AUSTRIAN
MARSHALL PLAN FOUNDATION
VIENNA | AUSTRIA

Motor &Cognitive Performance as a Predictor of PAD Vascular Surgical Outcomes

Academic Research Assignment by order of the Austrian Marshall Plan Foundation

Dipl.-Ing. Simon Höglinger, B.Sc.

Dipl.-Ing. Vanessa Hinko, B.Sc.

January 2017

Carried out at

Interdisciplinary **C**onsortium on **A**dvanced **M**otion **P**erformance (iCAMP)

Michael E. DeBakey Department of Surgery

Baylor College of Medicine

Houston, TX

Supervised by

FH-Prof. PD Dr. Thomas Haslwanter

Bijan Najafi, Ph.D., MSc.

Acknowledgement

by Simon Höglinger

We want to thank the Interdisciplinary Consortium of Advanced Motion Performance under the lead of Dr. Najafi and the Baylor College of Medicine for giving us the opportunity to join their surgical research team and to gain experience in biomedical research. Also we want to thank our team members for their helpful inputs and for their agreement to continue working on the study.

Additionally we want to thank Dr. Montero, Dr. Mills, Dr. West and Dr. Chung from the division of vascular surgery at the Baylor College of Medicine for their input and contribution to this project.

Also we want to thank our supervisor from the University of applied Sciences Upper Austria for his help and support to make this research stay possible.

Especially the authors wish to thank the Austrian Marshall Plan Foundation for the financial support. The MP Scholarship enabled us to take part in research project in the United States of America.

Content

Abstract

by Simon Höglinger

Background: Nowadays preoperative risk assessments lack in the possibility to capture the global health status of patients. Frailty is a concept, based on the physical reserve of a patient to describe his/her ability to withstand stressors. Several studies in the past have shown that frailty can be used as predictor of surgical outcomes in different patient groups. The evaluation of frailty may also be a highly important asset for vascular surgeons in characterizing the health status of patients and include this knowledge in their preoperative decision making process. The Upper Extremity frailty test is a very fast 20 seconds task to measure frailty. The usage of this highly innovative test might overcome well known issues such as time and usability problems and allows easy frailty measurements in many different patient populations such as PAD patients. **Methods:** Frailty-, vascular- and health status assessment were performed at baseline in twenty-six adults (mean age:64) undergoing arterial re-vascularization using the Upper Extremity Frailty-Test, Rutherford and WIFi classification, measurements of the subjects skin perfusion pressure as well as the SF-12 health survey and standardized questions regarding quality of life. Patients undergoing both, endovascular and open procedures were investigated. All participants were followed up for two weeks repeating the assessments described above and by the usage of a follow up health outcome questionnaire. The measured health outcomes included (1) death and major adverse events, (2) Re-interventions and re-admission (including minor and major amputations), (3) changes in the activity level and (4) residential changes. **Results:** Based on the Upper Extremity Frailty Index, 14 (54%) of the participants were frail and 10 (38%) non-frail. Frailty shows a significant relation to adverse events ($p=0.006$) and the frailty score is nearly doubled in patients with adverse events ($p=0.002$). Further significant difference between frail and non-frail subjects were found for the SF-12 mental component summary score ($p=0.010$).

Conclusion: The study demonstrated that preoperative measured frailty score as well as SF-12 health survey are significant predictors for postoperative adverse events in vascular surgical patients undergoing arterial revascularization.

1 Introduction

by Vanessa Hinko

Preoperative risk assessment is an important factor for the decision making process of surgeons. If postoperative complications occur, this causes increased health care costs, length of hospital stay and patient suffering. They can lead to a cascade of events resulting in disability of the patient, loss of independency, reduction of quality of life and higher mortality. [1, 2]
Currently preoperative risk evaluation strategies lack in the ability to capture the global health status of a patient. Historically it is based on the personal clinical experience of the surgeon. Nowadays different scoring systems are used to assist this subjective approach. Commonly used predictors of postoperative complications, mostly used in older adults, asses only single end-organ, organ-specific physiologic compromise or are subjective measures. Examples for those are the American Society of Anesthesiology (ASA) score or the Lee and Eagle criteria, which accounts for cardiac function only. Though these scoring systems are widely used there is a paucity of tools for accurately predict operative risk and postoperative outcomes. [1]
Age has been consistently associated with adverse outcomes in surgery, but age alone as a predictive metric is insufficient to characterize surgical outcomes in populations with numerous comorbidities and heterogeneity among health statuses such as the peripheral arterial disease (PAD) population [3, 4].

An evaluation of frailty, however, may be a highly important asset to vascular surgeons in characterizing the health status of their patients. Frailty is a concept most commonly referred to older adults (older than 65 years), describing the patients' ability to withstand stressors. It represents a state of decline in overall function and physiologic reserve. It is also a metric that attempts to evaluate susceptibility to adverse outcomes beyond traditional constraints of age or disability. By definition, frail individuals are at high risk for poor health outcomes. [5, 6]

Several studies have shown that frailty could be used to predict adverse events and outcomes after surgery. Robinson et al. investigated two hundred one subjects and found a correlation between postoperative complications after colorectal and cardiac operations and preoperative diagnosed frailty (nonfrail:21%, prefrail:40%, frail58%; P=0.016) [6]. They also found, that frail individuals had longer hospital stays and higher thirty-day readmission rates. Saxton et al. evaluated two hundred and twenty-six patients undergoing general surgery and found a higher

median preoperative frailty index (FI) for those patients having postoperative complications ($p=0.007$). They showed that the operation complexity, FI and the role-emotional domain were associated with and increased risk of postoperative complications. They also conclude that the evaluation of an functional status by the frailty index and the SF-36 health survey may help identifying patients at higher risk of postoperative complications [2]. Similar results could be shown by Makary et al., which studied 594 subjects undergoing elective surgery over a period of one year.

