Right or Left (circle one) _____ cm

Participant Namecode _____ Visit Date ___/___/___

Participant ID _____

5.	Details of Exercise Test *(based on treadmill familiarization)*	TM speed: _____ mph TM grade:_____ % incline
	Additional comments Current Exercise Routine	Participant was called about missed appointment? Yes No Reason for missed session: ☐ Hospitalized ☐ Forgot ☐ Other _____ ☐ Not feeling well ☐ Transportation problem Make-up date scheduled? Yes No (mm/dd/yy) _____ _____
6.	Pre-Exercise Blood Glucose	_____
7.	Baseline Measurements	Blood pressure _____ mmHg R or L Heart rate _____ bmp
8.	TM Test 1: TM Test 2: TM Test 3:	Pre BP _____HR _____ Post BP _____ HR _____ Walking Time _____minutes: seconds Recovery Time _____ minutes: seconds Pre BP _____HR _____ Post BP _____ HR _____ Walking Time _____minutes: seconds Recovery Time _____ minutes: seconds Pre BP _____HR _____ Post BP _____ HR _____ Walking Time _____minutes: seconds Recovery Time _____ minutes: seconds
9.	Baseline ABI	Right _____ *indicates testing leg Left _____

Participant Namecode _____ Visit Date ___/___/___
Participant ID _____

10.	Post-exercise ABI's	_____ immediate _____ 2 minutes _____ 5 minutes _____ 10 minutes
11.	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location

Participant Namecode _____ Visit Date ___/___/___
Participant ID _____

	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location

Participant Namecode _______________ Visit Date ___/___/___
Participant ID ______________________

	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location

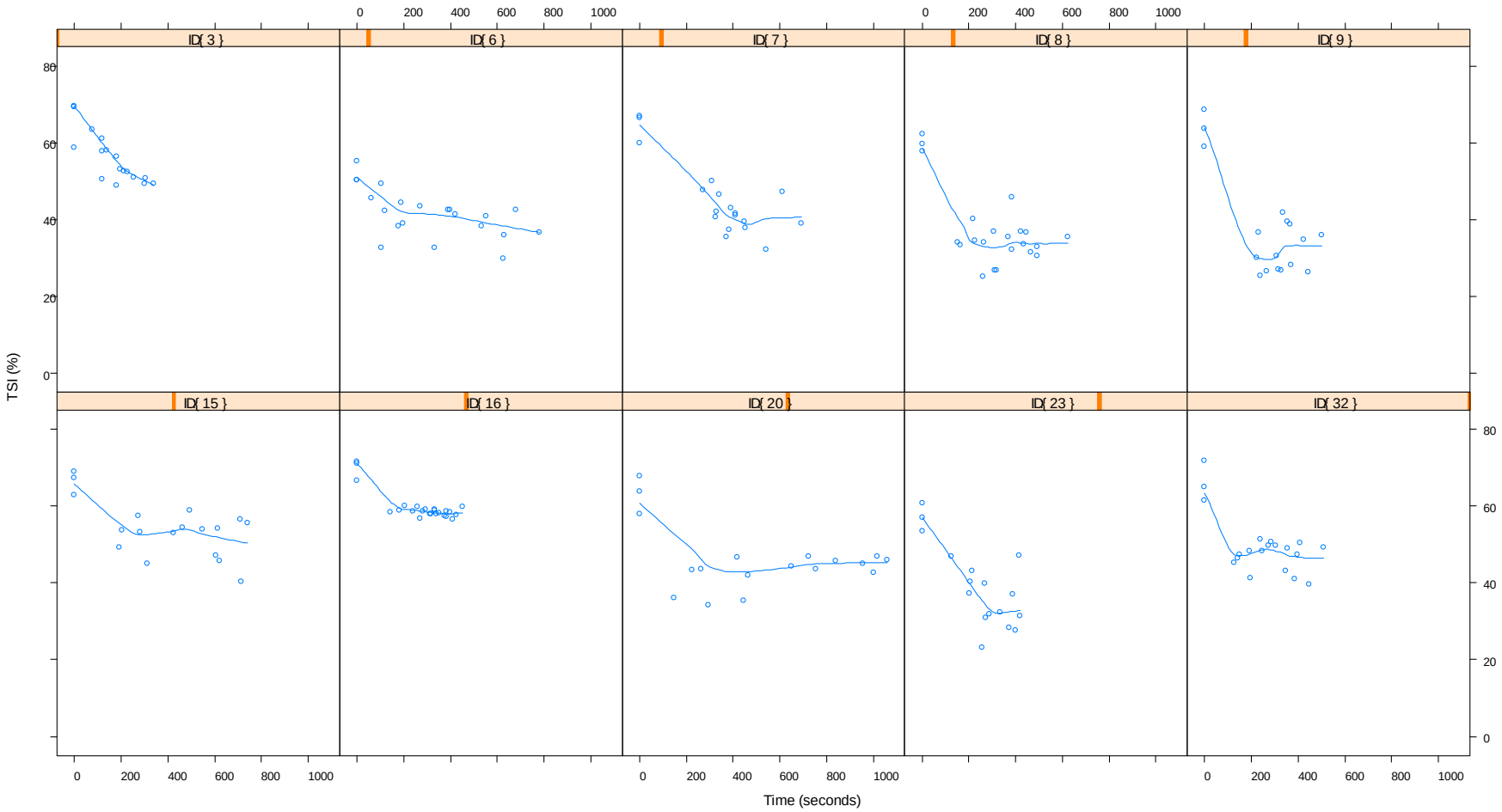
Participant Namecode _______________ Visit Date ___/___/___
Participant ID ______________________

	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
	Test # Exercise *OR* Rest Time	Intensity Descriptor Location
12.	Post-Exercise Blood Glucose	_____

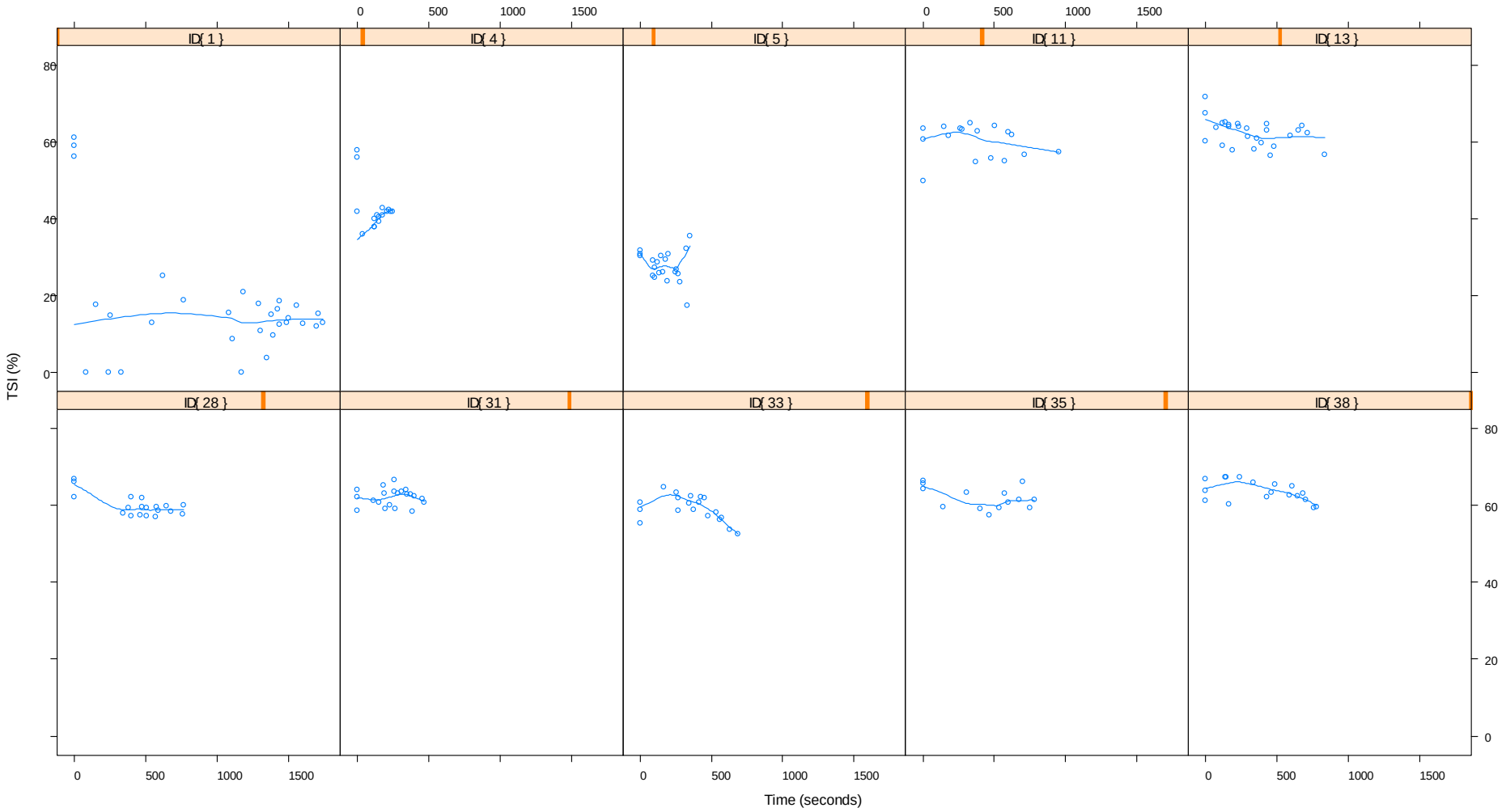
Participant Namecode _____ Visit Date ___/___/___
Participant ID _____

Appendix N
Individual Exercise Trajectories

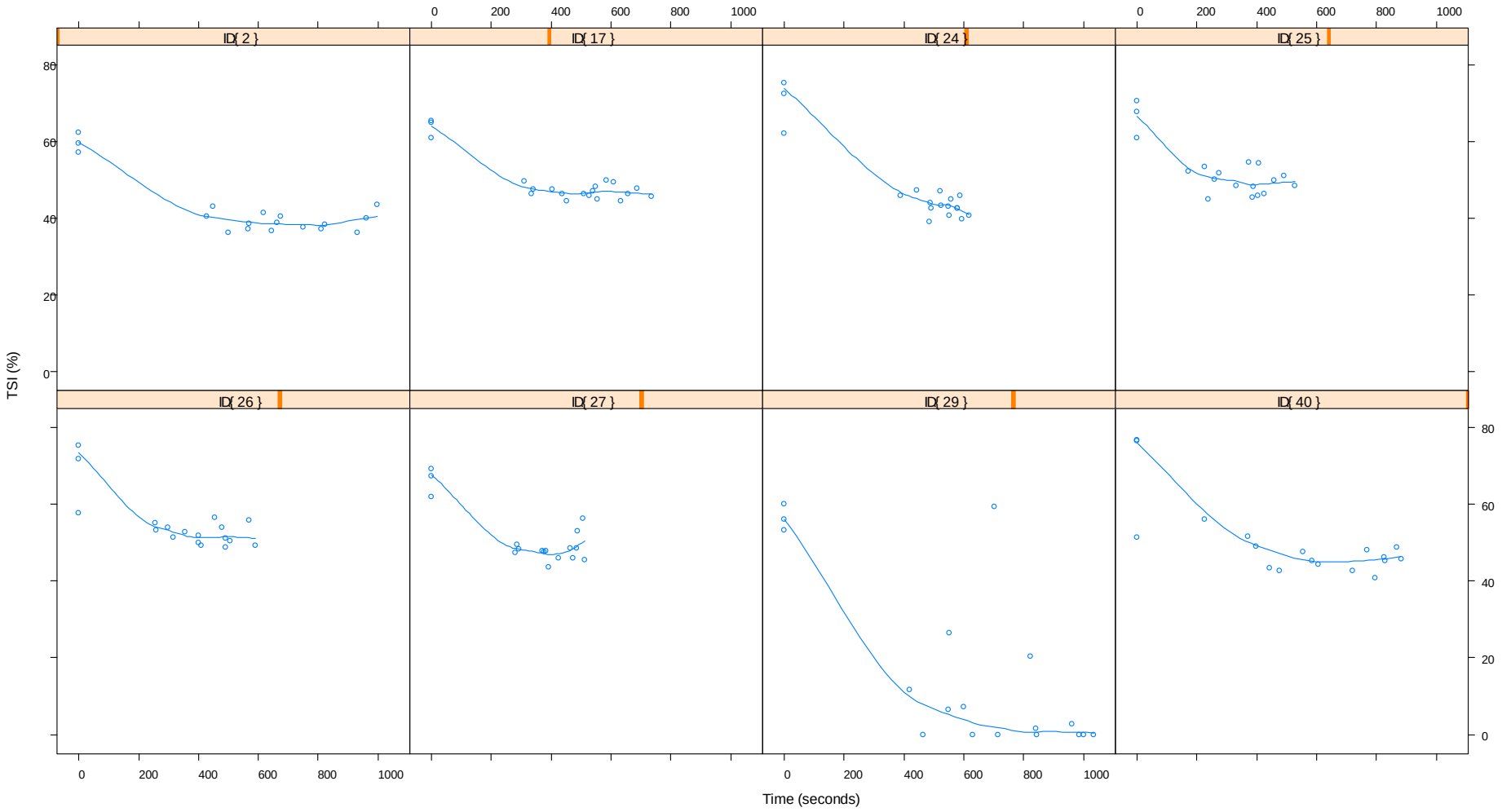
N1. An initial rapid decline in TSI, followed by slowly declining or relatively unchanged TSI values throughout exercise (*n*=10).



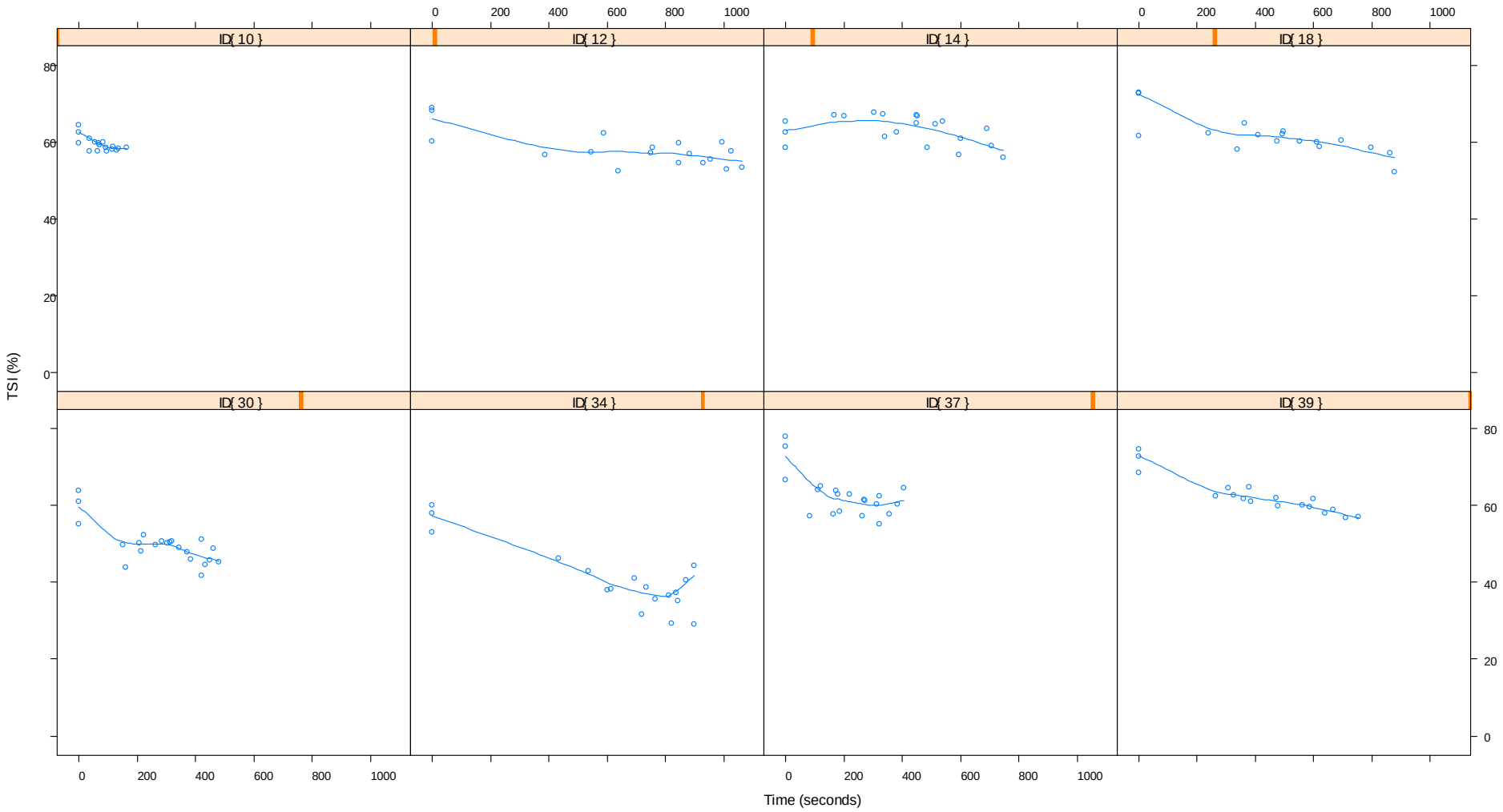
N2. Relatively unchanged TSI values during exercise (*n*=10).



