UPPER LIMB ISCHAEMIA: A TWELVE YEAR EXPERIENCE

by

Dr Johannes Marthinus du Toit
MBChB (Stell), FCS (SA)
Student Number: DTTJOH016

Submitted in fulfilment of the requirements for the degree:

Master of Medicine (Surgery)
by minor-dissertation

Department of Surgery: Vascular Unit
Faculty of Health Sciences, Groote Schuur Hospital
University of Cape Town

Supervisor: Dr NG Naidoo
MBChB, FCS (SA)
Head: Vascular Unit, Groote Schuur Hospital
The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.
DECLARATION OF AUTHENTICITY

I, Dr Johannes Marthinus du Toit, hereby declare that the work on which this dissertation is based, is my own. I have fully and specifically acknowledged sources from which material has been adapted. Furthermore, the information contained within this document, was gathered and utilized specifically to fulfil the purposes and objectives of this study and has not been previously submitted to any other university for a higher degree.

I understand that, if at any time it is shown that I have significantly misrepresented material within this document, any degree or credits awarded to me may be revoked.

Signature:

JM du Toit

Date: 8 September 2014
ABSTRACT

Upper limb ischaemia – a twelve year experience

Authors: Dr JM du Toit, Dr NG Naidoo (Department of Vascular Surgery, Groote Schuur Hospital)

Introduction: Upper limb ischaemia (ULI) is a relatively uncommon, but well recognized vascular entity. The sequelae of impaired function or amputation of an arm can be devastating to the individual with loss of independence and / or livelihood. There remains much to be learned that can only be established through good quality studies. This project was aimed at developing a comprehensive, but broad overview of ULI, specific to the population we serve.

Aims: The objective was to review the Vascular Surgery Unit’s experience with ULI, with particular emphasis on defining the pattern and distribution of disease and pathological profile, describing key demographic and clinical features and reporting on conventional clinical outcomes. Areas of interest, with the potential for further research, were identified.

Methods: Retrospective descriptive study. All patients that underwent a surgical intervention for ULI between January 2000 and December 2011, were included in the audit. Approval from the Department of Surgery Research Committee and Human Research Ethics Committee was obtained prior to accessing data (Appendix 1 & 2). A research folder was compiled for each patient. On completion of the data collection process, the findings were analyzed and compared to current literature on this topic.

Results: Sixty-four patients with ULI were managed surgically during the 12 year study period. A male: female ratio of 0.60 (as opposed to 0.96 from 2011 Census figures), was reported. The thrombo-embolic subgroup of patients (n=30), were notably younger than expected (mean age of 55 years) compared to the UEAOD subgroup (n=12, mean age of 57 years). Approximately 48% were of mixed ethnicity, correlating well with 2011 Census figures. Referrals were predominately received from Secondary Hospitals (84%) situated within the Cape Metropole. 55% Presented with acute ULI, of which 40% were classified as Rutherford grade IIa and 17% diagnosed with established compartment syndrome. Approximately 48% were of mixed ethnicity, correlating well with 2011 Census figures. 55% Presented with acute ULI, of which 40% were classified as Rutherford grade IIa and 17% diagnosed with established compartment syndrome. The majority of chronic ULI patients, presented with signs of tissue necrosis (48%). Other indications for intervention included upper extremity claudication symptoms (31%), rest pain (14%) as well as neuro-vascular symptoms (7%). A disproportionately high prevalence of cigarette smoking (83%, with an average of 31 pack years) was identified in the UEAOD subgroup. 27% Of patients were not receiving adequate pharmacological therapies aimed at addressing pre-existing risk factors, as proposed by the TASC II document. Thrombo-embolism was the single largest aetiological factor identified (47%), with the majority of occlusions (57%) occurring at the level of the brachial artery. A left-sided predominance with a ratio of 2:1, was noted. Approximately 47% of patients with UEAOD, were younger than 55 years. A clear proximal pattern of disease was observed (66% of lesions within the subclavian artery). Eighty-nine procedures were performed in 64 patients (78 open, 5 exclusively endovascular with a combined open / endovascular approach implemented in 6 patients). The 30-day mortality rate was 7.8%. Systemic complications were observed in 13% with 23% sustaining some form of procedural complication. Twenty amputations were performed in 64 patients, of which 6 were major amputations. The 30-day amputation rate after an attempt at revascularization, was 12.5%. Adherence to follow-up was poor (51% at 6 months), limiting interpretation of follow-up data.

