Dissertation

Vascular Trauma of the Extremities – Comparison of Outcome and Arterial Stability of the Upper and Lower Limbs

submitted by

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To Mama and Papa

STATUTORY DECLARATION

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz“.

02.05.2019 Dr.med.univ. Gloria Hohenberger eh

DISCLOSURE

Parts of this thesis have been published in the following articles:

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All co-authors have explicitly agreed to the use of their data in this thesis.

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ABBREVIATIONS

ADL	Activities of Daily Living
A_T	Adventitia thickness
AUVA	Allgemeine Unfallversicherungsanstalt
BABB	Benzyl alcohol/benzyl benzoate
CFS	Clinical Frailty Scale
CIA	Common iliac artery
CSHA	Canadian Study of Health and Aging
DASH	Disabilities of the Arm, Shoulder & Hand
EvG	Elastica van Gieson
FFB-Mot	Physical Fitness Questionnaire
F_z	Axial force
G	Shear modulus
H&E	Hematoxylin and Eosin
ID	Inner vascular diameter
I_H	Intimal hyperplasia thickness
ISS	Injury Severity Score
KCl	Potassium chloride
KH_2PO_4	Monopotassium phosphate
LE	Lower extremity
k_z	Axial Cauchy stress-pressure slope
k_θ	Circumferential Cauchy stress-pressure slope
MESS	Mangled Extremity Severity Score
M_T	Mean media thickness
Na_2HPO_4	Disodium phosphate
NaCl	Sodium chloride
NaH_2PO_4	Monosodium phosphate
OD	outer vascular diameter
ORIF	Open Reduction and Internal Fixation
p	Transmural pressure

PBS	Phosphat-buffered saline
PFA	Paraformaldehyde
p_i	Internal pressure
r	Correlation coefficient
SA	Subclavian artery
SHG	Second-harmonic generation
SPSS	Statistical Package for Social Sciences
UE	Upper extremity
α	Opening angle of circumferentially oriented strips
β	opening angle of axially oriented strips
$\Delta\lambda_\theta$	Circumferential distensibility
θ_{motor}	Angle of twist
κ_{ip}	In-plane dispersion parameter
κ_{op}	Out-of-plane dispersion parameter
λ^*	Inversion stretch
λ_z	Axial stretch
σ_{zz}	Axial Cauchy stress
$\sigma_{\theta\theta}$	Circumferential Cauchy stress

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ZUSAMMENFASSUNG

Hintergrund/Ziel: Bis dato wurde das posttraumatische funktionelle Outcome nach Gefäßverletzungen noch nicht zwischen oberer (UE) und unterer Extremität (LE) verglichen. Ziel unserer Studie war es, dieses zwischen den Extremitäten zu vergleichen. Hauptzielgrößen waren das Unvermögen an den präoperativen Arbeitsplatz zurückzukehren beziehungsweise (für Rentner) ein postoperativer Verlust von 10% der Punktzahl des Fragebogens zur Erfassung des motorischen Funktionsstatus (FFB-MOT).

Zusätzlich wurden die biomechanischen Eigenschaften der A. subclavia (SA) und A. iliaca communis (CIA) miteinander verglichen.

Material & Methoden: Alle Patienten, welche mittels arterieller Rekonstruktion bei Extremitätentraumata inklusive Gefäßläsion an einem Level-I-Traumazentrum und einem kooperierenden Level-III-Traumazentrum zwischen Jänner 2005 und Dezember 2014 behandelt worden waren, wurden bezüglich Studienteilnahme kontaktiert. Der jeweilige Mangled Extremity Severity Score (MESS) und der prä- und postoperative Score des FFB-Mot wurden erhoben. Unfähigkeit zur Wiederaufnahme der posttraumatischen Beschäftigung sowie ein postoperativer Verlust von zumindest 10% der Punktezahl des FFB-Mot (Rentner) wurden als primäre Outcome Größe festgelegt.

Als Präparate für den biomechanischen Teil der Studie wurden Arterienpaare (CIA und SA) von erwachsenen Körperspendern gewonnen. Kombinierte Extensions-Inflations-Torsionstests wurden unter variierenden axialen Dehnungen, intraluminalen Drücken und Torsionen durchgeführt. Die gewebeinhärenten Residualspannungen wurden in die Umfangs- und Längsrichtung der Arterien bestimmt. Histologische und mikrostrukturelle Untersuchungen mittels Second-Harmonic-Generation Imaging wurden an den Präparaten durchgeführt.

Ergebnisse: Bei den 27 eingeschlossenen Extremitäten war in 14 Fällen die UE und in 13 Fällen die LE traumatisiert. Bezüglich der MESS-Werte gab es keinen Unterschied zwischen UE (5.9; SD: 2.5) und LE (6.2; SD: 2.5). Das primäre Outcome-Event ereignete sich in 52% (14/27) der Fälle, ohne statistisch signifikanten Unterschied (p = 0.45) zwischen den Extremitäten (UE: 43%, 6/14; LE: 62%, 8/14). Jedoch zeigte die Differenz zwischen prä- und posttraumatischen FFB-Mot ein signifikant schlechteres Outcome (p = 0.012) nach Gefäßverletzungen an der LE (Verlust von 31.8%) im Vergleich zur UE (Verlust von 13.3%).

In den biomechanischen Untersuchungen wurden 17 SAs und CIAs von 17 Körperspendern eingeschlossen. Die CIA zeigte im Vergleich zur SA höhere Cauchy-Spannungen in Umfangs- und Längsrichtung. Die Residualspannungen in Umfangsrichtung waren signifikant kleiner in der SA als in der CIA bei Messungen nach 30 Minuten und 16 Stunden. Des Weiteren konnte durch die mikrostrukturellen Untersuchungen ein erhöhter Anteil an Kollagenfasern in der CIA festgestellt werden (CIA: 51,4%; SA: 44,3%).

Schlussfolgerungen: Die Ergebnisse lassen darauf schließen, dass Patienten, welche eine Gefäßverletzung an der LE erleiden, ein schlechteres Outcome als jene mit OE-Gefäßtraumen haben.

Die biomechanischen Unterschiede der untersuchten Arterien könnten auf das unterschiedliche biomechanische Umfeld der Arterien zurückgeführt werden.

ABSTRACT

Background/objective: There is limited evidence of the functional posttraumatic differences between upper (UE) and lower extremities (LE) after vascular injuries. This study aimed to compare the functional post-interventional results between UE and LE with inability to return to the preoperative workplace or postoperative loss of at least 10% of the physical fitness questionnaire (FFB-Mot) score (for retirees) as the primary outcome.

Further, a biomechanical comparison of the subclavian (SAs) and common iliac arteries (CIAs) was conducted.

Materials & Methods: All consecutive patients treated for arterial injuries with vascular reconstruction at a level-I trauma centre and a cooperating level-III trauma centre between January 2005 and December 2014 were assessed. The Mangled Extremity Severity Score (MESS) and the FFB-Mot were determined. The differences between pre- and posttraumatic values were compared statistically for UE and LE. Inability to return to the preoperative workplace (for working people) or postoperative loss of at least 10% of the FFB-Mot score (for retirees) was defined as the primary outcome event.

For the biomechanical investigation paired SAs and CIAs of human adult body donors were extracted. Extension-inflation-torsion experiments at different axial stretches, transmural pressures and torsions were conducted. Residual stresses in axial and circumferential direction were determined. Specimens were evaluated via histological and second-harmonic generation imaging investigations.

Results: Of 27 patients included in the study, 14 cases involved the UE and 13 the LE. There were no statistically significant differences ($p = 0.75$) between the mean MESS for UE (5.9; SD: 2.5) and LE (6.2; SD: 2.5). The primary outcome event occurred in 52% (14/27) without significant difference between UE (43%, 6/14) and LE (62%; 8/14) injuries ($p = 0.45$). However, the difference between the pre- and post-traumatic FFB-Mot scores showed a significantly poorer functional outcome after LE vascular injury (loss of 31.8%) in comparison to the UE (loss of 13.3%; p = 0.012).

The biomechanical trial involved arterial samples of 17 body donors. The CIA revealed higher Cauchy stresses in circumferential and axial directions when compared to the SA. The residual stresses in circumferential direction were significantly lower for SA than for CIA at measurements after 30 min and 16 h. The amount of collagen fibres was higher for the CIA (51.4%) when compared to the SA (44.3%) during microstructure evaluation.

Conclusions: Results indicate a poorer functional outcome after vascular extremity trauma to the LE than to the UE.

The evaluated biomechanical differences may be traced back to different mechanical environments of the arteries.

PREFACE

Vascular injuries concern approximately 3% of all civilian and military traumas and have been reported with an increasing prevalence in the recent decades. Thereof, 27 – 87% affect the extremities. (Farber et al. 2012, Yavuz et al. 2013) Therapeutic options have been improved through wartime surgery experiences (Farber et al. 2012, Fox et al. 2005) including a decrease of amputation rates from 53% in 1946 to about 1.5% in 1996 (Farber et al. 2012). However, peripheral vascular traumas remain potentially life- and limb-threatening injuries including challenging therapy, requiring rapid diagnosis and intervention (Doody et al. 2008, Menakuru et al. 2005, Rasouli et al. 2009).

With respect to post-interventional outcomes, various studies have determined concomitant injuries of the adjacent soft and skeletal tissues, especially neurological lesions, as the main reason for poor post-traumatic results (Myers et al. 1990, Sobnach et al. 2010, van der Sluis et al. 1997). Blunt vascular lesions have shown significantly higher amputation rates in comparison to penetrating traumas (Prichayudh et al. 2009). Nevertheless, the current literature lacks detailed information concerning possible post-traumatic differences between upper (UE) and lower extremities (LE) following vascular injuries.

As an objective criterion for limb salvage prediction, the Mangled Extremity Severity Score (MESS) was described by Johansen et al (Johansen et al. 1990). This assessment was primarily designed for severe LE traumas and later extended to UE injuries (Korompilias et al. 2009) and has since been evaluated by various authors for both, the upper and lower limbs (Prichayudh et al. 2009, Prasarn et al. 2012, Bernstein and Chung 2007, Mommsen et al. 2005). For post-operative evaluation, the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire (Gummesson et al. 2003), which was postulated by the American Academy of Orthopaedic Surgeons, forms a convenient tool for self-assessment of UE disability and symptoms which can detect even small changes after injuries of the upper limb. However, the current literature lacks information about possible relations between the MESS and the DASH questionnaire.

We therefore aimed to compare the post-traumatic results between UE and LE regarding various patient-related variables with the main focus on functional outcomes. Further on, we focussed on possible correlations between the MESS and DASH and evaluated if the described MESS threshold for amputation (≥ 7 points) was applicable for our collective.

Additionally we compared our results with a biomechanical analysis of arteries of the UE and LE.

1 BACKGROUND

1.1 Classification of vascular injuries

In 1965, Jörg Vollmar (Ludwig 1998) developed a classification for vascular traumas. This distinguishes between the following subgroups:

- Direct sharp injuries
- Direct blunt injuries
- Indirect injuries
- Chronic subsequent conditions

Hereinafter we focus on the first three categories since patients suffering from chronic alterations were not included in this thesis.

1.1.1 Direct sharp vascular injuries

These may be the result of stab injuries, impalement lesions, cutting damages as well as gunshot wounds. Further on, they may occur intraoperatively as iatrogenic vascular traumas. Direct sharp injuries may be subdivided into three subgroups with regard to degree of severity as follows (see Figure 1):

- Grade I: Partial dissection of the vascular wall without opening of the lumen. Here, the intima remains intact und the clinical symptomatic is mainly silent. False aneurysms represent one of their common consequences.
- Grade II: Partial dissection of the vascular wall with opening of the lumen. During this trauma, all layers of the arterial wall are dissected without interruption of vascular continuity. The resulting bleeding may either proceed to the surface or to the local soft tissues.

- ⇨ Grade III: Complete dissection of the vascular wall. Here, a curling of the intima occurs which results in maximal activation of local thrombogenesis and may induce haemostasis and complete vessel thrombosis.

Direct sharp vascular injuries always occur in combination with external wounds and therefore include the risk for development of infections. Regarding clinical symptomatic, grade II and III lesions commonly involve severe haemorrhage.

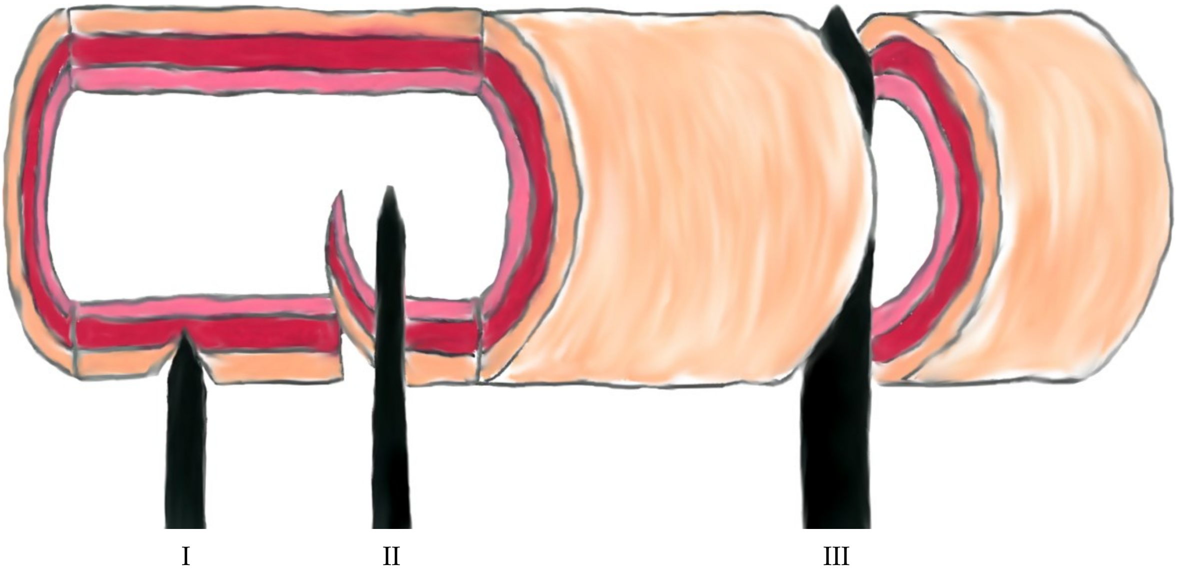

Figure 1: Scheme depicting direct sharp vascular injuries (© G. Hohenberger)

1.1.2 Direct blunt vascular injuries

Direct blunt vascular lesions are the result of dislocations, fractures and constricting bandages and may also be divided into three categories (Figure 2):

- ⇨ Grade I: Contusion or rupture of the intima.
- ⇨ Grade II: Rupture of intima and media.
- ⇨ Grade III: Contusion of all the layers of the arterial wall including possible curling of the inner layers and local thrombogenesis with vascular occlusion.

Most of these cases lack a superficial wound and they are commonly long-distance lesions. Typical clinical signs represent complete or incomplete ischemia as a result of the lumen thrombosis.

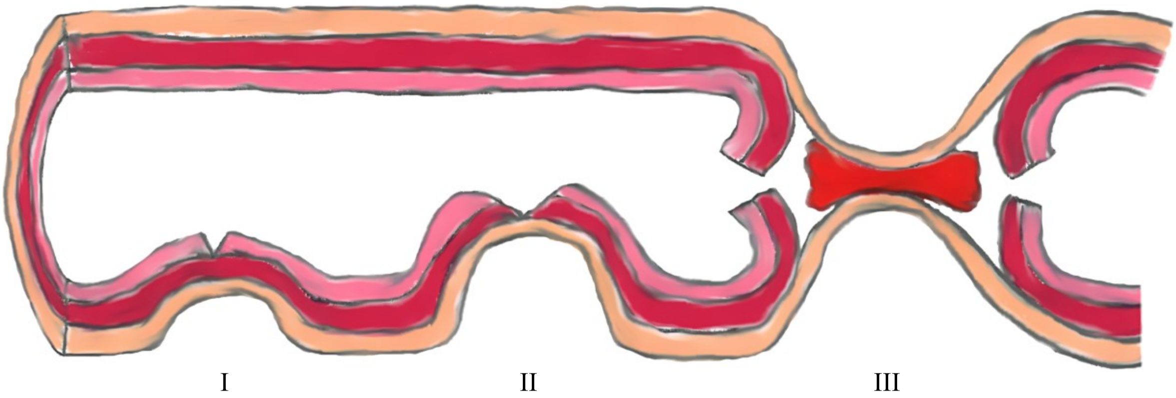

Figure 2: Classification of direct blunt vascular lesions (© G. Hohenberger)

1.1.3 Indirect vascular injuries

Here, one may distinguish between the following three patterns:

- ⇨ Deceleration injuries: These occur during sudden changes of movement or acceleration (e.g. traffic accidents) and mainly concern the thoracic portion of the aorta. Hereby either aneurysm formation or rupture of the vessel including severe thoracic haemorrhage take place.
- ⇨ Arterial spasm: This means a sudden constriction of the vessel resulting in a typical triad combined of coolness, paleness and pulselessness.
- ⇨ Vascular overstretching: Here, the main characteristics are ischemia as well as concomitant lesions (e.g. fractures, muscular injuries).

1.2 Details on age and gender

1.2.1 Military reports

Regarding recent military trauma reports, the average age of vascular trauma patients is located around 25 years (Beranger et al. 2017, Markov et al. 2012, Ratnayake et al. 2014, Scott et al. 2014), see Table 1. Dua et al. (2014) and Fox et al. (2005) reported about slightly older patients (mean 28 and 29, respectively). The amount of male patients ranges from 94 up to 100%.

Table 1: Age and gender distributions in recent trauma reports ("/" means that this information was not reported)

Authors	Hospital	Patients total	Males	Age mean (SD) (years)	Age median (years)	Age range (years)
Beranger et al. 2017	Kabul French Military Hospital	45	44 (98%)	/	25	12 – 50
Dua et al. 2014	Joint Theater Trauma Registry	46	46 (100%)	28 (/)	/	/
Fox et al. 2005	Walter Reed Army Medical Center	107	105 (98.1%)	29 (/)	/	19 – 64
Markov et al. 2012	Joint Theater Trauma Registry	380	/ (98.7%)	25.7 (6.5)	/	/
Ratnayake et al. 2014	Military Base Hospital, Sri Lanka	44	44 (100%)	/	24	18 – 42
Scott et al. 2014	Joint Theater Trauma Registry	214	210 (98%)	/	25	19 – 52
Siddique and Bhatti 2013	Combined Military Hospital, Pakistan	54	/ (94%)	26.8 (9.2)	/	9 – 67

1.2.2 Civilian reports

As displayed in Table 2, the average age of civilian trauma patients is slightly higher in comparison to military collectives. The male collective of Hafez et al. (2001) is an exception however it must be considered that these values concern South Africa. In their collective, males were much more frequently involved than females but these sex attributed differences were smaller than in combat settings.

Table 2: Details on recent civilian trauma reports ("/" means that this information was not reported)

Authors	Hospital	Patients total	Males	Age mean (SD) (years)	Age median (years)	Age range (years)
Dua et al. 2014	Joint Theater Trauma Registry	64	51 (80%)	35 (/)	/	/
Hafez et al. 2001	University of Natal Medical School, South Africa	550	480 (87.3%)	/	24 (males) 35 (females)	2 – 70 (males) 3 – 75 (females)
Klocker et al. 2010	Medical University of Innsbruck	89	71 (80%)	/	34.6	2.5 – 81.7
Klocker et al. 2012	Medical University of Innsbruck	56	43 (77%)	/	31.9	/
Klocker et al. 2014	Medical University of Innsbruck	152	127 (84%)	/	31.7	5.3 – 77.2
Markov et al. 2012	Joint Theater Trauma Registry	7,020	/ (82.8%)	32 (10.1)	/	/
Menakuru et al. 2005	Level III Centre North India	148	132 (89%)	39 (/)	/	7 – 65
Rasouli et al. 2009	Iranian National Trauma Project	113	101 (89%)	27.13 (13.87)	/	3 – 82
Wali 2002	Asir Central Hospital, Saudi Arabia	27	21 (78%)	27 (12.6)	/	2 – 65

1.3 Affected vessels

Concerning commonly affected vessels, there is a tendency towards the brachial and the popliteal and femoral arteries in military and civilian reports.

1.3.1 Military reports

Siddique and Bhatti (2013) evaluated 54 patients (21 UE; 33 LE) at the Combined Military Hospital in Pakistan. The brachial artery was by far the most commonly injured vessel of the UE (48%; 10/21). Regarding the LE, the femoral artery was affected in 42% (14/33) and the popliteal artery in 33% (11/33).

Şişli et al. (2016) found the combined injury of the femoral artery and vein as the most common type (12%; 11/90) in a collective of 90 cases with combat related vascular extremity traumas. The second most often traumatised vessels were the brachial artery, a combined injury of the axillary artery and vein, the femoral artery, and the combination of the popliteal artery and vein in nine cases each (10%).

1.3.2 Civilian reports

Wali (2002) reported the brachial artery as the most frequently affected vessel (41%; 11/27) followed by the ulnar artery in 19% (5/27) and the combination of the radial and ulnar arteries in 19% (5/27) during a half-year period in the Asir Central Hospital in Saudi Arabia.

Menakuru and colleagues (2005) reported data of 130 extremity vascular injuries treated in a level III centre in North India. Of these, the brachial artery was affected in 29% (38/130) and the femoral artery in 26% (34/130).

During a 10-year period, Hafez et al. (2001) collected characteristics of 550 patients with LE vascular injuries. Here, the most often affected vessel was the superficial femoral (37.2%) followed by the popliteal artery (30.7%).

In Klocker et al. (2014), authors presented 152 patients with arterial traumas of the extremities (UE: 68; LE: 90) who had undergone vascular interposition. The brachial artery was the most commonly affected vessel on the UE (51%; 35/68) and the popliteal artery of the LE (63%; 57/90). In a study concerning blunt traumas of the UE, Klocker and colleagues (2010) found the brachial artery again as the most often traumatised vessel in 50% of all cases.

Jagdish et al. (2014) performed a seven-year retrospective trial including 45 patients with extremity vascular injuries. The popliteal (33%; 15/45) and the brachial arteries (20%; 9/45) were most often injured.

1.4 Trauma mechanism

1.4.1 Military reports

As one may expect, the recent literature describes more penetrating traumas including vascular lesions in military settings in comparison to civilian samples.

Dua et al. (2014) compared popliteal artery injuries between military patients from the Joint Theater Trauma Registry (41.8%; 46/110) and civilian patients from a level I trauma centre (58.2%; 64/110). The military subgroup suffered significantly ($p < .0001$) more penetrating traumas (96% versus 30%).

Siddique and Bhatti (2013) evaluated 54 patients at a Combined Military Hospital in Pakistan over a two-year period and found penetrating trauma as the most common cause of injury (62.9%).

Markov et al. (2012) searched the Joint Theater Trauma Registry for arterial traumas in Iraq and Afghanistan (between 2003 and 2006) and compared these data with civilian trauma patients whose characteristics were gained from the National Trauma Data Bank for the same time interval. Regarding the military collective, the main injury mechanism was explosion (68.7%) followed by penetrating (28.2%) and blunt (3.2%) traumas. The civilian subgroup showed blunt and penetrating traumas in each 50% but no explosion injuries.

Fox et al. (2005) evaluated 107 patients with vascular injuries that had been treated at the Walter Reed Army Medical Centre from December 2001 till March 2004. The most common mechanism was injury due to explosive devices (64%; 68/107) including landmines, grenades and others. This was followed by high-velocity gunshot wounds (25%; 27/107).