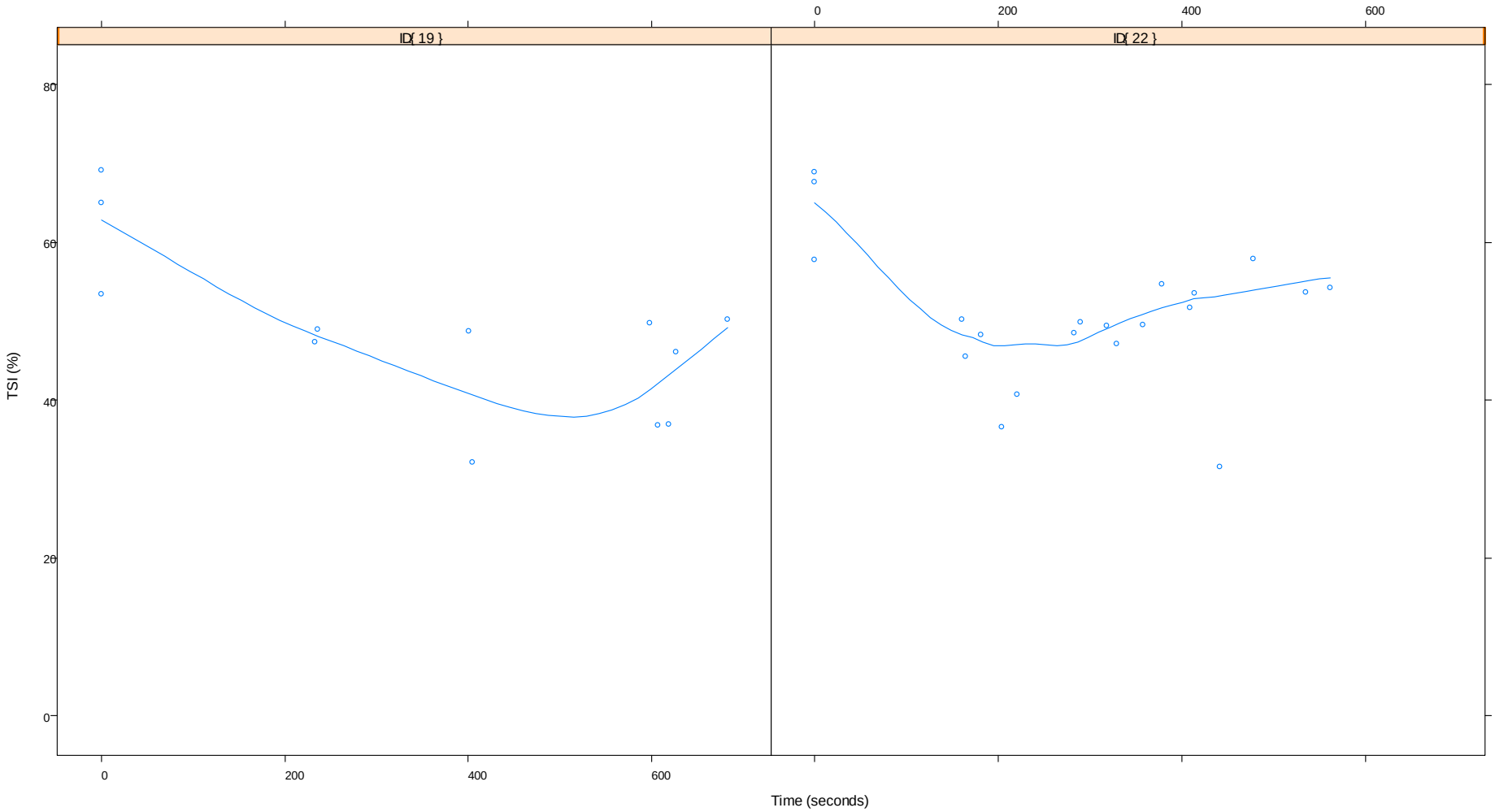
N3. Exponentially declining TSI values during exercise (*n*=8).



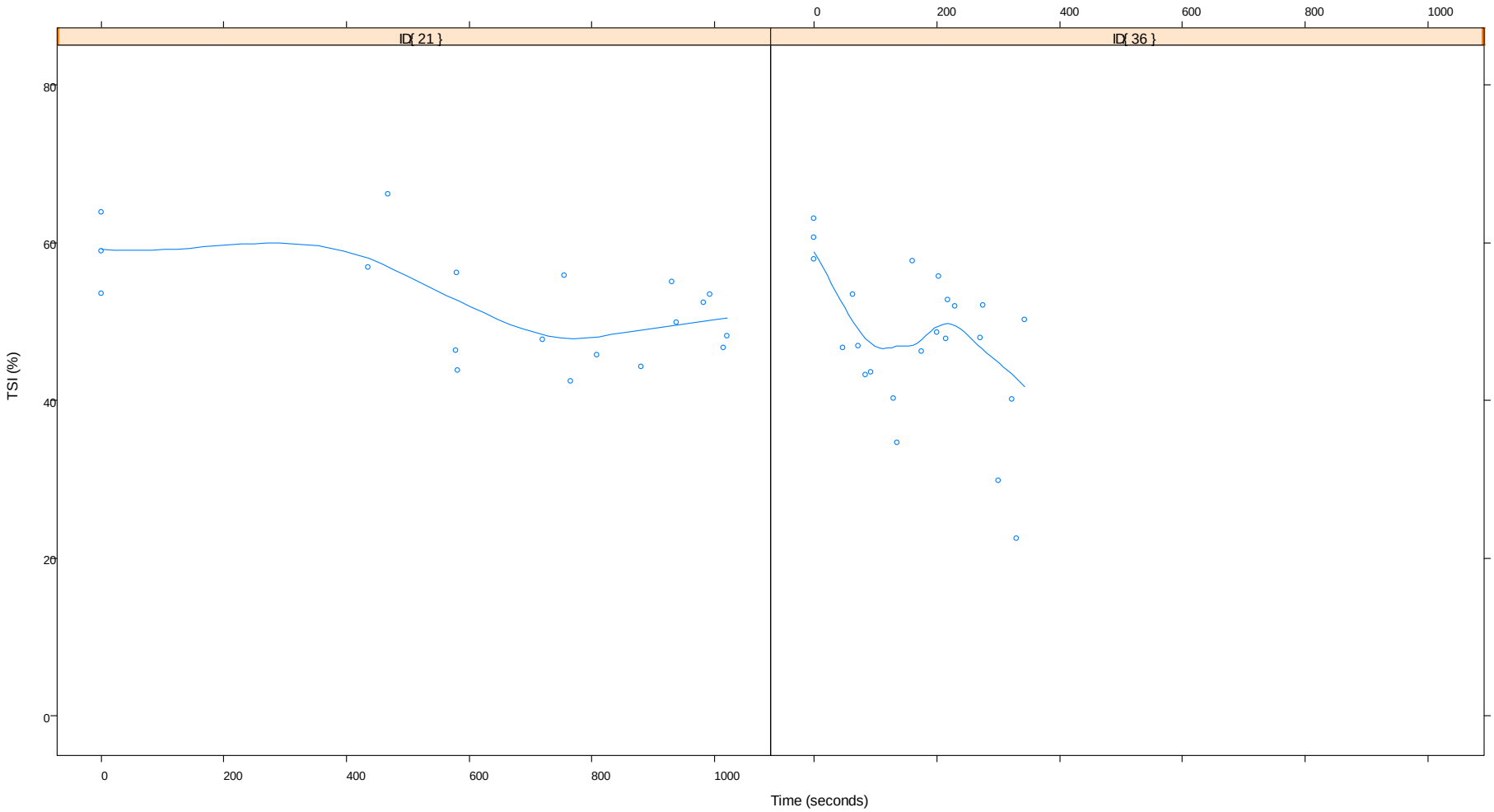
N4. Gradual decline in TSI values throughout the exercise phase (*n*=8).



N5. Quadratic change in TSI values during exercise (*n*=2).

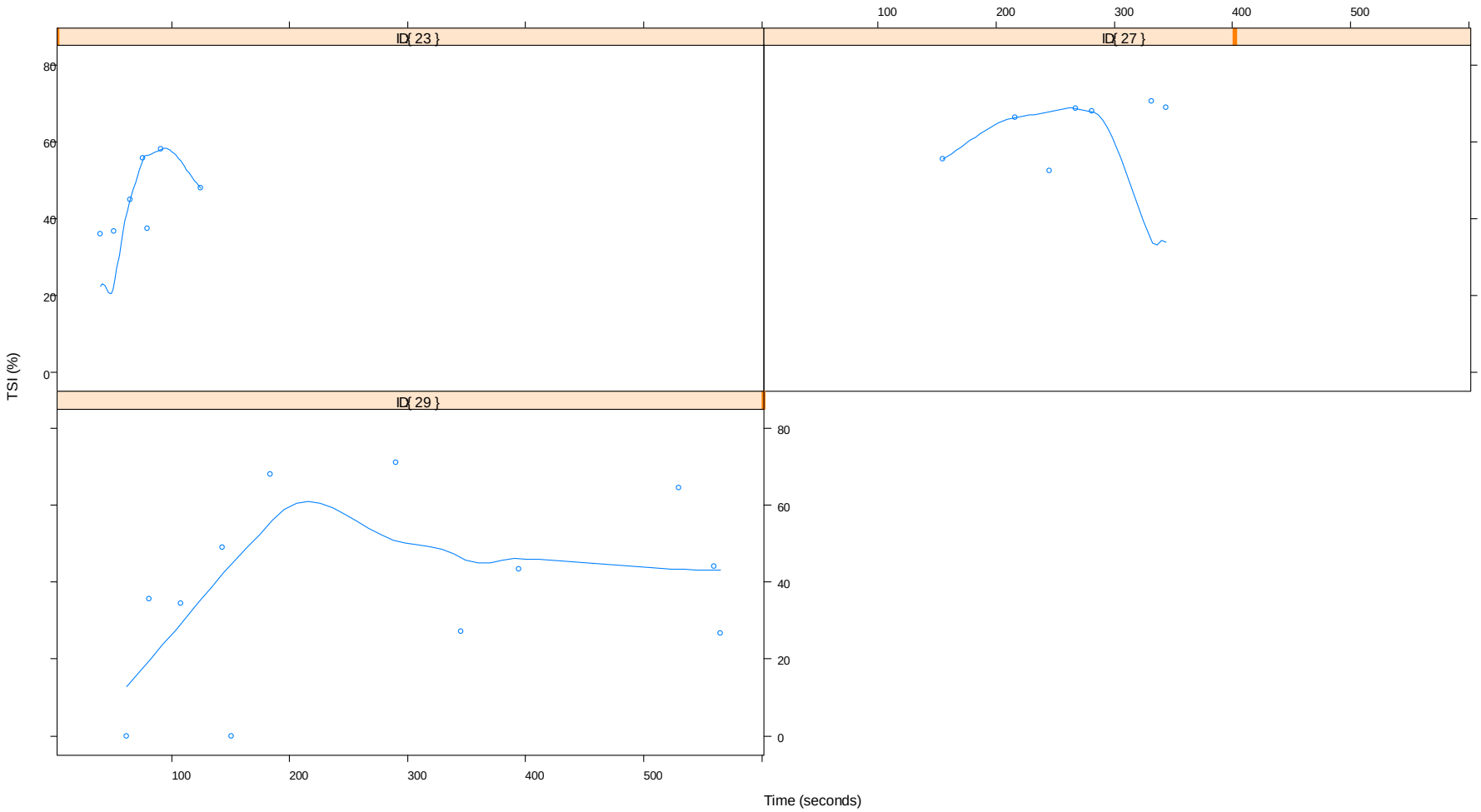


N6. Cubic change in TSI values during exercise (*n*=2).

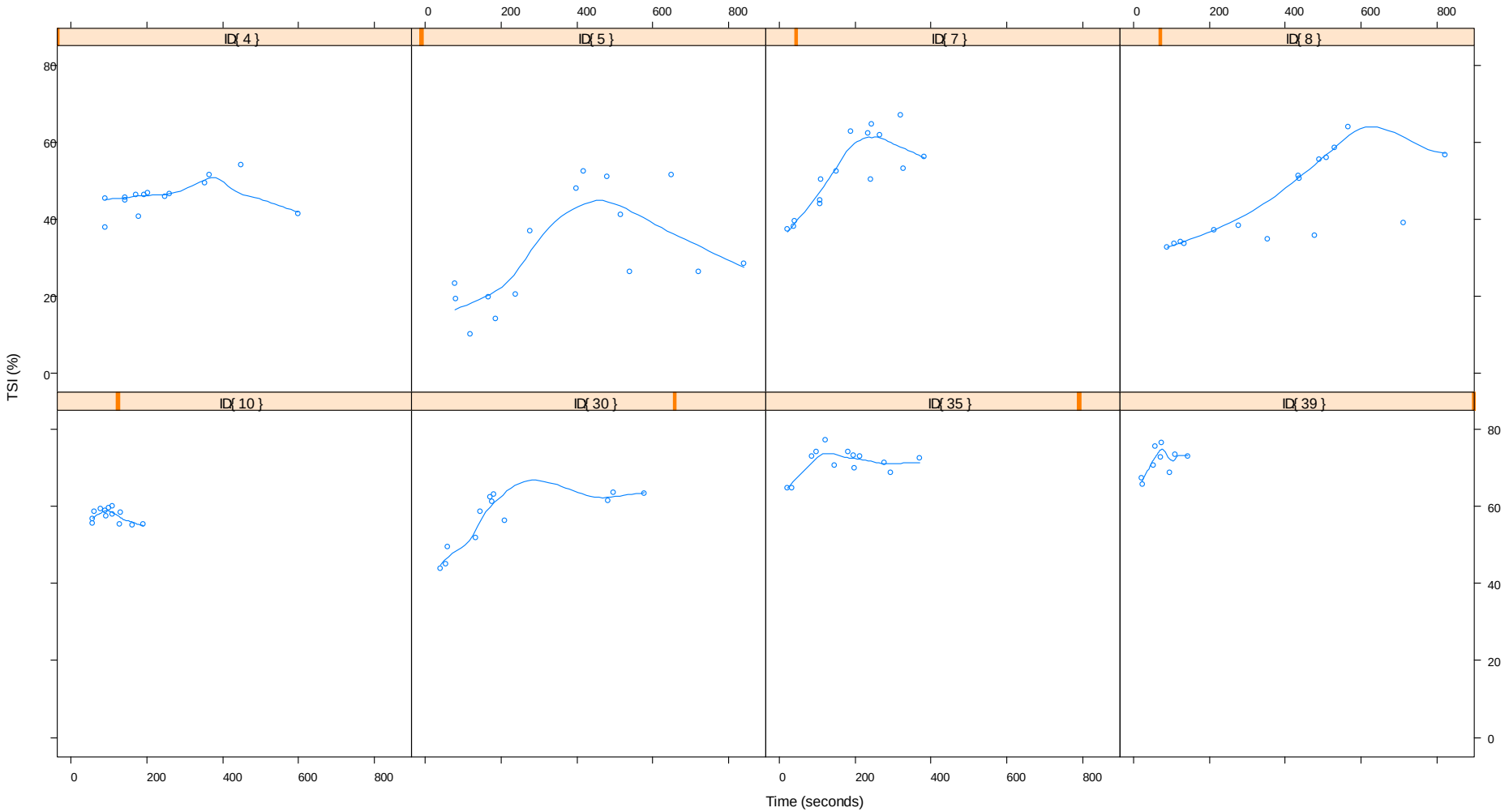


Appendix O
Individual Recovery Trajectories

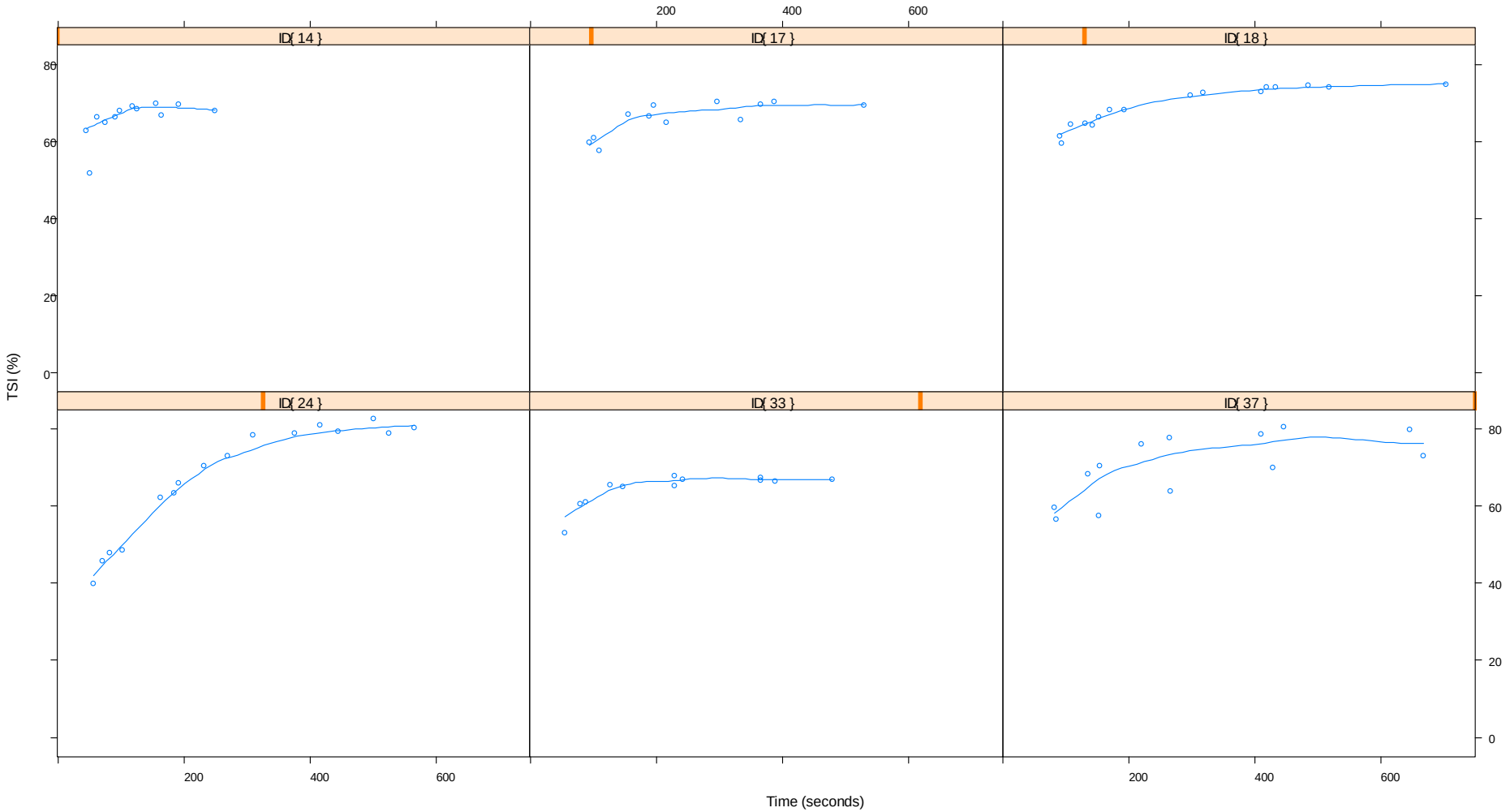
O1. Rapid peak TSI during recovery (*n*=3).