In 2015 Toosizadeh and colleagues introduced a new innovative approach to identify frailty, called Upper Extremity Frailty Meter. They invented a wearable sensor based method which allows identifying frailty with a short 20 seconds upper extremity exercise. The method uses a so called Upper Extremity Frailty (UEF) Index as a measure of frailty. This index is based on speed of elbow flexion, power of movement and speed variation. In 2016 Toosizadeh et al. showed that this UEF index was a significant predictor of several medical related outcome measures except hospital length of stay ($p<0.010$) in older adults hospitalized for ground-level falls [7].
Nevertheless frailty as a predictor of adverse events and health outcomes is only studied for mostly generalized surgical patient populations. There is still a need to further investigate specialized patient populations such as patients undergoing vascular surgery. In the past, standardized frailty assessments were hardly applicable to patients diagnosed with PAD since most of these tests require gait assessments and are time consuming. The highly innovative UEF test overcome these problems and allows easy frailty measurements in many different patient populations such as PAD patients.

1.1 Aims and Goals

The purpose of this study is to explore the association between preoperative frailty assessment using the Upper Extremity Frailty Meter and the occurrence of postoperative complications and severe postoperative events. Further whether frailty could be used as a metric to predict postoperative outcomes and adverse events in patients with lower extremity PAD is investigated. In detail, the aims of the study are:

<u>Aim1:</u> Investigate the association between frailty with health & adverse events of patients undergoing vascular surgery

H1: Those with poor motor-cognitive performance (frail individuals) have a high likelihood to have complications post-surgery

H2: Those with more complications post-surgery have lower cognitive performance prior surgery

H3: Vascular intervention may delay progression toward frailty and loss of mobility in non-frail and pre-frail adults diagnosed with peripheral arterial disease

<u>Aim2:</u> Assessing objective motor & cognitive performance post-surgery to evaluate postoperative outcomes

H4: Sensor-derived parameters (motor and cognitive performance) are sensitive metrics to assess functional outcomes in response to surgery

The results of this study will allow significant progress in the field of vascular surgery research. If the aims of this project are achieved:

(i) Early, quick, and accurate assessment of frailty in the care setting without the need of gait assessment would be possible. This would aid in planning discharge disposition and hospital resource allocation among PAD patients, who often have plantar wounds that limit them from undergoing gait assessment.

(ii) Technical capability to predict outcomes and adverse events and to develop best practices for specific clusters of peripheral arterial disease patients will help establish prevention and preoperative strategies to improve both short-term and long-term outcomes in these patients.

2 Theoretical Background

by Vanessa Hinko

2.1 Peripheral arterial disease

Peripheral arterial disease (PAD) is a common vascular condition that affects both life expectancy and quality of life. The term PAD is used to describe the impairment of arterial blood flow to the extremities. More detailed, it is a disease in which plaque made up of fat, cholesterol, calcium, fibrous tissue, and other substances in the blood builds up in the arteries outside the heart and the brain[1] . The resulting condition is called arteriosclerosis[2]. Over time, plaque can harden and grow in size leading to a narrowing in the arteries and therefore limiting the flow of oxygen-rich blood to organs and extremities of the body. Atherosclerosis can involve almost all major arteries in the body. Common locations for PAD are the iliac, femoral, popliteal and tibial arteries.

An insufficient blood supply to the legs could cause muscle cramping, fatigue, heaviness and pain in the hips, thighs or calves while walking or performing exercises. This leg pain is known as intermittent claudication. Claudication is a sensation described as aching, burning heaviness or tightness in the muscles of the leg. It typically starts after walking a certain distance, walking up a hill, climbing stairs or general exercise and typically relieves by rest. Patients with severe PAD may experience claudication pain after walking short distances or even have pain at rest or while lying in bed. [8]

Additionally PAD can increase the risk of getting infections in the affected limb. Because of the reduced blood flow in the affected area these infections may heal worse and need significant more time to heal. If severe enough or untreated over long periods, blocked blood flow can cause gangrene (tissue death) or score (ulcer) that will not heal on its own. In very serious cases, this can lead to leg amputation [9]. All of these mentioned symptoms have in common to result in a decreased quality of life.

[1] Atherosclerosis (blood flow blockage) of the arteries of the heart is known as coronary artery disease. 8. Gornik, H.L., *Peripheral Arterial Disease.* Circulation, 2005. **111**(13): p. e169-e172.

[2] In this report, PAD refers to atherosclerosis of the lower extremities. Other terms used for this condition are peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease.

2.1.1 Risk factors of peripheral arterial disease [9,16]

Major risk factors for peripheral arterial disease are smoking, older age, and having certain diseases or conditions. With a around four times increased risk, smoking is the main risk factor for PAD. The risk to suffer from PAD increases for smokers and patients with a history of smoking compared to non-smokers. Smokers and people with diabetes mellitus are at the highest risk for peripheral arterial disease complications. The appearance of tissue death (gangrene), caused by a decreased blood flow, in the lower extremities is more common in those patients.

Older age is another well known risk factor for PAD. The building of plague in the arteries together with other risk factors, such as smoking and diabetes, leads to a higher risk for PAD. Also high cholesterol contributes to the build-up of plaque in the arteries. This plague can block the arteries and can significantly reduce the oxygen rich blood flow to the extremities. High cholesterol is an important risk factor for peripheral arterial disease.

Obesity and physical inactivity are other significant factors that are often related to peripheral arterial disease. In general, people with a body mass index (BMI) of 25 or higher are more likely to develop heart diseases or a stroke. A high BMI can also be connected to a higher risk of PAD. The increase of daily physical activity in patients already diagnosed with PAD can help to increase walking distances and decrease the risk of a heart attack or a stroke. As describes in chapter 2.1.3 supervised exercise programs are one of the treatments for PAD patients.

Besides the risk factors described above many diseases and conditions can raise the risk for peripheral arterial disease. This includes high blood pressure, coronary heart disease, stroke and the metabolic syndrome.

2.1.2 Epidemiology, Mortality and Costs

The incidence of peripheral arterial disease varies over the general population. Between 3%-10% of people younger than age 70 years suffer from peripheral arterial disease. The incidence rises up to 15%-20% in people older than 70 years [10].