Beranger et al. (2017) reviewed 45 patients with combat-related vascular injuries at Kabul French military hospital from January 2009 to April 2013. Sixty-seven percent (30/45) of wounds resulted from gunshots and further 24% (11/45) from explosive devices.

1.4.2 Civilian reports

In Vielgut et al. (2015), 64 cases of popliteal artery injuries were evaluated at the University Hospital Vienna. The sustained trauma was blunt in 55% (35/64) and penetrating in 45% (29/64) of all cases. Regarding blunt injuries, motorcycle accidents were the most common reason (40%; 14/35). Wounds inflicted by knifes or sharp metal objects were the most common (48%; 14/29) reason for penetrating trauma.

Klocker and colleagues (2012) reviewed 56 patients with previous UE vascular repair. Blunt trauma was the most common mechanism with 89% (50/56). In 2014, the authors surveyed 152 patients and found blunt injuries in even 91% (138/152).

Jagdish et al. (2014) conducted a seven-year retrospective analysis on 45 patients with vascular injuries. These resulted from blunt trauma in 84.4% (38/45) of all cases. Patients mainly sustained motor vehicle accidents (80%). Klocker et al. (2010) found sports accidents in 35% of all cases followed by work injuries (29%)

and traffic accidents (27%) in 89 patients who had undergone vascular reconstruction of the UE.

Over ten years, Hafez et al. (2001) prospectively collected data on 550 patients who had sustained LE vascular traumas. In men, firearm injuries were the most common mechanism (68%) and in women this was blunt trauma (45.7%). Although these data were not collected in a military setting, they concern cases from South Africa where an increased violence rate may be supposed.

1.5 Outcomes

1.5.1 Upper extremity trials

In Klocker et al. (2010), 89 patients were retrospectively analysed following vascular reconstruction due to blunt UE trauma. Seventeen percent had concomitant venous lesions and 43% accompanying nerve injuries. The limb salvage rate was 98% whereby only primary amputations were conducted.

In 2012, Klocker et al. reviewed all UE vascular traumas which had been treated at their institution since 1990. These were asked to complete the Cold Intolerance Symptom Severity and the DASH questionnaires. In total, 56 patients completed both assessments. In this mainly blunt trauma group, 41% of all patients reported an abnormal cold intolerance and also had worse functional outcomes in comparison to the subgroup without. Further, cold intolerance was more commonly observed in patients who had sustained nerve lesions.

Paryavi et al. (2014) evaluated a collective consisting of 38 patients with humeral fractures and concomitant brachial artery injuries at a level I trauma centre from 1999 to 2012. The amputation rate was 5%. Immediate Open Reduction and Internal Fixation (ORIF) did not have negative effects on limb salvage.

Simmons et al. (2008) conducted a retrospective evaluation of 41 brachial artery trauma patients during a 6-year interval. Authors reported a death and amputation rate of each 9.8%. The mean MESS was higher in the amputation group (7 versus 4.3 points).

Rasouli et al. (2009) reported about a collective of 113 patients with UE vascular injuries. The amputation rate was 2.7% and five patients died as a result of severe concomitant injuries.

1.5.2 Lower extremity trials

Dua et al. (2014) compared 46 military popliteal traumas from the Joint Theater Trauma Registry collected during a period of five years to 64 civilian popliteal injury patients from a level I centre which had been collected between 2002 and 2009. In the military subgroup the trauma mechanism was mainly penetrating, the MESS and the secondary amputation rate (29% versus 13%) were significantly higher in comparison to the civilian collective.

Vielgut et al. (2015) evaluated a collective of 64 popliteal artery injuries at an urban level I trauma centre over a 20-year period regarding functional outcome by use of the Functional Independence Measure questionnaire. Authors concluded that blunt traumas were more frequently associated with polytraumatised patients, higher amputation rates and worse results regarding the Functional Independence Measure questionnaire than penetrating traumas.

Hafez et al. (2001) surveyed a collective of patients with LE injuries including vascular trauma over a period of ten years. Concomitant injuries were bone traumas (35.1%) and nerve injuries (7.6%). The limb salvage rate was 83.8% and graft occlusion, associated compound fractures were risk factors for amputation among others.

Ratnayake and colleagues (2014) evaluated all consecutive popliteal artery injuries at a Military Base Hospital in Sri-Lanka over an interval of eight months. Of the 39 included patients, eleven sustained primary and four delayed amputations.

1.6 Classification systems

1.6.1 The Physical Fitness Questionnaire (FFB-Mot)

The FFB-Mot was designed by Bös et al. (2002). Its main goal is to evaluate the motoric function status of normal populations of males and females through self-assessment (Morfeld et al. 2008). The assessment of its results is based on age- and gender-specific comparative values. Through repetition, this tool may also be used to evaluate the functional status over a time period. (Bös et al. 2002)

The assessment involves the subcategories strength, endurance, mobility and coordination (Mess and Walter 2013). The standard version consists of 20 questions (items 2 – 6 of each subcategory). Four additional items with the lowest difficulty level (e.g. “Are you able to get up from a chair without using your arms?”; questions 1, 8, 15 and 22) form an ADL-score (Activities of Daily Living) and four questions with the highest degree of difficulty (e.g. “Are you able to run a marathon [42 kilometres]?”; questions 7, 14, 21 and 28) built a sports scale. The standard version enables assessment of normal populations. The ADL- and the sports scale may be used to evaluate frail respectively very sportive persons. (Bös et al. 2002)

The respective test person assesses each question with the possible categories “I am not able to perform this activity” (1 point), “I have major problems performing this activity” (2 points), “I have moderate problems performing this activity” (3 points), “I have minor problems performing this activity” (4 points) or “I have no problems performing this activity” (5 points). (Bös et al. 2002)

Each subcategory (strength, endurance, mobility and coordination) consists of five questions with a value range of 5 up to 25 points. Therefore, the full scale of the standard version ranges from 20 to 100 points. The ADL- and the sports scale (each four questions) have a range from 4 to 20 points. (Bös et al. 2002)

For this study, the standard version was used. The full questionnaire can be seen in the appendix.

1.6.2 The Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (CFS)

The CFS was developed as a 7-point assessment by Rockwood et al. (2005) through evaluation of 2.305 elderly patients who participated in the CSHA.

The scale enables evaluation of a participant's degree of frailty based on clinical data such as cognitive and motoric function and co-morbidities (Hayek et al. 2016, Moorhouse and Rockwood 2012). With the now modified 9-point ordinal scale (Figure 3) elderly patients can be assessed as very fit (level 1), well (level 2), managing well (level 3), vulnerable (level 4), mildly frail (level 5), moderately frail (level 6), severely frail (level 7), very severely frail (level 8) or terminally ill (level 9). (Provencher et al. 2016)

The CFS has been shown to be an easy tool with good inter-rater reliability and effective evaluation of frailty (Gregorevic et al. 2016, Rockwood et al. 2005).

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing**, and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Figure 3: The CSHA Clinical Frailty Scale (Rockwood et al. 2005, reprinted with permission of Kenneth Rockwood)

1.6.3 The Mangled Extremity Severity Score (MESS)

The MESS was popularised by Johansen et al. (1990) as a simple and objective rating scale for or against LE amputation (Gummesson et al. 2003, Prichayudh et al. 2009). Here, four different variables were included: skeletal and soft tissue injury, limb ischemia, shock as well as patient age (Table 3).

The score was designed in a civilian setting on a retrospective analysis of 25 patients who had sustained mangled LEs and on a prospective study on 26 trauma patients (Johansen et al. 1990, Schirò et al. 2015). During the retrospective analysis, the patients with salvaged extremities had a mean MESS of 4.88, whereas the amputation group showed a mean of 9.11, which was significantly higher. These findings were confirmed by their prospective trial and the authors concluded that a value of 7 or more points predicted amputation with 100% accuracy (Johansen et al. 1990). Up to now, the MESS has been extended to the UE and has been evaluated for both, upper and lower limbs.

Generally, the use of the MESS and the cut-off point of ≥7 points as an indicator for amputation remain controversial. Edge and colleagues (2015) stated the MESS not to be predictive in combat related UE and LE trauma including open fractures. Sheean et al. (2014) found a MESS of at least seven points as a positive predictive value in 50% regarding LE traumas and recommended against its use in the military setting. In contrary, Sharma et al. (2003) described a MESS ≥7 as positively predictive in 100% regarding their evaluation on 50 patients with mangled LEs. However, they found the score lacking prediction of successful extremity salvage and functional outcomes since many of their observed extremities with a MESS ≤ 7 had to undergo delayed amputation. Prichayudh and colleagues (2009) postulated that the decision for or against limb amputation should rather be based on individual clinical signs since they were able to avoid amputation in 12 out of 19 patients with UE traumas and a MESS of at least 7 points. In Fochtmann et al.'s (2014) evaluation of 93 third-degree open tibia shaft fractures, the MESS proved to be significantly higher in the subgroup requiring amputation. However, the authors concluded that the threshold of 7 points should be discussed and possibly revised. As a potential solution, Yeh et al. (2016) suggested the additional use of the Injury Severity Score (ISS) in cases of MESS between 7 and 9 points. If this exceeds 18 points, amputation should be considered and if it is less than 18 points, salvage of the extremity could be attempted in approximately 60% with reference to the authors.

Table 3: Details on the MESS (Johansen et al. 1990)

Variables	Points
A. Skeletal/soft-tissue injury	
Low energy (stab wound, simple fracture, "civilian" gun-shot wound)	1
Medium energy (open or multiple fractures, dislocations)	2
High energy (close-range shotgun or "military" gun-shot wound, crush injury)	3
Very high energy (above + gross contamination, soft-tissue avulsion)	4
B. Limb ischemia	
Pulse reduced or absent but normal perfusion	1*
Pulselessness, paraesthesia, diminished capillary refill	2*
Coolness, paralysis, numbness	3*
C. Shock	
Systolic pressure always > 90 mmHg	0
Hypotensive transiently	1
Persistent hypotension	2
D. Age (years)	
< 30	0
30 – 50	1
> 50	2

*** score doubled for ischemia > 6 hours**

1.6.4 The Disabilities of the Arm, Shoulder and Hand (DASH) Questionnaire

The DASH questionnaire was introduced by Hudak and colleagues (1996). It is a self-assessment questionnaire which has become very popular for evaluation of conditions of the UE. It forms a convenient tool for assessment of UE disability and symptoms which can detect even small changes after interventions of the upper limb (Gummesson et al. 2003).

The standard form consists of 30 questions concerning disabilities and symptoms of both UEs. The questionnaire offers two further optional sections. One is a Work Module and the other a Sports/Performing Arts Module, see appendix. (Aasheim and Finsen, 2013)

Since then the DASH has been evaluated by various authors. Töpel and colleagues (2009) performed a follow-up of 33 patients who had undergone arterial reconstruction for UE vascular lesions. Exclusion criteria involved iatrogenic traumas and arterial injuries distal to the wrist joint. The authors compared the collective's functional outcomes (e.g range of wrist and finger motion) to their respective DASH results and found a strong correlation between these two assessments. Here, patients showing severe functional deficits had significantly higher DASH scores (mean: 35.82 points) in comparison to the participants without or with minor deficits (mean: 11.82 points). A higher rate of functional deficits (56%) occurred in the subgroup showing concomitant neural injuries which consisted of 27 patients (81% of all participants).

Joshi et al. (2007) conducted a retrospective trial using the DASH score as the mean outcome measure for 17 patients who had sustained blunt or penetrating UE traumas including arterial injuries. Their limb salvage rate was 94%. The authors observed a higher (though not statistically significant) DASH score in the subgroup who had suffered from blunt (61.8 points) versus penetrating traumas (22.8 points) which they traced back to more often occurring neural and orthopaedic concomitant injuries in the blunt trauma subgroup.

Frech et al. (2016) conducted a follow-up of 65 patients who had sustained arterial reconstruction due to UE injuries. Patients with associated neural traumas gained significantly higher DASH scores (mean: 40.3 points) in comparison to the group without these injuries (mean: 0.8 points). However, the authors did not find worse clinical outcomes in patients with brachial plexus injuries in comparison to the subgroup with peripheral neural traumas.

2 CLINICAL TRIAL

2.1 Patients and Methods

2.1.1 Inclusion criteria

The study analysed all patients with extremity traumas including vascular lesions treated at our level I trauma centre (State Hospital and Medical University of Graz) and a cooperating level III trauma centre (AUVA Trauma Hospital Graz) between January 1st, 2005 and December 31st, 2014. The included vascular injuries were limited to vessels situated proximal to the wrist respectively upper ankle joint. All iatrogenic lesions were excluded. Only patients who had undergone vascular reconstruction were included.

2.1.2 Outcome assessment

The main target size for comparison of the outcome between UE and LE was defined as the post-operative re-entrance to the pre-traumatic workplace. Further on, the pre- and post-traumatic scores of the FFB-Mot, as an appraisal for the respective grade of mobility, were evaluated for each participant. A post-traumatic loss of 10% was determined as the main target size for retirees and regarded equal to the not occurrence of re-entrance to the pre-traumatic workplace.

2.1.3 Patient recruitment and retrospective data analysis

Primarily, the patients fulfilling the inclusion criteria were detected via the respective institutional software packages openMEDOCS and ASTRA. Their personal details (name, date of birth and patient number) were exported into encrypted Microsoft Excel sheets (Microsoft Excel 2013; Microsoft, Redmond, WA, USA). Patients' datasets were checked for accuracy and completeness. Patients were contacted telephonically, respectively per mail if their telephonic details were not available, and invited to participate in the study.

Regarding the retrospective data collection, each patient's individual MESS was evaluated by use of the clinical records. The characteristics listed in Table 4 were gathered for each study participant.

Table 4: Details on evaluated patient characteristics

Target	Details
Age	in years
Gender	male; female
Body side	right; left
Extremity	upper; lower
Mechanism of accident	traffic accident, sport accident etc.
Mechanism of vascular injury	direct blunt respectively penetrating
Details on vascular lesion	rupture, laceration etc.
Injured vessel	respective name
Further injured vessels	arterial/venous; respective name
Concomitant injuries	muscular, nervous and bone
Vascular surgical interventions	vascular suture, venous interposition etc.
Further surgical interventions	bone/nervous/muscular
Duration of surgical intervention	in minutes
Secondary surgical interventions	step-wise wound closure, secondary fracture fixation etc.
Duration of hospital stay	in days
Duration of intensive care unit stay	in days
Sickness absence rate	in days
Secondary amputation	yes; no

2.1.4 Questionnaire survey

Patients agreeing to participate in the survey were re-called to the Department of Orthopaedics and Trauma of the Medical University of Graz. After detailed information about the implementation of the study, its aims and the possibility of withdrawal from the survey at any time, patients were asked to sign informed consent.

During the follow-up interview, patients were asked for their current work status. Post-traumatic re-education was regarded equal to post-traumatic inability to work.

The FFB-Mot was completed by the investigator during the interviews with all participants for the pre- as well as for the post-traumatic status. To attain results comparable to the international literature, the pre- and post-interventional grade of the CSHA CFS were evaluated additionally for each patient. Patients were also interviewed regarding post-traumatic sensory disturbances.

2.1.5 Comparison of MESS and DASH

The actual DASH questionnaire was evaluated for each patient in order to assess possible correlations with the MESS. The total MESS as well as the DASH Work Module and the DASH Sports/Performing Arts Module were filled in together with the patients if this was applicable.

2.1.6 Statistical analysis

All calculations were performed with Statistical Package for Social Sciences (SPSS) 15.0. Fisher's exact test was used for comparison between UE and LE regarding the occurrence of an event as well as for the calculation of a possible influence of concomitant injuries on the occurrence of an event. Spearman's rank correlation coefficient was used for evaluation of the relation between the FFB-Mot and the CFS. T-test for unpaired samples was utilised for analysis of differences between UE and LE regarding MESS, pre- and post-traumatic FFB-Mot score, FFB-Mot difference and influence of concomitant injuries on the FFB-Mot difference. Since the data for the MESS and the DASH questionnaire did not reveal standard distribution, Spearman's rank correlation coefficient was used for analysis. *p*-values below 0.05 were considered as statistically significant.

2.2 Results

2.2.1 Patient collective

Between 2005 and 2014, 71 patients with extremity traumas were treated including vascular reconstruction at the University Hospital Graz and the AUVA Trauma Hospital Graz. Hereof, 39 involved UEs and 32 LEs. Forty-four of these could not be included in our study. The respective reasons are listed in Table 5.

Table 5: Reasons for exclusion from the study

	UE	LE
Death prior to study	7	0
Refusal to participate	3	2
No reply to written study invitation	11	12
No availability of contact data	2	3
No availability by phone after first telephonic consultation	2	2

Twenty-seven patients signed informed consent and could be re-evaluated for the study. The patient group had a mean age of 34.4 years (SD 17.4; range 15.3 – 67.4) at the time of the trauma. There was a high proportion of male gender with 24 (89%) male and 3 (11%) female patients.

2.2.2 Injury mechanism

Traffic accidents represented the most common trauma mechanism with ten cases (37%). Further causes are listed in Table 6.

Table 6: Details on injury mechanism (percentages and extremities)

Mechanism	UE	LE	n (percentages)
Traffic accident	2	8	**10 (37%)**
Work accident	5	4	**9 (33%)**
Fall	4	0	**4 (15%)**
Sport accident	2	1	**3 (11%)**
Incised wound	1	0	**1 (4%)**
	14 (52%)	**13 (48%)**	**27 (100%)**

Fourteen traumas (52%) concerned the UE and thirteen (48%) the LE. Twenty-two injuries (81%) affected right and five (19%) left extremities, whereas 14 cases (52%) concerned the dominant and 13 traumas (48%) the non-dominant side. However, there was no statistically significant connection between handedness and the traumatised body side (p = .618).

2.2.3 Vascular injuries and management

The study sample showed five direct penetrating and twenty-two direct blunt vascular injuries regarding the classification of Jörg Vollmar. Among these, the brachial (26%; 7/27) and the popliteal (29%; 8/29) arteries proved to be the most commonly affected vessels, followed by the subclavian (9%; 3/27) and the posterior tibial (11%; 3/27) arteries. Details are displayed in Table 7.

Table 7: Distribution of injured arteries (cases and percentages)

Vessel	n	Percentages
Subclavian artery	3	11
Brachial artery	7	26
Cubital artery	2	7
Ulnar artery	1	4
Radial artery	1	4
Common iliac artery	1	4
Femoral artery	1	4
Popliteal artery	8	29
Posterior tibial artery	3	11
Total	**27**	**100**

The most frequent vascular injury pattern was traumatic vascular obstruction (Table 8).

Table 8: Specific vascular injuries

Injury Type	UE	LE	Total
Traumatic vascular obstruction	6	5	**11**
Rupture	1	6	**7**
Laceration	6	0	**6**
Traumatic arterio-venous fistula	0	1	**1**
Spasm	1	0	**1**
Contusion	0	1	**1**
Total	**14**	**13**	**27**

Vascular reconstruction techniques included venous interposition or bypass (63%; 17/27), arterial suture (14%; 4/27), venous patch plasty (7%; 2/27) and closure of a fistula, thrombectomy, prosthesis application and balloon dilatation in respectively one case (each 4%), see Table 9. All of these interventions were performed by a vascular surgeon or an experienced traumatologist with assistance of a vascular surgeon.

Table 9: Vascular reconstructions with regard to extremity

Vascular Intervention	UE	LE	Total
Venous interposition or bypass	7	10	**17 (63%)**
Arterial suture	3	1	**4 (14%)**
Venous patch plasty	2	0	**2 (7%)**
Fistula closure	0	1	**1 (4%)**
Thrombectomy	1	0	**1 (4%)**
Prosthesis application	0	1	**1 (4%)**
Balloon dilatation	1	0	**1 (4%)**
Total	**14 (52%)**	**13 (48%)**	**27 (100%)**

Twelve cases (44%) showed a concomitant vascular lesion. Here, 75% (nine patients) concerned veins and 25% (three cases) arteries and each six cases concerned the UE and LE. The respective injury patterns per extremity are displayed in Table 10. The concerned vessels represented a highly heterogenic collective (Table 11).

Table 10: Vascular injury patterns

Injury Type	UE	LE	Total
Rupture	2	3	**5 (41.66%)**
Laceration	4	0	**4 (33.33%)**
Traumatic arterio-venous fistula	0	1	**1 (8.33%)**
Traumatic vascular obstruction	0	1	**1 (8.33%)**
Contusion	0	1	**1 (8.33%)**
Total	**6 (50%)**	**6 (50%)**	**12 (100%)**

Table 11: Concomitant vascular injuries

Vessel	n
Radial artery	1
Anterior tibial artery	1
Fibulary artery	1
Cephalic vein	1
Medial or lateral brachial vein	3
Median cubital vein	1
Common iliac vein	1
Femoral vein	1
Popliteal vein	1
Posterior tibial vein	1
Total	**12**

Regarding these further injuries, the most common vascular interventions proved to be vascular sutures as well as venous interposition (each 4 cases/8.33%).

Table 12: Interventions concerning concomitant vascular injuries

Vascular Intervention	UE	LE	Total
Venous interposition or bypass	2	2	**4**
Arterial suture	3	1	**4**
Ligature	1	0	**1**
Fistula closure	0	1	**1**
Thrombectomy	0	1	**1**
Prosthesis application	0	1	**1**
Total	**6**	**6**	**12**

2.2.4 Concomitant injuries

2.2.4.1 Muscular trauma

Nine patients (33%) sustained additional injuries of the adjacent musculature. Hereof, six cases (67%) concerned the UE and three (33%) the LE.

Regarding the injury pattern, seven patients (78%) had muscular lacerations, one participant sustained a combined muscle and tendon lesion (11%) and one further patient had a periosteal avulsion of a tendinous origin (11%).

Seven of these patients (78% of 9) underwent surgical muscular interventions. Five cases received a muscular suture, one patient underwent a combined muscular and tendinous suture and in one case, re-fixation of the tendinous origin was conducted.

2.2.4.2 Neural trauma

In thirteen of our patients (48.1%), injury of either one nerve (18.5%; 5/27) or at least two nerves (29.6%; 8/27) could be observed.

Table 13: Depiction of the neural injuries with concomitant vascular injuries (vessel 1, artery under reconstruction; vessel 2, concomitant vascular lesion)

n	Vessel 1	Vessel 2	Mechanism	Nerve(s)	Side
1	subclavian artery	0	avulsion	brachial plexus (median and inferior trunk)	right
2	radial artery	cephalic vein	laceration	ulnar & median nerves	right
3	ulnar artery	radial artery	laceration	ulnar & median nerves & superficial branch of the radial nerve	left
4	brachial artery	0	sensory lesion	median nerve	right
5	popliteal artery	popliteal vein	blunt lesion	peroneal nerve	right
6	popliteal artery	0	blunt lesion	peroneal nerve	left
7	popliteal artery	peroneal artery	blunt lesion	peroneal nerve	left
8	subclavian artery	0	avulsion	brachial plexus	right
9	subclavian artery	0	avulsion	brachial plexus	right
10	common iliac artery	common iliac vein	subtotal avulsion	sacral plexus	left
11	brachial artery	0	contusion	superficial branch of the radial nerve	right
12	brachial artery	brachial vein	laceration partial laceration	radial nerve median nerve	left
13	brachial artery	0	laceration	median nerve	left

Neural reconstruction was conducted in five patients. Here, one anastomosis of the brachial plexus, three neural sutures and one sural-nerve-interposition were conducted.

2.2.4.3 Bone trauma

Ten of the patients (37%) sustained one or more fractures on the concerned extremity. Hereof, six cases had closed whereas four showed open fractures of diverse grading.

The number ranged from single fractures up to five bone traumas. Six patients had only one fracture, whereas there were at least two fractures in the further four cases. Fractures concerned the UE of four patients and the LE in six cases (details in Table 14).