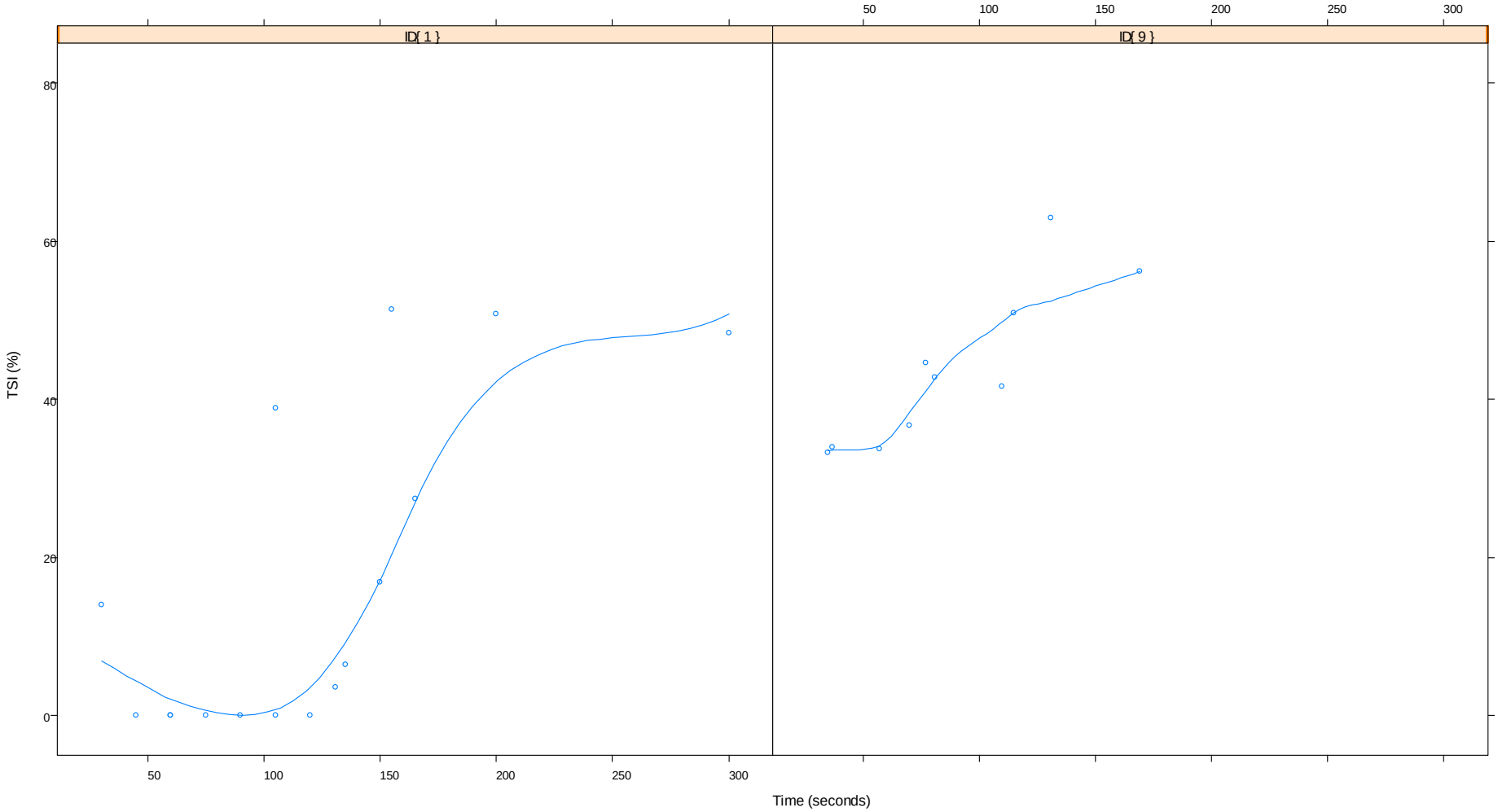
O2. Prolonged TSI recovery with a less pronounced peak (*n*=8).



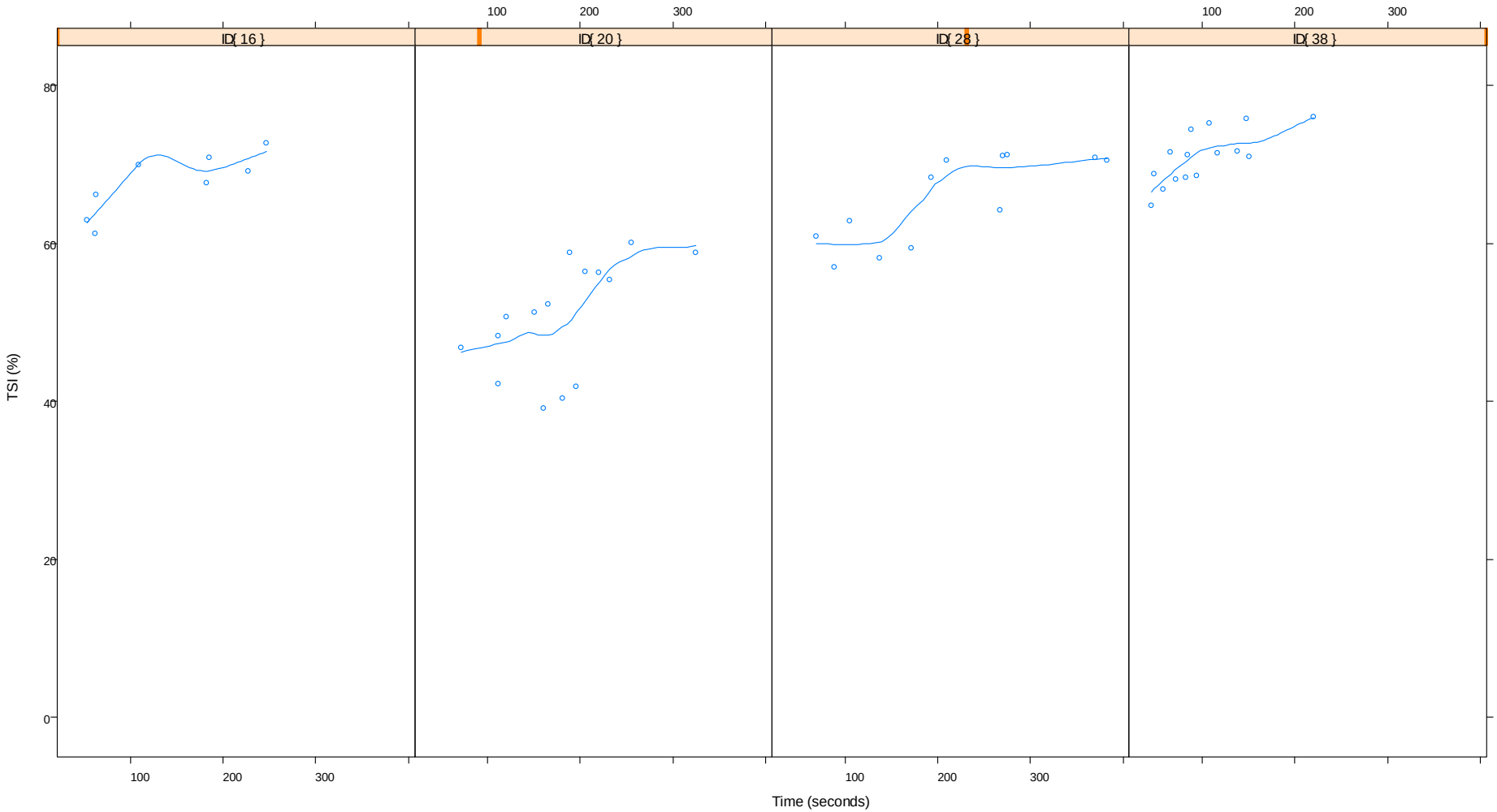
O3. Exponential TSI recovery (*n*=6).



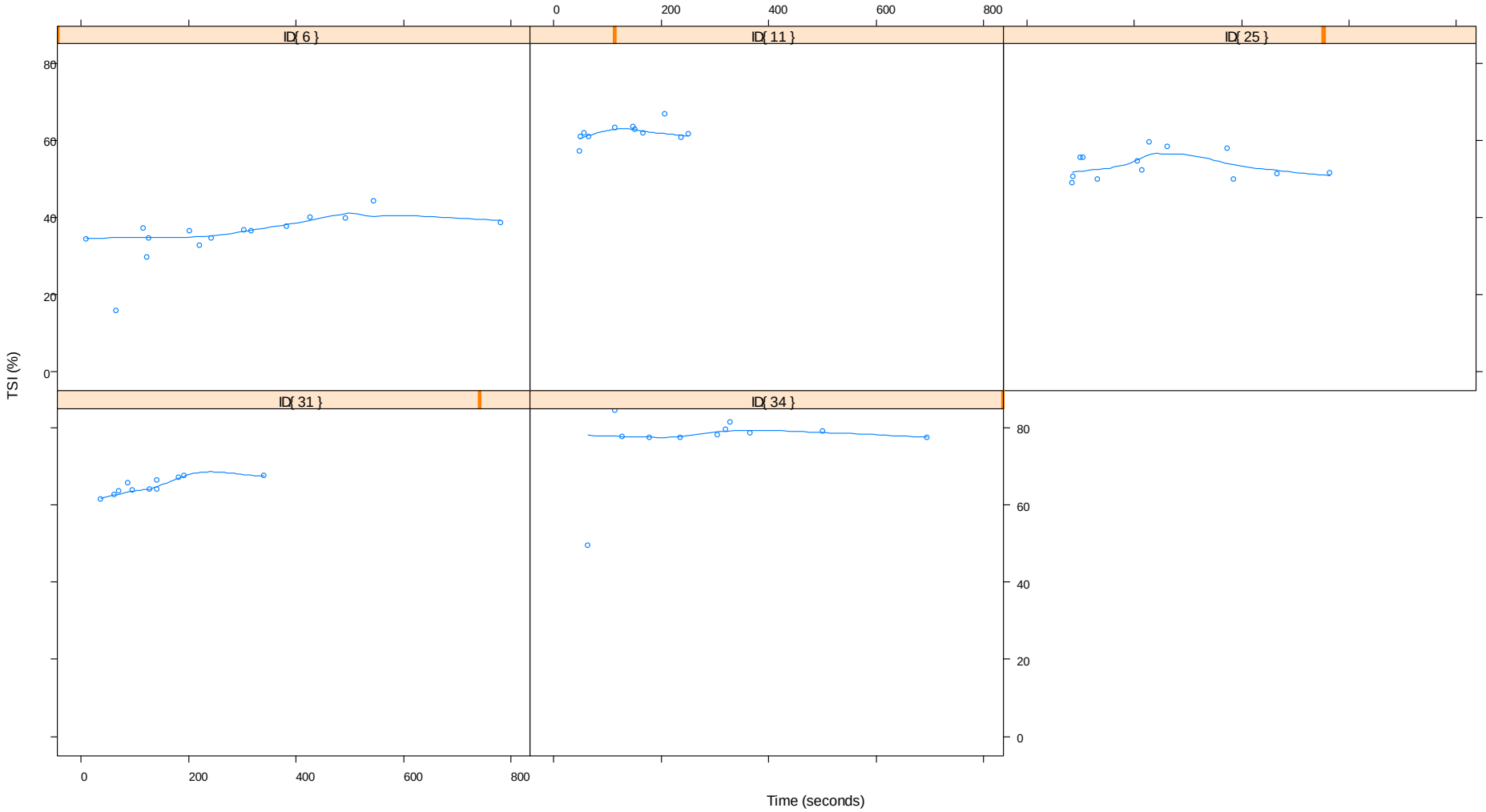
O4. Rapid cubic TSI recovery (*n*=2).



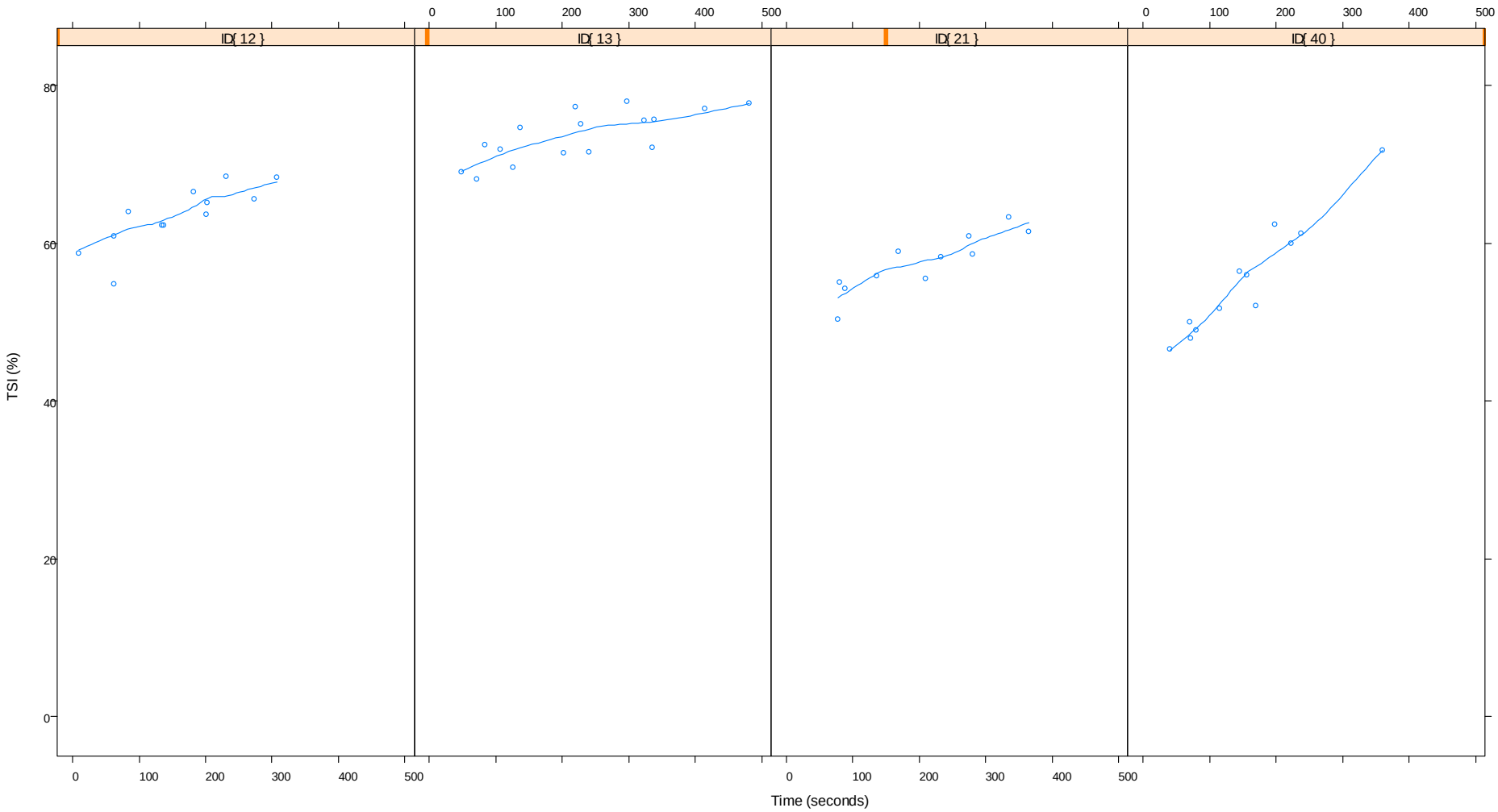
O5. Slower cubic TSI recovery (*n*=4).