Conclusion: Although few firm conclusions could be drawn, this review has expanded our overall perspective of ULI, specific to the population we serve. It is anticipated that the publication of our institutional data will create a clinical awareness and facilitate future research projects in this field. A collaborative research effort between South African vascular units will facilitate comparison of different institutional experiences and enable pooled data analysis, perhaps further defining the pattern of upper limb vascular disease by identifying distinct geographical confounders.
AKNOWLEDGEMENTS

I am grateful to everyone who supported me throughout the course of this MMed dissertation.

In particular, I would like to thank my supervisor, Dr NG Naidoo, for his aspiring guidance, invaluably constructive criticism and illuminating views throughout this project.

To my parents, thank you for your continual support and encouragement.

Dr PE Eloff, for the initial identification of participants from an operative database.

Mrs Katherine Manning, for her expert and friendly assistance with the use of the relevant data-analysis software.

Professor D Kahn and the Department of Surgery, Groote Schuur Hospital, for creating a favourable clinical environment and relevant support structure, conducive to performing research.
UPPER LIMB ISCHAEMIA: A TWELVE YEAR EXPERIENCE

by

Dr Johannes Marthinus du Toit
# TABLE OF CONTENTS

**Chapter 1: Introduction**  
1

**Chapter 2: Literature review**  
2  
General considerations and overview  
2  
Incidence and demographics  
3  
Predisposing conditions  
6  
Aetio-pathology  
12  
Anatomical basis of disease  
41  
Clinical presentation and management pathways  
43  
Outcome  
48

**Chapter 3: Aim**  
55

**Chapter 4: Methods**  
56

**Chapter 5: Results**  
61  
Incidence and demographics  
61  
Risk factors  
66  
Aetio-pathology  
69  
Initial clinical presentation  
74  
Surgical interventions  
76  
Outcome  
82

**Chapter 6: Discussion and future research perspectives**  
90

**Chapter 7: Conclusion**  
93

**References**  
94

**Appendix 1: Departmental Research Committee approval**  
107

**Appendix 2: Human Research Ethics Committee approval**  
108

**Appendix 3: Data collection sheet**  
109

(iv)
LIST OF TABLES AND FIGURES

Chapter 2: Literature review

Page 7
Table 1: Studies evaluating incidence of risk factors in atherosclerotic occlusive disease

Page 8
Figure 1: Approximate odds ratio range for atherosclerotic risk factors as depicted by the TASC II document

Page 9
Figure 2: Comparative abstinence rates for bupropion, nicotine replacement therapy or both versus placebo

Page 13
Table 2: A proposed aetio-pathological classification of upper limb ischaemia

Page 19
Table 3: Conditions associated with secondary Raynaud’s phenomenon

Page 22
Figure 3: Schematic representation of collateral circulation around the shoulder joint

Page 29
Figure 4: Schematic representation illustrating the anatomical relations of structures to the interscalene triangle, costoclavicular triangle and the subcoracoid space

Page 30
Table 4: Causative mechanisms described in TOS
Table 5: Summary of underlying bony pathology encountered in ATOS

Page 31
Figure 5: Schematic representation illustrating the anatomical relations and sequelae of a chronically compressed SCA

Page 32
Table 6: Spectrum of arterial pathologies associated with ATOS

Page 33
Figure 6: Schematic representation illustrating the anatomical relations of the quadrilateral space

Page 36
Figure 7: DSA of a 49-year-old recreational baseball player’s right hand

(v)
Figure 8: Axial anatomy, demonstrating vulnerability of the terminal ulnar artery and accompanying nerve, to repetitive trauma

Figure 9: Anatomic relations of an aberrant right SCA

Figure 10: A proposed anatomical approach to the aetiology of upper limb ischaemia

Table 7: Suggested classification of acute limb ischaemia

Table 8: Relationship between arm-function and duration of ischaemia

Table 9: Summary of major publications on upper limb bypass procedures

Table 10: Summary of studies reporting on SCA / BCA stent placement

Chapter 5: Results

Figure 11: Patients receiving surgical intervention

Figure 12: Western Cape population growth according to recent Census statistics

Table 11: Comparative demographic details according to prevailing aetiologies

Table 12: Demographic comparison of TED versus UEAOD subgroups

Figure 13: Race prevalence

Table 13: Source of referral according to province

Table 14: Level of referring facility

Table 15: Specific referring facility
Table 16: Studies evaluating incidence of risk factors in atherosclerotic occlusive disease