Dislocations occurred in eleven patients (41% of 27). Four times the elbow and seven times the knee was dislocated. Only one of these cases proved to be a dislocation fracture. Six of these lesions were treated surgically through bridging external fixation. These included four knee dislocations, one elbow dislocation and the dislocation fracture, whereas here also primary ORIF of the proximal tibia was conducted.

Table 14: Classification of fractures (n #, number of fractures)

n	Side	Open/Closed	n #	Side of #	Dislocation
1	right	open (II°)	1	clavicle	no
2	left	open (III°)	1	tibia shaft	no
3	left	closed	2	proximal tibia, distal tibia	yes
4	right	closed	2	scapula, clavicle	no
5	left	closed	1	tibia	no
6	right	open (II°)	1	distal humerus	no
7	left	closed	2	proximal tibia, fibula head	no
8	right	open (III°)	1	tibia	no
9	left	closed	5	proximal tibia, fibula head	no
10	right	closed	3	scapula, clavicle, humeral shaft	no

All of the cases underwent surgical intervention for either one or more of the fractures. Due to the heterogeneity of the collective, details for the respective injury patterns and therapies are listed in Tables 14 and 15.

Table 15: Primary and secondary fracture treatment (#, fracture)

n	Side of #	Primary Intervention	Secondary Intervention
1	clavicle	primary plating	none
2	tibia	primary plating	none
3	proximal tibia distal tibia	primary plating of proximal tibia and external fixator	plating of the distal tibia
4	scapula clavicle	primary plating of clavicle and scapula remained conservative	none
5	tibia	external fixator	secondary plating
6	distal humerus	external fixator	secondary plating
7	proximal tibia fibula head	external fixator and fibula remained conservative	secondary plating
8	tibia	primary plating and temporary external fixator	none
9	proximal tibia fibula head	external fixator	none
10	scapula clavicle humeral shaft	primary plating of clavicle, scapula remained conservative and external fixator upper arm	none

2.2.5 Fasciotomy rate

In total, ten patients (37% of 27) underwent fasciotomy. Hereof, eight were conducted prophylactically during primary surgical intervention (each four for UE and LE) and two as a result of verified compartment syndrome. The latter concerned the LE, whereas fasciotomy was once performed during the initial intervention and for the other case, compartment syndrome developed during the in-patient course and fasciotomy was performed as a secondary intervention.

2.2.6 Vascular reconstruction in relation to orthopaedic fixation

Concerning fractures and/or articular instabilities, eleven patients (41% of 27) underwent internal and/or external fixation. Eight of these were conducted secondary to vascular intervention while three preceded vessel reconstruction.

2.2.7 Post-interventional course

Regarding the primary surgical intervention including vascular reconstruction, the collective had a surgery time which ranged from 49 up to 452 minutes with a mean of 235 minutes (SD 111). Fourteen patients (51.9% of 27) underwent further surgeries (step-wise wound closure, secondary fracture treatment etc.) on the concerned extremity.

The mean hospital stay was 22.5 days (SD 16.9; range: 4 – 68) and the mean intensive care unit stay proved to be 5.1 days (SD 7.4; range 0 – 28).

The mean sickness absence rate amounted for a mean of 297 days (SD 238.3) with a range from 5 to 853. Here, two patients who had been retirees before and after trauma, two patients who had been pupils at the time of injury and three persons who proved to be unemployable after the injury, were not included in the evaluation of this value.

2.2.8 Post-operative sensory disturbances

Twenty-one (78% of 27) patients stated post-traumatic peripheral sensory disorders. Of these, twelve concerned the UE (57% of 21) and nine the LE (43% of 21).

2.2.9 Amputation rate

In the patient group a rate of delayed amputations of 11% (3/27) occurred. All of these concerned the LE of male patients.

The first patient sustained a knee dislocation with rupture of the popliteal vessels. His MESS lay at 8 with a prolonged ischemia time (> 6h). The patient underwent venous interpositions for both the popliteal artery and vein, lower leg fasciotomy and received a bridging external fixator at the knee. Eighteen days after primary surgical intervention, the respective extremity was amputated just proximal to the knee joint due to muscular necrosis concerning the upper and lower legs. The patient had to change his workplace. His FFB-Mot score fell from 94 pre-traumatically to 54 points post-traumatically.

The second case also had a knee dislocation with traumatic occlusion of the popliteal artery. His MESS lay at 5 including doubled score for the ischemia time. At primary surgical intervention, he underwent a bypass operation, primary fixation of the proximal tibia and received an external fixator. Due to the development of an infectious hematoma around the medial ankle, the lower leg was amputated at a height of approximately 15 centimetres distal to the knee joint. Here, the specific durance until amputation could not be evaluated since it was conducted in another federal state. In this case, the FFB-Mot went from 100 to 87 points, the patient remained at his pre-traumatic workplace and is still very sportive. The small decline of FFB-Mot points confirms the well-known excellent functional prognosis after below knee amputations.

The third patient was transferred to the hospital with a contaminated, extensive soft tissue wound of the thigh including rupture of the common iliac artery and vein, type C pelvic injury and subtotal pelvic plexus avulsion. Here, the MESS proved to be 8 without prolonged ischemic time. The vascular damage was reconstructed with arterial and venous prosthetic bypass interposition. Due to the occurrence of soft tissue necrosis, the patient underwent above knee amputation six days after primary intervention. His FFB-Mot fell from 100 to 58 points and he had to change his workplace.

2.2.10 Functional outcomes

2.2.10.1 Comparison of the extremities

With respect to the MESS, the UE had a mean value of 5.93 (SD 2.46) and the LE showed a mean of 6.23 (SD 2.49). T-test for independent samples did not show a statistically significant difference ($p = .754$). Therefore, the extremities were regarded as equal with respect to sustained trauma for the statistical analysis. Further, the pre-traumatic scores of the FFB-Mot were 87.86 (SD 7.47) for the UE and 92.31 (SD 24.74) for the LE. Here, *t*-test for independent samples did not reveal statistically significant differences ($p = .327$) between the limbs regarding mobility.

2.2.10.2 Evaluation of the working status

Eleven patients (41% of 27) returned to their pre-traumatic workplace, further eleven participants (41% of 27) had to change their employment and three patients

(11% of 27) were incapable of working after the incident. Two participants had been retirees before and after the trauma.

2.2.10.3 Results of the FFB-Mot

The post-traumatic score of the FFB-Mot amounted for 76.2 points (SD 15.6) for the UE and 62.5 points (SD 20.3) for the LE.

The difference of the pre- and post-traumatic values revealed a post-operative loss of 22.2% of the FFB-Mot's points for the whole sample. Regarding the UE, the patients experienced an average loss of 13.3%, whereas for the LE, the loss amounted for 31.8%. Here, the *t*-test for independent samples showed a statistically significant difference between UEs and LEs. Therefore, the UE had a significant worse outcome in comparison to the UE ($p = .012$).

Regarding the concomitant injuries, Fisher's exact test did not show an impact of muscular ($p = .988$), bone (0.724) or neural ($p = .267$) injuries on the FFB-Mot difference.

Further, linear regression did not reveal a statistically significant coherence between the FFB-Mot difference and the intensive care unit stay ($p = .09$). However, the FFB-Mot difference was statistically significantly influenced by the durance of the hospital stay ($p = .006$).

2.2.10.4 Defined Events

The defined events which meant the lack of post-traumatic re-entrance into the former workplace, respectively a loss of 10% of the FFB-Mots points for retirees occurred in 14 patients (52% of 27). Here, eight cases concerned the LE and six the UE. However, Fisher's exact test did not show statistically significant differences ($p = .449$).

Muscular lesions co-existed with an event in five cases. However, these had no significant influence on the events ($p = 1.00$). This was the same with bone traumas ($p = .695$), which occurred together with an event in six cases. Neural lesions occurred in combination with an event in eight cases and did not have a significant influence on these targets ($p = .449$).

Further, linear regression did not reveal a statistically significant coherence between the event and the intensive care unit stay ($p = .095$) and the durance of the hospital stay ($p = .14$).

2.2.10.5 Analysis of coherence between CHSA-CFS & FFB-Mot

The pre-traumatic mean value for the CFS was 1.44 (SD 0.69) with a range from 1 to four. Spearman's rank correlation coefficient showed a highly significant correlation between this outcome and the pre-traumatic FFB-Mot values of the collective ($p < 0.001$). The post-interventional mean for the CFS proved to be 2.29 (SD 1.14; range 1 – 4). Also this outcome correlated statistically significantly with the post-operative FFB-Mot value ($p < .001$).

2.2.10.6 Analysis of correlation between MESS & DASH questionnaire

Since the DASH questionnaire enables evaluation of UE function, its results were for sure compared solely to the MESS results of the 14 UEs. Here, the mean MESS proved to be 5.93 (SD 2.37; range: 2 – 11) and regarding the DASH questionnaire, the mean score was 30 points (SD 29.63) with a range from 0 to 94.2, for details see Table 16. Spearman's rank correlation coefficient revealed no statistically significant correlation between the total MESS and the total DASH score ($p = .075$).

Further on, seven cases had prolonged time of ischemia (> 6 hours). Here, the mean MESS was 6.85 and the DASH proved to be 43.7 points (SD 35.45; range 0 – 94.2). Spearman's rank correlation coefficient was .86, which was statistically significant ($p = .013$). Additionally, patients who had sustained neural traumas had significantly higher DASH scores in comparison to the group that lacked these injuries (43.1 vs. 6.5 points, $p = .02$).

The Sports/Performing Arts Module of the DASH could be evaluated in twelve cases, whereas the further two patients did not perform any sports or arts.

The mean score was 39.1 (SD 38.2; range: 0 – 100) and had a statistically significant correlation with the respective MESS (*p* = .006) including a correlation coefficient of 0.74.

The DASH Work Module could be analysed for eleven patients, while one patient used to be a retiree before and after the trauma and two patients had become incapable of working due to their injuries. Its mean value was 14.2 (SD 20.2; range: 0 – 56.3) and did not correlate significantly with the MESS (correlation coefficient: 0.57; *p* = .063). For a detailed depiction of the analysis see Table 16.

Further on, four cases had a MESS of at least seven points (see Table 17). Hereof, patient number 14 had a total MESS of 7 points. Here, the post-interventional total DASH was 18.3 points and the patient was still employed at his pre-traumatic work place. Patient number 4 had a score of 8. His post-operative total DASH proved to be 20.8 points, whereas the Sports Module was at 56.3 points. The patient became incapable of working, whereby he had been marginally employed prior to the trauma. Next, patient number 8 had sustained a rupture of the brachial plexus including sensorimotor malfunction. His MESS was 10 points and his post-operative total DASH was at 75. Despite the dysfunction of the UE, the patient showed a very good compensation and even changed his bureau job into work at a construction site. Patient number 7 had a MESS of 11. He was incapable of returning to his work place and his total DASH and the DASH Sports Module had values of 94.2 and 75 points, respectively. Further, he had sustained a burst fracture of the 12th thoracic vertebra leading to spinal canal stenosis and paraplegia and a complete rupture of the brachial plexus resulting in motoric dysfunction of the concerned UE.

Table 16: Comparison of the scores (Hohenberger et al. 2019)

	MESS	**DASH**	***r***	***p***
Total scores	5.93	30	.49	.075
Cases with prolonged ischemia time	6.85	43.7	.86	.013
Cases with applicable Sports/Performing Arts DASH	6.16	39.1	.74	.0006
Cases with applicable Work DASH	5.27	14.2	.58	.063

Table 17: Schedule of MESS and DASH-Score details for each patient (* means duplication of points due to ischemia > 6 hours) (Hohenberger et al. 2019)

Patient	**Skeletal and soft tissue injury**	**Limb ischemia**	**Shock**	**Age**	**Total MESS**	**DASH Score**	**DASH Work Module**	**DASH Sports/ Performing Arts Module**
1	2	4*	0	0	6	62.5	0	75
2	1	0	0	1	2	6.7	0	0
3	2	2	0	2	6	0.8	not applicable	0
4	1	3	2	2	8	20.8	not applicable	56.3
5	1	2	1	0	4	39.2	0	0
6	2	2*	1	0	5	6.7	0	43.8
7	2	6*	2	1	11	94.2	not applicable	75
8	2	6*	2	0	10	75	43.8	100
9	4	2*	0	0	6	24.2	0	81.3
10	2	2*	0	1	5	0	0	0
11	2	2	0	1	5	27.5	31.3	not applicable
12	2	1	0	0	3	0.8	0	0
13	1	4*	0	0	5	43.3	25	not applicable
14	4	2	0	1	7	18.3	56.3	37.5

2.3 Discussion

The surgical management of vascular extremity trauma is challenging. Haemorrhage control as well as maintenance of arterial and venous circulation are the main goals. The incidence of vascular injury has increased during the last decades with reference to large trauma centre reports (Dragas et al. 2009). However, treatment strategies from wartime experiences have led to improvement of interventional coping strategies including a decrease of reported amputation rates (Huynh et al. 2006, Menakuru et al. 2005).

Regarding trauma mechanism, penetrating vascular lesions have been reported to be more frequent in comparison to blunt injuries (Rasouli et al. 2009). Dua et al. (2014) conducted a comparison between civilian versus military popliteal artery injuries, whereof the military group showed a significantly higher incidence of penetrating traumas (96%; 44/46) in comparison to the civilian group (30%; 19/64). In Huynh et al. (2006), the trauma mechanism was mostly (74%; 42/57) blunt in a civilian sample with LE vascular injuries. These findings are comparable to our blunt trauma rate (77%; 21/27). Contrastingly, Myers et al. (1990) reported a perforating trauma rate of 64% in a civilian collective of 80 patients, but their completely different wound type distribution was due to a high amount of gunshot (11/80), stab (7/80) and glass cut wounds (29/80). These injury types were not seen in our cases at all.

In contrast, amputation rates are higher for vascular lesions due to blunt mechanisms (Prichayudh et al. 2009). Klocker et al. (2010) evaluated a limb salvage rate of 98% in a sample of 89 patients who had sustained blunt UE injuries. This value is comparable to our sample since we observed no amputation in the UE subgroup. Popliteal artery injuries carry the highest amputation rates amongst all LE vascular injuries for both, civilian and military patients (Dua et al. 2014, Ratnayake et al. 2014). Ratnayake et al. (2014) observed a significantly higher delayed amputation rate after popliteal artery injuries for military (29%) in comparison to civilian patients (13%). Accordingly, the delayed amputation rate in our sample following popliteal artery injury was 25% (2/8). Liang and colleagues (2016) reported delayed amputation in 26% (11/43) of their evaluated popliteal artery injuries whereas these patients had sustained significantly more blunt traumas in comparison to the primary amputation group. These results are comparable to our collective (two amputations/eight popliteal artery injuries; 25% amputation rate).

As a simple and objective rating scale the MESS was introduced by Johansen et al. in 1990. The assessment was primarily constructed for the LE and later extended to UE injuries. The authors stated that a score of 7 points or more predicted amputation with 100% accuracy. The score and its threshold for amputation have been evaluated in various trials since then.

Prichayudh et al. (2009) managed limb salvage in 12 out of 19 patients with UE trauma including a MESS of 7 or higher and postulated that the decision for or against limb salvage should rather be based on clinical examination. Loja and colleagues (2017) re-evaluated 230 patients with LE vascular injuries with an amputation rate of 18.7% (primary and delayed amputations). The authors found no statistically significant differences between the median MESS of the amputated (MESS: 6 points) and salvaged (MESS: 4 points) limb group after exclusion of confounding variables. Fochtmann et al. (2014) concluded that the threshold for amputation of 7 points should possibly be revised. In our sample, three delayed amputations (all concerning the LE) were conducted. Two of these patients had a MESS of 8 points and lost 43%, respectively 42% of their pre-traumatic FFB-Mot Score. The third patient had a primary MESS of 5 and a surprisingly good clinical outcome with only 13% loss of FFB-Mot points but this underlines the well-known good functional prognosis after below knee amputation. The mean loss of FFB-Mot points within the amputation group was 33% (SD: 13.8; range: 13 – 42) and the mean MESS was at 7 points (range: 5-8). Nine further patients (9/27) were evaluated with MESS values of 7 or more points (mean: 8.4; SD: 1.49; range: 7 – 11) and did not receive amputation. Their mean loss of FFB-Mot points was 37% (SD: 20.3; range: 8 – 69).

Concerning affected vessels, Dua et al. (2014) observed the popliteal artery as the most commonly injured structure on the LE (22%). For the UE, reports either reveal the brachial artery as the most common affected vessel with rates from 34.6% up to 55% (Dragas et al. 2009, Prichayudh et al. 2009), or combined injuries of the radial and ulnar arteries (Myers et al. 1990). Among our patients, 50% (7/14) of all UE injuries concerned the brachial artery and for the LE, 62% (8/13) of the collective sustained a popliteal artery trauma. Lesions of a second vessel occurred in 12 cases (44% of 27), 75% of these were adjacent veins. This is a much higher rate in comparison to Markov et al. (2012) who observed an incidence of 23.4% of associated venous injuries in a civilian study group.

With regard to patient age, data of military and civilian samples differ widely. Military reports include younger patients with age range from eight to 42 years (Ratnayake et al. 2014, Salamon et al. 2016) whereas civilian patients' age ranged from five up to 68 years (Huynh et al. 2006, Menakuru et al. 2005, Prichayudh et al. 2009). Our collective was comparable to the latter with a mean age of 34 years (SD: 17.4; range: 15 – 68) at time of trauma. Concerning gender distribution, vascular traumas tend to affect males more often with up to 89% (Menakuru et al. 2005), which was the same in our sample (89%; 24/27) and may be attributed to male risk behaviour (Paquette et al. 2016).

Dua et al. (2014) observed a significantly lower rate of knee dislocations in combination with popliteal artery lesions in their military collective (2%; 1 out of 46 patients) in comparison to the civilian study group (30%; 19 of 64 patients). The knee dislocation rate within our popliteal artery injuries was much higher compared to the latter (75%, 6/8). This might be traced back to our higher MESS in the LE (6.2 in our sample and 5.1 in their civilian study group).

Associated fractures in patients with femoral artery injuries have been described as a risk factor for poor outcomes (Yavuz et al. 2013). Dragas et al. (2009)

reported fractures of UE bones and brachial plexus injuries to be significant factors for limb loss. In our patients, muscular and neural lesions as well as fractures did neither statistically influence the main target sizes nor the FFB-Mot differences. The impact of concomitant lesions on the amputation rate could not be evaluated statistically due to the low number of cases (three LE major amputations).

The CFS has been proposed as a specific assessment for frailty (Rockwood et al. 2005). Up to now, literature only describes pre- and post-traumatic changes of its values only in elderly patients (Masud et al. 2013, Provencher et al. 2016). Provencher and colleagues (2016) evaluated a collective with extremity fractures regarding their pre- and post-injury CFS. Their data are hardly comparable to ours since they used patients with at least 65 years (this study: mean of 34 years). Their pre-trauma values of the CFS were 1 or 2 points in 56.6%, 3 or 4 in 32.2% and 5 and/or 6 in 11.1% whereas this study sample had values of either 1 or 2 points in 96.3% of cases.

As a limitation of our study, only 27 out of 71 patients matching the defined inclusion criteria could be re-evaluated. It is possible that our sample is a positive selection of all treated patients since patients with satisfactory clinical results are more likely to accept invitations for follow-up studies than those with bad outcomes. Seven patients (10%; 7/71) had already died at the onset of this trial. More heavily injured patients have a worse life expectancy and therefore our study participants are likely to represent a positive selection. Because of the partially long-time interval between trauma and follow-up assessment (mean: 75.7; SD: 33.6; range: 16 – 124 months) patients may have forgotten or upgraded their pre-traumatic FFB-Mot and CFS values. Regarding the FFB-Mot, only two questions (10%; 2/20) focus mainly on the UE whereas seven (35%; 7/20) concern the LE and eleven sub-items (55%; 11/29) involve combined (LE, UE and trunk) activities. Due to this construction of the FBB-Mot a more detailed evaluation of the LE becomes possible and may have influenced our outcomes.

In our patient group, correlation between the MESS (mean 5.9 points) and DASH score (mean 30 points) did not reveal statistically significant but remarkable results (p = .075). This was also observed for the eleven patients with completed DASH Work Module (p = .063). For the seven patients with ischemia time exceeding 6 hours, the MESS (mean 6.85 points) and the DASH questionnaire (mean 43.7 points) correlated significantly (p = .013). Regarding the twelve patients who completed the DASH Sports/Performing Arts Module, the two scoring systems strongly correlated and the results were statistically significant (p = .0006), with a mean MESS of 6.2 and a mean DASH of 39.1. To our knowledge, this is the first study that correlates these two assessment tools, thus no direct comparison with literature is possible.

Töpel et al. (2009) evaluated the outcomes of 33 patients who had undergone arterial reconstruction for major UE vascular injuries. Similar to our study, iatrogenic and injuries distal to the wrist joint were excluded. In Töpel's study, 73% of all traumas involved arteries of the forearm, while in our patient population, the brachial artery was the most commonly injured vessel, which reflects the increased severity of injuries captured in our cohort. Authors compared the patients' functional outcomes based on physical exam (e.g. range of wrist and finger motion) to the respective DASH scores and found a strong correlation between these two assessments. Patients showing severe functional deficits had a significantly higher DASH score (35.8 points) in comparison to participants with minor or no deficits (11.8 points). In our study, despite the involvement of more proximal vessels, the mean post-traumatic DASH score was lower, with an average of 30 points. However, in the subgroup of patients with prolonged ischemia time, a higher mean DASH score was observed (43.7 points). Töpel et al. demonstrated a higher rate of functional deficits (56%) in patients with concomitant nerve injuries (27 patients/81%). In our study, the three patients who had sustained injuries of the brachial plexus also had the worst functional outcomes and the highest DASH scores (62.5, 75 and 94.2 points respectively).

Joshi et al. (2007) performed a retrospective review using the DASH score as the mean outcome assessment tool for 17 patients who had sustained blunt or penetrating UE traumas with associated major arterial injuries. Comparable to our results, their patients were predominantly males and underwent reconstruction with vein grafts in the majority of cases. Furthermore, the most commonly affected vessel proved to be the brachial artery in 65% of cases, which was almost the same for our cohort (64%). Their limb salvage rate of 94% was also comparable to our patient series (100%). Higher, though not statistically significant DASH scores were observed in the subgroup of patients who had suffered blunt trauma with a mean score of 61.8 points, compared to patients with penetrating injuries, with a mean score of 22.8 points. The authors suggested that higher DASH scores in the blunt trauma group were the result of concomitant nerve and orthopaedic injuries, often associated with crash or other types of blunt trauma. Interestingly, in our study, the means of the total DASH score between these two subgroups demonstrated minor differences (blunt: 31 ± 32.4 points; penetrating: 27.5 ±14.7 points). Concomitant nerve injury was present in 64% (9/14) of our patients, which is relatively high in comparison to Klocker et al.'s (2010) results with 43% (38/89).

Frech et al. (2016) conducted a retrospective review of prospectively collected data, assessing the results of the DASH questionnaire of 65 patients who had sustained arterial reconstruction due to UE injuries. Patients with associated nerve traumas scored significantly higher (mean of 40.3 points) in comparison to the group without nerve injuries (mean of 0.8 points). These findings were confirmed by our results (43.1 vs. 6.5 points, $p = 0.02$). However, the authors of this study did not find worse clinical outcomes in patients with brachial plexus injuries in comparison to the subgroup with peripheral neural traumas, even though patients with such lesions showed the highest DASH scores in our study.