PAD is estimated to affect around 4.6% of the American population—an estimated 8.5 million individuals. It is also highly prevalent among the elderly population of the United States; roughly 12%-20% of individuals older than sixty are affected by PAD. [3]

In a study conducted in 2004 Selvin and colleagues investigated the prevalence of PAD. They used the results from the National Health and Nutrition Examination Survey between 1999 and

2000. Regarding their results the prevalence of peripheral arterial disease among individuals aged ≥ 40 years is around 4.3%. The prevalence of PAD dramatically increases with age. Among individuals aged ≥ 70 years the prevalence raised up to 14.5%, which correlated to around four million individuals.[17]

There is no clear gender difference in the PAD prevalence. Though, the prevalence appears to be lower in women. This differences decrease with an increase in age. Also there are no clear differences regarding race/ethnic groups. [17,18]

Selvin et al, could show that the smoking status of individuals can be associated with the prevalence of peripheral arterial disease. They found a prevalence of 6.8% for current smokers, 4.4% for former smokers and only 3.1% in never-smokers. Even greater differences were found for individuals with diabetes. 10.8% of individuals with diabetes had PAD compared to 3.6% of individuals without diabetes. The prevalence among individuals which self-reported a history of cardiovascular disease was 12.9%. [17]

Costs

There are only little published data on the use of healthcare resources and the associated costs for the diagnosis, treatment and prevention of PAD. Margolis and colleagues investigated the costs of PAD over around 30,000 patients. Over a period of ~ 25 months the annual total mean PAD-related costs were $5,955 per patient per year (PPPY). Hospitalization was the major cost causing category, accounting for approximately 75% of the total PAD-related costs with an average of $4,442 PPPY. Disease correlated non-coronary procedures showed average costs of $729 PPPY and PAD-related medications totaled $610, including costs for anti-hypertensives ($313 PPPY) and lipid-lowering therapy ($207PPPY).[19]

2.1.3 Treatment of peripheral vascular disease [11]

Treatment of patient's lower extremity PAD is done in two steps, first addressing the risk factors of generalized atherosclerosis and second interventions such as pharmacotherapy, endovascular therapy or surgical interventions. The treatment of symptoms should always be chosen on the basis of the severity of the patients symptoms. For patients with symptomless disease an invasive intervention is never appropriate, but the presence of the disease can serve as a marker of generalized atherosclerosis. Therefore, therapy should address the primary prevention of systemic

complications. Patients showing mild or moderate symptoms are normally treated with lifestyle changing measures such as an exercise program. Additionally pharmacotherapy can be used to improve walking distance for patients showing intermittent claudication.

For patients with chronic critical limb ischemia, surgical revascularization is unquestioned appropriate. Surgical intervention is rarely indicated in patients with intermittent claudication alone. Only in patients where their symptoms interfere with their lifestyle or performance of an occupation the benefits of surgical revascularization outweigh the risks. When surgery is considered as treatment, there are two basic choices - endarterectomy and bypass grafting. Endarterectomy is mostly chosen for truly local disease otherwise bypass grafting is more appropriate.

Endovascular interventions, including balloon angioplasty and stent placement, is an attractive alternative to open surgical procedures as described above. Indications for such procedures are liberalized, arguing with the minimally invasive nature of these procedures.

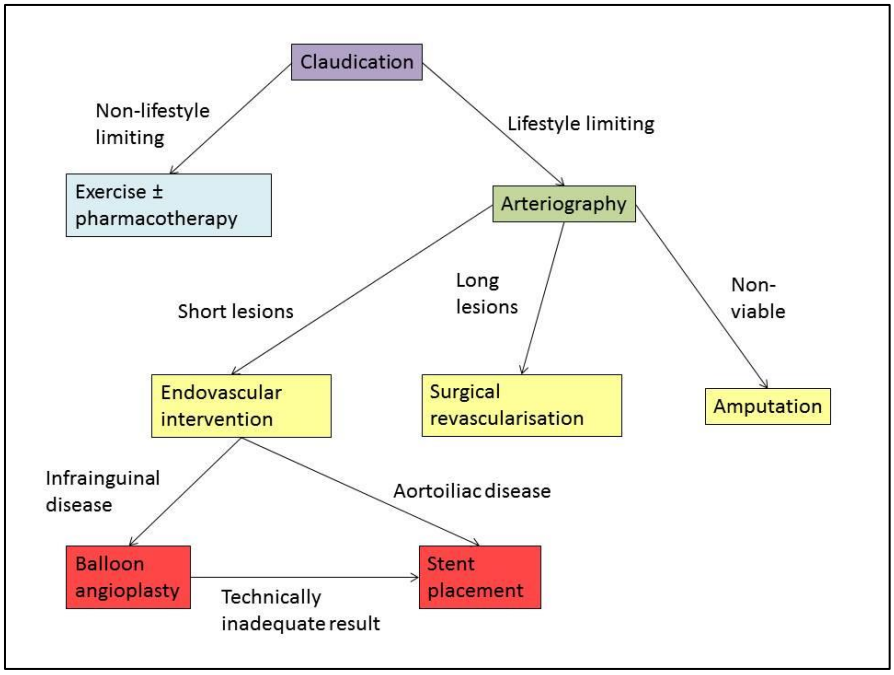

Figure 1Algorithm for managing patients with peripheral arterial disease [11]

2.2 Rutherford and WIFi classification

2.2.1 Rutherford Classification

The Rutherford classification, first published in 1986 (with revision in 1997) is a symptomatic classification system for peripheral arterial disease. The system classifies PAD into acute and chronic limb ischemia. This is to emphasize the need of different treatments to each presentation of the disease. Also this classification system includes objective measures including Doppler, arterial brachial indices and pulse volume recordings. [15]

Recording to Rutherford's chronic limb ischemia classification, the evaluation of patients with chronic limb pain should include the character and onset of the patients' pain, the onset of claudication, verified by walking or treadmill tests and ankle brachial indices. To differentiate claudication from pseudoclaudication in patients showing exertional leg symptoms treadmill exercise testing, if possible, including pre- and post-exercise ABIs can be performed. Treadmill testing may also be useful to objectively document the magnitude of symptom limitation in patients with claudication. Table 1 shows the Rutherford classification for chronic limb ischemia. [15]

Table 1 Rutherford Classification for chronic limb ischemia

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic—no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mm Hg but at least 20 mm Hg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mm Hg
II	4	Ischemic rest pain	Resting AP < 40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mm Hg
III	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mm Hg
	6	Major tissue loss—extending above TM level, functional foot no longer salvageable	Same as category 5

In contrast to Rutherford's classification of chronic limb ischemia, Rutherford's acute limb ischemia classification splits the effected limb into three categories: viable, threatened and irreversibly damaged. Patients categorized within category 1 and 2a ischemia, showing an onset within 14 days and a low risk of myo-necrosis are often treated with endovascular methods. Patients of category 2b require more immediate intervention due to the higher risk of permanent nerve or tissue damage. Category 3 patients already showing major tissue loss or permanent nerve damage are treated with amputation. Table 2 shows Rutherford's acute limb ischemia classification. [15]

Table 2 Rutherford's classification for acute limb ischemia

Category	**Description/Prognosis**	**Findings**		**Doppler signal**	
		Sensory loss	**Muscle weakness**	**Arterial**	**Venous**
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis	Inaudible	Inaudible

2.2.2 Wound, Ischemia, and Foot Infection – WIFi classification

As even more and more patients with critical limb ischemia are diabetic patients, the Society for Vascular Surgery developed a new classification system that combines PAD classification schemes based on PAD perfusion patterns and foot ulcer schemes. There are several grading systems to characterize foot ulcer, all based on the size and depth of ulcers and foot gangrene.