Table 17: Summary of cases according to the underlying aetio-pathology
Table 18: Summary of cases according to underlying aetio-pathology, by Deguara et al

Figure 14: Comparative diagram (Eyers et al vs Current series) translating the incidence of arterial occlusion within relevant arterial segments

Table 19: Summary of underlying arterial lesions in UEAOD subgroup

Table 20: Summary of ATOS presentations

Table 21: Summary of AULI presentations, according to severity of ischaemia
Figure 15: Incidence of compartment syndrome in AULI subgroup

Figure 16: Summary of CULI presentations

Figure 17: Summary of ablative and minor procedures performed

Table 22: Breakdown of procedures performed for thrombo-embolic disease

Table 23: Breakdown of procedures performed for UEAOD

Table 24: Breakdown of procedures in patients presenting with ATOS

Table 25: Summary of 30-day post- surgical outcome

Table 26: Summary of 6-month post- surgical outcome

Table 27: Summary of long term (>6 months) post- surgical outcome

Table 28: Comparison of TED- and UEAOD- subgroups
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AULI</td>
<td>Acute upper limb ischaemia</td>
</tr>
<tr>
<td>CULI</td>
<td>Chronic upper limb ischaemia</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>UEAOD</td>
<td>Upper extremity atherosclerotic occlusive disease</td>
</tr>
<tr>
<td>TED</td>
<td>Thrombo-embolic disease</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>HPT</td>
<td>Hypertension</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>CCA</td>
<td>Common carotid artery</td>
</tr>
<tr>
<td>BCA</td>
<td>Brachio-cephalic artery</td>
</tr>
<tr>
<td>SCA</td>
<td>Subclavian artery</td>
</tr>
<tr>
<td>RSA</td>
<td>Retro-oesophageal subclavian artery</td>
</tr>
<tr>
<td>ATOS</td>
<td>Arterial thoracic outlet syndrome</td>
</tr>
<tr>
<td>ASM</td>
<td>Anterior scalene muscle</td>
</tr>
<tr>
<td>PSD</td>
<td>Post-stenotic dilatation</td>
</tr>
<tr>
<td>TAO</td>
<td>Thromboangiitis obliterans</td>
</tr>
<tr>
<td>RP</td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>RS</td>
<td>Raynaud’s syndrome</td>
</tr>
<tr>
<td>RD</td>
<td>Raynaud’s disease</td>
</tr>
<tr>
<td>HHS</td>
<td>Hypothenar hammer syndrome</td>
</tr>
<tr>
<td>PFO</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>ASD</td>
<td>Atrial septal defect</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>MVP</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>IE</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>CMO</td>
<td>Cardio-myopathy</td>
</tr>
<tr>
<td>MD-CTA</td>
<td>Multi-detector computed tomography arteriogram</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic resonance arteriogram</td>
</tr>
<tr>
<td>ERNA</td>
<td>Equilibrium radionuclide angiography</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>PTA</td>
<td>Percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>ePTFE</td>
<td>Expanded polytetrafluoroethylene</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
</tbody>
</table>
CHAPTER ONE:
INTRODUCTION

Upper limb ischaemia is a relatively uncommon, but well recognized vascular entity caused by a wide range of aetiological factors. However, the sequelae of impaired function or amputation of an arm can be devastating to the individual with loss of independence and/or livelihood. There remains much to be learned that can only be established through good quality studies.

Due to the relative infrequency of this condition, few clinicians are familiar with the different aspects of diagnosis, investigation and treatment. The occupational ramifications and impact on quality of life in those affected can be substantial. A thorough understanding of this condition is essential if significant improvement in surgical outcome and limb functionality is to be made. These considerations were the inspiration behind the current study, with the purpose of improving colleagues’ (as well as the author’s) insight into the disease by defining the pattern and distribution of disease and pathological profile, describing key demographic and clinical features and reporting on conventional clinical outcomes.