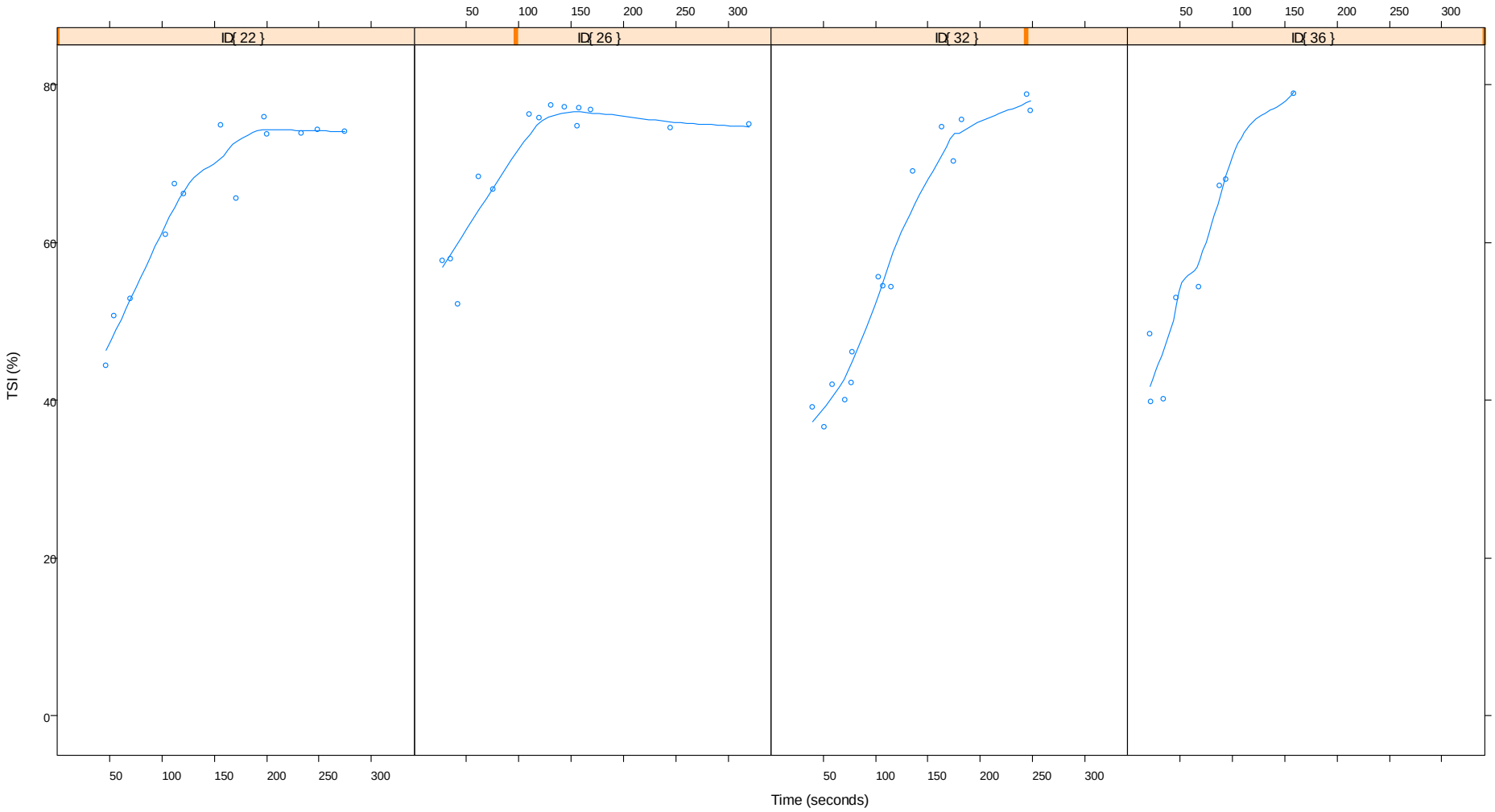
O6. Relatively unchanged TSI values throughout the recovery phase (*n*=5).



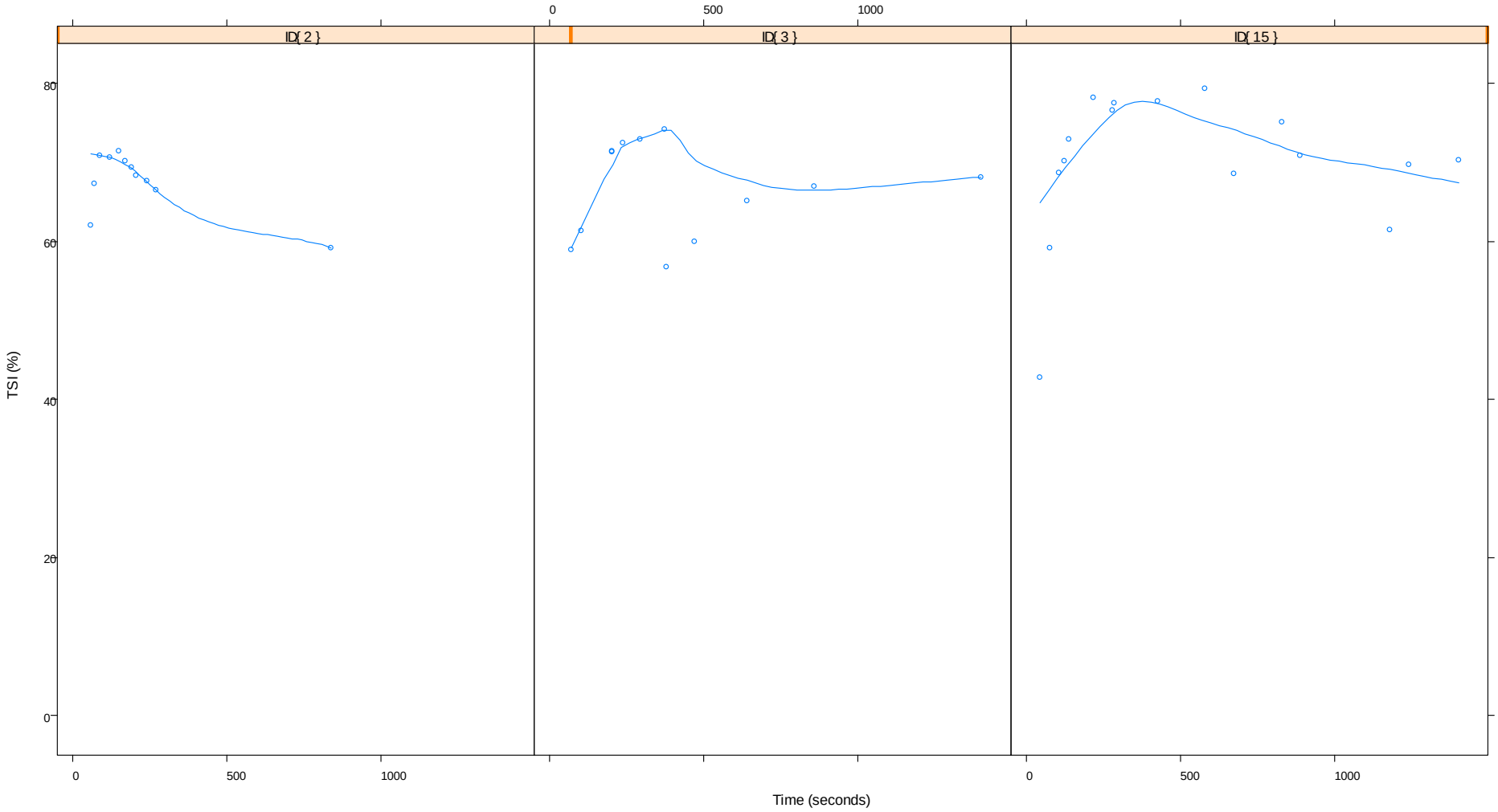
O7. Linear TSI recovery (*n*=4).



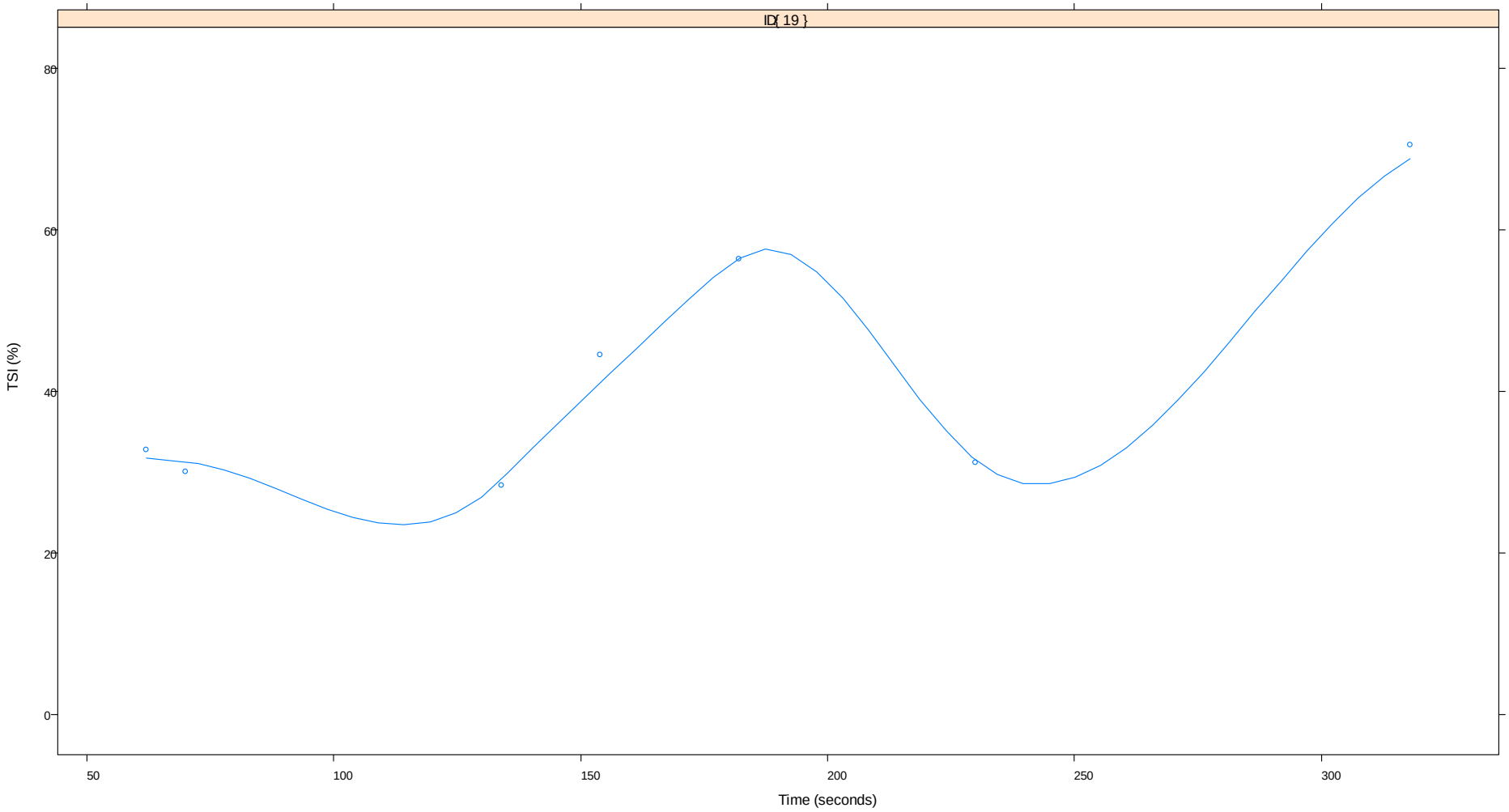
O8. Rapid initial and full recovery (*n*=4).



O9. Rapid initial TSI recovery, followed by gradually declining TSI values (*n*=3).



O10. Unique recovery pattern (*n*=1).



Appendix P

Individual Exercise Phase Summary

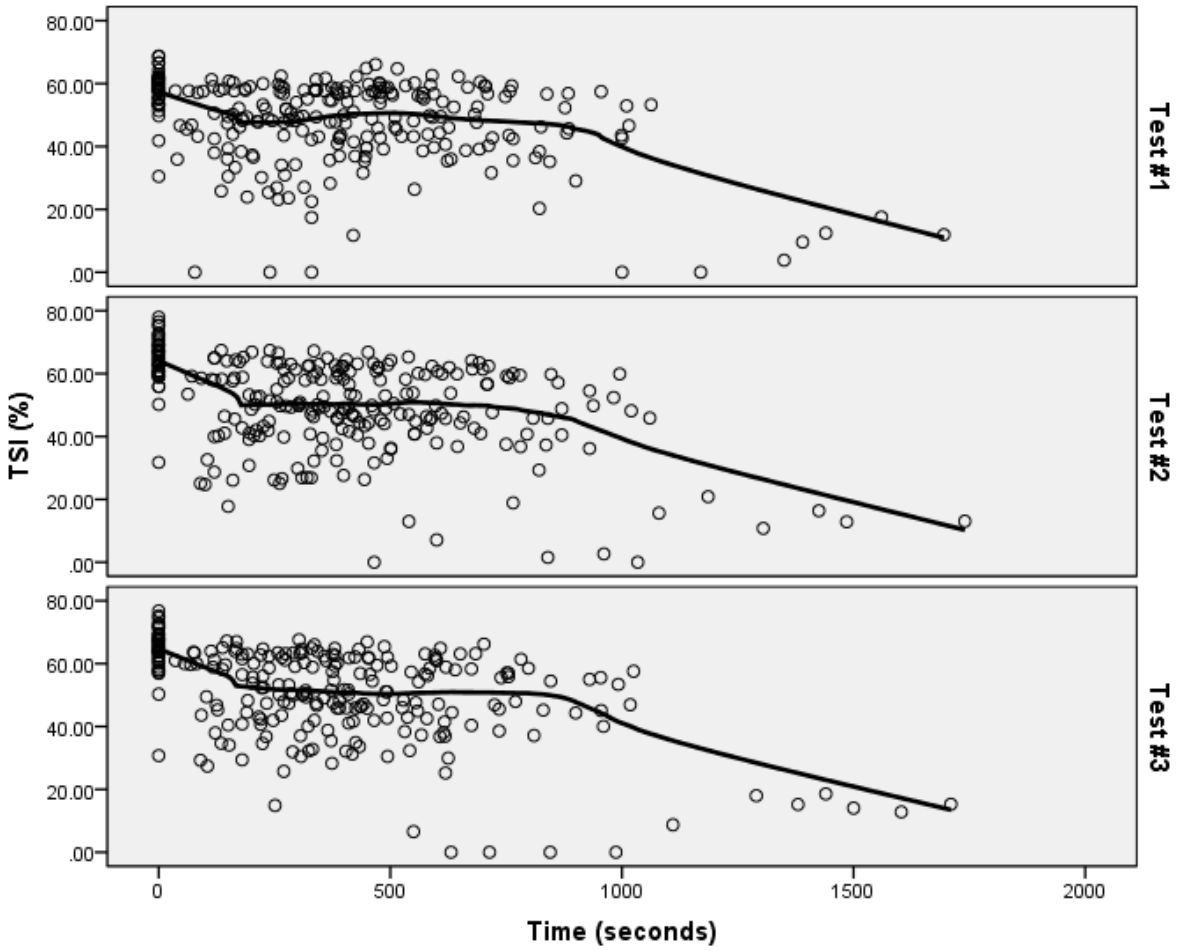
ID #	Gender	Age	ABI	BMI Category	Ratings	*M* TSI	(*SD*)	Min.	Max.
1	Male	55	0.65	Normal	30	17.12	(15.50)	00.00	61.12
2	Male	63	1.03	Overweight	18	42.50	(8.25)	36.19	62.41
3	Male	65	0.50	Obese	17	56.06	(6.68)	48.95	69.55
4	Male	68	0.30	Overweight	16	42.50	(5.92)	35.94	57.90
5	Female	79	0.41	Overweight	21	27.72	(3.90)	17.41	35.54
6	Male	62	0.63	Underweight	21	41.67	(6.35)	29.93	55.29
7	Male	81	0.64	Normal	18	45.31	(9.96)	32.34	66.99
8	Male	68	0.48	Normal	22	37.43	(10.17)	25.08	62.20
9	Male	77	0.60	Normal	17	37.67	(13.63)	25.39	68.71
10	Male	81	0.53	Obese	17	59.40	(1.87)	57.57	64.51
11	Male	58	1.05	Normal	17	60.14	(4.37)	49.76	64.87
12	Male	55	1.12	Normal	18	58.12	(4.63)	52.49	68.40
13	Male	73	1.15	Overweight	26	62.34	(3.47)	56.38	71.60
14	Male	62	0.91	Overweight	20	63.11	(3.76)	55.84	67.63
15	Male	58	0.94	Obese	18	54.30	(7.39)	40.28	68.99
16	Female	78	0.94	Overweight	24	59.76	(4.03)	56.50	71.51
17	Male	52	0.87	Overweight	20	49.39	(6.40)	44.34	65.39
18	Male	83	0.57	Overweight	17	61.59	(5.04)	52.29	72.93
19	Male	83	0.62	Overweight	12	48.71	(10.75)	32.13	69.07
20	Male	63	0.63	Normal	18	46.19	(8.86)	34.27	67.69
21	Male	65	1.15	Overweight	19	51.95	(6.72)	42.42	66.12
22	Male	79	0.90	Normal	20	50.86	(8.84)	31.58	68.85
23	Male	77	1.64	Obese	17	39.29	(10.83)	23.14	60.80
24	Male	68	0.68	Overweight	18	47.73	(10.74)	39.16	75.31
25	Male	64	0.66	Obese	18	52.42	(7.26)	44.81	70.47
26	Male	66	0.90	Overweight	18	54.88	(7.28)	48.83	75.26
27	Male	67	0.75	Obese	17	51.39	(7.72)	43.54	69.28
28	Male	49	0.94	Obese	19	59.88	(2.84)	56.96	66.89
29	Male	58	0.68	Normal	18	16.94	(23.36)	00.00	60.07
30	Male	72	0.46	Overweight	22	49.77	(5.11)	41.63	63.76
31	Male	68	1.27	Obese	21	62.03	(2.19)	58.41	66.54
32	Male	68	0.74	Overweight	20	49.78	(7.97)	39.55	71.76
33	Female	78	0.95	Overweight	19	59.20	(3.30)	52.58	64.79
34	Male	63	0.90	Overweight	18	40.82	(8.81)	29.05	60.02
35	Male	57	0.56	Normal	14	61.92	(2.92)	57.39	66.37
36	Male	79	1.04	Overweight	23	47.54	(9.65)	22.51	63.02
37	Female	75	0.64	Obese	20	62.56	(5.70)	55.12	77.95
38	Female	63	1.14	Obese	18	63.57	(2.71)	59.31	67.37
39	Male	59	1.06	Obese	18	62.57	(4.96)	56.67	74.58
40	Male	63	0.66	Overweight	18	50.11	(10.34)	40.72	76.74