The WIFi classification system uses three components for classification. Separate grades are given for foot wound (presence, size and depth), ischemia (including ABI indices, toe pressure or transcutaneous oximetry) and infection (reaching from local to systemic). The three grades can be combined to give an estimation of the risk of amputation within one year and the potential benefit of revascularization. Table 3, Table 4, Table 5 and Table 6 show the WIFi classifications and WIFi estimations. [15]

Table 3 WIFi classification for wounds

Wound		
Grade	Ulcer	Gangrene
0	No ulcer	No gangrene
1	Small, shallow ulcer on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene
2	Deeper ulcer with exposed bone, joint, or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full-thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving the forefoot/midfoot; full-thickness heel necrosis ± calcaneal involvement

Table 4 WIFi classification for ischemia

Ischemia			
Grade	ABI	Ankle systolic pressure	TP, $TcPO_2$
0	≥ 0.80	> 100 mm Hg	≥ 60 mm Hg
1	0.6–0.79	70–100 mm Hg	40–59 mm Hg
2	0.4–0.59	50–70 mm Hg	30–39 mm Hg
3	≤ 0.39	< 50 mm Hg	< 30 mm Hg

Table 5 WIFi classification forinfection

Infection	
Grade	Clinical manifestation of infection
0	No symptoms or signs of infection Infection present, as defined by the presence of at least two of the following items: • Local swelling or induration • Erythema 0.5–2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Local infection involving only the skin and the subcutaneous tissue Exclude other causes of an inflammatory response of the skin (trauma, gout, acute Charcot, fracture, thrombosis, venous stasis)
2	Local infection with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues, and no systemic inflammatory response signs
3	No systemic inflammatory response signs Local infection with the signs of SIRS, as manifested by two or more of the following: • Temperature > 38 or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg • White blood cell count > 12,000 or < 4,000 cu/mm or 10% immature bands

Table 6 WIFi classification estimations for risk of amputation and likelihood of benefit or requirement for revascularization

Estimate risk of amputation at 1 y																
	Ischemia 0				Ischemia 1				Ischemia 2				Ischemia 3			
W-O	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fL0	fL1	fL2	fL3	fL0	fL1	fL2	fL3	fL0	fL1	fL2	fL3	fL0	fL1	fL2	fL3

Estimate likelihood of benefit of/requirement for revascularization (assuming infection can be controlled first)																
	Ischemia 0				Ischemia 1				Ischemia 2				Ischemia 3			
W-O	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	fL0	fL1	fL2	fL3	fL0	fL1	fL2	fL3	fL0	fL1	fL2	fL3	fL0	fL1	fL2	fL3

3 Materials and Methods

by Simon Höglinger

3.1 Study Design and Subjects

A prospective preliminary study of vascular surgical patients undergoing arterial revascularization in the lower extremities was conducted. Participants were consented and the baseline measurements were performed prior to surgical intervention. To overcome problems with time critical patient recruitment the consenting process and the baseline measurements were performed and will be performed at the patients preoperative clinic visit or directly on the day of their surgery. All emergency patients were consented and measured right before surgery.

To investigate long term outcomes (including adverse events, health status and functional outcomes), all participants will be followed up for 12 months using follow up visits. Follow Ups will be performed two weeks, 3 months, 6 months and 12 months after the participants' intervention. If the intervention requires a postoperative stay in the hospital also a 1-to-3 day follow up visit will be performed (Figure 2).

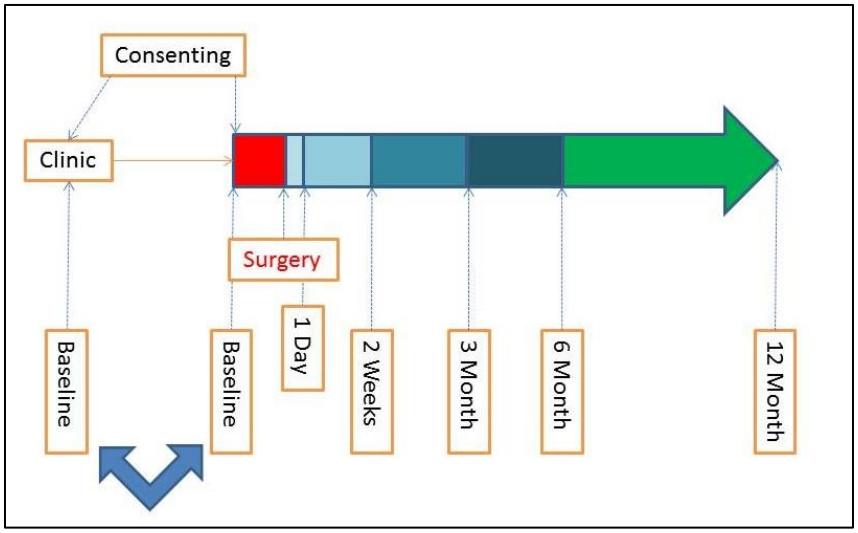

Figure 2 Overview study design; Individuals will be interviewed and consented at baseline (clinic or at the day of surgery).Long-term health outcomes will be assessed using 4-to-5 follow up visits. The displayed one-day follow up will only be performed for hospitalized patients.

Participants

Individuals included in this report were recruited over a four month period (09/2016 – 12/2016) from the division of vascular surgery at Baylor Clinic at Baylor College of Medicine and from the Department of Surgery at Baylor St. Lukes Episcopal Hospital. Written informed consent according to the principals expressed in the declaration of Helsinki was obtained from all participants. The protocol of the study has been approved by the Institutional Review Board of Baylor College of Medicine.