The project was aimed at developing a comprehensive, but broad overview of upper limb ischaemia, specific to the population we serve. Areas of interest, with the potential for further research, were identified.
CHAPTER TWO:
LITERATURE REVIEW

1) GENERAL CONSIDERATIONS AND OVERVIEW

A computerized search of the National Library of Medicine and the National Institutes of Health MEDLINE database was undertaken using the Entrez PubMed (www.pubmed.gov) interface, followed by a secondary manual search of the article reference lists. The primary search strategy was developed to retrieve English language articles focusing on upper limb ischaemia published between 2000 and 2013; letters to the editor, editorials and other items of general commentary were excluded from the search. Studies reporting on upper limb ischaemia related to primary Raynaud’s phenomenon and trauma were excluded, as they were beyond the scope of this review.

The above literature search resulted in a heterogeneous group of articles related to upper limb ischaemia. No randomized trials or prospective studies were identified. Clinical data were limited to case reviews derived from a range of sources, including district general hospitals, regional centres as well as specialist vascular units. Most of these publications reported on a single clinical (either acute or chronic) or aetiological (either traumatic or non-traumatic) aspect of upper limb ischaemia. Understandably, series that combine acute and chronic ischaemia are rare.\textsuperscript{[1,5-7]} Often, by attempting to discuss two distinctly different disease processes concurrently, important individual characteristics may be obscured.
Popular research themes subsumed within the published surgical series, included comparisons of different management pathways (particularly operative versus non-operative management of acute upper limb ischaemia), clinical outcome of different interventional modalities (specifically percutaneous versus open surgical procedures) as well as reviews of specific aetiological entities. The applicable articles were reviewed, including relevant references from the perused material.

Due to the wide spectrum of underlying aetiologies and clinical presentations, it is of utmost importance that interesting findings from the literature are presented in a logical and structured manner. This may be accomplished by implementing a rigid clinical or aetiological framework. Instead, the relevant findings will be presented under the following headings, in order to accommodate for the complexities and heterogeneity associated with this condition.

- Incidence and demographics
- Risk factors
- Aetio-pathology
- Anatomical basis of disease
- Clinical presentation and related management pathways
- Outcome

2) INCIDENCE AND DEMOGRAPHICS

Patients managed non-surgically are often excluded from these series. This prevailing limitation adds to the difficulty in determining the true incidence of upper limb ischaemia as well as establishing an accurate ratio of acute to chronic presentations. Most authors
agree that ischaemic conditions of the lower extremity are much more common than those of the upper extremity.\textsuperscript{[1-3]} Upper limb revascularization procedures comprise approximately 4% of all vascular procedures performed and constitute around 15-18% of all interventions performed for critical limb ischaemia.\textsuperscript{[4,5]}

There seem to be unique demographic differences between upper and lower extremity bypass populations.\textsuperscript{[8-10]} Hughes et al\textsuperscript{[9]} reviewed their single centre experience and noted that patients presenting for upper extremity revascularization do so at a relatively early age (average age 57 years) with a slight female preponderance of 55%, a fairly consistent finding throughout the literature.\textsuperscript{[2,5]} In contrast, a contemporary cohort of lower extremity bypass patients from the same institution, had a mean age of 67 years with a primarily male preponderance of 62%.

The bypass population is not the only subgroup of patients reflecting subtle epidemiological differences between upper and lower limb cohorts. When considering acute limb ischaemia (defined as a sudden decrease in limb perfusion posing a potential threat to limb viability, presenting within 2 weeks of an acute event)\textsuperscript{[11]}, it is clear that this condition affect the lower limbs much more commonly (reported incidence of 1.3 cases per 100 000 per year),\textsuperscript{[4]} than the upper limbs. Acute upper limb ischaemia (AULI) occurs in a slightly different patient population than acute lower limb ischemia,\textsuperscript{[12]} partially explained by an unequal distribution of atherosclerotic occlusive disease, mostly affecting the lower limbs. AULI is also found in a more heterogeneous group of patients, presenting as a clinical manifestation of conditions such as inflammatory vasculitides, iatrogenic
disorders (drug related, arterial catheterization and radiation fibrosis), arterial thoracic outlet syndrome and atherosclerotic occlusive disease.