Appendix Q
Individual Recovery Phase Summary

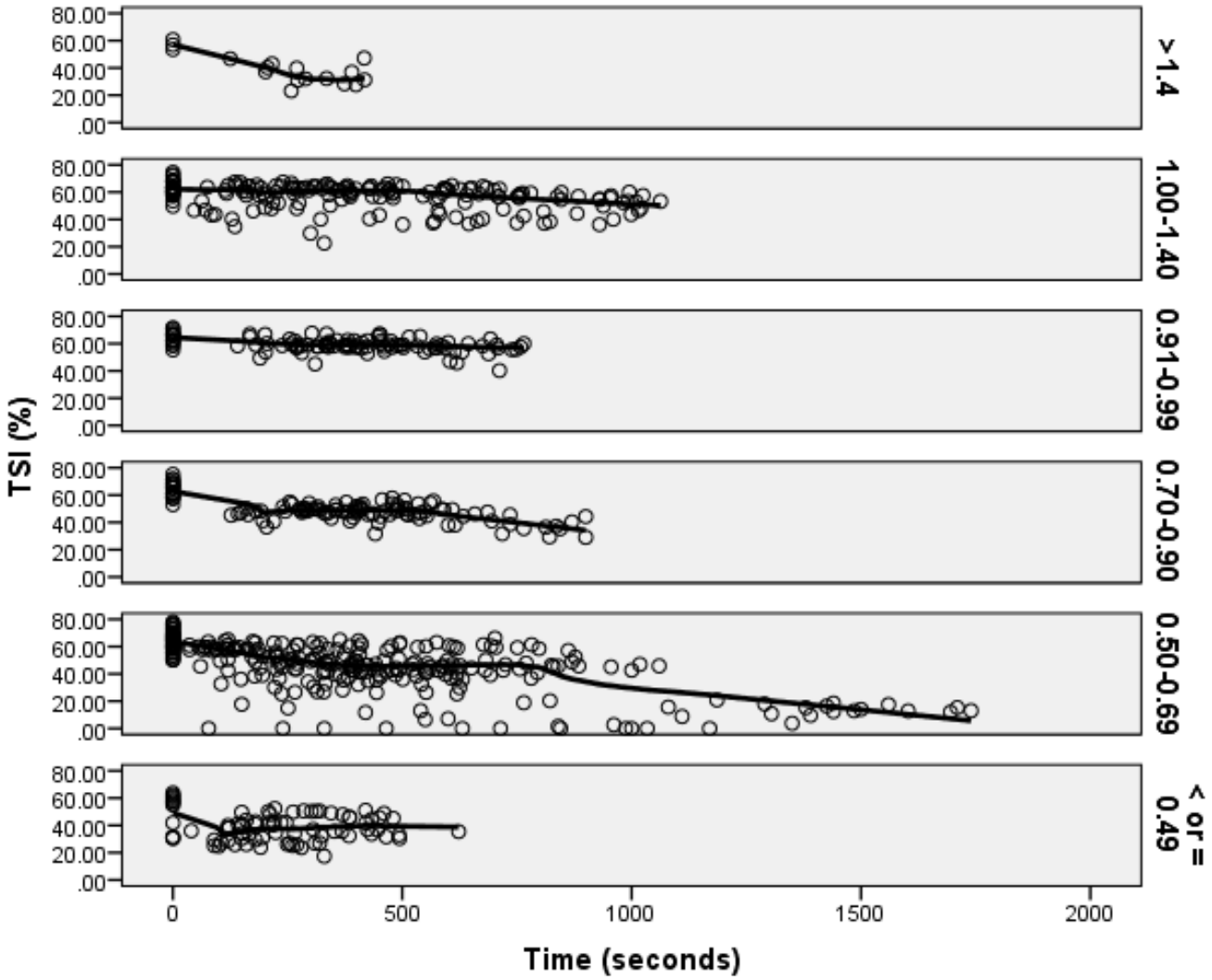
ID #	Gender	Age	ABI	BMI Category	Ratings	*M* TSI	(*SD*)	Min.	Max.
1	Male	55	0.65	Normal	16	16.10	(20.33)	00.00	51.37
2	Male	63	1.03	Overweight	11	67.57	(3.85)	59.17	71.45
3	Male	65	0.50	Obese	12	66.60	(6.10)	56.69	74.11
4	Male	68	0.30	Overweight	14	45.91	(4.15)	37.85	53.98
5	Female	79	0.41	Overweight	15	31.29	(14.39)	10.18	52.45
6	Male	62	0.63	Underweight	15	35.25	(6.34)	15.81	44.15
7	Male	81	0.64	Normal	15	52.31	(10.02)	37.37	67.01
8	Male	68	0.48	Normal	16	44.47	(11.04)	32.81	63.84
9	Male	77	0.60	Normal	10	43.65	(10.20)	33.25	62.91
10	Male	81	0.53	Obese	13	57.55	(1.77)	55.13	60.07
11	Male	58	1.05	Normal	11	61.95	(2.35)	57.25	66.88
12	Male	55	1.12	Normal	12	63.35	(3.94)	54.81	68.40
13	Male	73	1.15	Overweight	16	73.55	(3.22)	68.11	77.96
14	Male	62	0.91	Overweight	12	65.97	(4.88)	51.85	69.78
15	Male	58	0.94	Obese	16	69.92	(9.25)	42.74	79.26
16	Female	78	0.94	Overweight	8	67.54	(3.95)	61.19	72.66
17	Male	52	0.87	Overweight	12	65.94	(4.37)	57.68	70.31
18	Male	83	0.57	Overweight	16	69.10	(5.15)	59.56	74.77
19	Male	83	0.62	Overweight	7	41.93	(16.13)	28.34	70.50
20	Male	63	0.63	Normal	15	50.57	(7.18)	39.13	60.03
21	Male	65	1.15	Overweight	11	57.48	(3.73)	50.37	63.28
22	Male	79	0.90	Normal	13	65.73	(10.54)	44.36	75.89
23	Male	77	1.64	Obese	7	45.23	(9.15)	35.99	58.03
24	Male	68	0.68	Overweight	16	67.23	(14.49)	39.92	82.70
25	Male	64	0.66	Obese	13	53.47	(3.60)	48.84	59.53
26	Male	66	0.90	Overweight	14	70.52	(8.65)	52.11	77.42
27	Male	67	0.75	Obese	7	64.34	(7.21)	52.55	70.44
28	Male	49	0.94	Obese	12	65.40	(5.59)	56.99	71.24
29	Male	58	0.68	Normal	12	38.68	(23.43)	00.00	71.16
30	Male	72	0.46	Overweight	12	56.67	(7.34)	43.74	63.66
31	Male	68	1.27	Obese	11	64.85	(2.04)	61.52	67.49
32	Male	68	0.74	Overweight	15	57.03	(15.69)	36.62	78.77
33	Female	78	0.95	Overweight	12	64.32	(4.27)	52.96	67.77
34	Male	63	0.90	Overweight	12	77.43	(9.43)	49.46	88.49
35	Male	57	0.56	Normal	13	71.28	(3.60)	64.68	77.07
36	Male	79	1.04	Overweight	8	56.22	(14.03)	39.80	78.87
37	Female	75	0.64	Obese	13	70.07	(8.54)	56.43	80.56
38	Female	63	1.14	Obese	15	70.88	(3.39)	64.78	75.98
39	Male	59	1.06	Obese	9	71.48	(3.67)	65.74	76.48
40	Male	63	0.66	Overweight	12	55.38	(7.39)	46.50	71.73

Appendix R
Grouped Exercise Trajectories

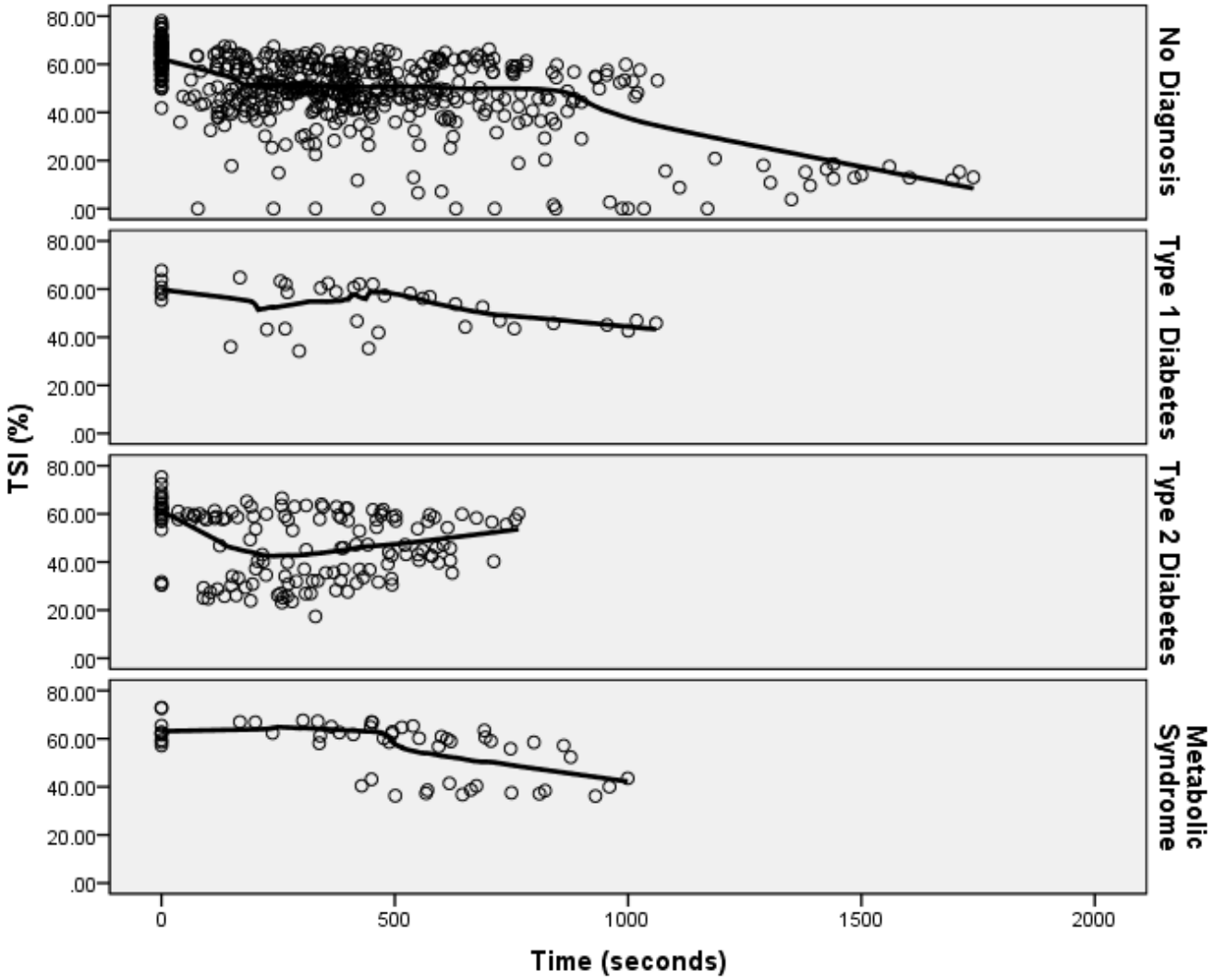
R1. Treadmill Test



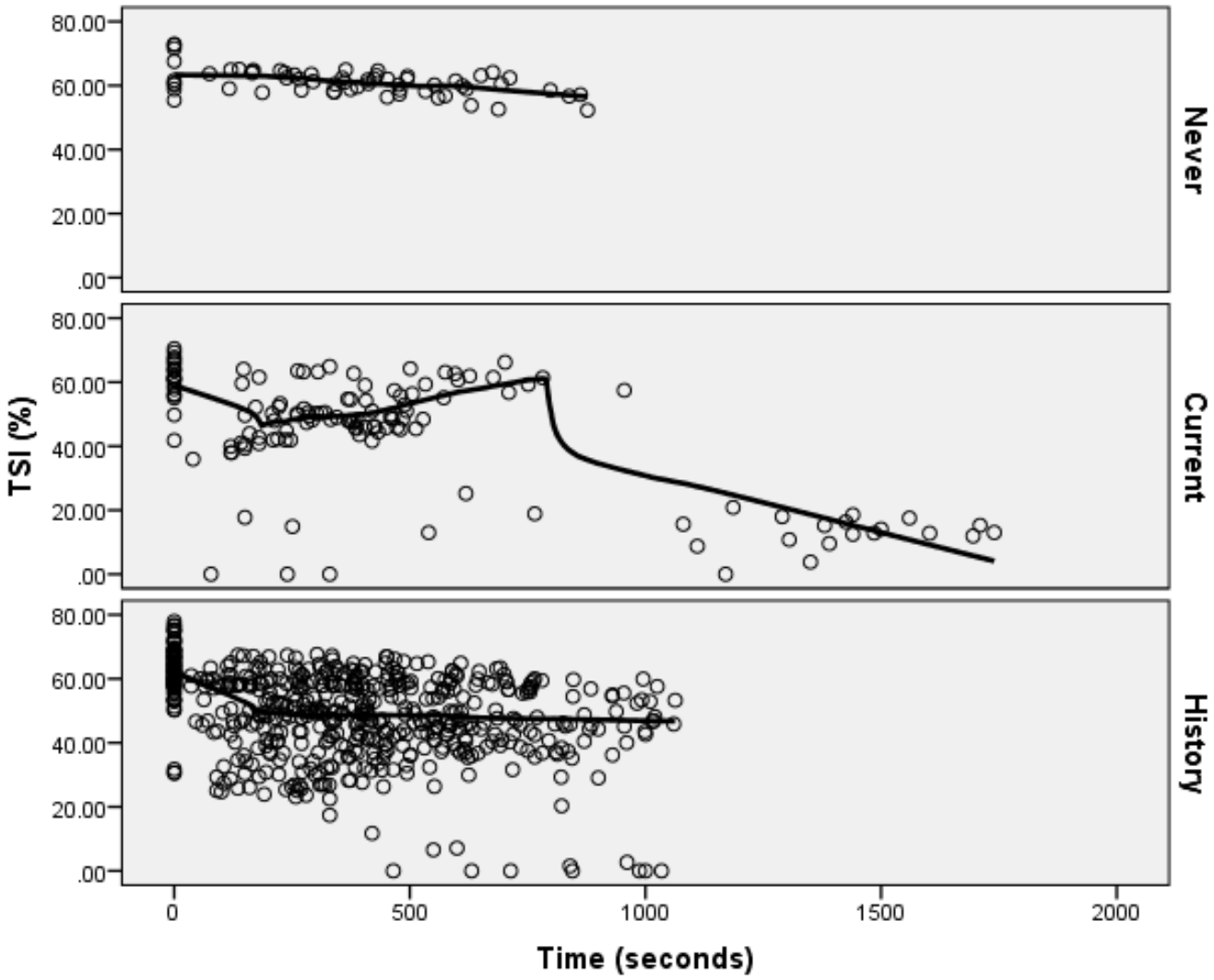
R2. ABI


TSI (%)
80.00
60.00
40.00
20.00
.00
>1.4
1.00-1.40
0.91-0.99
0.70-0.90
0.50-0.69
< or = 0.49
0
500
1000
1500
2000
Time (seconds)

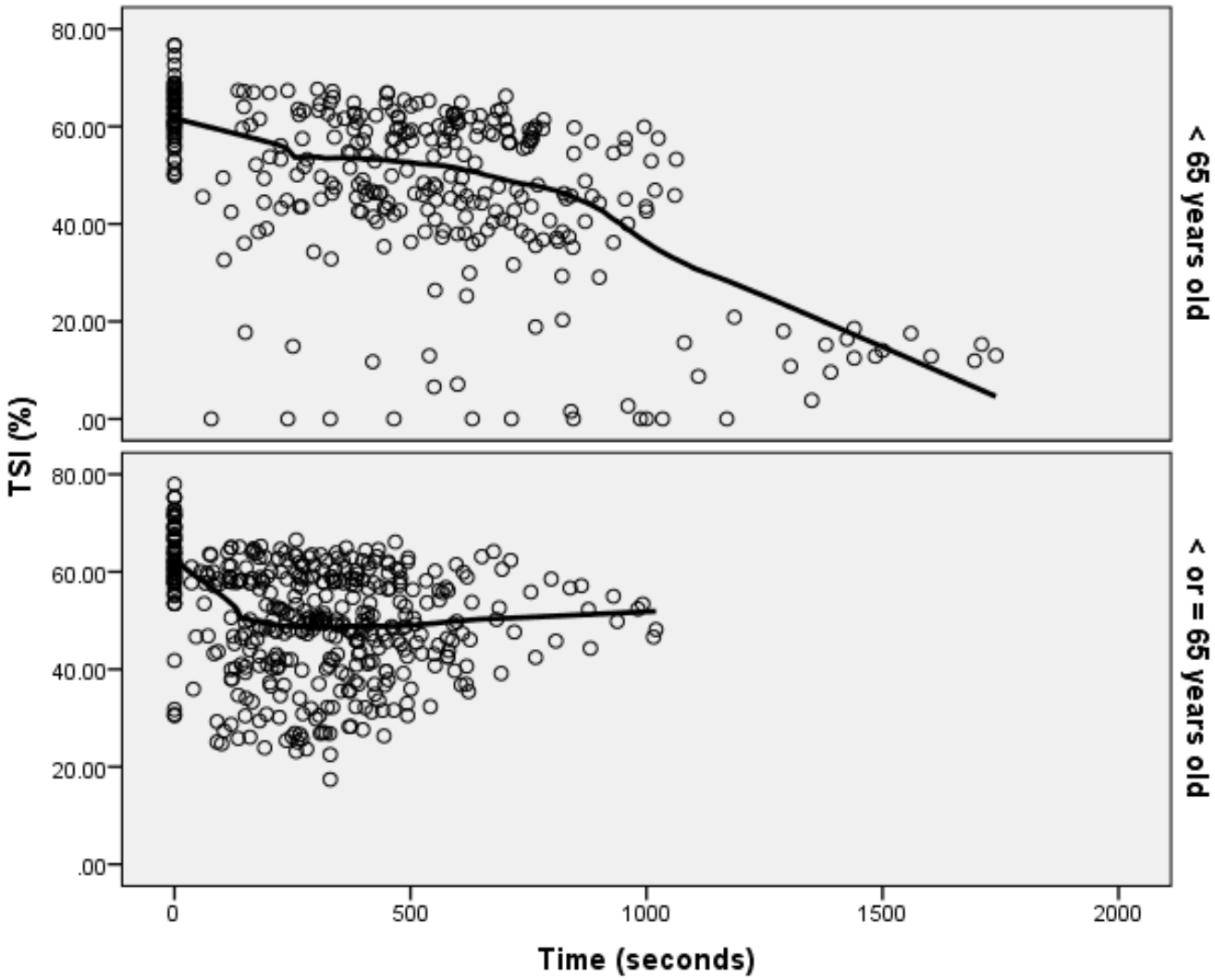
R3. Diabetes


TSI (%)
80.00
60.00
40.00
20.00
.00
No Diagnosis
Type 1 Diabetes
Type 2 Diabetes
Metabolic Syndrome
0
500
1000
1500
2000
Time (seconds)