Inclusion criteria for the participants were (1) diagnosis of peripheral arterial disease (ICD-10-CM I73.9) and (2) planned uni- or bilateral revascularization – including surgical revascularization and endovascular interventions - of the lower extremities. Participants were excluded if they had significant bilateral upper extremity disorders (e.g., bilateral amputation or bilateral fractures) that precluded them from performing the upper extremity frailty test. Also if patients did not want to perform the UEF test due to pain or personal preferences and therefore no kinematic data could be collected, these patients have been excluded from the statistical analysis. Even though frailty is a concept most commonly used for the elderly, it is also true that some younger patients (<65 years old) can be considered as frail. Based on this, we decided not to limit our study based on an arbitrary age cutoff. [2]

3.2 Experimental Paradigm and Analysis

Participants underwent a standardized preoperative interview, SF-12 Health survey, frailty assessment and vascular assessment performed by a research assistant. During the interview demographic information including the occupation and education level of the patient, pain assessment, medical history including current prescriptive and over the counter medications as well as HbA1C and albumin, pre-albumin laboratory results, history of foot ulcer and amputations, history of fall, outside home activity and usage of gait assisting devices and the patients preoperative living situation were obtained. A fall was defined as an incident in which a participant unintentionally came to rest on a lower surface. We also collected variables about the operative procedure: endovascular versus open bypass surgery, length of surgery/ anesthesia as well as length of hospital stay.

3.2.1 Upper extremity frailty assessment

We evaluated frailty based on a validated method using wearable technology to measure upper- and forearm motion. A tri-axial wearable inertial motion unit (IMU) sensor (BioSensics LLC, Boston, MA, USA; dynamic range ±2,000 ˚/s; sample frequency: 100 Hz) was attached directly above the elbow and one at the wrist, using strap bands. Participants performed two twenty seconds trials of elbow flexion, within which they repetitively flexed and extended their elbow to full flexion and extension as fast as possible. The test can be performed both while sitting or while lying on bed. Before the actual test, the protocol was explained to participants and they were encouraged to do the test as fast as possible. The first trail performed consists of the motion performance only (single task).

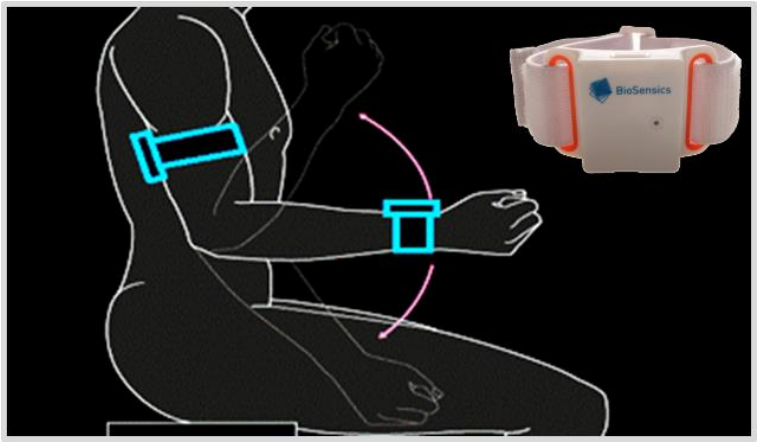

Figure 3 Upper Extremity Frailty Meter; Two IMU-sensors will be attached on the arm of the participants, one at the wrist and another one above the elbow. The subjects get introduced to perform an arm flexion and extension for 20seconds.

Several kinematic measurements of elbow and forearm motion were derived using angular velocity and anthropometric data including the participants' body mass and height. The outcome measures included (1) speed, (2) flexibility, (3) power, (4) rise time, (5) moment, (6) speed variability, (7) speed reduction and (8) flexion number. See Table 7 for an overview and further explanation of this measures. Based on UEF parameters an UEF Index was calculated, which represents the continuous frailty index and categorical frailty status (frail or non-frail). The UEF index is a 0-to-1 score, were 0 is representing minimal frailty symptoms and 1 maximum frailty symptoms. Those with a score of ≤0.27 are considered non-frail, those with a score > 0.27 are frail. Of note, only speed, power and speed reduction (reduction in angular velocity within 20 seconds) were used to develop the UEF index, as they showed the best association with the modified Rockwood questionnaire, the TSFI. This parameter represent "slowness", "weakness" and "exhaustion" frailty markers respectively[3]. [13]

[3] For more details regarding the validation of UEF using a motion capture system and for a detailed description of parameter calculations and UEF index calculation, please see 7. Toosizadeh, N., J. Mohler, and B. Najafi, *Assessing Upper Extremity Motion: An Innovative Method to Identify Frailty.* Journal of the American Geriatrics Society, 2015. **63**(6): p. 1181-1186. and 12. Toosizadeh, N., et al., *Assessing Upper-Extremity Motion: An Innovative, Objective Method to Identify Frailty in Older Bed-Bound Trauma Patients.* J Am Coll Surg, 2016. **223**(2): p. 240-8.

Table 7 Upper Extremity Frailty Parameter [13]

Parameter	Definition
Speed	Mean value of the elbow angular velocity range (maximum minus minimum speed)
Flexibility	Mean value of the elbow flexion range
Power	Mean value of the product of the angular acceleration range and the range of angular velocity
Rise time	Mean value of the time required to reach maximum angular velocity
Moment	Mean value of the maximum moments on the elbow within each flexion/extension estimated from the moment of inertia of the forearm and hand, and elbow motion
Speed variability	Coefficient of variation (standard deviation divided by the mean) of the angular velocity range
Speed reduction	Difference in angular velocity range between the last and the first 5s of elbow flexion as a percentage of the initial angular velocity range
Flexion number	Number of flexions/extensions during 20s

For the second trial, directly followed by the first one, participants were asked to count numbers backwards out loud by ones from a number chosen by the research assistant (but never lower than 30) while performing the elbow flexion (dual – task). Participants were asked to maintain their usual speed for the test, while counting numbers backwards by an individually selected rhythm [14].