The MESS was introduced by Johansen et al. (1990) as a simple and objective rating scale determining the need of LE amputation after significant vascular trauma (Sharma et al. 2003, Togawa et al. 2005). Four different variables were included: skeletal and soft tissue injury, limb ischemia, shock as well as patient age. The score was designed in a civilian setting based on a retrospective analysis of 25 patients who had sustained mangled LEs and on a prospective study of additional 26 trauma patients with devastating vascular LE injuries. During the retrospective analysis, the patients with salvaged extremities had a mean MESS of 4.9, whereas the amputation group had a mean of 9.1, which was significantly higher. These findings were confirmed by their prospective trial, and the authors concluded that a value of seven or more points predicted amputation with 100% accuracy. (Johansen et al. 1990) Up to now, the MESS has been applied to UE injuries and has been evaluated for both, upper and lower limbs (Mommsen et al. 2010, Prasarn et al. 2012, Prichayudh et al. 2009).

The use of the MESS and the cut-off point of ≥7 points as an indicator for amputation remain controversial. Ege and colleagues (2015) stated the MESS not to be predictive in combat related UE and LE trauma including open fractures. Similarly, Sheean et al. (2014) demonstrated that a MESS of at least seven points has a positive predictive value of 50% only in patients with LE traumas in the military setting and disadvised its use. To the contrary, Sharma et al. (2003) suggested that a MESS ≥7 positively predicts need for amputation in 100% of patients after examining 50 patients with mangled LEs. However, they found the score lacking prediction of successful extremity salvage and functional outcomes since many of the patients with a MESS ≤ 7 required delayed amputation. Prichayudh and colleagues (2009) postulated that the decision for or against limb amputation should rather be based on individual clinical signs, since they were able to avoid amputation in 12 out of 19 patients with limb threatening UE traumas with a MESS of at least 7. In Fochtmann et al.'s (2014) evaluation of 93 third-degree open tibia shaft fractures, the MESS proved to be significantly higher in the subgroup requiring amputation. However, the authors concluded that the threshold of 7 points should be reassessed and possibly revised. In a follow-up study, Yeh et al. (2016) suggested the additional use of the ISS in cases of MESS between 7 and 9 points. If the ISS exceeds 18 points, amputation should be considered and if it is less than 18 points, salvage of the extremity should be attempted, with approximately 60% success rates based on the authors’ experience.

In our study, none of the critically injured extremities underwent amputation, even though four patients had a MESS of at least seven points. Patients with borderline MESS of 7 or 8 points achieved satisfactory long-term results, based on their post-operative total DASH scores (18.3 and 20.8, respectively). Regarding the highest MESS scores (10 and 11 points), both patients had sustained a complete rupture of the brachial plexus leading to motor and sensory dysfunction of the injured extremity. One patient had become incapable of working, however he had also sustained paraplegia due to a burst fracture of the 12th thoracic vertebra, so it is difficult to draw conclusions regarding the actual cause of his disability. Regarding the threshold of 7 MESS points for amputation, 50% of our patients with MESS of 7 or higher had satisfactory functional outcomes and the other half had a sensorimotor deficit of the UE as a result of their direct brachial plexus lesions.

The wider applicability of the results of this retrospective study is limited by the inherent bias of this type of study. Additionally, the included patient group was small and concerned exclusively civilian traumas. Therefore, our results can only be compared to studies including patients with similar injury mechanisms. Furthermore, follow-up time showed a wide range from 17 to 124 months (mean 70.1 months; SD 35.8).

2.4 Conclusion

Concluding from our results, functional outcome after limb trauma with arterial reconstruction is worse for the LE compared to the UE. When assessed with the FBB-Mot, there was a significant difference ($p = .012$). This worse functional outcome was not associated with a higher rate of patients that were unable to return to their pre-traumatic workplace. The mean loss of FFB-Mot points was 33% in the amputation group which had a mean MESS of 7 points at time of admission. In comparison, nine further patients showed MESS values of 7 or more points with a mean of 8.4 and did not undergo amputation. The mean loss of FFB-Mot points of this subgroup was 37%. As indicated by this outcome, the threshold for amputation of 7 points of the MESS might need revision.

In patients with vascular trauma of the UE, the DASH Sports/Performing Arts Module correlates positively and significantly with the respective MESS. Furthermore, the DASH score correlated positively and significantly with the MESS in patients with prolonged ischemia time (> 6 hours). The use of a MESS of 7 or more points as an indication for primary amputation is not justified, as half of our patients with a MESS ≥ 7 achieved satisfactory functional outcomes at long term follow-up. Early intervention and decreased ischemia time may increase chances of limb salvage. Further studies including more patients need to be conducted to verify our results and lead to firm conclusions regarding accurate predictors of poor outcomes, indicating amputation in patients suffering such injuries.

3 BIOMECHANICAL TRIAL

3.1 Material and Methods

3.1.1 Specimen harvesting

3.1.1.1 Preface

The specimens for the biomechanical tests were extracted from human adult cadavers during routine autopsies at the Institute of Pathology of the Medical University of Graz. As structures of interest, we chose the subclavian (SAs) and common iliac arteries (CIAs), both branches arising from the aorta.

The resection of the vessels was conducted unilaterally (alternately the SA and CIA were excised from the right respectively left side). Further, only segments without palpable wall calcifications were included. Arteries showing signs of atherosclerosis during autopsy were rejected. Therefore, dissection of appropriate arteries was carried out between May, 11th 2016 and March, 21st 2017.

Regarding details on the respective specimen donors, targets such as age, cause of death, underlying disease and the individual status of atherosclerosis (which was determined by the assigned pathologist) were selected from the autopsy report.

3.1.1.2 Dissection protocol

Opening of the thoracic and abdominal cavities was performed through a Y-cut in a typical manner. Next, dissection of the skin and subcutaneous tissues was performed until the bone structures of the torso and the intercostal musculature were exposed. The thoracic cage was then opened via scissors bilaterally whereby the cut was stopped directly at the sternoclavicular joint to avoid injury of the SA.

The sternoclavicular joint was then cautiously opened and the clavicle was lifted to depict the underneath situated vascular bundle. After identification of the artery, its course was traced as far lateral as possible and the vessel was resected. On the medial side, the cut-off was placed directly at the exit from the pericardial sac, respectively at the division from the brachiocervical trunk. The medial ending was marked with a simple interrupted suture for orientation. After removal of the viscera, the CIA was dissected. Here, marking of the proximal end was again conducted with a suture.

Immediately after specimen collection, the respective arteries were transported to the Institute of Biomechanics at the Graz University of Technology in small containers filled with Phosphate-buffered saline (PBS). Here, they were tested at the day of dissection.

3.1.2 Biomechanical tests

3.1.2.1 Preparation

Prior to the biomechanical tests photo documentation was conducted for each specimen. As depicted in Figure 4, a straight segment of approximately 40 mm in length was gained from the SA, respectively the CIA for the extension-inflation-torsion tests. Additionally, two circular segments were cut off from the used arteries for the later conducted histological analysis, residual stress measurements and the second-harmonic generation (SHG) imaging microscopy. For the biomechanical tests, preferably straight arterial segments were used since curved vessels tend to lead to buckling including wrong test results.

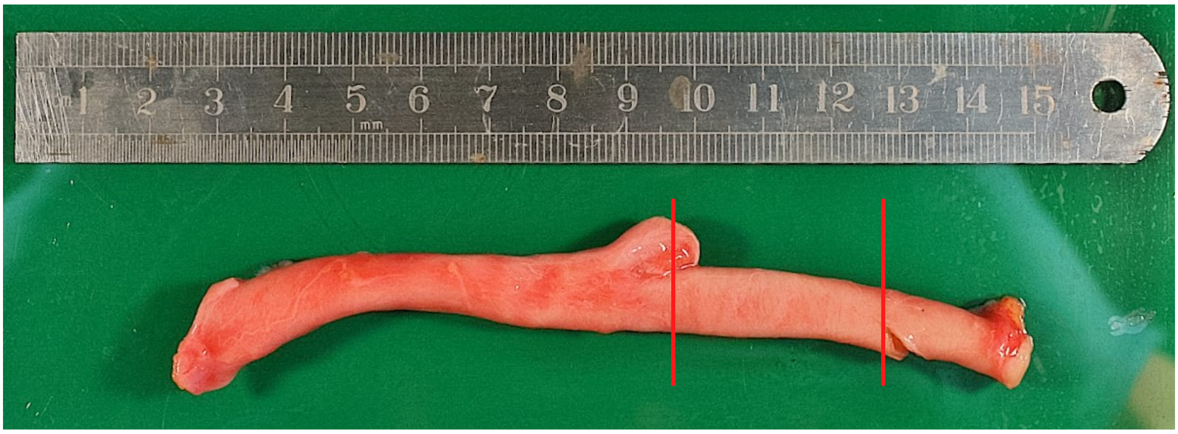

Figure 4: Photodocumentation of a left CIA (red boundaries represent segment for extension-inflation-torsion tests). Reproduced from Sommer et al. (2018) with permission of Elsevier.

Regarding measurement of the axial deformation, special biological tissue dye was used to generate a tracking pattern on the specimens for videoextensometer measurements.

For fixation of the specimens in the testing apparatus, both of their endings were cannulated with individually designed tube connectors. For ideal match with the respective vessel diameter, the arterial endings were tied through corduroy strings to these. The whole construct was then inserted in the testing machine where the arteries were submerged in 37°C warm PBS solution. All tests were performed at 37°C temperature.

3.1.2.2 Extension-Inflation-Torsion test protocol

The specimens underwent tests using an extension-inflation-torsion machine (µSTRAIN AU 14-0406, Messphysik; Fürstenfeld, AUSTRIA; see Figure 5). The prepared vessels were tested at transmural pressures (p) with a range from 0 up to

26.6 kPa (200 mmHg). Here, the transmural pressure, axial force (F_z), outer diameter and gage length of the arterial segments were continuously measured.

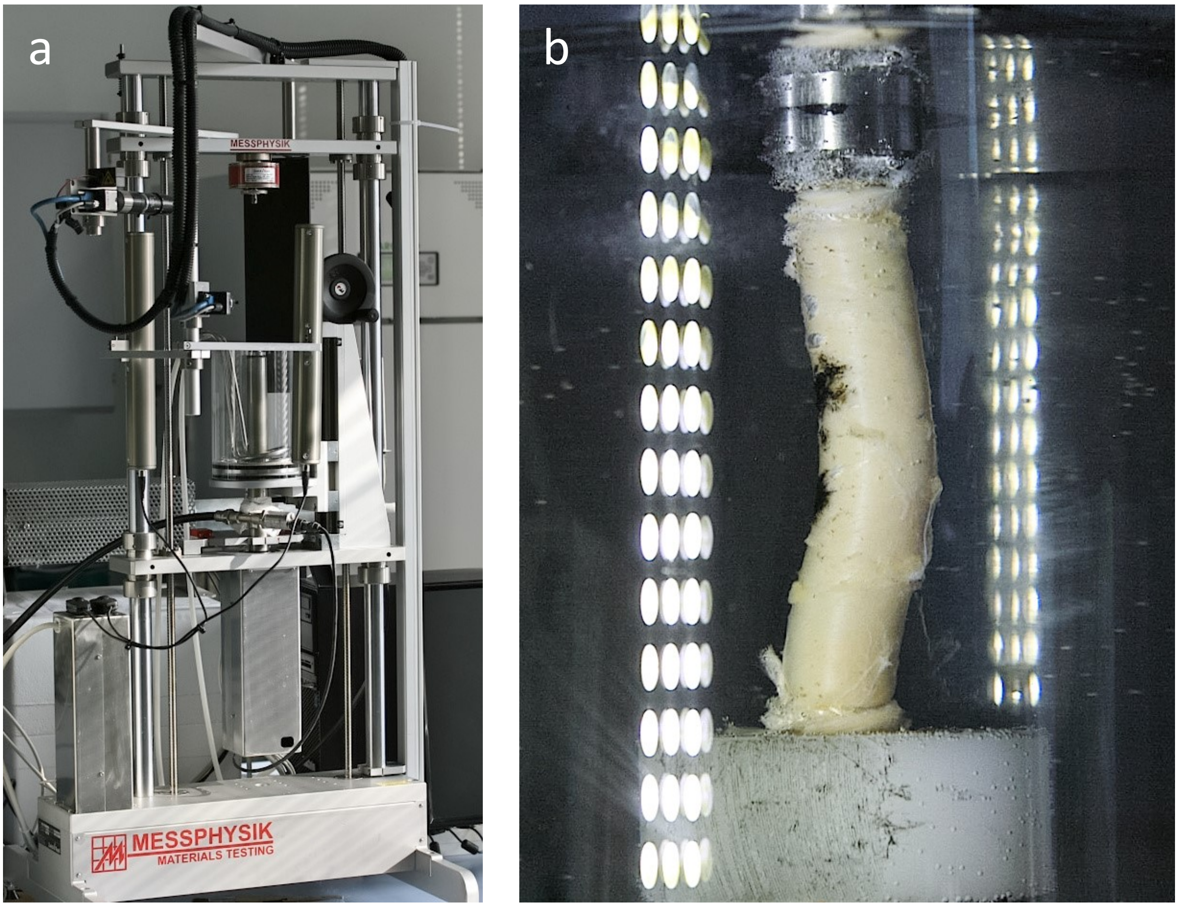

Figure 5: Test protocol. a) Test apparatus. b) Inserted specimen.

3.1.2.3 Preconditioning protocol

During each increase of the axial stretch, the arterial wall underwent axial as well as circumferential preconditioning. This was initially conducted through five axial stretch cycles with a range from the initial condition of 0% axial stretch to 10% stretch, which was then held. An axial stretch of 10% was chosen since preliminary tests have shown an axial *in vivo* pre-stretch of about 10%.

3.1.2.4 Test protocol

After preconditioning the measurement protocol was started. The arteries were stretched axially from $\lambda_z = 1$ to $\lambda_z = 1.2$ in 0.05 increments. At each axial stretch, the pressure was increased from 0 kPa to 26.66 kPa in steps of 3.33 kPa. At each pressure step a twist in the range of ±25° was applied to the artery.

3.1.2.5 Statistical analysis

A *t*-test was used to compare the values for SA and CIA. The α-level was set at 5%, therefore *p*-values below .05 were considered statistically significant.

3.1.3 Histology

3.1.3.1 Tissue preparation and staining

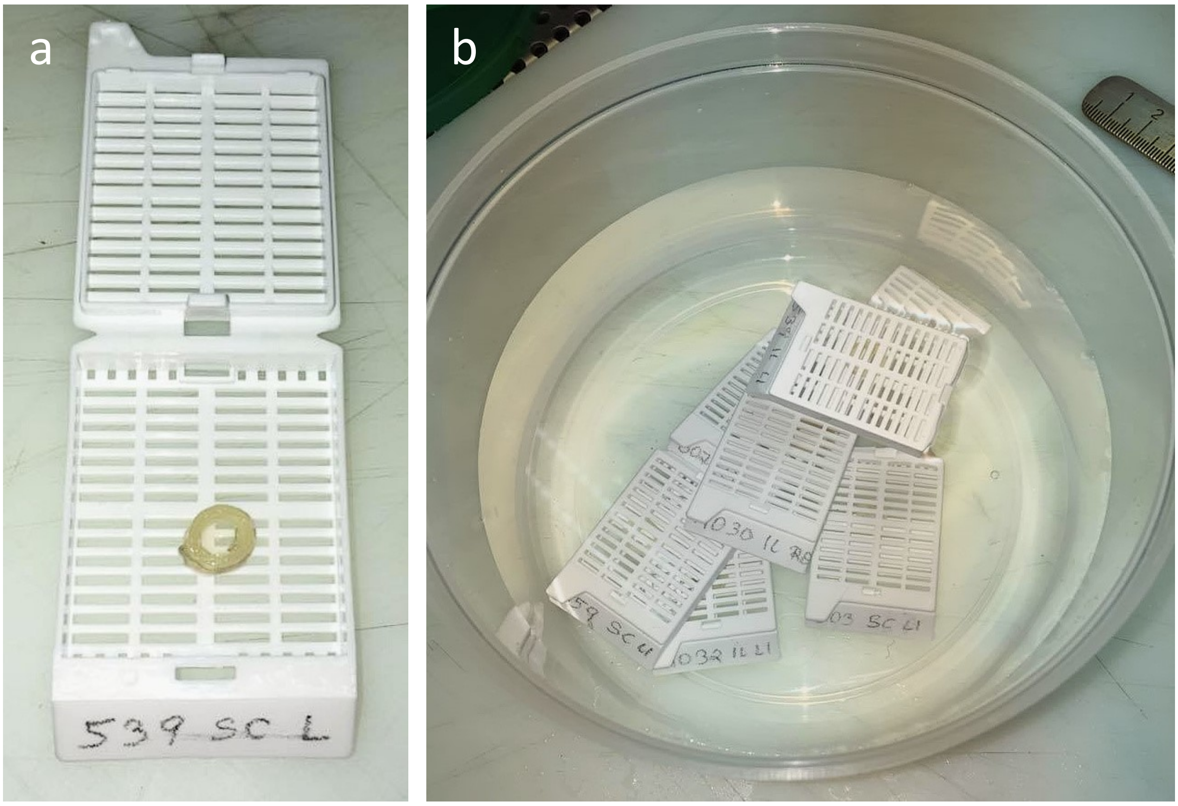

Figure 6: Annular sections in small containers for tissue preparation, histological staining and investigation. a.) Section of a left SA. b.) Various sections of arterial specimens in buffered 4% formaldehyde solution.

Before tissue preparation for the mechanical tests, one annular section was cut off from each specimen and fixed in formaldehyde. For histological assessment, seven pairs (each consisting of one SA and one CIA) were utilised. The evaluation was conducted at the Institute of Pathology of the Medical University of Graz. Here, the prepared sections were transferred into liquid-permeable tissue containers and stored in a buffered 4% formaldehyde solution (pH 7.4) filled receptacle for fixation (see Figure 6). Afterwards, they were embedded in paraffin and sectioned at about 43 µm. Following these standard procedures the samples were stained with Hematoxylin and Eosin (H&E), as routine staining in histology/pathology, and Elastica van Gieson (EvG) to highlight especially elastic fibres. These are stained in black whereas collagen fibres are stained red, and other tissue elements including smooth muscle cell cytoplasm are stained yellow/orange.

3.1.3.2 Histological analysis

The sections were examined under a light microscope and assessed for differences between the SAs and CIAs regarding fractions of elastin and collagen as well as atherosclerotic plaque formations. Further, they were photographed and analysed with regard to their components by use of an image analysis routine within the Aperio ImageScope software package (version 12.0).

3.1.4 Second-harmonic generation (SHG) imaging microscopy

Taken from our testing sample, nine specimen pairs underwent SHG microscopy. Before SHG imaging, the specimens were optically cleared to enhance the penetration depth of the microscope.

3.1.4.1 Reagent preparations

The following solutions were fabricated for the optical clearing process:

- ⇨ PBS: For fabrication of 1000 mL of PBS, 1.44 g of monosodium phosphate (NaH_2PO_4), 0.24 g of monopotassium phosphate (KH_2PO_4), 0.24 g potassium chloride (KCl), 8 g of sodium chloride (NaCl) and 1000 mL of distilled water were mixed.

- 4% Paraformaldehyde (PFA): To get 900 mL of PFA, 7.8 g of disodium phosphate (Na_2HPO_4), 1.87 g of NaH_2PO_4 and 100 mL of formaldehyde (36 – 40%) were mixed and filled up to 900 mL with distilled water.
- Ethanol series: we created a 50% ethanol, 70% ethanol, 95% ethanol and 100% ethanol by combining ethanol and distilled water.
- Benzyl alcohol/benzyl benzoate (BABB) solution: hereof, a 1:2 solution was mixed.
- Ethanol-BABB-solution: this 1:1 solution of ethanol and BABB was mixed under the fume hood.

3.1.4.2 Optical tissue clearing protocol

Primary, rectangular pieces were extracted from the SAs, respectively CIAs (Figure 7 A/B). For fixation, these were put into a 4% PFA solution for approximately twelve hours at room temperature (Figure 7 C).

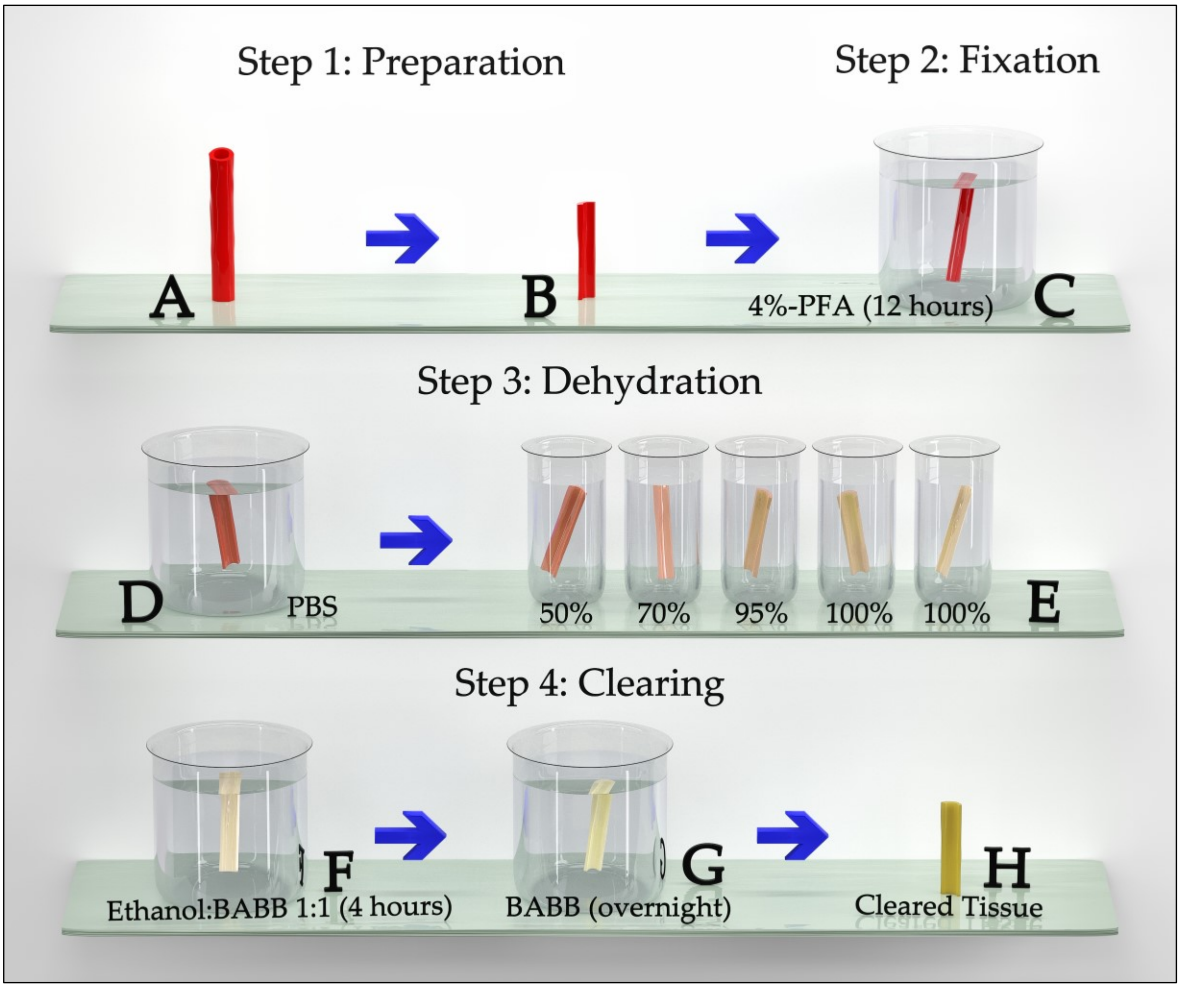

Figure 7: Schematic depiction of the optical tissue clearing protocol

Afterwards, the specimens were shortly rinsed twice with PBS for purification from the 4% PFA (Figure 7 D). The next step was the dehydration process, whereby the tissues were brought into an ethanol series with each step lasting 45 minutes. This included 50%, 70%, 95% and 100% twice (Figure 7 E). The specimens were air-dried for a few minutes after each step.