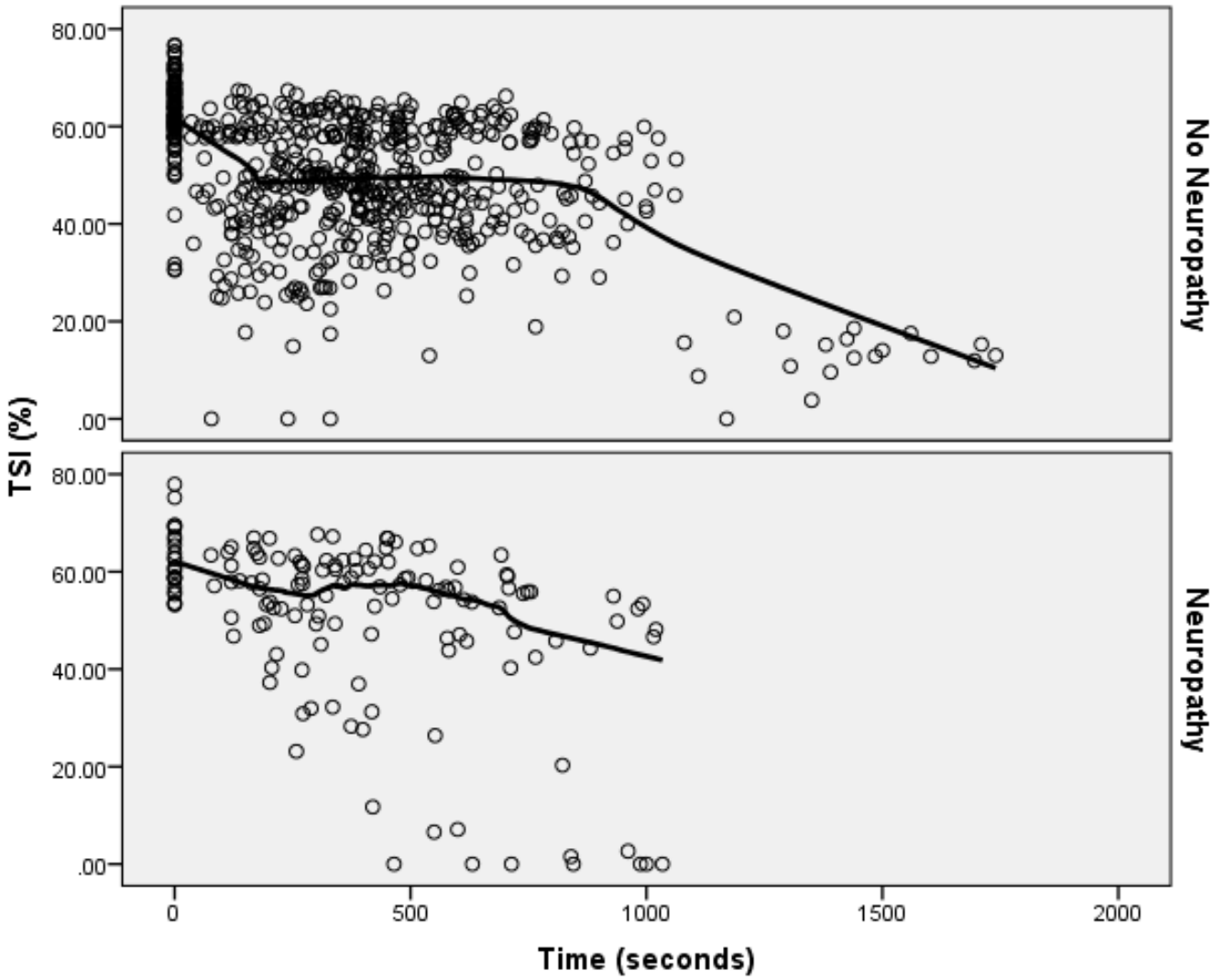
R4. Smoking Status



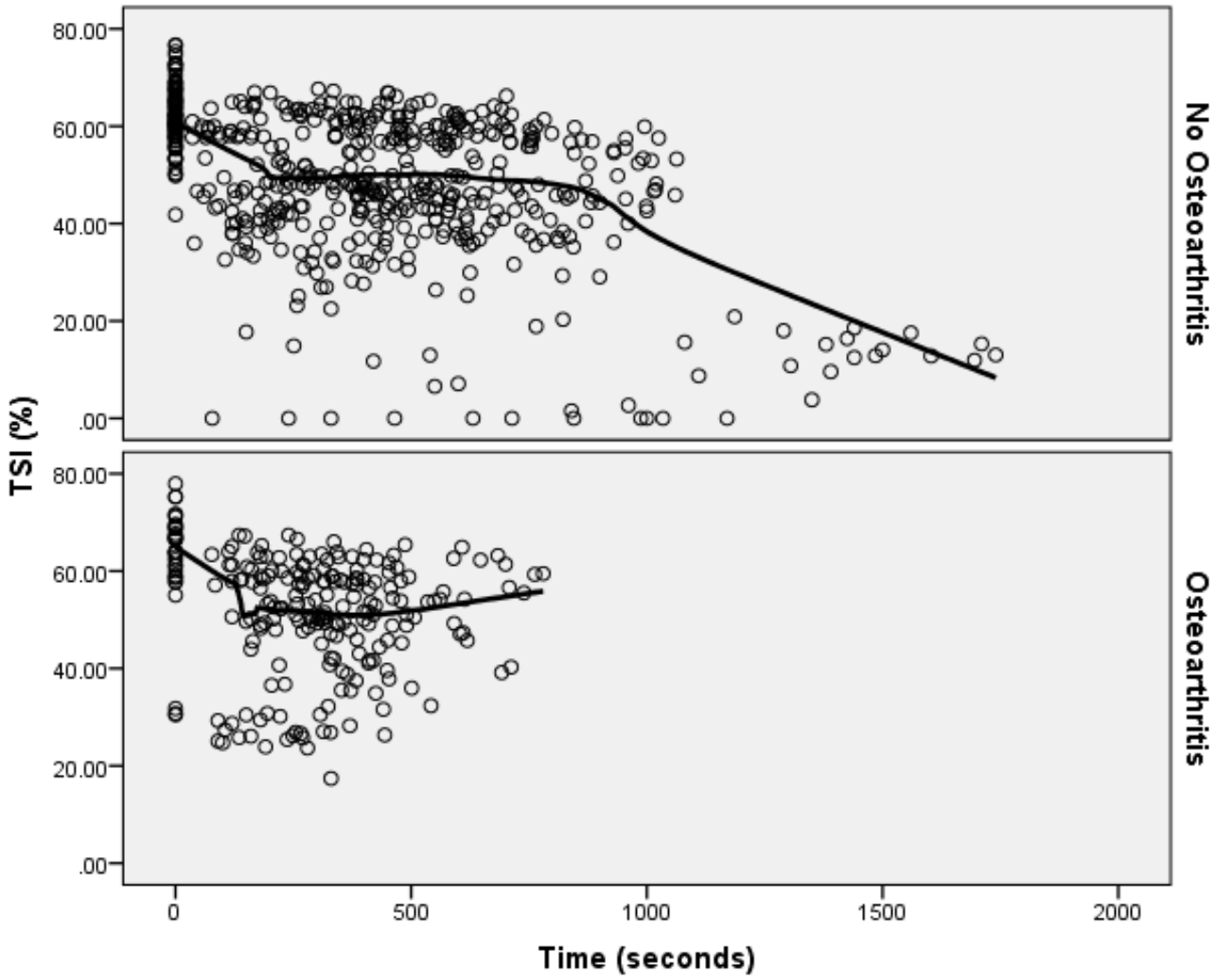
R5. Age


80.00
60.00
40.00
20.00
.00
TSI (%)
< 65 years old
< or = 65 years old
0
500
1000
1500
2000
Time (seconds)

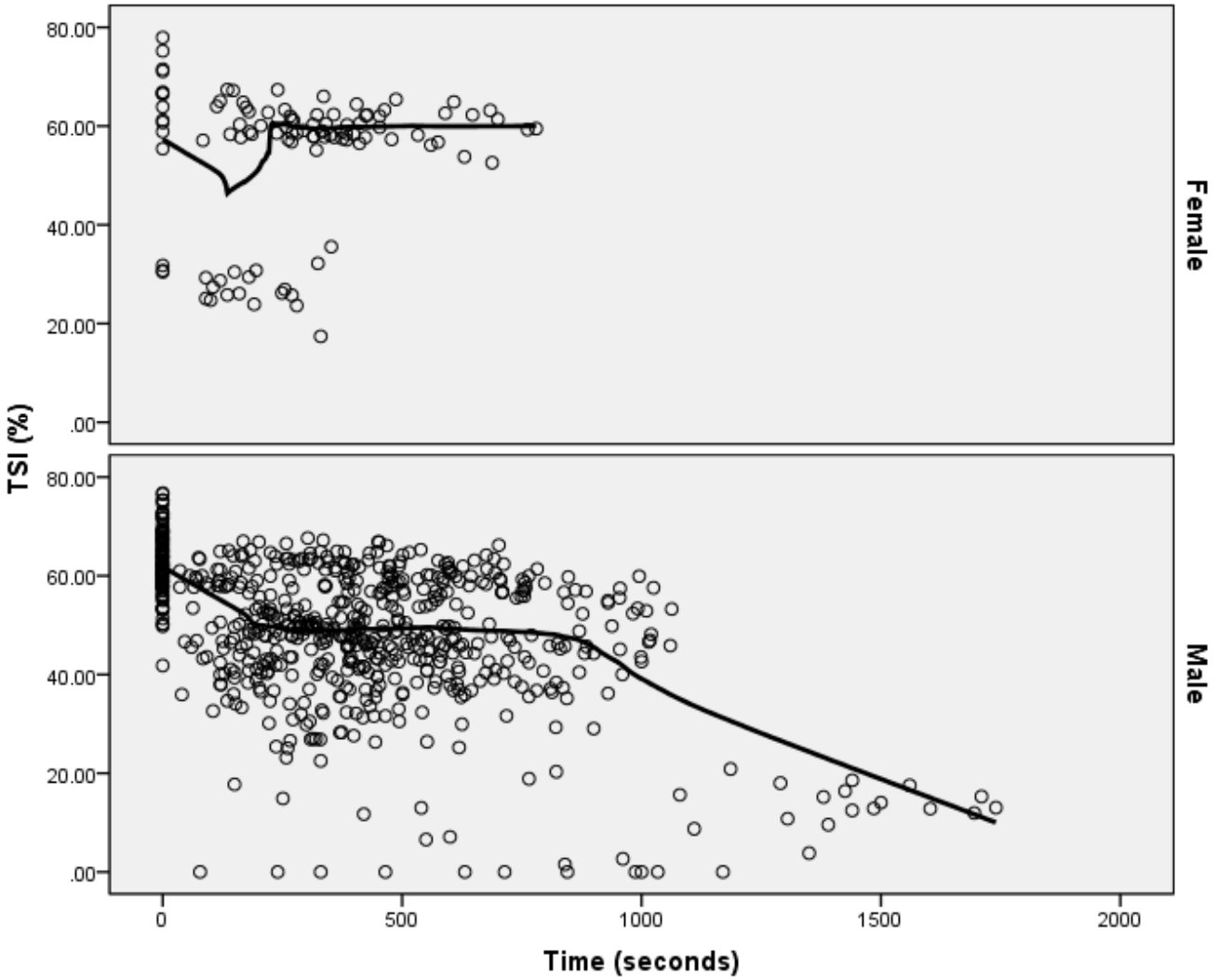
R6. Neuropathy



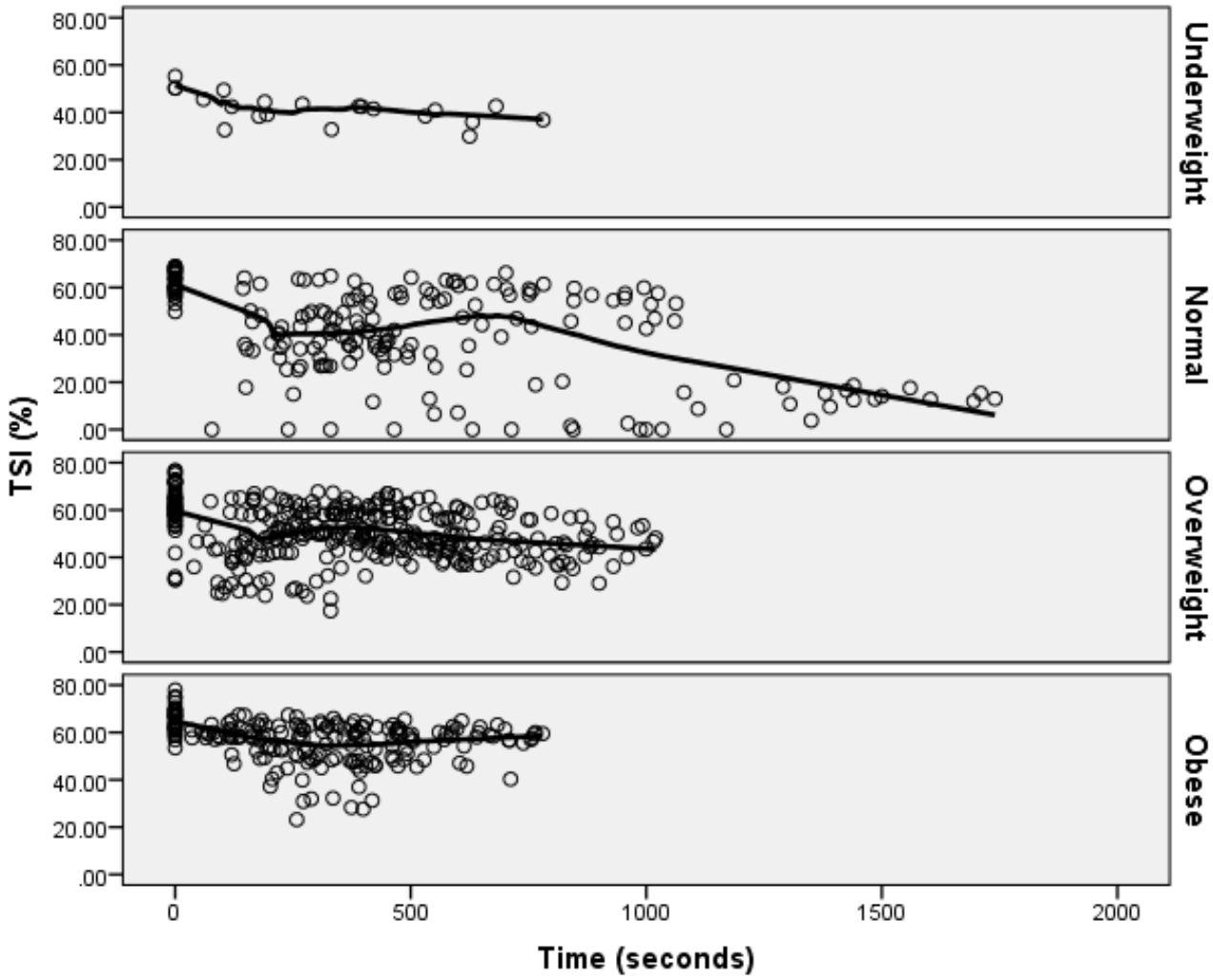
R7. Osteoarthritis



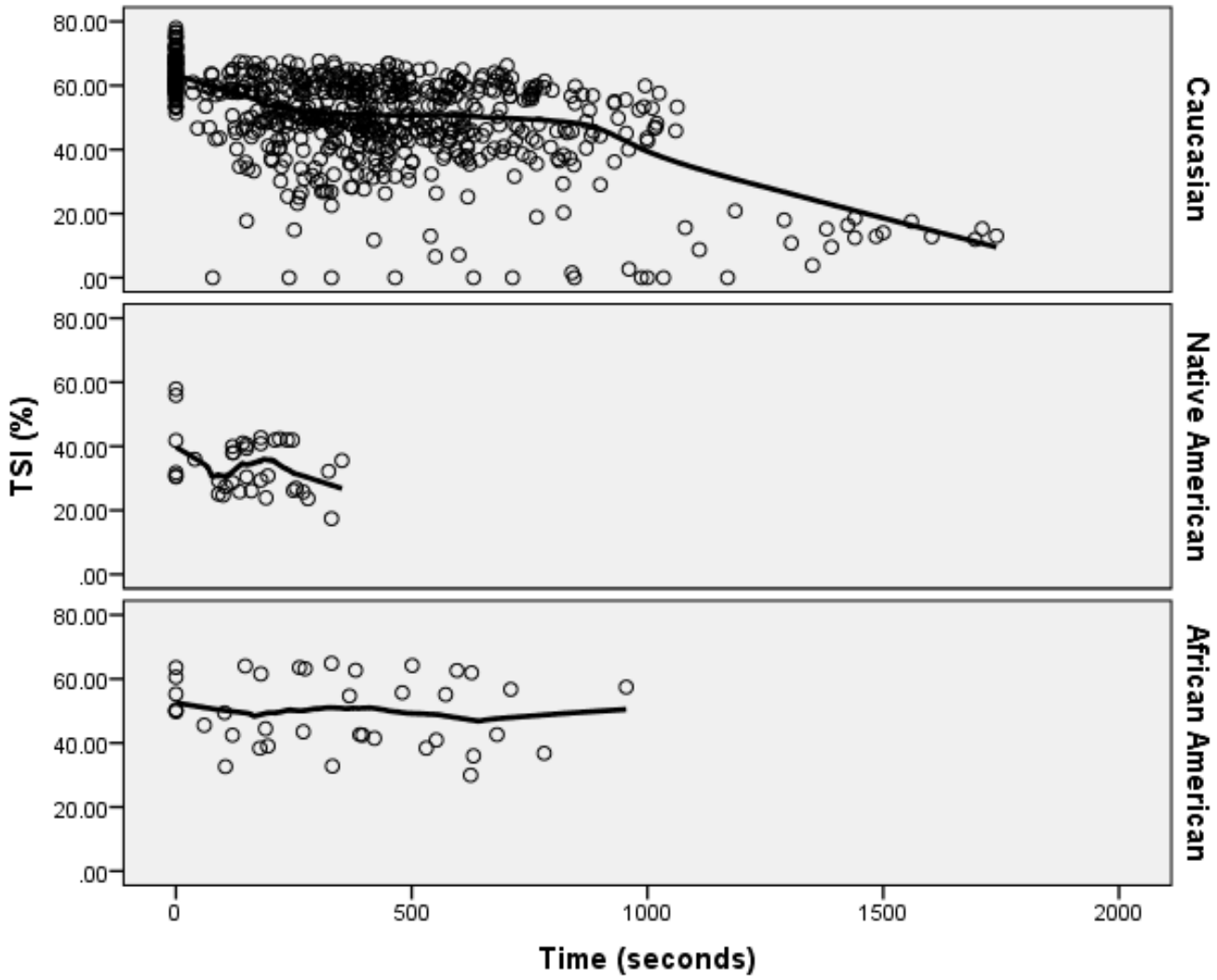
R8. Gender


80.00
60.00
40.00
20.00
.00
Female
TSI (%)
80.00
60.00
40.00
20.00
.00
Male
0
500
1000
1500
2000
Time (seconds)