By including this second trial, the evaluation of the cognitive cost was enabled. Counting backwards was chosen, as it involves working memory and, therefore, is more related to executive functions compared to tasks such as naming objects or animals. Also counting is a rhythmic task and therefore may highly interfere with other rhythmic tasks, such as arm flexion, performed at the same time. Beachet et al. showed, that counting backwards by one is more appropriate for older adults, because of its simplicity. To better represent the natural environment in performing daily activities, there was no instruction to prioritize either the counting or the movement during performing the task. [14]

Equation 1 Calculation of dual task cost [14]

$$Parameter_{dual-task\ cost} = \frac{Parameter_{dual-task} - Parameter_{single-task}}{Parameter_{single-task}} * 100$$

To assess the changes in individual's performance from single to dual-task (first to second trail), the dual-task "cost" was calculated as percentage of change for all parameters.
To assure that a higher positive percentage value of dual-task cost represents deteriorated motor performance for all parameters, the dual-task cost values were multiplied by -1 for rise time, speed reduction, and speed variability UEF parameters. [14]

3.2.2 Vascular assessment and PAD classification

To assess the quality of the participants' lower extremity blood flow skin perfusion pressure (SPP) was measured using a FDA approved system named SensiLase (Väsamed). Participants were asked to lie flat and relax their feet during the measurement. SensiLase provides a fully automated, quantitative evaluation of the microcirculatory perfusion in the skin. The test uses a laser Doppler sensor and pressure cuffs to measure reactive hyperemia. The used outcomes of the system are a displayed graph of perfusion over pressure during cuff deflation and the pressure at which skin perfusion was detected. The blood perfusion pressure was measured at the lateral side of the lower extremity around two to five centimeters above the ankle.
For the classification of PAD the widely clinically used Rutherford classification as well as the so called WIFi classification system was used. Both were assessed for all participants before intervention by their treating physician. WIFi classification was also assessed for all follow up visits. For a closer description of both classification systems see section 2.2.

3.2.3 Health Outcome Assessment

All follow up visits (see Figure 1), SF-12 Health survey (expect for 1-3 day follow up visits), frailty assessment, vascular assessment and health outcome assessment were measured. The measured health outcomes included (1) Death and major adverse events (heart attack and stroke), (2) Amputations since the patients surgery (including only amputations of the same limb as that of the surgery and splitting between minor – below ankle – and major – above ankle – amputations), (3) Re-interventions (major interventions such as a new surgical bypass graft,

thrombolysis and major surgical revisions and minor interventions including endovascular procedures without thrombectomy or other minor surgical revisions), (4) readmission, (5)changed residence (favorable: home, no change or return to home, unfavorable: discharge or movement to skilled nursing facility or family assisted living), and (6) length of hospital stay. The length of hospital stay was defined as nights spent in the hospital after surgical procedure. Therefore the length of stay for all outpatients that left the hospital after their intervention was defined as zero. Re-admission was assessed from the day of discharge. Additionally fall injuries, changes in the outside home activity and usage of gait-assisting-devices was recorded. Of note, for statistical analysis death, heart attack, stroke, readmission, revascularization (major interventions) as well as major amputations were defined as adverse events.

3.2.4 Statistical Analysis

Statistical analysis was performed using SPSS statistical software. Differences between groups in demographic information and adverse health outcomes for the two frailty groups – frail or non-frail (i.e., non-frail: UEF index ≤ 0.27; frail: UEF >0.27) was determined using two-sided fishers exact test. Furthermore analysis of variance (One-Way ANOVA) for nominal data as well as two-sided fishers exact test for categorical data were performed to investigate the relationship between several demographic and UEF parameter with health outcome (adverse events). Therefore the data has been split into two groups, those patients that showed adverse events and those that did not show any adverse events as defined in section 3.2.3.

4 Results

by Simon Höglinger

A total of twenty-six adults (average age of 64; range 52-to-81) were recruited over a four month period (09/2016 – 12/2016) for the current study. The mean body-mass-index was 27.9 and 16 (62%) participants were male and 10 (38%) female. Endovascular surgery was performed in 20 patients (77%), open surgery in 3 patients (11.5%) of the total group. Three (11.5%) of the patients haven't had an intervention at the time of analysis.

Based on the Upper Extremity Frailty Index, 14 (54%) of the participants were frail and 10 (38%) non-frail. For two of the participants frailty calculation was not possible, one wasn't able to perform the upper extremity frailty test, another rejected to perform the test due to pain. As mentioned in section 3.1 those participants were excluded from the statistical analysis of the kinematic motion data used to determine frailty and the frailty score.

As indicated in Table 8 and Table 10, the percentage of participants who had adverse health outcomes following their vascular intervention was greater in the frail than in the non-frail group. Differences reached significance ($p=0.006$). All those who had adverse events (including dead, stroke, major amputation and re-intervention) were frail according to the Upper Extremity Frailty test. Only 37.5 % of patients who didn't have adverse event were frail. The calculated frailty score shows a significant relation to adverse events ($p=0.002$) and is almost doubled in patients experiencing any adverse event (mean non-frail: 0.264 versus mean frail: 0.455). Another significant between-group difference for adverse events is the preoperative SF-12 mental component summary score ($p=0.010$). Statistical analysis showed a difference in the mean score of 53.3 ± 9.6 in the group with no adverse event versus 41.3 ± 10.1 in the group with adverse events.

None of the demographic or clinical data that were analyzed are significant predictors of adverse events. Those patients with adverse events tend to be older (9%, $p=0.134$), had 18.2% longer length of intervention ($p=0.475$), had 20.4% higher score on Rutherford classification ($p=0.202$), showed more severity in wound (WIFi $W= 0.8 \pm 1.2$ in the no adverse events group versus WIFi $W= 2.0 \pm 1.2$ in the group with adverse events, $p=0.061$), and had higher pain on average by 64% ($p=0.211$). None of these variables achieved statistical significant level in our sample ($p<0.050$).

Table 9 provides a comparison of several health outcome measures for the frailty groups as defined by the UEF index. There are two health measures which show a significant difference between the frailty groups. Only 18.2% of the non-frail group were hospitalized patients, while

61.5% of the frail group were hospitalized prior or after surgery (p=0.047). Another significant between-group difference is the occurrence of postoperative adverse events (p=0.006). Neither the type of adverse events (death, stroke, major amputation, re-intervention or re-admission) nor other unfavorable health outcomes reached significance level (p<0.050).