Following the dehydration process, the specimens were placed in a 1:1 ethanol:BABB solution for four hours (Figure 7 F). After this interval, the tissues were put into 100% BABB solution overnight (Figure 7 G). On the following morning, the arterial sections were kept in BABB-filled small containers, wrapped with aluminium sheets in order to prevent chemical changes of the BABB due to exposure to light. Figure 8 shows the end result of a cleared specimen.

Figure 8: Photography of a cleared specimen

3.1.4.3 Conduction of SHG microscopy

SHG microscopy was performed at the Institute of Science and Technology in Klosterneuburg. It was conducted via a picosecond Chameleon Titan:Sapphire laser source (Coherent, Inc., USA) and an optical parametric oscillator (picoEmerald, Germany), which had been integrated into a TriM Scope II confocal microscope (LaVision BioTec GmbH, Germany). For induction of second harmonic generation of collagenous fibres, the laser was turned to 880 nm. Signal detection was conducted with a non-descanned detector under use of an emission filter (469/50 nm). Images for evaluation were taken with a Leica IMM CORR CS2 20x 0.68 water immersion objective appropriate for deep tissue imaging.

3.2 Results

3.2.1 Patient collective

The analysed group consisted of 17 patients, respectively six male and 11 female cadavers. Their age ranged from 43 to 96 with a mean of 65.3 (SD 17.23). The macroscopic findings of their arteries, their causes of death and underlying diseases are listed in Tables 18 and 19.

Table 18: Vascular sample with respective causes of death and underlying diseases

n	Gender	Age	Side	Death Cause(s)	Underlying Disease(s)
1	M	48	L	AMI, GCD	VT
2	F	46	R	CSVT	AR, SH
3	F	63	R	PT	TAA
4	F	49	L	SH	AD
5	F	96	L	PB, RVD	OC, PEM
6	M	82	L	TP	MSCS
7	F	52	L	HF	MRC, PE
8	M	58	L	HF (LV), MI	CH
9	F	50	L	TP	MAL
10	F	61	L	CF	PEM (HG), HC
11	M	50	R	GCD, TP	CUP
12	M	43	R	sepsis, MOV	peripheral PE
13	F	92	L	pneumonia, HF (RV)	MMC
14	F	75	L	pneumonia	BCC
15	M	78	L	CF	BP
16	F	88	L	RVD	peripheral PE, PI
17	F	79	R	RVD	pneumonia, PEM

AD, autoimmune disease (unclear); AMI, acute myocardial infarction; AR, aneurysm rupture; BCC, basal cell carcinoma; BP, bronchopneumonia; CF, cardiorespiratory failure; CH, cor hypertonicum; CSVT, cerebral sinus venous thrombosis; CUP, cancer of unknown primary; F, female; GCD, global cardial dilatation; HC, hypopharyngeal carcinoma; HF, heart failure; HG, high-grade; L, left; LV, left ventricular; M, male; MAL, metastasising adenocarcinoma lung; MMC, metastasising mammary carcinoma; MOV, multi-organ failure; MI, myocardial ischemia; MRC, metastasising rectal cancer; MSCS, metastasising spindle cell sarcoma; n, number; OC, oral cancer; PE, pulmonary embolism; PEM, pulmonary emphysema; PI, pulmonary infarction; PT, pericardial tamponade; PB, purulent bronchitis; R, right; RV, right ventricular; RVD, right ventricular dilatation; SH, subarachnoid haemorrhage; TAA, thoracic aortic aneurysm; TP, tumor progression; VT, ventricular tachycardia

Table 19: Status of atherosclerosis of the respective specimen donors per arteries. Data were stated by the assigned pathologist (HG, high-grade; LG, low-grade; M, moderate; NC, no comment)

n	Basal Cerebral Arteries	Coronary Arteries	Kidney Arteries	Aorta and Branches	Pulmonary Arteries
1	LG to M	M	LG	M	NC
2	NC	NC	NC	NC	NC
3	NC	HG	NC	HG	HG
4	LG	LG	LG	LG	NC
5	LG	M	NC	HG	NC
6	NC	HG	NC	M	NC
7	LG to M	NC	NC	NC	NC
8	LG to M	M	LG to M	M to HG	LG to M
9	NC	NC	NC	NC	NC
10	LG	LG	LG	HG	NC
11	LG	LG to M	LG	M to HG	LG to M
12	LG	LG to M	NC	LG to M	LG to M
13	M	HG	M	HG	NC
14	LG to M	M	M	M to HG	NC
15	LG	LG	NC	M to HG	NC
16	LG to M	LG	HG	HG	LG to M
17	LG to M	LG	LG to M	HG	LG

3.2.2 Biomechanical tests

3.2.2.1 Extension-inflation tests

3.2.2.1.1 Preconditioning

As displayed in Figure 9, axial forces were clearly increased for the CIA in comparison to the SA during axial preconditioning.

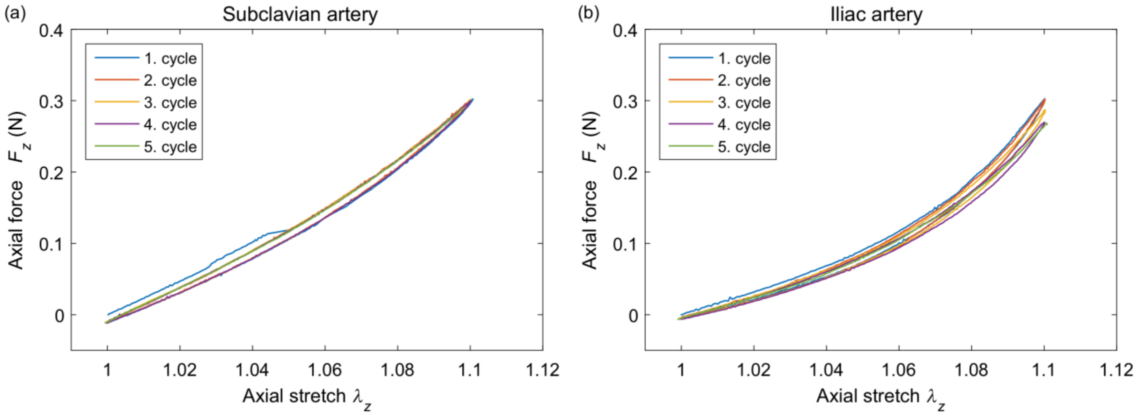

Figure 9: Typical axial force versus axial stretch behaviour of a representative SA (a) and CIA (b) during five cycles of preconditioning (up to $\lambda_z = 1.1$)

During circumferential preconditioning, the SA (Figure 10a) showed stiffer behaviour in the circumferential direction than the CIA (Figure 10b). On the other hand, axial stretches slightly decreased during circumferential preconditioning (Figures 10c and 10d).

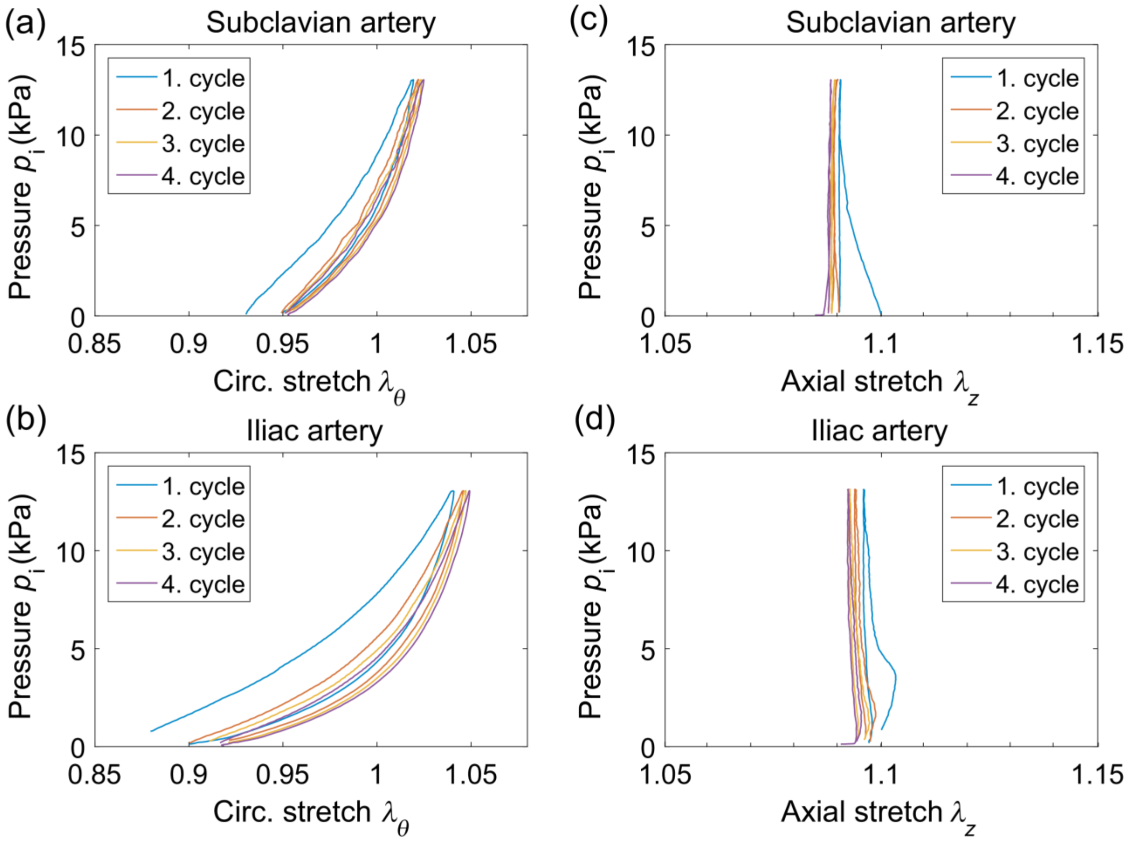

Figure 10: Representative preconditioning behaviour in terms of pressure versus circumferential and axial stretch plots of SA (a & c) and CIA (b & d) during preconditioning cycles up to 13.3 kPa (initial axial stretch of $\lambda_z = 1.1$)

3.2.2.1.2 Extension-inflation behaviour

Figures 11 and 12 show representative pressure versus circumferential stretch and pressure versus axial stretch behaviours resulting from inflation up to 26.6 kPa.

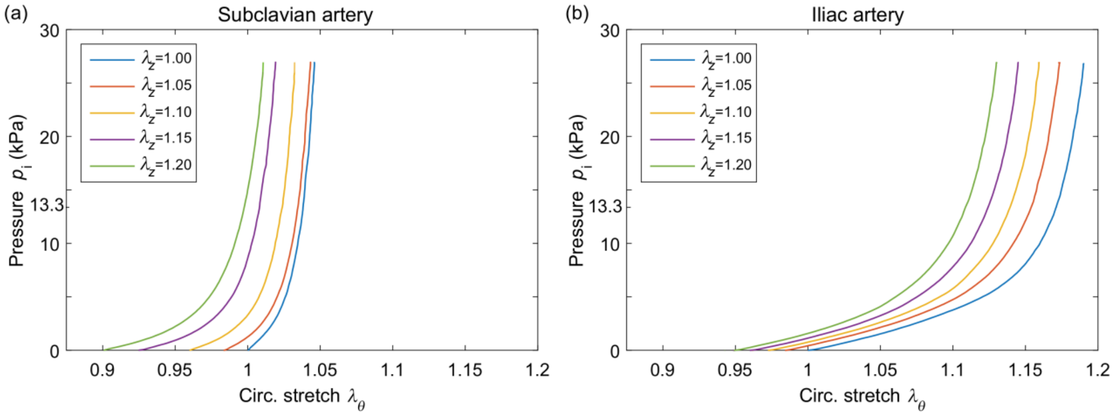

Figure 11: Inflation pressure versus circumferential stretch plots for SA (a) and CIA (b) at varying axial pre-stretches (λ_z = 1.0 – 1.2 in 0.05 increments). Reproduced from Sommer et al. (2018) with permission of Elsevier.

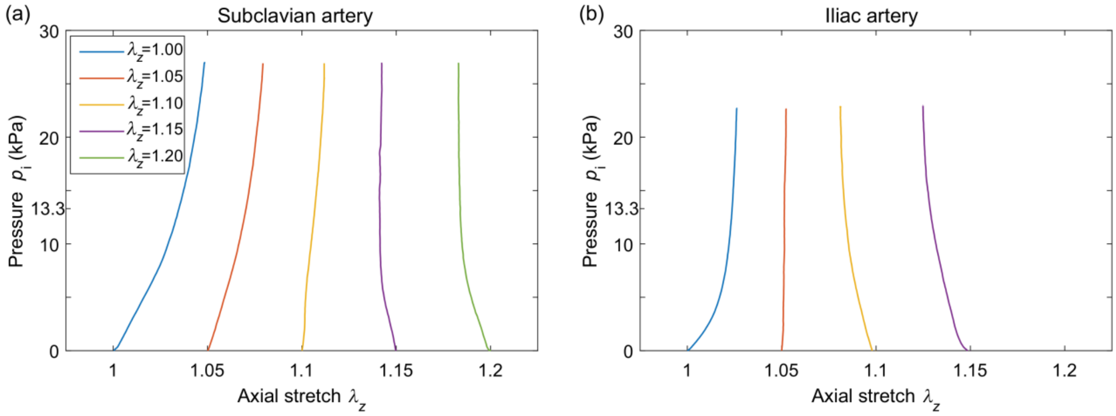

Figure 12: Inflation pressure versus axial stretch plots for SA (a) and CIA (b) at different axial pre-stretches. Reproduced from Sommer et al. (2018) with permission of Elsevier.

As depicted in Figure 11, the CIA was more compliant in the circumferential direction when compared to the SA. In the pressure-axial stretch plot of Figure 12, the SA showed elongation at axial pre-stretches of λ_z = 1.0, 1.05 and 1.1. Further, the SA shortened at λ_z = 1.15 and 1.2 during inflation indicating an inversion stretch (λ^*)

between $\lambda_z = 1.10$ and 1.15 for this specimen. The CIA elongated at $\lambda_z = 1.0$ and kept a constant length at $\lambda_z = 1.05$ showing that this axial stretch is similar to the inversion stretch.

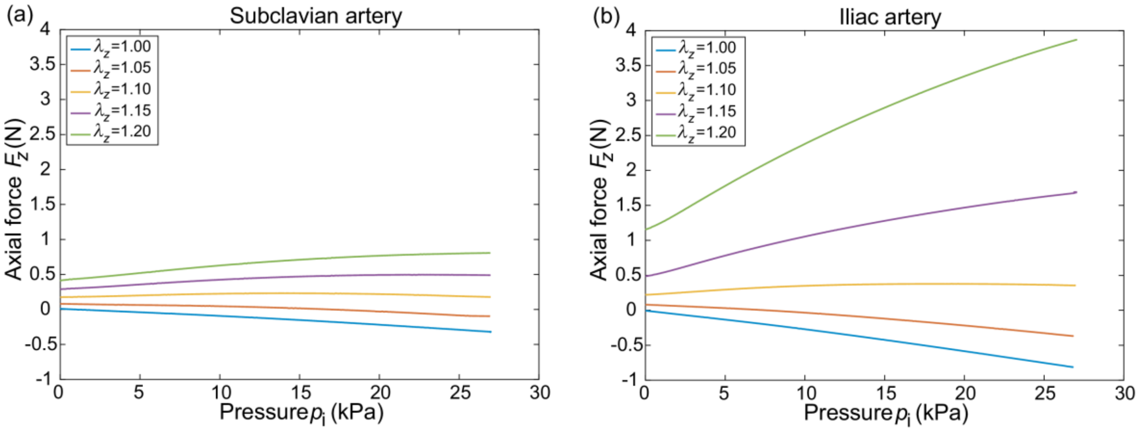

Figure 13: Axial force versus pressure behaviour of SA (a) and CIA (b) at different pre-stretches in a representative specimen (horizontal lines represent the inversion stretch)

As seen in Figure 13, the axial force decreased with inflation below the inversion stretch and increased with inflation above it. The CIA (Figure 13a) showed stiffer axial behaviour than the SA (Figure 13b).

3.2.2.2 Inversion stretch

All performed tests showed that the intersection point of the axial force and axial stretch curves correspond to the inversion stretch of the respective artery (see Figure

14). In the depicted axial force-axial stretch plots the inversion stretch was larger for the SA when compared to the CIA.

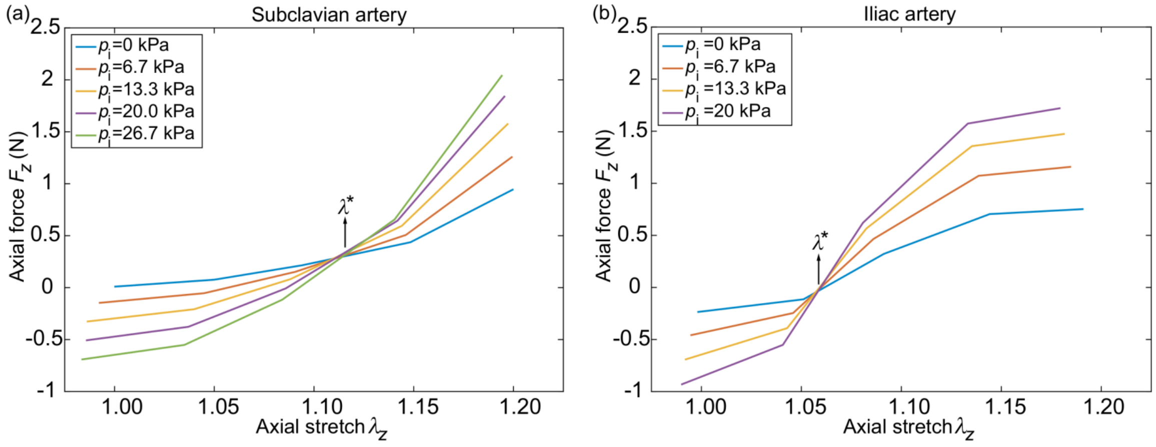

Figure 14: Axial force-axial stretch diagrams for different pressures (represented by the different curves). Reproduced from Sommer et al. (2018) with permission of Elsevier.

Table 20 gives details on the inversion stretches of SA and CIA. The mean value was 1.10 for the SA and 1.07 for the CIA sample. The listed measures did not show significant differences between the SA and CIA (*p* = .21). Further, no statistically significant linear correlations with age could be found for both SA (*r* = −.14; *p* = .7) and CIA (*r* = −.40; *p* = .18).

Table 20: Inversion stretches of SA and CIA

	SA	**CIA**
Median	1.11	1.05
[Q1;Q3]	[1.06;1.13]	[1.04;1.09]
Mean	1.10	1.07
SD	0.05	0.05

3.2.2.3 Circumferential distensibility

Changes of circumferential stretch or circumferential distensibility ($\Delta\lambda_\theta$) were measured for comparison of the mechanical stiffness and properties of the arteries during inflation tests. Table 21 displays circumferential distensibilities of both SA and CIA at an axial stretch of $\lambda_z = 1.1$ and internal pressures (p_i) of 13.3 kPa and 26.7

kPa. Here, larger median circumferential distensibilities were observed in the CIA at both pressures however the differences were not significant (13.3 kPa: p = .55; 26.7 kPa: p = .98).

Table 21: Circumferential distensibilities for SA and CIA at 13.3 kPa ($\Delta\lambda_{\theta,\,13.3}$) and 26.7 kPa ($\Delta\lambda_{\theta,\,26.7}$) at λ_z = 1.1

	$\Delta\lambda_{\theta,\,13.3}$		$\Delta\lambda_{\theta,\,26.7}$	
	SA	**CIA**	**SA**	**CIA**
Median	0.08	0.14	0.12	0.17
[Q1; Q3]	[0.07; 0.16]	[0.07; 0.17]	[0.10; 0.18]	[0.07; 0.18]
Mean	0.10	0.12	0.13	0.14
SD	0.05	0.06	0.05	0.07

3.2.2.4 Inter-specimen variation, circumferential and axial compliances and influence of age

Load-deformation behaviour showed high variation among specimens. Figure 15 shows data from a specimen of a young donor in comparison to an artery of an old donor.

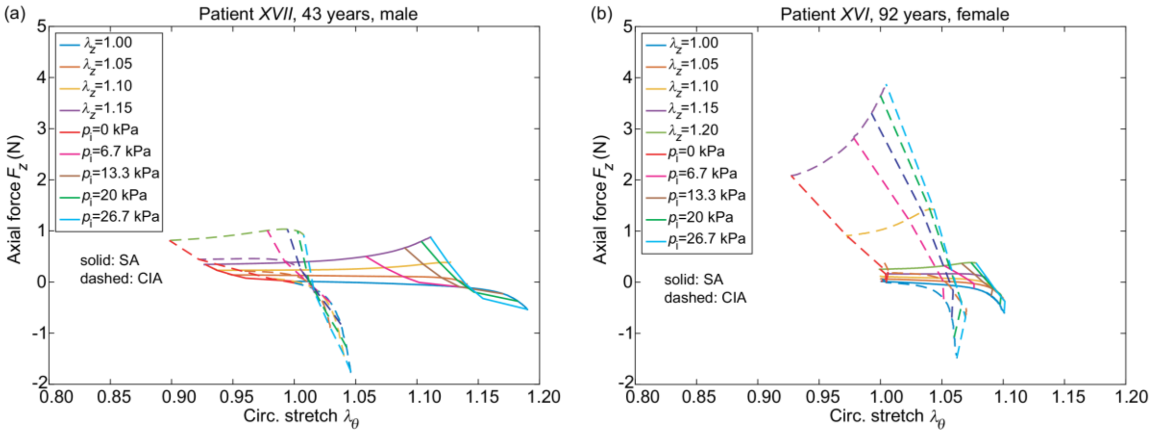

Figure 15: Axial force versus circumferential stretch behaviour of SA (solid) and CIA (indicated by dashed lines) of a young (43 years) and an elder (92 years) patient

For each tested specimen 25 data points are plotted being connected through five lines which indicate different pressure levels (0, 6.7, 13.3, 20, 26.7 kPa). Further five lines represent different axial pre-stretches (1.0, 1.05, 1.1, 1.15, 1.2 kPa). For both donors, the SA showed larger compliances in the circumferential and axial directions when compared to the corresponding CIA.

Pearson's correlation coefficient between age and circumferential distensibility was significant for the CIA ($r = -.61$; $p = .05$) but not for the SA ($r = -.37$; $p = .26$). Correlation between age and axial force range was not significant for both arteries (SA: $r = -.22$, $p = .55$; CIA: $r = .45$, $p = .16$).

3.2.2.5 Stress analysis

Circumferential ($\sigma_{\theta\theta}$) and axial Cauchy stresses (σ_{zz}) as a function of the inflation pressure at different axial pre-stretches are displayed in Figure 16. Both increased with increasing pre-stretch. At no inflation pressure (0 kPa), non-zero axial stretches were obtained due to axial pre-stretching.