R9. Body Mass Index (BMI)

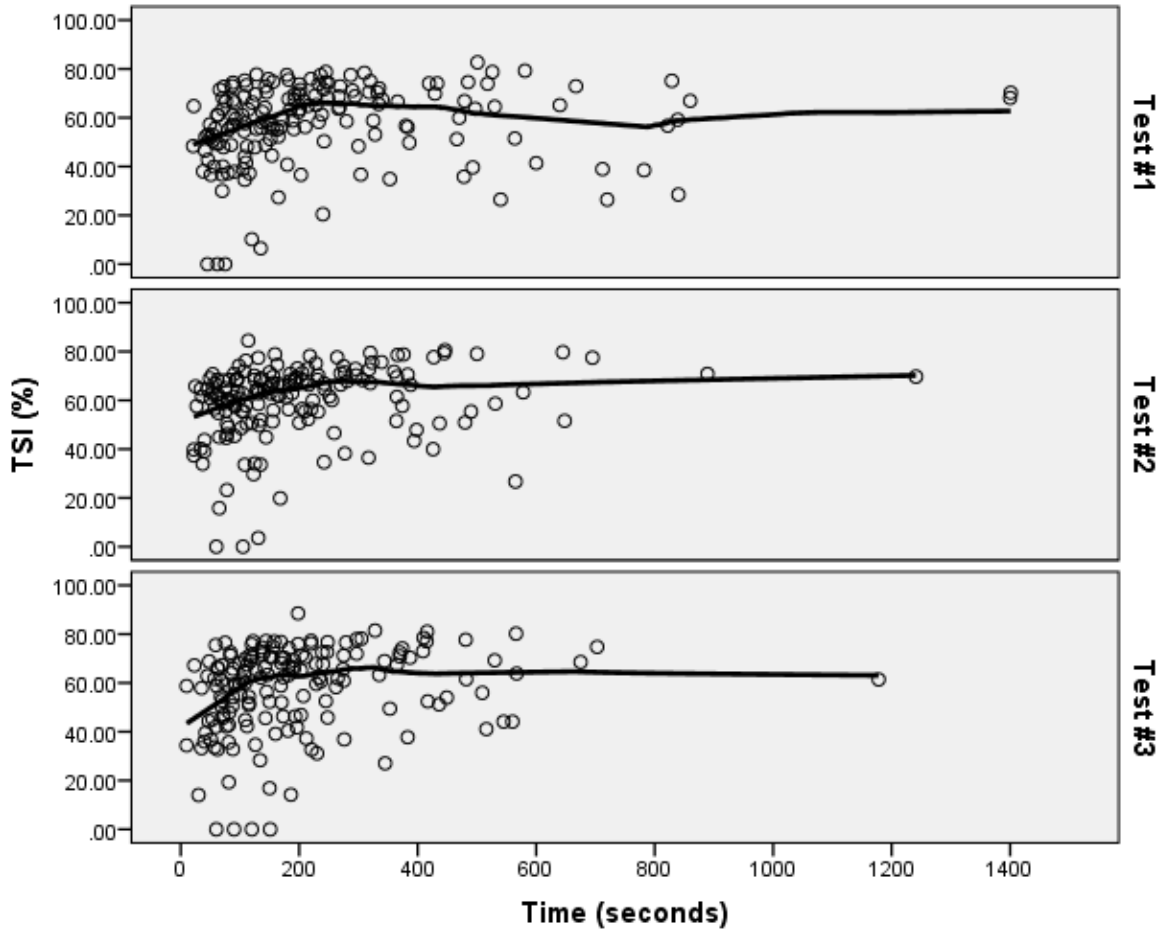


R10. Ethnicity

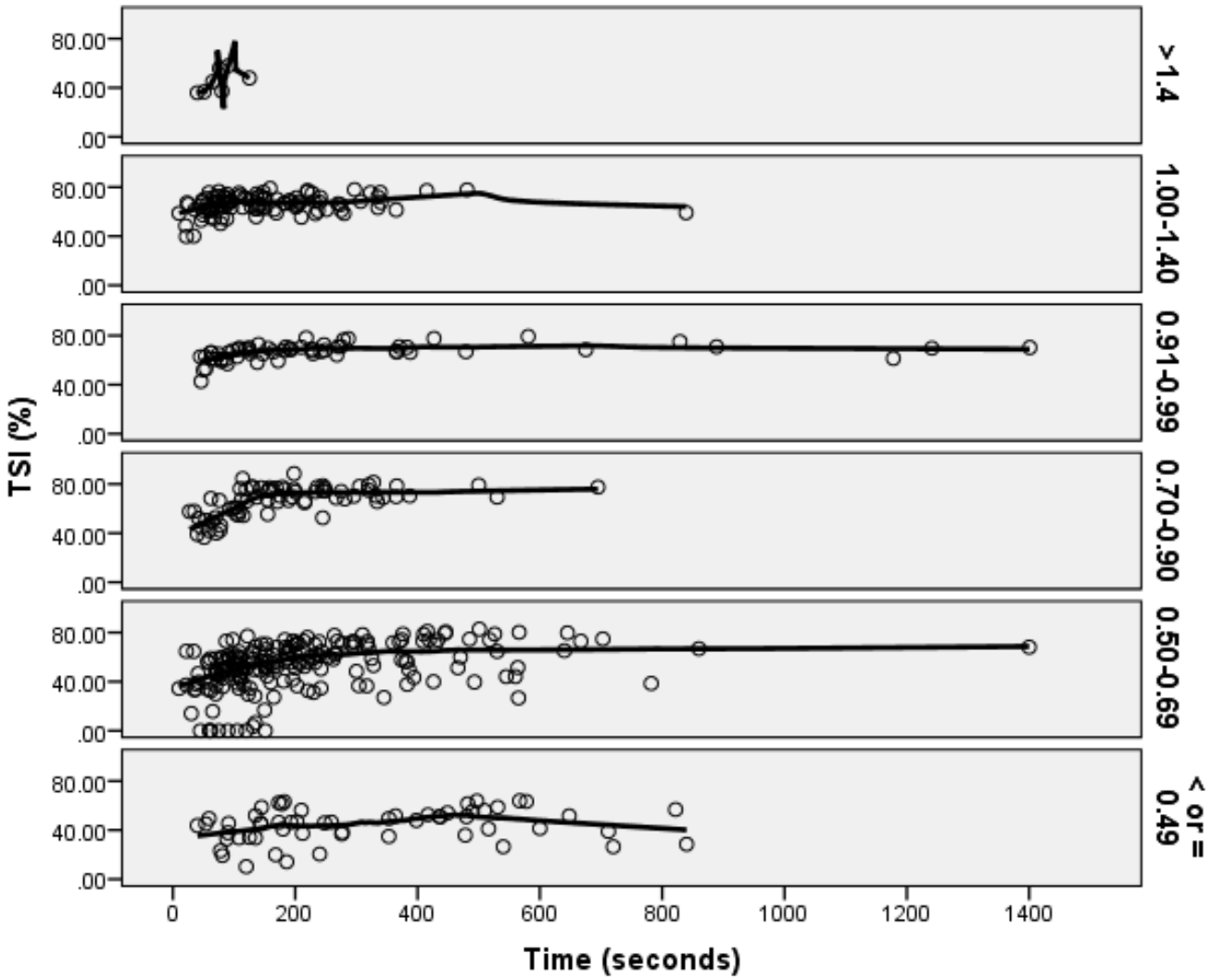


Appendix S
Grouped Recovery Trajectories

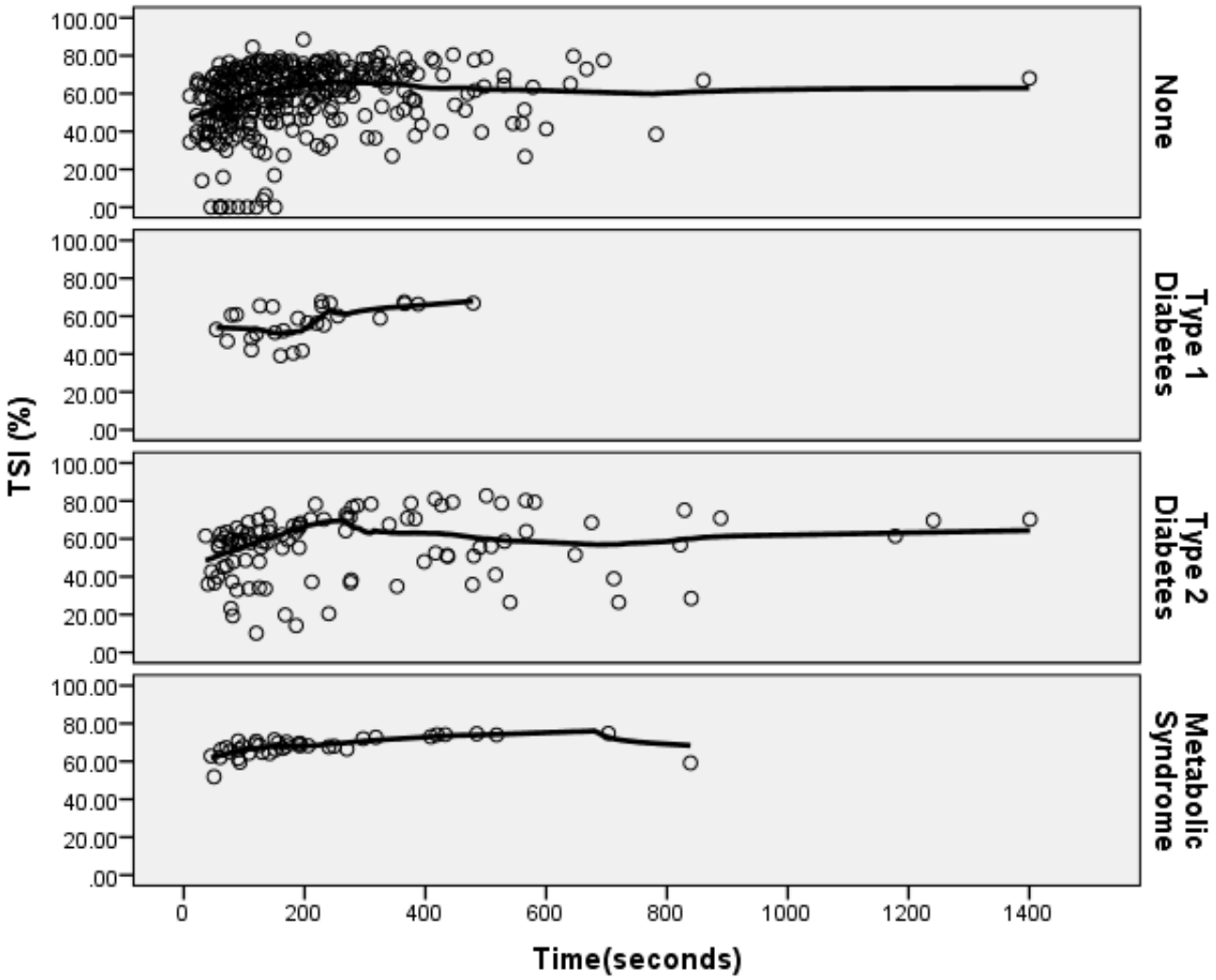
S1. Treadmill Test



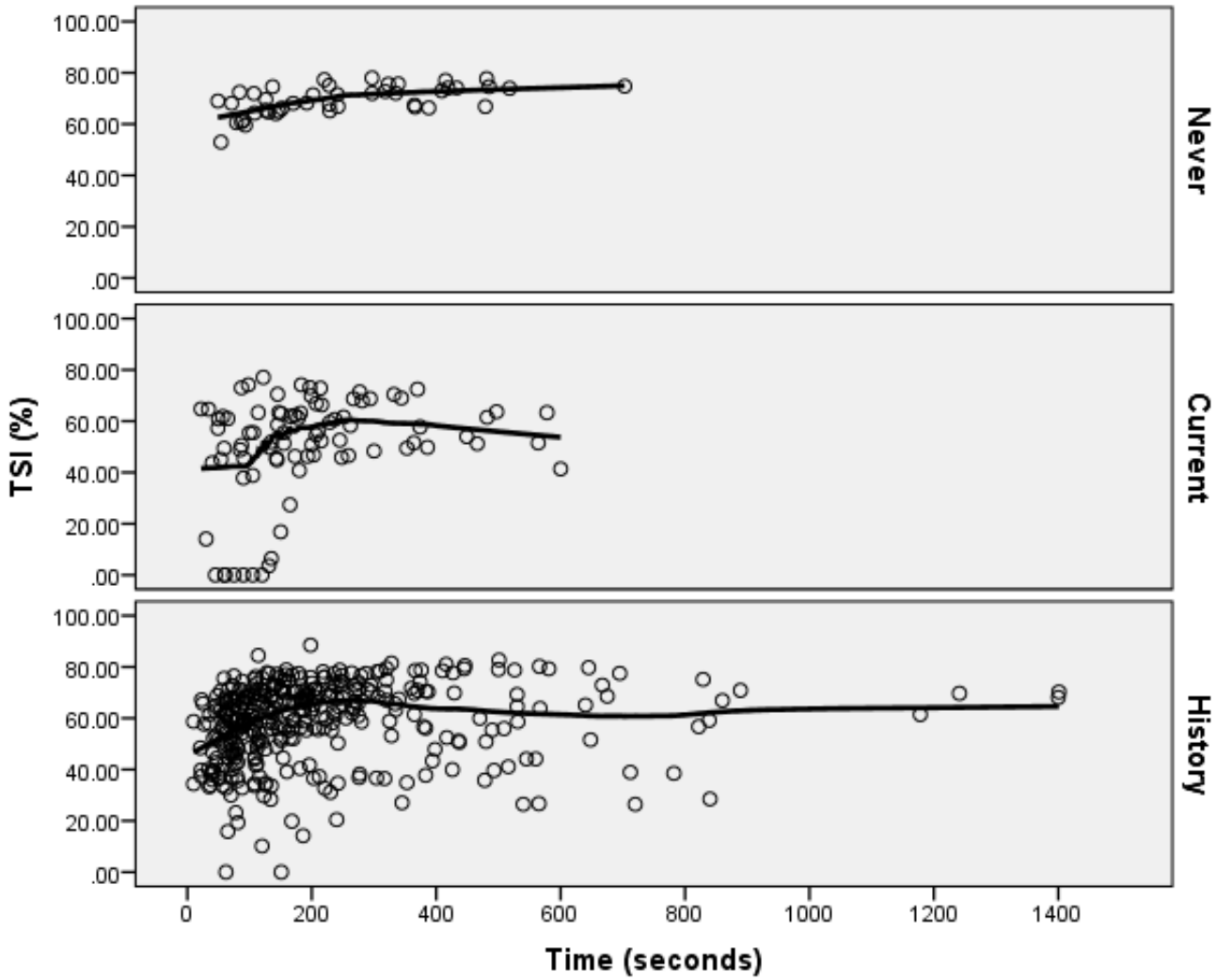
S2. ABI


TSI (%)
80.00
40.00
.00
0
200
400
600
800
1000
1200
1400
Time (seconds)
>1.4
1.00-1.40
0.91-0.99
0.70-0.90
0.50-0.69
< or = 0.49