Table 8 Association between demographic and UEF parameter and adverse health outcomes (categorical data)

Characteristic	Adverse Events		p-value
	No	Yes	
Male	68.8%	44.4%	0.397
Female	31.3%	55.5%	0.397
Frailty	37.5%	100%	0.006*
Tabaco Use	18.8%	11.1%	1.000
Tabaco History	61.5%	62.5%	1.000
History of Foot Ulcer	43.8%	11.1%	0.182
Diabetes	93.8%	100%	1.000
Hypertension	87.5%	55.6%	0.142
Open Intervention	15.4%	11.1%	1.000
Hospitalized patients	31.3%	75%	0.082
Wound present	33.3%	62.5%	0.221
History of falls	25%	37.5%	0.647

*Significant between-group difference

Table 9 Health outcome measures for the frailty groups as defined by the UEF index

	Non-frail group, % (n=10)	Frail group,% (n=14)	p-value
In-patient	18.2	61.5	0.047*
Adverse Event	0	57.1	0.006*
Death	0	23.1	0.223
Stroke	0	7.1	1.000
Major Amputation	0	7.1	1.000
Re-intervention	0	35.7	0.053
Re-admission	0	7.1	1.000
Usage of gait assisting devices 2 weeks after intervention	33.3	40	1.000
Change in outside home activity 2weeks after intervention	50	60	1.000

UEF, upper extremity frailty *Significant between-group difference

Table 10 Association between demographic and UEF parameter and adverse health outcomes (nominal data)

	Adverse Events No 0;Yes1	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		p-value
					Lower Bound	Upper Bound	
BMI	0	28.7	6.7	1.7	25.1	32.2	
	1	29.5	8.0	2.8	22.8	36.3	.777
Age	0	62.1	8.4	2.1	57.7	66.6	
	1	67.7	8.8	2.9	60.9	74.4	.134
UEF-Index	0	.264	.113	.028	.203	.324	
	1	.455	.148	.052	.331	.579	.002*
Length of	0	2.2	.662	.184	1.8	2.6	
Intervention [h]	1	2.6	1.933	.644	1.125	4.097	.475
Rutherford	0	4.083	1.311	.379	3.250	4.917	
classification	1	4.917	1.114	.455	3.747	6.086	.202
SF-12 - PCS	0	32.9	11.7	3.0	26.4	39.4	
	1	30.7	8.1	2.9	23.9	37.4	.639
SF-12 - MCS	0	53.3	9.6	2.5	48.0	58.7	
	1	41.3	10.1	3.6	32.9	49.7	.010*
HbA1c	0	8.042	2.4194	.6984	6.504	9.579	
	1	7.200	1.6523	.6245	5.672	8.728	.428

Albumin	0	5.636	7.8086	2.3544	.390	10.882	
	1	3.400	.6419	.2620	2.726	4.074	.501
Wound volume	0	2.1	2.9	2.1	-24.2	28.5	
(cm3)	1	.611	.015	.011	.477	.744	.541
WIFI: Wound	0	.80	1.229	.389	-.08	1.68	
	1	2.00	1.155	.436	.93	3.07	.061
WIFI: Ischemia	0	2.10	1.287	.407	1.18	3.02	
	1	2.43	1.134	.429	1.38	3.48	.595
WIFI: Foot	0	.40	.699	.221	-.10	.90	
Infection	1	.43	.535	.202	-.07	.92	.929
SPP - R	0	57.64	30.978	9.340	36.82	78.45	
[mmHg]	1	47.40	32.020	14.320	7.64	87.16	.554
SPP - L	0	55.00	20.418	5.894	42.03	67.97	
[mmHg]	1	78.67	13.614	7.860	44.85	112.49	.083
Pain	0	3.93	4.114	1.062	1.66	6.21	
Assessment	1	6.43	4.467	1.688	2.30	10.56	.211

*Significant independent association ; MCS mental component summary; PCS physical component summary; UEF Upper Extremity Frailty; BMI Body Mass Index

5 Discussion

by Simon Höglinger

The concept that frailty results in adverse events in older adults is well established [6]. For years it has been recognized that some older adults might not have the physiological reserve to withstand an operation. Anyhow the approach of using frailty to forecast adverse events is relatively new. Further using frailty as a predictor of postoperative adverse events not only in older adults, but rather in younger adults as well is new to best of our knowledge. Using a simple objective sensor-based test to identify frailty and make use of this for preoperative risk assessment would have a high impact on future surgical decision making and postoperative medical care. We think that this has a high potential to improve patient oriented medical care and augment other risk assessment models. It also might help to explain why some patients recover far worse than expected and others better than expected.

As hypothesized, within the current sample of vascular surgical patients, post-operative adverse events were significantly associated with frailty as measured using the UEF-index. The results confirm that being frail significant increase the likelihood of adverse events post vascular intervention.

Further the results show that the SF-12 MCS score is a significant predictor for adverse events. We assume this correlates with the cognitive part of the UEF-test. This assumption is based on the general knowledge about the definition of frailty. There are many physical and cognitive factors and parameter that contribute to frailty. Especially the cognitive performance plays an important role. Several studies reported that subjects can still be considered as frail if their motor performance is at or above the average but their motor-cognitive performance is weak. Since mental and cognitive ability are closely related to each other, we assume a correlation between the mental outcome of the SF-12 (MCS) and the motor-cognitive performance of the UEF test.
We also found, that the described UEF-test is feasible to be performed in a busy physician clinics or surgical day. It takes only three minutes to conduct the assessment and shows a high usability as the test can be performed using an easy application installed on a tablet.

Limitations

First, we recognized some study limitations in upper-extremity frailty measures. Any upper-extremity disability or injury may limit the ability to perform measurements. We found this to be the case for two out of twenty-six individuals, who were excluded from the analysis because they were not able to perform the UEF test. Further due to attachment of vital sign-monitoring or health improving equipment attached on the dominant arm of the participant, one of the participants was not able to perform the UEF-test on his dominant arm. However, this is likely to be less important as other studies demonstrated similar prediction qualities for assessing frailty using either the dominant or the non-dominant arm [7].
Second, we were only able to evaluate short-term outcomes and did not evaluate the impact on long-term functional outcomes and quality of life measures. However, the investigation of long-term health outcomes is part of this study and will be performed in the following months. For a closer description of the outlook and future assessments see section 6 “Outlook”.
Third, the providers were blind to the results of the UEF-test as well as the SF-12 health survey. We do not know how and how much this knowledge would have influenced medical care.
Lastly, we were not able to show that frailty could be used as a predictor of the type of adverse event, or any other minor but unfavorable health outcome.