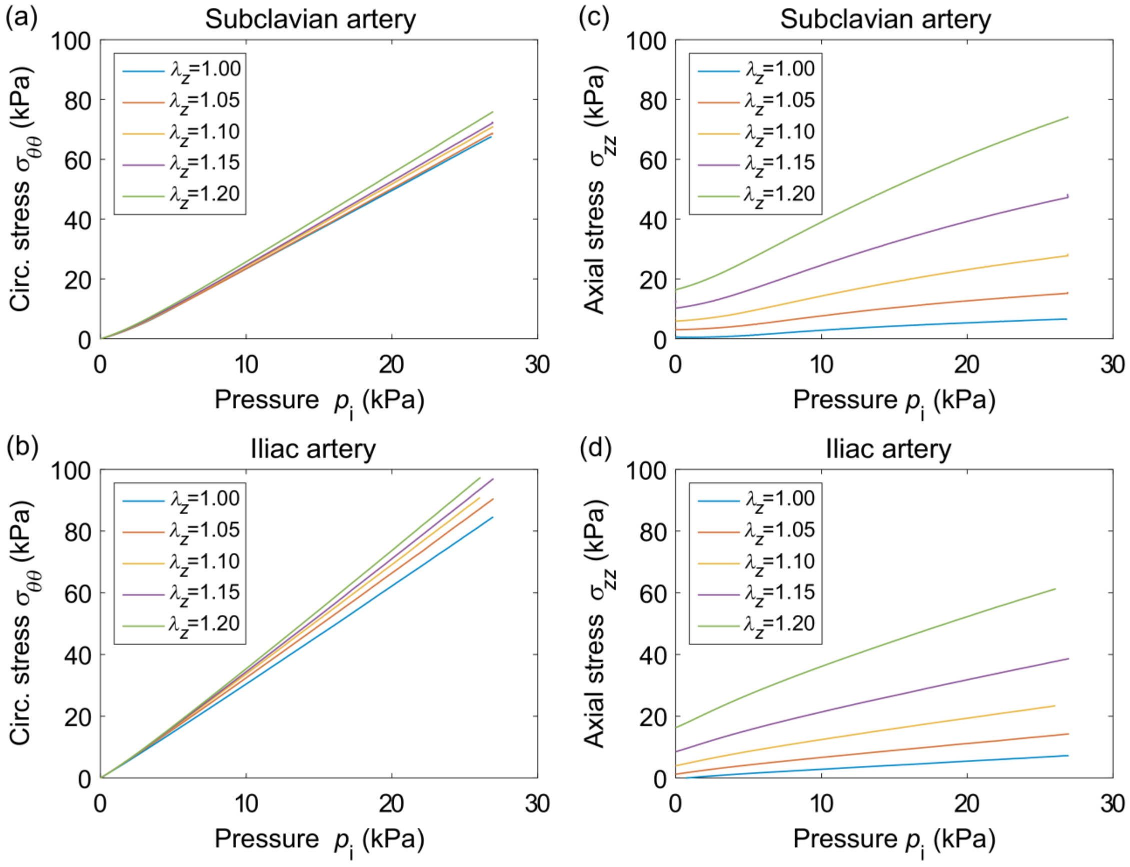

Figure 16: Representative circumferential (a, b) and axial Cauchy stresses (c, d) of SA (a, c) and CIA (b, d) at different axial pre-stretches. Reproduced from Sommer et al. (2018) with permission of Elsevier.

Table 22 shows the Cauchy stress-pressure slopes k_θ and k_z of all utilised specimens at different axial stretches λ_z. The difference between the slopes (k_θ and k_z) was highly statistically significant for both SA (p = .003) and CIA (p = .002).

Table 22: Parameters of circumferential k_θ and axial stress-pressure slopes k_z of the arteries at different axial pre-stretches

		$\lambda_z = 1.00$		$\lambda_z = 1.05$		$\lambda_z = 1.10$		$\lambda_z = 1.15$		$\lambda_z = 1.20$	
		SA	**CIA**	**SA**	**CIA**	**SA**	**CIA**	**SA**	**CIA**	**SA**	**CIA**
Circ. slopes k_θ	**Median**	3.0	2.6	4.0	2.7	3.6	3.6	3.8	3.5	3.7	3.6
	Q3-Q1	1.7	1.1	1.4	1.6	1.5	0.8	1.4	0.9	1.5	0.9
	Mean	3.3	2.8	3.8	2.8	3.4	3.4	3.4	3.7	3.4	4.0
	SD	1.1	0.9	1.3	0.9	1.2	1.1	1.3	1.1	1.3	0.9
Ax. slopes k_z	**Median**	0.4	0.5	0.8	0.9	1.1	1.6	1.5	2.5	2.4	2.8
	Q3-Q1	0.7	0.2	0.8	0.5	0.8	1.0	1.3	1.1	2.3	1.3
	Mean	0.6	0.5	1.3	0.9	1.4	1.7	2.2	2.4	3.9	2.8
	SD	0.5	0.3	1.6	0.4	1.1	0.6	2.3	1.0	4.8	1.1

Figure 17 shows changes of circumferential and axial stresses with increasing axial pre-stretch λ_z. Stresses increased with increasing pre-stretch which was more visible in the circumferential than in the axial stresses.

Table 23 displays the Cauchy stresses in circumferential $\sigma_{\theta\theta}$ and axial directions σ_{zz}, circumferential k_θ and axial stress-pressure slopes k_z and the respective corresponding slope values. The median circumferential stresses $\sigma_{\theta\theta}$ were slightly increased in the CIA sample (p = .56). However, the median axial stresses σ_{zz} were significantly larger in the CIA when compared to the SA (p = .02).

Regarding the median circumferential and axial Cauchy stresses, we found no statistically significant difference between the arteries.

At $\lambda_z = 1.1$ the median circumferential-to-axial stress slope ratios $SR = k_\theta / k_z$ were 2.8 (for the SA) and 2.2 (CIA) which indicates that both arteries were more compliant in the axial than in the circumferential direction.

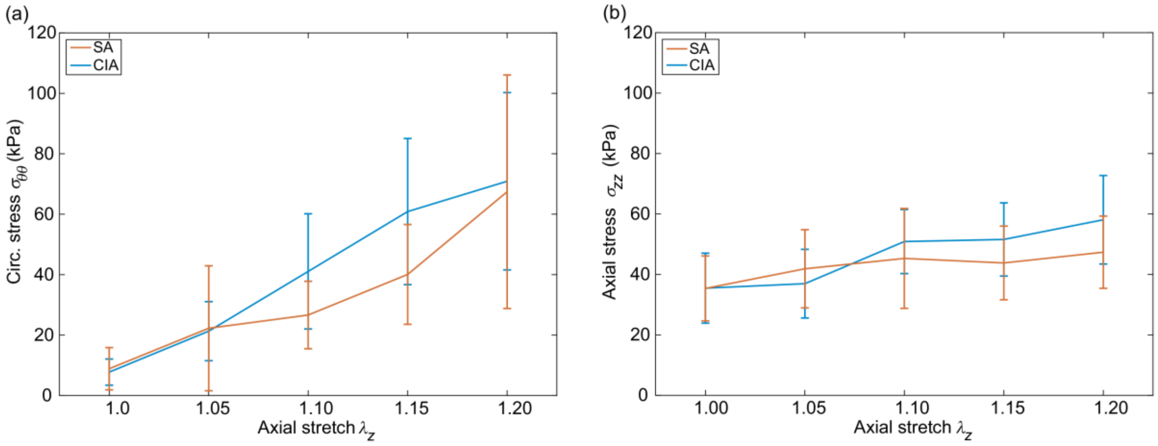

Figure 17: Cauchy stress-axial stretch diagrams (a, b) of the SA (orange) and CIA (blue) at different axial pre-stretches

Table 23: Cauchy stresses (in kPa), stress-pressure slopes and corresponding slope ratios for both SA and CIA at $p_i = 13.3$ kPa and $\lambda_z = 1.1$ (Sommer et al. 2018)

		SA			**CIA**		
	Median	**[Q1;Q3]**	**Mean ± SD**	**Median**	**[Q1;Q3]**	**Mean ±SD**	p
$\sigma_{\theta\theta}$	45.5	[34.2;43.8]	45.3±16.5	45.5	[45.2;57.8]	50.9±10.6	0.56
σ_{zz}	23.7	[17.8;35.3]	26.7±11.2	34.5	[31.0;58.8]	41.1±19.1	0.02
k_θ	3.6	[2.8;4.3]	3.4±1.2	3.6	[2.9;3.6]	3.5±1.1	1.00
k_z	1.1	[0.8;1.6]	1.4±1.1	1.6	[1.2;2.3]	1.7±1.6	0.20
SR	2.8	[1.9;3.9]	2.8±1.4	2.2	[1.7;2.3]	2.3±1.2	0.31

3.2.2.6 Residual stresses

Figures 18 and 19 illustrate the changes of the opening angles α (circumferentially oriented strips) and β (axially oriented strips) for both SA and CIA over time. For both values a pronounced nonlinear residual stress release over time was observed. At the start of the tests, the opening angles of the circumferential/axial strips increased/decreased fast during the primary 30 minutes and reached their zenith after approximately six hours.

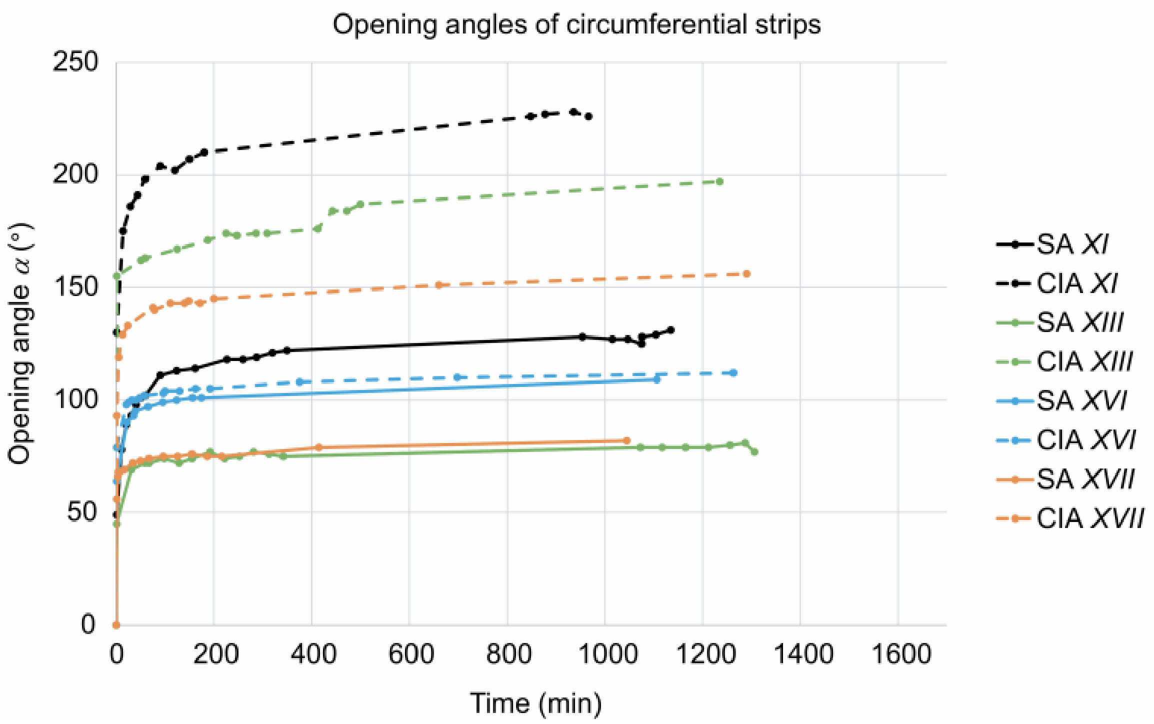

Figure 18: Change of α over the time for SA (solid lines) and CIA (dashed lines). Different colours indicate different body donors.

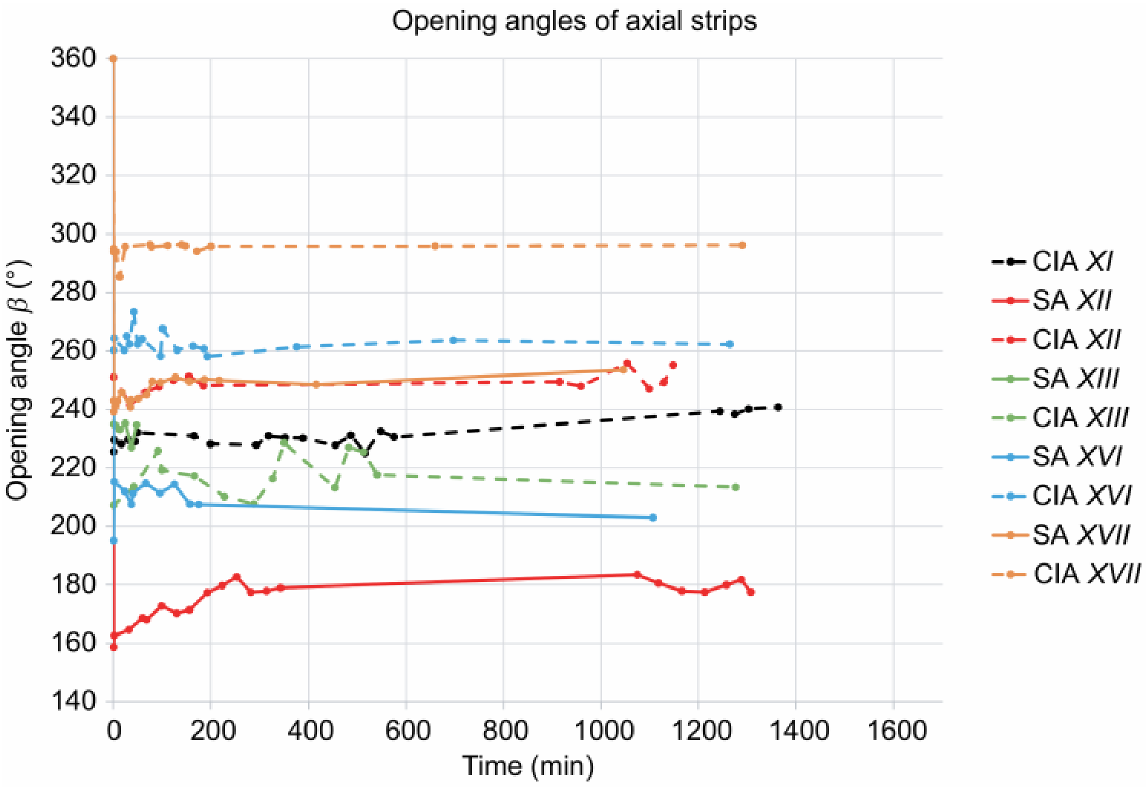

Figure 19: Change of β over the time for SA (solid lines) and CIA (dashed lines). Different colours represent different body donors.

Table 24 presents opening angles α and β of SA and CIA after 30 minutes and 16 hours. The SA sample showed significantly smaller values for α when compared to the CIA specimens after 30 minutes (p = .02) and 16 hours (p = .001) which indicates smaller circumferential residual stresses in the SA. The differences of the median values of β did not differ significantly between the arteries after 30 minutes (p = 1) and 16 hours (p = .73).

Table 24: Opening angles α and β from SA and CIA

	α				β			
	30 min		16 h		30 min		16 h	
	SA	CIA	SA	CIA	SA	CIA	SA	CIA
Median	93	135	79	157	235	230	242	260
IQR	37	37	42	27	81	79	55	24
Mean	94	130	86	155	219	221	247	258
SD	27	39	30	30	57	58	47	34

3.2.2.7 Torsional behaviour

Figure 20 illustrates the representative torque versus twist behaviour of the SA and CIA at a constant pressure of 13.3 kPa and different axial pre-stretches. The curves show the torque behaviour during torsion with an angle of twist θ_{motor} in the range of ±25°. For all axial pre-stretches hysteresis areas during torsion cycles were pronounced. The slopes of the curves in (a) and (b) correspond to the shear modulus G (higher G corresponds to higher torsional stiffness of the artery).

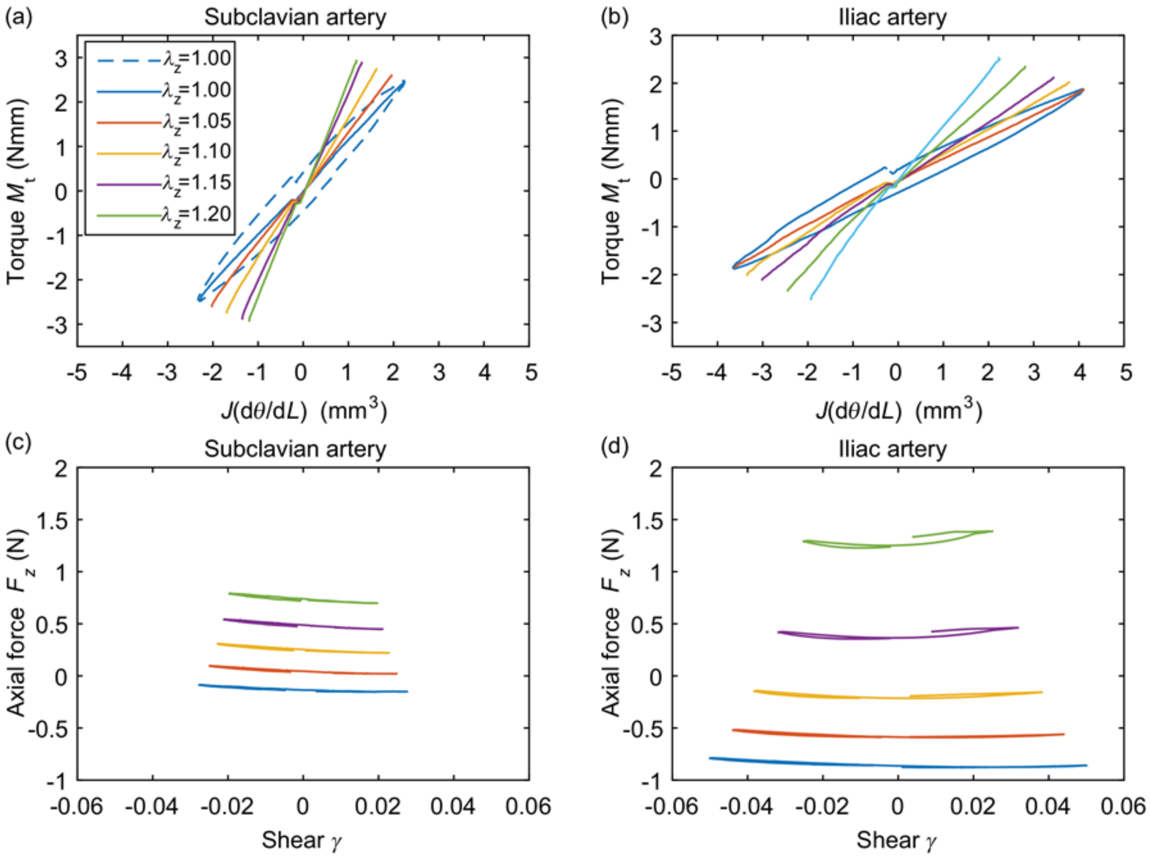

Figure 20: Torque versus "rate of twist" behaviour of a SA (a) and CIA (b) at different axial pre-stretches. The slopes of the curves indicate the respective shear modulus. Sections c and d show the axial force-amount of shear diagrams of an SA (c) and the respective CIA (d) at different axial pre-stretches. Reproduced from Sommer et al. (2018) with permission of Elsevier.

In sections (c) and (d) of Figure 20, the typical axial force versus the amount of shear behaviour is plotted. Here, the highest axial forces were reached at the maximum absolute values of the amount of shear.

Table 25 shows the shear moduli *G* of SA and CIA at different axial pre-stretches at a constant pressure of p_i = 13.3 kPa. During tests, *G* increased with increasing axial pre-stretch and increasing inflation pressure in both arteries.

Table 25: Shear modulus *G* of SA and CIA at 13.3 kPa and different axial stretches

	Shear modulus *G* (kPa)									
	$\lambda_z = 1.00$		$\lambda_z = 1.05$		$\lambda_z = 1.10$		$\lambda_z = 1.15$		$\lambda_z = 1.20$	
	SA	**CIA**	**SA**	**CIA**	**SA**	**CIA**	**SA**	**CIA**	**SA**	**CIA**
Median	435	188	497	334	654	445	848	1193	1303	875
Q3-Q1	228	345	611	423	824	572	1555	1121	1276	505
Mean	576	432	714	627	963	781	1365	1611	1606	1046
SD	357	461	513	757	768	859	1014	1668	893	615

Table 26: Shear modulus *G* at different axial pre-stretches at p_i = 13.3 kPa

	Shear Modulus *G* (kPa)				
	SA		CIA		
λ_z	**Median**	**Mean**	**Median**	**Mean**	**p**
1.00	435	576	188	432	0.27
1.05	497	714	334	627	0.36
1.10	654	963	445	781	0.58
1.15	848	1365	1193	1611	0.95
1.20	1303	1606	875	1046	0.41

G was larger for the SA in comparison to the CIA at all axial stretches except λ_z = 1.15, though without statistical significance. Table 27 shows the shear modulus for different pressures at an axial stretch of λ_z = 1.1. All differences did not differ significantly.

Table 27: Shear modulus G at different internal pressures at $\lambda_z = 1.1$

	G (kPa)				
	SA		CIA		
p_i (kPa)	Median	Mean	Median	Mean	p
0	155	207	114	188	0.44
3.3	194	308	154	295	0.72
6.7	402	488	251	483	0.65
10.0	529	714	328	619	0.57
13.3	681	942	387	734	0.57
16.7	846	1272	405	806	0.28
20.0	1135	1533	483	869	0.32
23.3	1036	1604	499	690	0.53
26.7	1411	1883	545	646	0.24

3.2.3 Geometrical and histological investigations

The utilised sample cohort consisted of seven specimen pairs gained from five female and two male body donors with an average age of 60.9 years (SD 10.96; median: 59; range 50 – 86) at time of death.

The average outer vascular diameter (OD) was 6.07 mm (SD 0.89; median: 5.6; range: 5.0 – 7.5) for the SA (Figure 21) and was clearly smaller than for the CIA (Figure 22) with an average OD of 7.9 mm (SD 1.07; median: 7.7; range: 6.7 – 9.6). Additionally, the average inner vascular diameter (ID) was determined to be 4.54 mm (SD 0.84; median: 4.3; range: 3.5 – 5.9) for the SA (Figure 21) and 6.28 mm (SD 1.34; median: 6.2; range: 4.5 – 8.5) for the CIA (Figure 22). Regarding the inner diameter, one CIA section could not be assessed due to artefacts.

The mean media thickness (M_T) was similar for both SA (mean: 0.52 mm; SD 0.08 mm; median: 0.51 mm; range: 0.44 – 0.7 mm) and CIA (mean: 0.54 mm; SD: 0.10 mm; median: 0.58 mm; range: 0.32 – 0.66 mm). Further, the amount of elastic fibres was higher in the SA (six cases with +++; one artery with ++) in comparison to the CIA (five specimens showing +; one case with ++; one case with ++[+]). The mean percentage of collagen fibres was determined to 44.3% (SD 5.0; range: 40 – 50) in the SA and 51.4% (SD 8.3; range: 40 – 60) in the CIA specimens. Further the amount of smooth musculature revealed a mean of 55.7% (SD 5.0; range: 50 – 60) in the SA and 48.6% (SD 8.3; range: 40 – 60) in the CIA. For a graphic depiction see Figures 23 and 24.