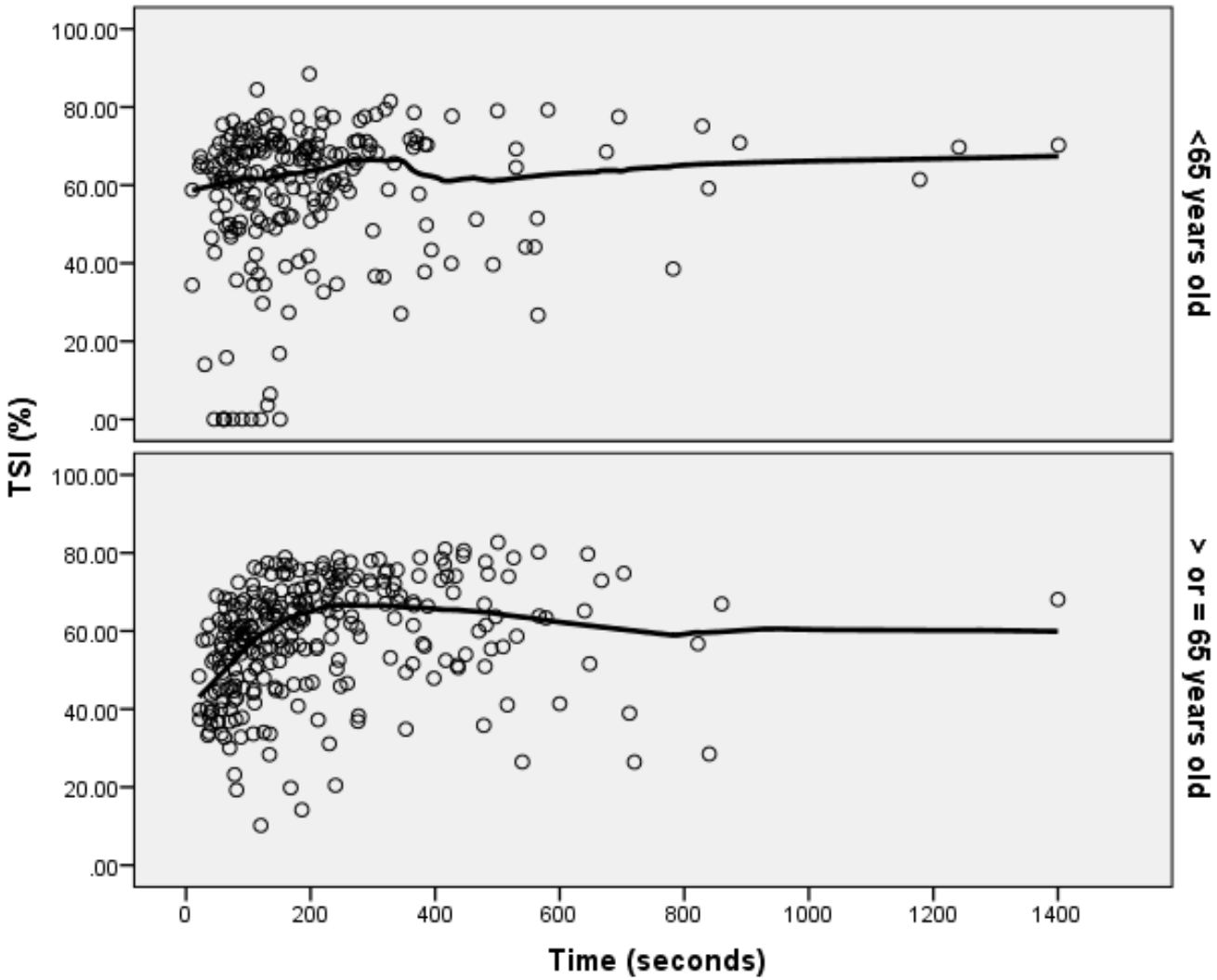
S3. Diabetes


TSI (%)
100.00
80.00
60.00
40.00
20.00
.00
None
Type 1 Diabetes
Type 2 Diabetes
Metabolic Syndrome
0
200
400
600
800
1000
1200
1400
Time(seconds)

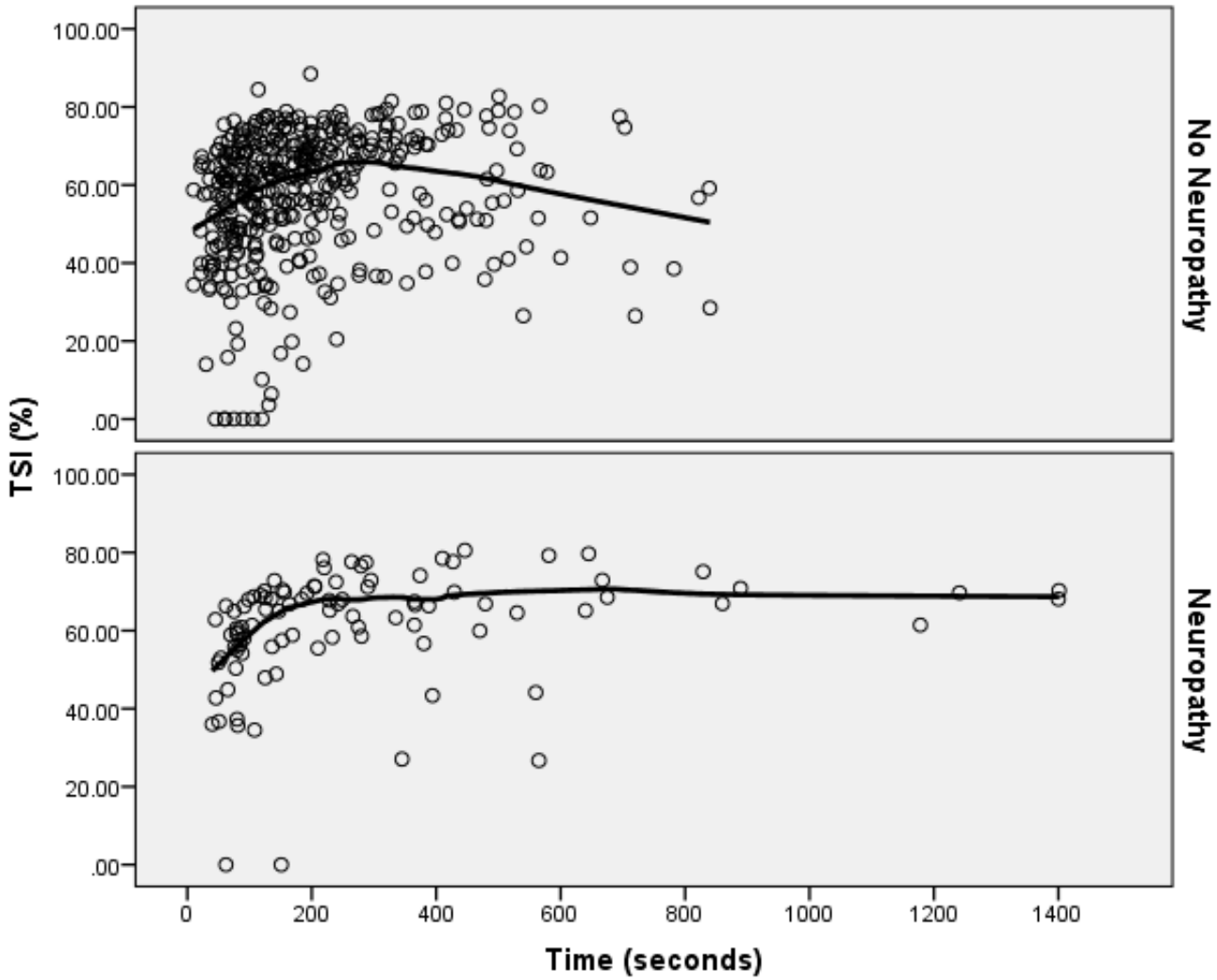
S4. Smoking Status



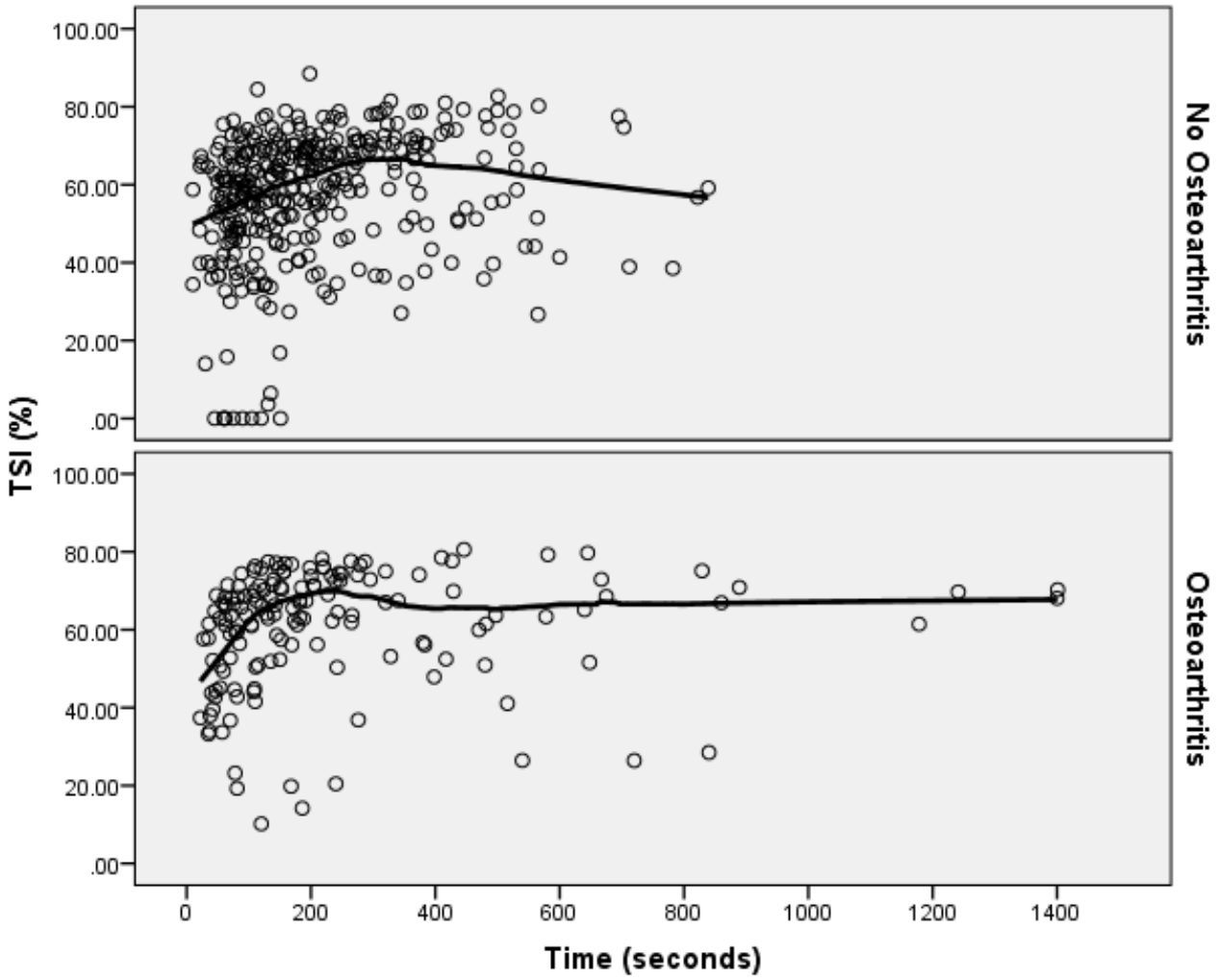
S5. Age


TSI (%)
100.00
80.00
60.00
40.00
20.00
.00
<65 years old
> or = 65 years old
0
200
400
600
800
1000
1200
1400
Time (seconds)

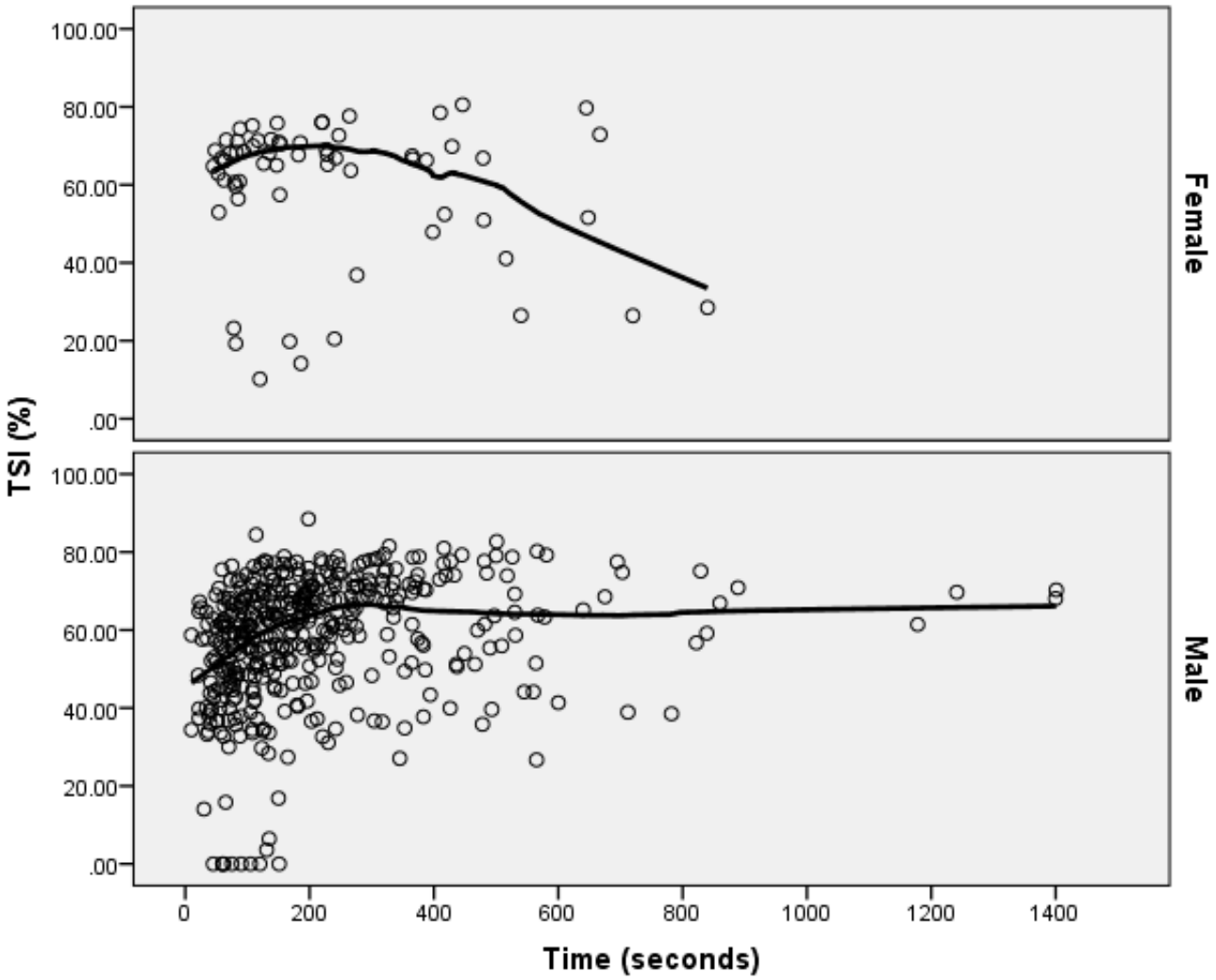
S6. Neuropathy



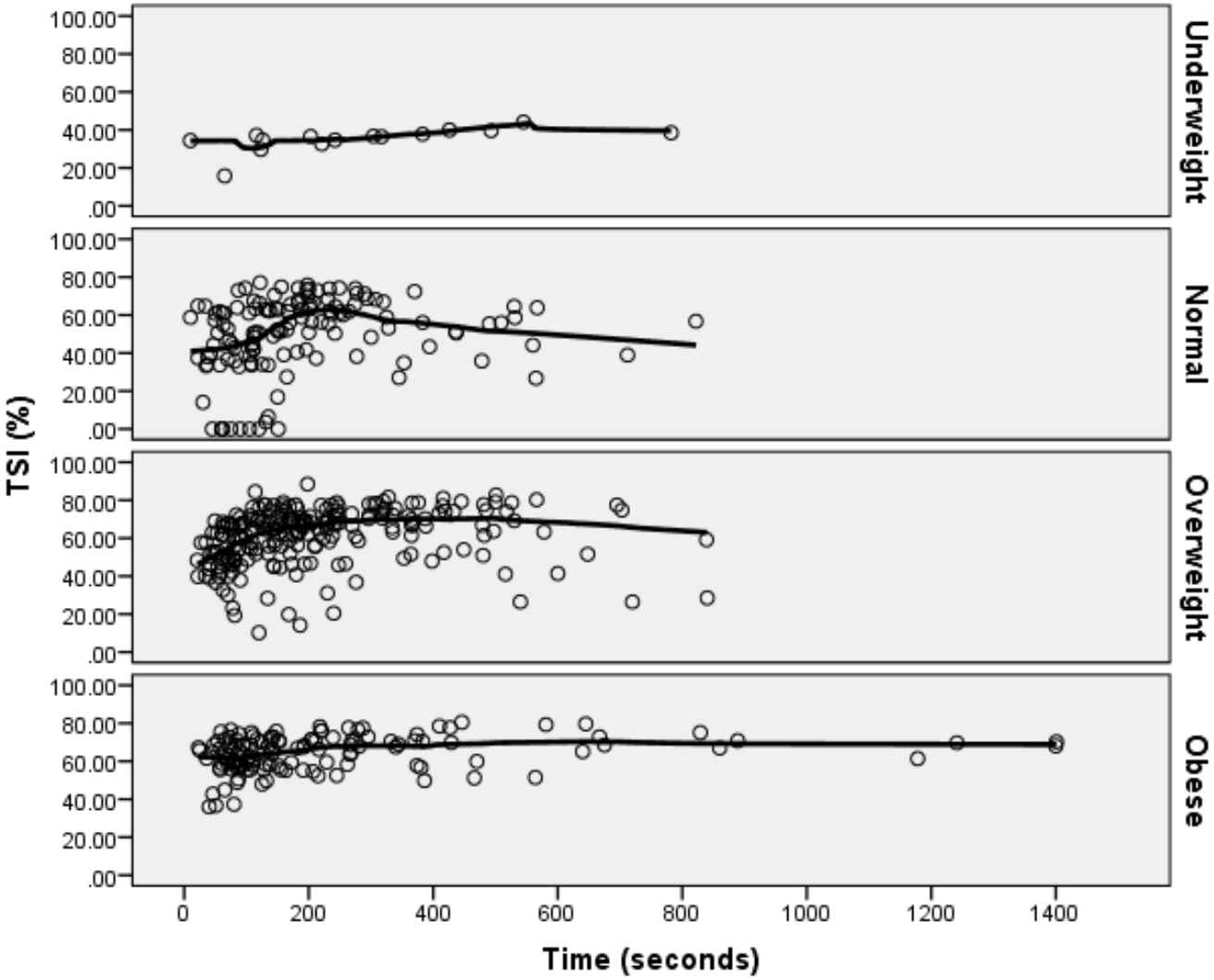
S7. Osteoarthritis



S8. Gender


100.00
80.00
60.00
40.00
20.00
.00
Female
Male
TSI (%)
0
200
400
600
800
1000
1200
1400
Time (seconds)

S9. Body Mass Index (BMI)



S10. Ethnicity