In summary, frailty seems to be a common condition in vascular surgical patients. Frailty as assessed by the UEF-test is significantly related with the occurrence of postoperative

complications and can be used as a predictor for those. Furthermore the standardized assessment of the health status by the SF-12 heath survey shows the ability to strengthen the predictive ability of the UEF-test. Making the UEF-test a standardized measure of frailty and including this into preoperative risk assessment can help in vascular surgical decision making and strengthens patient oriented medical care.

6 Outlook

by Simon Höglinger

As mentioned in chapter 3.1 this study is designed in a way that all participants will be followed up for 12 months. As this report covers only the short-time investigation of health outcomes, future researcher will continue on assessing long-term health outcomes over the full period of 12 months. Also patient recruitment over an overall time of one year will be continued by those researchers. Based on the new data collected in near future a new analysis of the data will be performed.

Further also vascular patients undergoing minor or major amputation as a treatment for their PAD/ inviable ischemia might be included in this study. The inclusion of patients from other medical facilities than the Baylor Clinic of Baylor College of Medicine and Baylor St. Lukes Episcopal is also a topic of discussion at this time and might be performed in the future.

Lastly, all four hypotheses as described in chapter 1.1 will be evaluated and analyzed. To proof hypothesis 2 (H2: Those with more complications post-surgery have lower cognitive performance prior surgery) already and future collected data of the UEF-dual-task will be analyzed. Dual-task cost will be calculated and a between-group analysis for patients with /without complications will be performed. To proof the hypothesis that vascular intervention may delay progression toward frailty and loss of mobility in PAD non-frail adults, an extensive analysis of non-frail patients and health outcomes including quality of life measures as well as activity measures will be performed. A similar analysis based on parameters selected by the UEF-test will be performed for the proof of hypothesis four.

7 Author's Contribution

by Vanessa Hinko

Vanessa Hinko: Literature review | Study conception and design | Acquisition of data | Analysis and interpretation of data

Writing following sections of the report:

1. Introduction
2. Theoretical Background
7. Author's Contribution

Simon Höglinger: Literature review | Study conception and design | Acquisition of data | Development of tests and UEF-index calculation | Analysis and interpretation of data |

Writing following sections of the report:

Acknowledgement

Abstract

3. Materials and Methods
4. Results
5. Discussion
6. Outlook

List of Figures

Equations

Tables

References

1. Makary, M.A., et al., *Frailty as a Predictor of Surgical Outcomes in Older Patients.* Journal of the American College of Surgeons, 2010. **210**(6): p. 901-908.
2. Saxton, A. and V. Velanovich, *Preoperative Frailty and Quality of Life as Predictors of Postoperative Complications.* Annals of Surgery, 2011. **253**(6): p. 1223-1229.
3. Roger, V.L., et al., *Heart Disease and Stroke Statistics--2011 Update: A Report From the American Heart Association.* Circulation, 2010. **123**(4): p. e18-e209.
4. Fried, L.P., et al., *Frailty in older adults: Evidence for a phenotype.* J Gerontol A Biol Sci Med Sci., 2001.
5. Jarrett, P.G., et al., *Illness presentation in elderly patients.* Archives of Internal Medicine, 1995.
6. Robinson, T.N., et al., *Simple frailty score predicts postoperative complications across surgical specialties.* The American Journal of Surgery, 2013. **206**(4): p. 544-550.
7. Toosizadeh, N., J. Mohler, and B. Najafi, *Assessing Upper Extremity Motion: An Innovative Method to Identify Frailty.* Journal of the American Geriatrics Society, 2015. **63**(6): p. 1181-1186.
8. Gornik, H.L., *Peripheral Arterial Disease.* Circulation, 2005. **111**(13): p. e169-e172.
9. National Institute of Health and Human Services *Peripheral Artery Disease,* 2016. Retrieved from https://www.nhlbi.nih.gov/health/health-topics/topics/pad/atrisk, Dec 2016
10. Abdulhannan, P., D.A. Russell, and S. Homer-Vanniasinkam, *Peripheral arterial disease: a literature review.* British Medical Bulletin, 2012. **104**(1): p. 21-39.
11. Ouriel, K., *Peripheral arterial disease.* The Lancet, 2001. **358**(9289): p. 1257-1264.
12. Toosizadeh, N., et al., *Assessing Upper-Extremity Motion: An Innovative, Objective Method to Identify Frailty in Older Bed-Bound Trauma Patients.* J Am Coll Surg, 2016. **223**(2): p. 240-8.
13. Joseph, B., et al., *Upper-Extremity Function Predicts Adverse Health Outcomes among Older Adults Hospitalized for Ground-Level Falls.* Gerontology, 2016.
14. Toosizadeh, N., et al., *Upper-Extremity Dual-Task Function: An Innovative Method to Assess Cognitive Impairment in Older Adults.* Front Aging Neurosci, 2016. **8**: p. 167.
15. Hardman, R., et al., *Overview of Classification Systems in Peripheral Artery Disease.* Seminars in Interventional Radiology, 2014. **31**(04): p. 378-388.
16. American Heart Association *Understand Your Risk for PAD,* 2016. Retrieved from http://www.heart.org/HEARTORG/Conditions/VascularHealth/PeripheralArteryDisease/Understand-Your-Risk-for-PAD_UCM_301304_Article.jsp, Dec 2016
17. Elizabeth Selvin, MPH; Thomas P. Erlinger; *Prevalence of and Risk Factors for Peripheral Arterial Disease in the United States - Results From the National Health and Nutrition Examination Survey,1999 –2000;* Circulation. 2004;110:738-743
18. C. Cimminiello; *PAD Epidemiology and pathophysiology*; Thrombosis Research, Volume 106, Issue 6, 1 June 2002, p. V295–V301
19. Margolis, B.J., et al.; *Health care resources and costs for treating peripheral artery disease in a managed care population: results from analysis of administrative claims data.* J Manag Care Pharm. 2005 Nov-Dec;11(9):727-34.