In our collective, the intimal hyperplasia thickness (IH) was on average 0.35 mm (SD 0.45; median: 0.1; range: 0.07 – 1.40) regarding the SA respectively 0.42 mm (SD 0.20; median: 0.38; range: 0.22 – 0.83) in the CIA. The amount of intimal hyperplasia was with a mean value of 83% (SD 26.6; range: 25 – 100) more pronounced in the CIAs than in SAs (see Figures 21 and 22) with a mean value of 71% (SD 35.0%; range: 10 – 100%). Intima calcification could only be observed in one pair of specimens gained from a female 61-year-old body donor. The mean adventitia thickness (AT) was 0.28 mm (SD 0.06; median: 0.3; range: 0.17 – 0.35) for the SA and 0.42 mm (SD 0.09; median: 0.45; range: 0.22 – 0.51) for the CIA. In all intima and adventitia analyses, one single CIA specimen had to be discarded due to artefacts. For a summarisation of the arterial characteristics see Table 28.

Table 28: Depiction of arterial characteristics

	Measure	Mean	SD	Median	Min	Max
SA	ID	4.54	0.84	4.3	3.5	5.9
	OD	6.07	0.89	5.6	5.0	7.5
	IH	0.35	0.45	0.1	0.07	1.40
	MT	0.52	0.08	0.51	0.44	0.7
	AT	0.28	0.06	0.3	0.17	0.35
CIA	ID	6.28	1.34	6.2	4.5	8.5
	OD	7.9	1.07	7.7	6.7	9.6
	IH	0.42	0.20	0.38	0.22	0.83
	MT	0.54	0.10	0.58	0.32	0.66
	AT	0.42	0.09	0.45	0.22	0.51

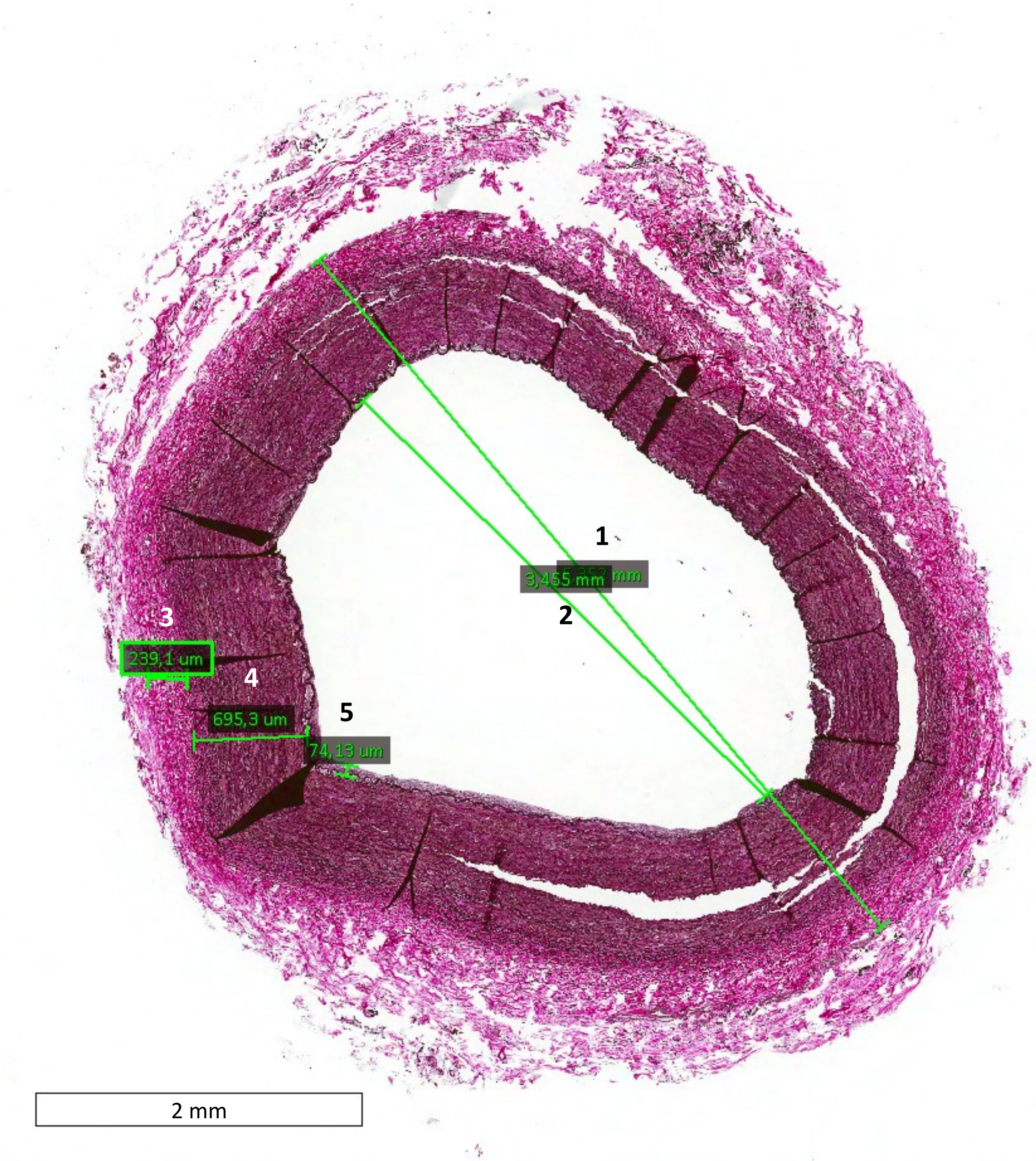

Figure 21: Histological section of a SA in EvG staining (1, outer vascular diameter; 2, inner vascular diameter; 3, adventitia thickness; 4, media thickness; 5, intimal hyperplasia thickness)

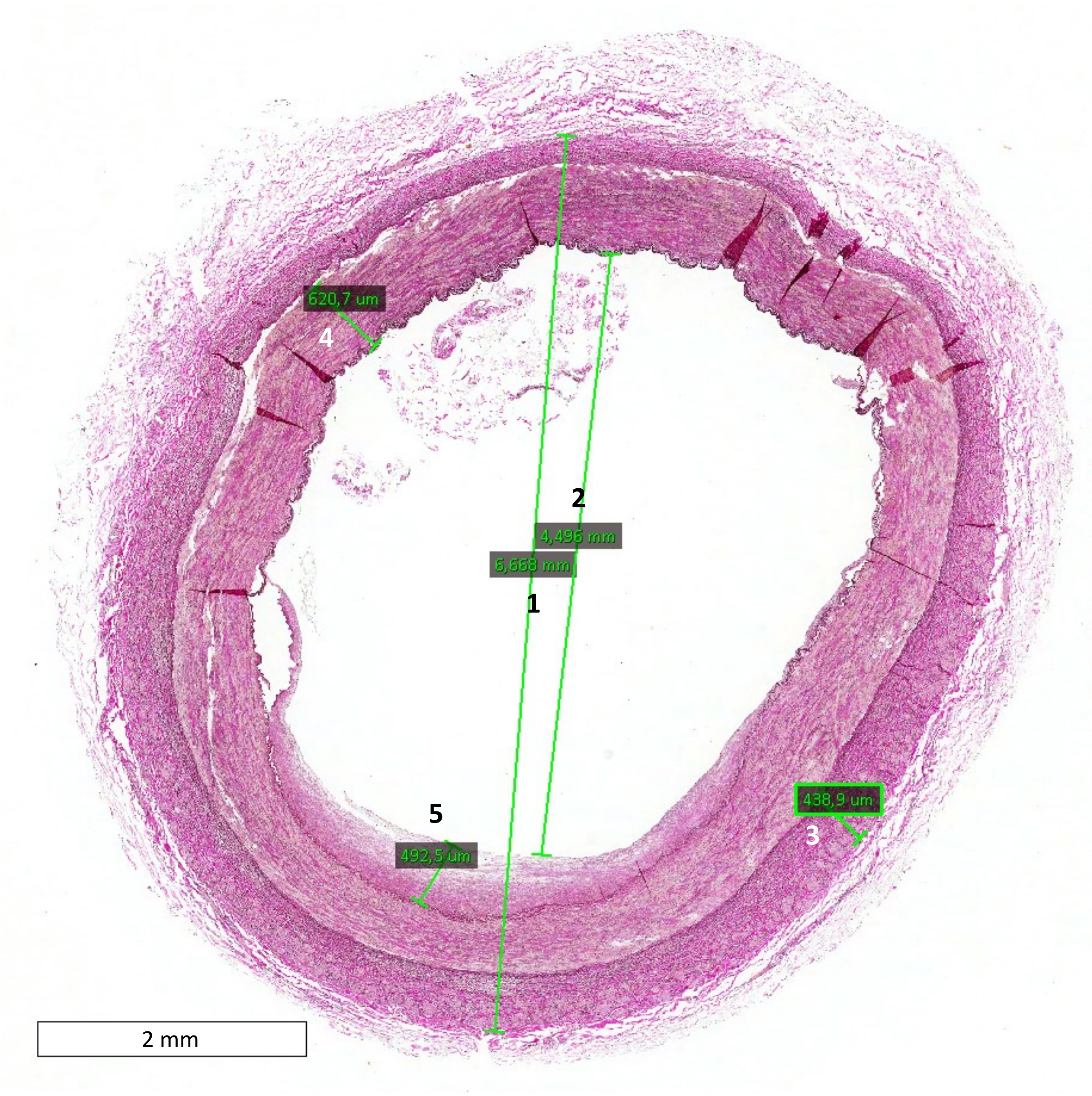

Figure 22: Histological section of a CIA in EvG staining (1, outer vascular diameter; 2, inner vascular diameter; 3, adventitia thickness; 4, media thickness; 5, intimal hyperplasia thickness)

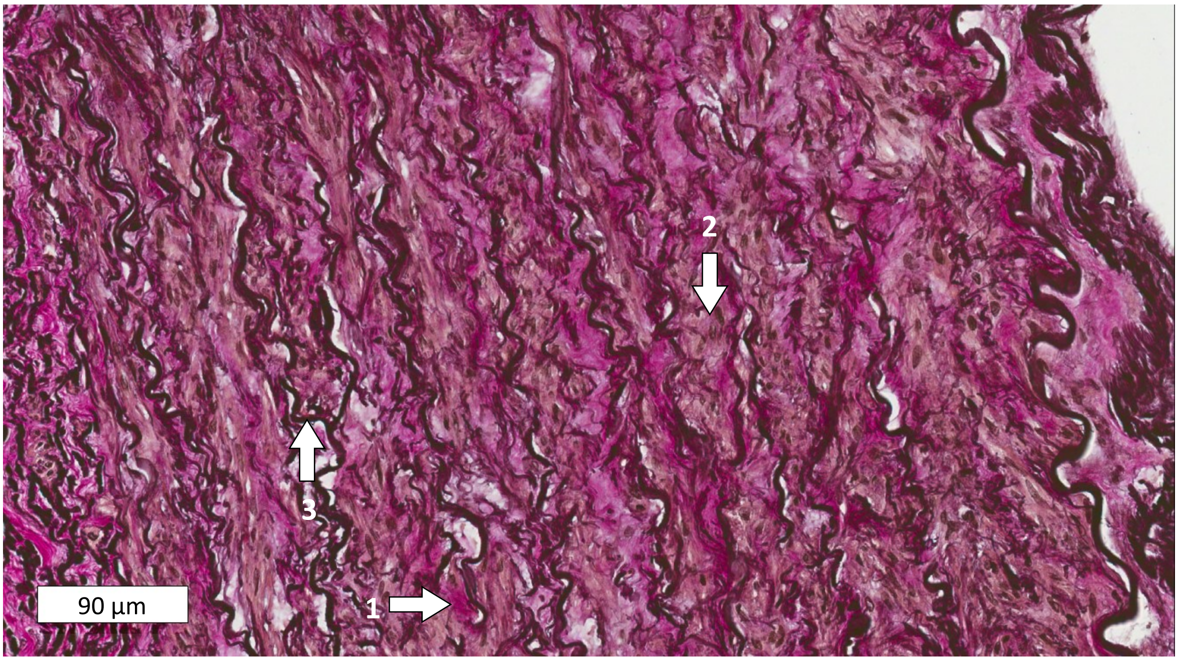

Figure 23: Media section of a SA with elastin content +++ in EvG staining (1, collagenous fibre [pink]; 2, smooth muscle cell [orange cytoplasm]; 3, elastic fibre [black])

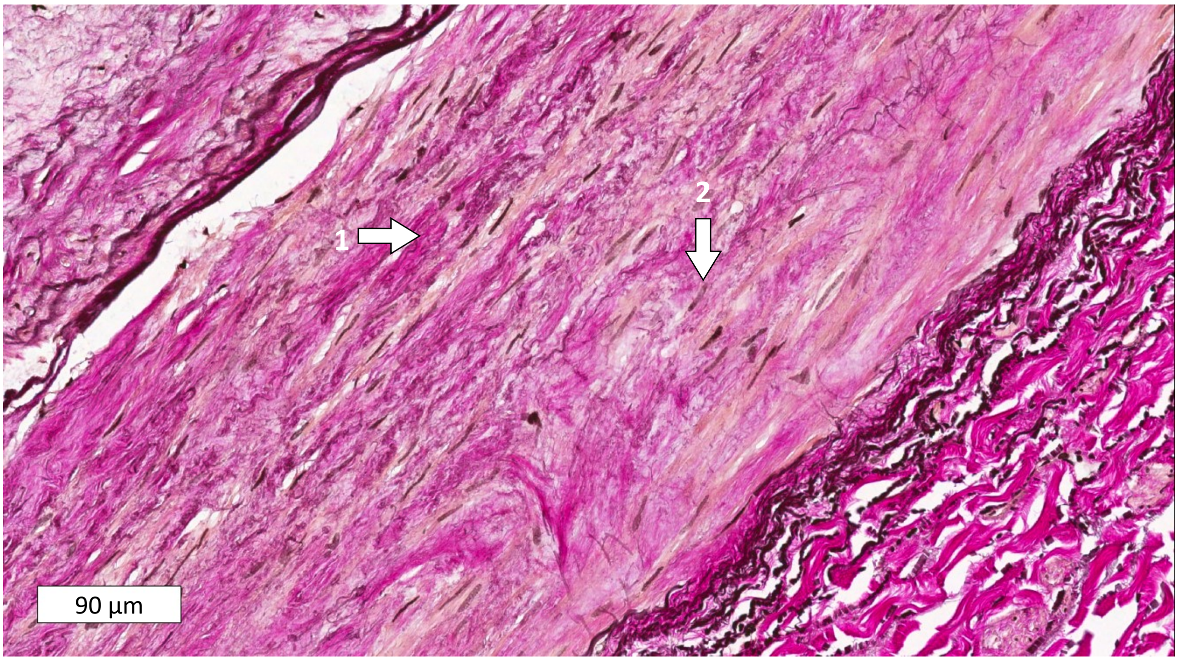

Figure 24: Media section of respective CIA including elastin content + in EvG staining (1, collagenous fibre [pink]; 2, elastic fibres [black]; smooth muscle cell [orange cytoplasm])

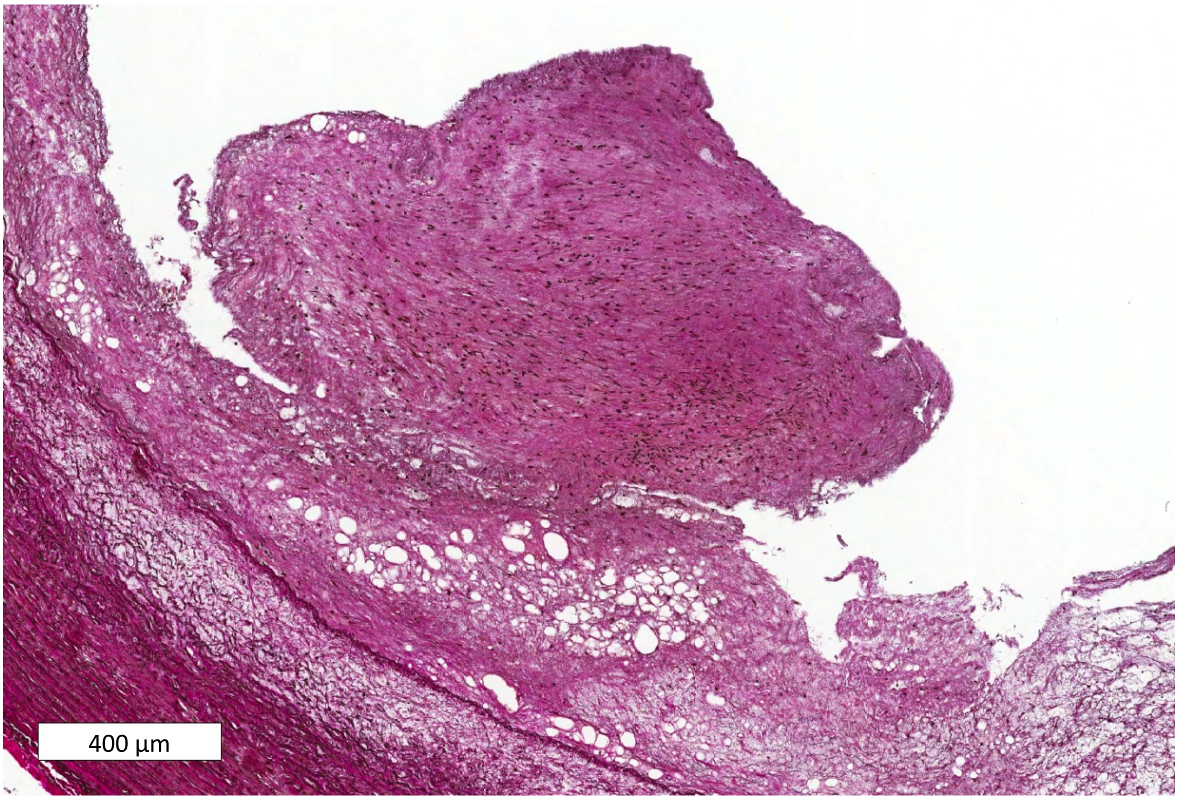

Figure 25: Plaque formation in a SA (EvG staining)

3.2.4 Microstructure

As depicted in Figure 26, the CIA sample tended to have a relatively dispersed collagen fibre structure throughout the intima. In the media, fibres were orientated closely to the circumferential direction ($\alpha = 0°$). However, the adventitia showed increased dispersion and fibre direction towards the axial direction.

The SA specimens in comparison only had a thin intimal layer and a higher angle towards the circumferential direction as compared to the CIA. In the adventitia, fibres were less dispersed in comparison to the CIA while also being orientated towards the axial direction.

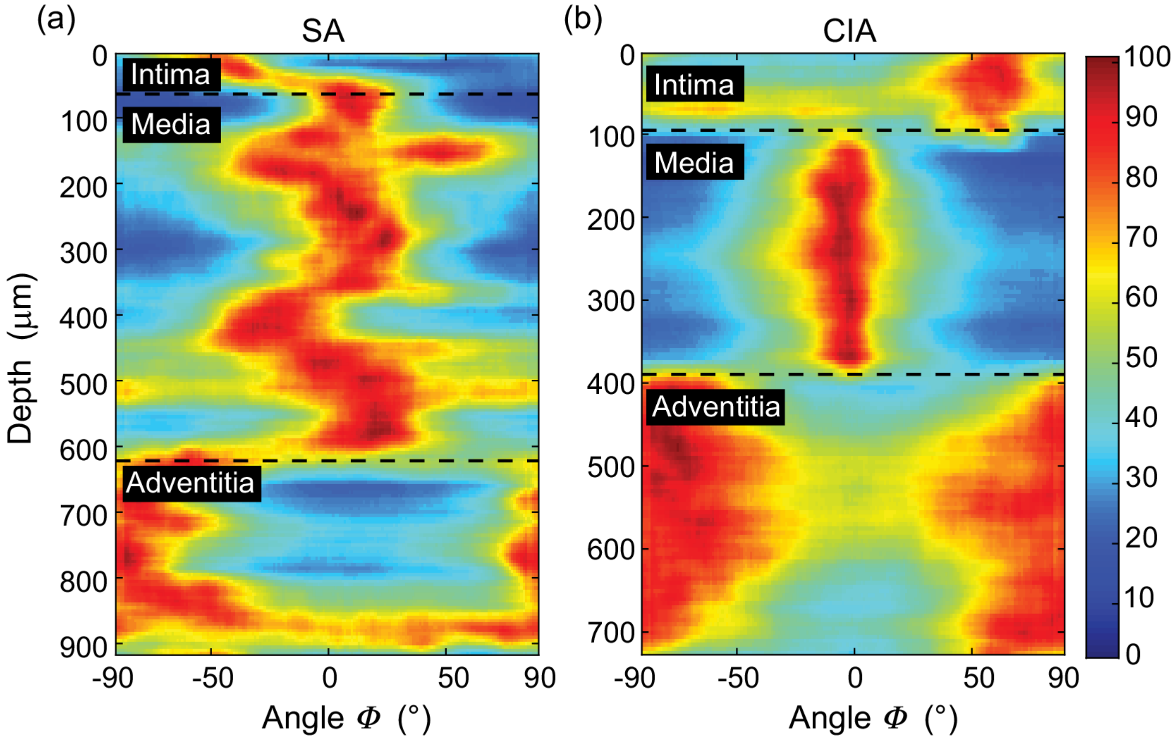

Figure 26: Intensity plots depicting collagen fibre orientation and dispersion throughout the wall of an arterial pair in a representative donor. Dark-red coloured parts represent no dispersion with all fibres pointing in the same direction whereas blue coloured parts depict that there were no fibres in this direction. Reproduced from Sommer et al. (2018) with permission of Elsevier.

Figure 27 shows the box-plots concerning the in-plane dispersion parameter κ_{ip} (a), the out-of-plane dispersion parameter κ_{op} (b) and the mean fibre angle α for media and adventitia of CIA and SA.

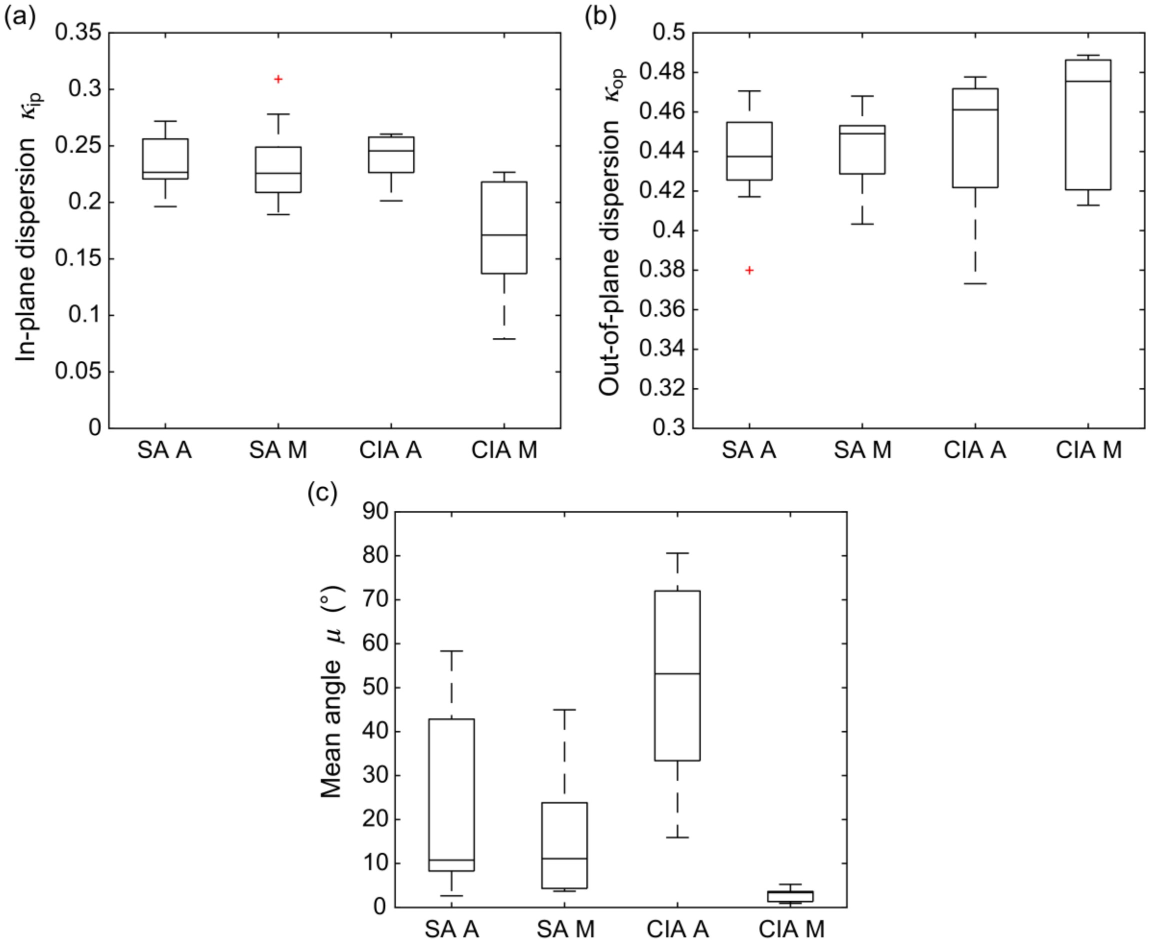

Figure 27: Box-plots of structural characteristics of media and adventitia (both CIA and SA). Reproduced from Sommer et al. (2018) with permission of Elsevier.

Regarding the CIA, the κ_{ip} was significantly ($p = .001$) reduced in its media (0.071 ± 0.05) in comparison to its adventitia (0.236 ± 0.03). In the SA, no significant differences between the respective layers could be found. However, the κ_{ip} was significantly ($p = .03$) higher in the SA media (0.226 ± 0.03) in comparison to the CIA media. κ_{op} on the other hand showed no significant differences regarding the vessels.

Further, the mean fibre angle was significantly ($p < .001$) lower in the CIA media (3.38 ± 1.37) in comparison to its adventitia (53.15 ±21.18). In the SA, no significant differences between the layers could be seen. α was significantly ($p = .03$) lower in the SA adventitia (10.77 ± 20.32) when compared to the CIA adventitia and also significantly lower ($p < .001$) for the CIA media in comparison to the SA media (11.09 ± 13.30).

3.3 Discussion

3.3.1 Biomechanical tests

3.3.1.1 Circumferential distensibility

The CIA showed slightly increased mean values ($\Delta\lambda_\theta = 0.12$) for the circumferential distensibility in comparison to the SA ($\Delta\lambda_\theta = 0.10$). Kamenskiy et al. (2014) observed higher average values for both arteries (SA: 0.23; CIA: 0.16) during planar biaxial extension tests. Differences of the results could be traced back to the different testing methods. Further, a significant correlation between age and circumferential distensibility was observed in the CIA sample ($r = -.61$, $p = .05$). A similar correlation was stated by Schulze-Bauer et al. (2003).

3.3.1.2 Stresses

Both average Cauchy stresses were increased in the CIA when compared to the SA, though without statistical significance. These results are comparable to Kamenskiy et al.'s (2014) results. The mean axial stress of the CIA (41.1 kPa) was well comparable to Schulze-Bauer et al.'s (2003) value (42.2 kPa). However, the mean circumferential stress was larger (50.9 kPa) than their reported outcome (43.5 kPa). Regarding the SA, no data could be found in the literature.

3.3.1.3 Torsional behaviour

During torsional tests, the shear modulus increased with increasing axial pre-stretch and increasing inflation pressure in both SA and CIA. This phenomenon was also observed in rat thoracic aortas by Deng et al. (1994) and in porcine coronary arteries by Lu et al. (2003). Kas' yanov and colleagues (1978) described a shear modulus of 220 kPa for human carotid arteries at 120 mmHg and in situ stretch in a very young donor sample. We observed clearly larger values of 1272 kPa (SA) and 806 kPa (CIA) which indicates an increase of the torsional stiffness with age.

3.3.1.4 Residual stresses

We found a larger average opening angle for the CIA (130 ± 39°) for the circumferential strips in comparison to the literature. Schulze-Bauer et al. (2003) and Kamenskiy et al. (2014) reported values of 94 ± 41° and 91 ± 36°, respectively. Our mean opening angle of 94 ± 27° (30 minutes) was smaller when compared to Kamenskiy and colleagues (102 ± 26°).

3.3.1.5 Limitations

One main problem was arterial buckling which happened at low axial pre-stretches and may have led to measurement errors. This phenomenon occurred as a result of increasing pressure.

Furthermore, measurement of the arterial opening angles proved to be difficult since they were not of circular shape anymore.

3.3.2 Histology

The structure of most of all vessels (with exception of the terminal vessels) may be structured into three layers:

- Tunica intima (intima): consisting of endothelial cells and subendothelial layer
- Tunica media (media): smooth musculature
- Tunica adventitia (adventitia): connective tissue

Additionally, an elastic layer is situated between intima and media as well as between media and adventitia (internal, respectively external elastic membrane).

Regarding functionality and the main components of the media two main types may be distinguished:

- ⇨ Arteriae elastotypicae: arteries adjacent to the heart including the aorta and the pulmonary arteries and their stems.
- ⇨ Arteriae myotypicae: peripheral arteries

Concerning arteriae elastotypicae, the media consists layers of concentric elastic fibres and smooth muscles (in the thoracic aorta 50 up to 70 of these layers can be depicted). Further, collagen fibres provide stabilisation. Their tunica intima is mostly thicker in comparison to arteriae myotypicae, due to its enlarged subendothelial layer. The high amount of elastic fibres enables the continuous bloodstream (so-called bagpipe function). (Junqueira 2005, Lüllmann-Rauch 2009)

In our study we compared the main histological characteristics between CIA and SA in seven specimen pairs. The inner and outer diameters were clearly smaller for the SA in comparison to the CIA and the amount of elastic fibres was higher in the SA. The amount of intimal hyperplasia was at a mean of 83% in the CIA specimens and at on average 71% in the SA. The literature lacks comparable data.

3.3.3 Microstructure

The inversion stretch was lower for the CIA ($\lambda^* = 1.05$) when compared to the SA ($\lambda^* = 1.11$) which might be traced back to the axially oriented collagen fibres in the CIA adventitia in comparison to the circumferentially oriented fibres of the SA adventitia. This orientation also may correlate with the larger axial stresses in the CIA. Further, the larger shear moduli in the SA may be explained via its higher dispersion of collagenous fibres and less oriented fibres towards the circumferential direction.

3.4 Conclusion

In conclusion, our evaluated mechanical differences between SA and CIA might be traced back to their different mechanical loadings caused by their anatomical location and their respective *in vivo* movements.

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APPENDIX

The FFB-Mot (Bos et al., 2002)

(Translation into English with permission and final approval of the authors)

For self-assessment of motor skills related to endurance, strength, mobility and coordination.

Choose the appropriate answer (1 – 5) to each of the following 28 questions:

1 I am not able to perform this activity.
2 I have major problems performing this activity.
3 I have moderate problems performing this activity.
4 I have minor problems performing this activity.
5 I have no problems performing this activity.

The simplest (1, 8, 15, 22) and most difficult (7, 14, 21, 28) activities are not included in your final score, but may help you to assess your degree of fitness.

Questions. Are you able to…

Self-assessment of strength

1 get up from a chair without using your arms?
2 carry a heavy shopping basket (8 kilos) up several floors?
3 carry a full beverage carton down the basement?
4 lift your upper body from supine position without using your arms (sit-up)?
5 lift a heavy suitcase above your head (e.g. onto the baggage rack on a train)?
6 carry two heavy suitcases up several floors?

Self-assessment of endurance

7 lift a dumbbell that is as heavy as you are?
8 walk several blocks quickly?
9 go up several floors without stopping?
10 walk two kilometres fast without stopping?
11 jog one kilometre without stopping?
12 jog 30 minutes without stopping (about 5 kilometres)?
13 jog one hour without stopping (about 10 kilometres)?
14 run a marathon (42 kilometres)?

Self-assessment of mobility

15 get in and out of a tight pullover and socks by yourself?
16 touch the floor with both hands while sitting on a chair?
17 tie your shoes on standing?
18 touch your shoulder blade with your hand from below?
19 touch the floor with both hands while standing (knees locked)?
20 touch your locked knees with your head while standing?
21 do the splits?

Self-assessment of coordination

22 go down stairs without using the handrail?
23 stand on a one leg without holding on?
24 do a somersault?
25 dribble a ball while walking fast?
26 vault over a one-metre high fence?
27 do a somersault off a one-metre diving board?
28 do a cartwheel?

Interpretation after adding the total points (questions 1, 8, 15, 22, 7, 14, 21 and 28 are not included):

Women

under 40 years of age

- ⇨ up to 62 points: significantly below average
- ⇨ 63 – 71 points: below average
- ⇨ 72 – 80 points: average
- ⇨ 81 – 88 points: above average
- ⇨ 89 – 100 points: significantly above average

40 until 60 years of age

- ⇨ up to 48 points: significantly below average
- ⇨ 49 – 60 points: below average
- ⇨ 61 – 69 points: average
- ⇨ 70 – 77 points: above average
- ⇨ 78 – 100 points: significantly above average

older than 60 years of age

- ⇨ up to 28 points: significantly below average
- ⇨ 29 – 41 points: below average
- ⇨ 42 – 51 points: average
- ⇨ 52 – 60 points: above average
- ⇨ 61 – 100 points: significantly above average

Men

under 40 years of age

- ⇨ up to 62 points: significantly below average
- ⇨ 63 – 72 points: below average
- ⇨ 73 – 82 points: average
- ⇨ 83 – 90 points: above average
- ⇨ 91 – 100 points: significantly above average

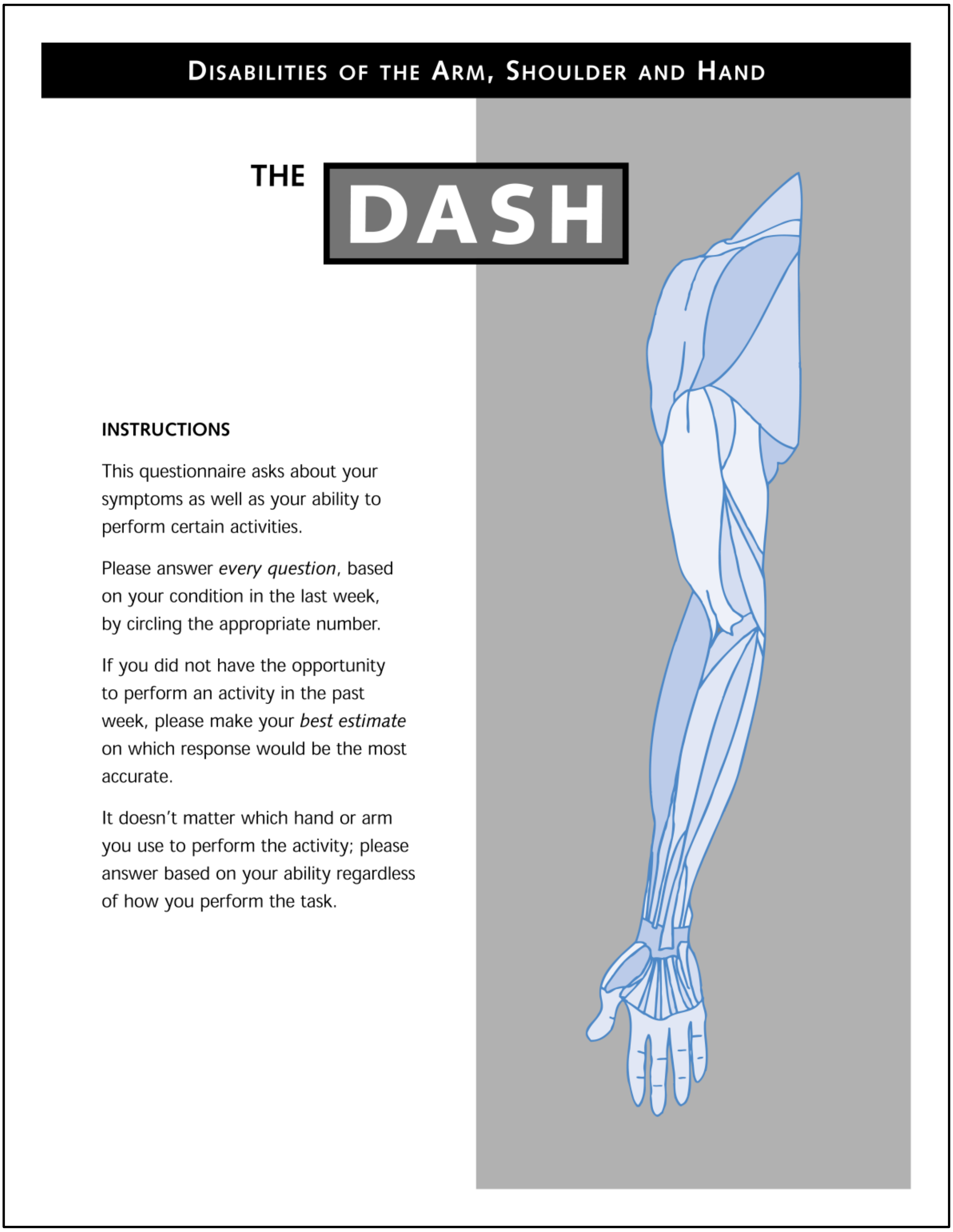
40 until 60 years of age

- ⇨ up to 51 points: significantly below average
- ⇨ 52 – 61 points: below average
- ⇨ 62 – 71 points: average
- ⇨ 72 – 82 points: above average
- ⇨ 83 – 100 points: significantly above average

older than 60 years of age

- ⇨ up to 29 points: significantly below average
- ⇨ 30 – 41 points: below average
- ⇨ 42 – 53 points: average
- ⇨ 54 – 64 points: above average
- ⇨ 65 – 100 points: significantly above average

The DASH Outcome Measure



DISABILITIES OF THE ARM, SHOULDER AND HAND

THE DASH

INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* on which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.

www.dash.iwh.on.ca

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DISABILITIES OF THE ARM, SHOULDER AND HAND

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	**1**	**2**	**3**	**4**	**5**
2. Write.	**1**	**2**	**3**	**4**	**5**
3. Turn a key.	**1**	**2**	**3**	**4**	**5**
4. Prepare a meal.	**1**	**2**	**3**	**4**	**5**
5. Push open a heavy door.	**1**	**2**	**3**	**4**	**5**
6. Place an object on a shelf above your head.	**1**	**2**	**3**	**4**	**5**
7. Do heavy household chores (e.g., wash walls, wash floors).	**1**	**2**	**3**	**4**	**5**
8. Garden or do yard work.	**1**	**2**	**3**	**4**	**5**
9. Make a bed.	**1**	**2**	**3**	**4**	**5**
10. Carry a shopping bag or briefcase.	**1**	**2**	**3**	**4**	**5**
11. Carry a heavy object (over 10 lbs).	**1**	**2**	**3**	**4**	**5**
12. Change a lightbulb overhead.	**1**	**2**	**3**	**4**	**5**
13. Wash or blow dry your hair.	**1**	**2**	**3**	**4**	**5**
14. Wash your back.	**1**	**2**	**3**	**4**	**5**
15. Put on a pullover sweater.	**1**	**2**	**3**	**4**	**5**
16. Use a knife to cut food.	**1**	**2**	**3**	**4**	**5**
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	**1**	**2**	**3**	**4**	**5**
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	**1**	**2**	**3**	**4**	**5**
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	**1**	**2**	**3**	**4**	**5**
20. Manage transportation needs (getting from one place to another).	**1**	**2**	**3**	**4**	**5**
21. Sexual activities.	**1**	**2**	**3**	**4**	**5**

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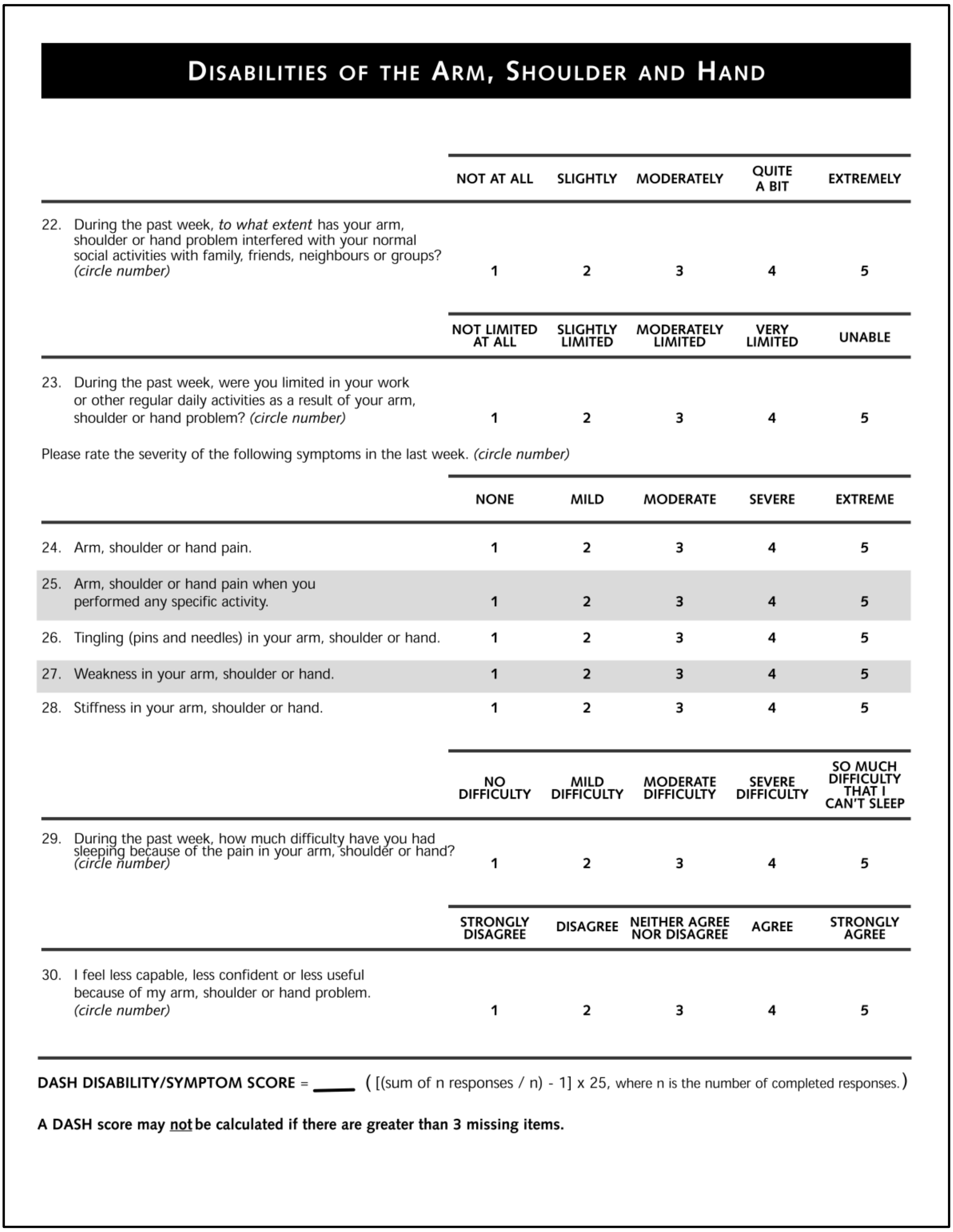

DISABILITIES OF THE ARM, SHOULDER AND HAND

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = _____ ([(sum of n responses / n) - 1] x 25, where n is the number of completed responses.)

A DASH score may not be calculated if there are greater than 3 missing items.

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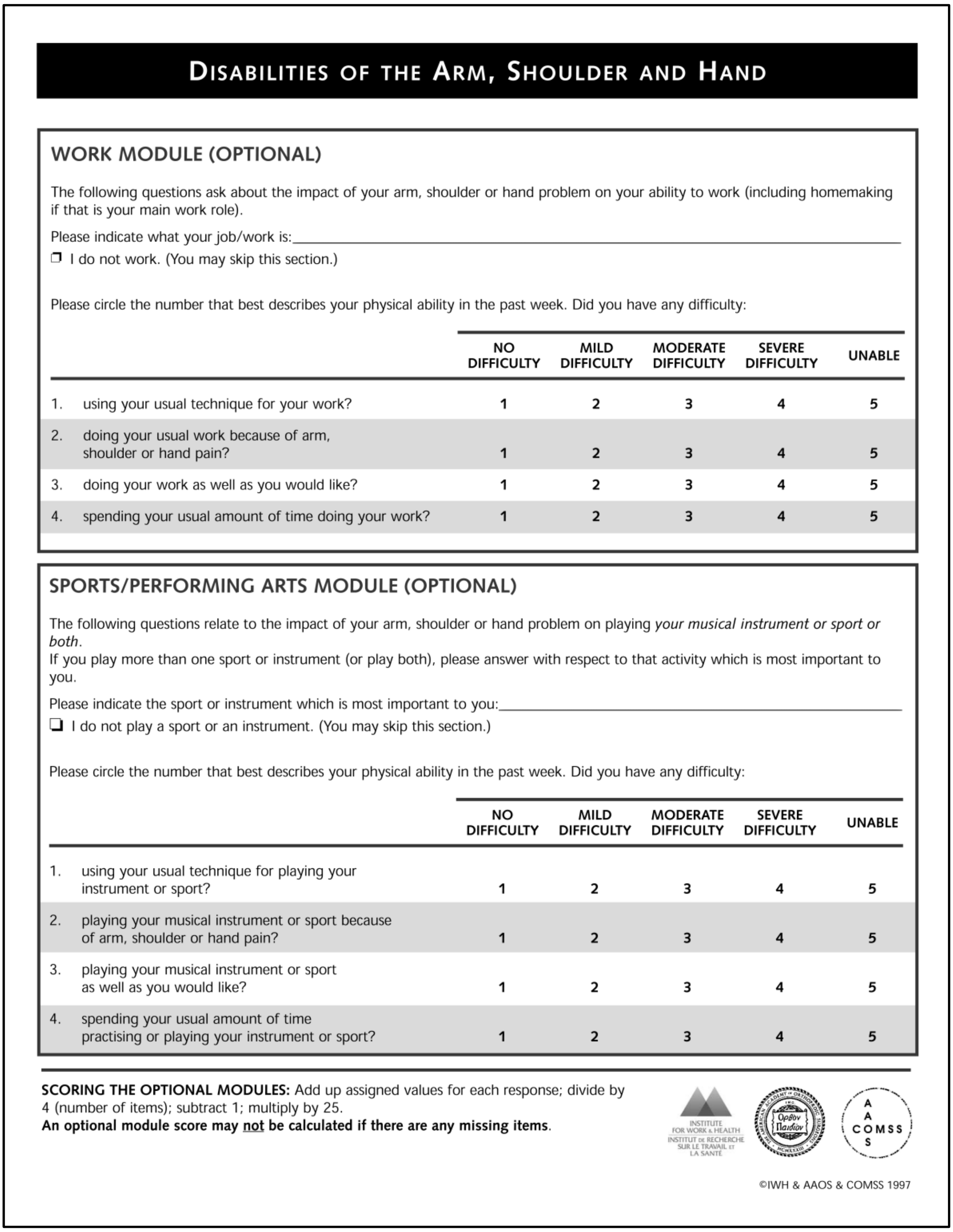

DISABILITIES OF THE ARM, SHOULDER AND HAND

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including homemaking if that is your main work role).

Please indicate what your job/work is:______________________________

☐ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*.
If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:______________________________

☐ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may <u>not</u> be calculated if there are any missing items.

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