Embolic disease affect the upper limbs more frequently.\textsuperscript{[13]} \textit{Emboli are the most frequent cause of upper limb ischaemia}. Of all arterial embolizations, between 10 and 20\% involve the upper limbs. However, a number of recent studies have estimated the frequency of peripheral arterial embolic occlusions, to be on the decrease.\textsuperscript{[14,15]} Multiple factors are at play, continuously influencing the incidence of embolic phenomena. Even though the frequency of systemic emboli due to ischaemic heart disease is on the increase, the absolute number of embolic events is believed to have declined, mostly due to a decrease in the number of rheumatic heart disease patients as well as widespread use of long-term anticoagulation in the management of rheumatic heart disease and atrial fibrillation.\textsuperscript{[16-18]}

As previously stated, series that combine both acute and chronic upper limb ischaemia are rare.\textsuperscript{[1,5,18,19]} The largest of these included 172 patients undergoing revascularization procedures for upper limb ischaemia over a 20 year period.\textsuperscript{[1]} The age of presentation depended heavily on the underlying aetiology at hand. The mean age of presentation of patients with thrombo-embolic disease was appreciably older (72.4 years) than those presenting with upper extremity atherosclerotic occlusive disease (62.5 years). This may partly explain the higher incidence of severe comorbid disease observed in patients presenting with thrombo-embolism, as opposed to atherosclerotic occlusive disease.
3) PREDISPOSING CONDITIONS

When considering the prevalence and contribution of predisposing conditions, it is important to interpret them in terms of the underlying aetio-pathology at hand. For instance, the presence of atrial fibrillation is a strong predisposing factor for cardio-embolic events, but not the development of atherosclerotic occlusive disease. This section will focus on traditional risk factors for atherosclerotic occlusive disease and their applicability to UEAOD.

3.1) Risk factors for atherosclerosis and the development of upper extremity atherosclerotic occlusive disease (UEAOD)

The best quality evidence regarding this topic takes the form of multiple consensus documents (including the TASC II document, American Heart Association and American College of Cardiology guidelines). However, it is important to note that most data pertaining to risk factors for non-coronary atherosclerotic arterial disease, have been extrapolated from studies primarily focusing on coronary artery disease (CAD), such as the Framingham Heart Study, Atherosclerosis Risk in Communities Study (ARIC), Honolulu Heart Study, and the Strong Heart Study. With rare exception, the evidence from these studies suggests that risk factors for non-coronary atherosclerotic arterial disease are generally similar and independent of the end organ affected.

Despite the superfluous reports on the effects of atherosclerotic risk factors in lower extremity arterial disease, none such studies specific to UEAOD could be identified. The prospect of generating good quality population based data in future (specific to the UEAOD cohort), are unlikely, particularly in light of a recent (2008) document produced
by the American Heart Association.[22] In an attempt to clarify nomenclature pertaining to non-coronary atherosclerotic arterial disease, they suggested that the term PAD should incorporate both lower and upper extremity atherosclerotic arterial disease.

Recently published surgical series on UEAOD (Table 1), have reported the following prevalence of traditional atherosclerotic risk factors.

Table 1: Studies evaluating prevalence of risk factors in UEAOD

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Smoking(%)</th>
<th>HPT(%)</th>
<th>DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes et al, 2013 [9]</td>
<td>55</td>
<td>35</td>
<td>Not reported</td>
<td>29</td>
</tr>
<tr>
<td>Hughes et al, 2007 [9]</td>
<td>20</td>
<td>Not reported</td>
<td>45</td>
<td>40</td>
</tr>
</tbody>
</table>

Hughes et al[9] noted a statistically significant difference in the prevalence of diabetes mellitus in upper extremity bypass patients (40%) compared to the lower extremity bypass population (83%). Differences in the prevalence of hypertension, coronary artery disease, congestive cardiac failure and tobacco use were not statistically significant.[9,23]

The criteria used to support a risk factor for UEAOD (as opposed to a strong association), require a prospective, controlled study showing that modifying the factor alters the development or course of the disease. Until such studies are produced, the best evidence on the impact of traditional risk factors on the development and progression of UEAOD, takes the form of extrapolated data from non-coronary atherosclerotic arterial disease.
studies. The rest of this section will attempt to shortly review these traditional risk factors, including proposed therapeutic targets in the presence of disease.

Figure 1: Approximate odds ratio range for atherosclerotic risk factors as depicted by the TASC II document\textsuperscript{[24]}

3.1.1) Tobacco products

The relationship between smoking and PAD has been recognized since 1911, when Erb reported that intermittent lower limb claudication was three times more common among smokers than non-smokers.\textsuperscript{[24]} Tobacco use is particularly prevalent in patients with UEAOD and seems to have a stronger causative association than the aforementioned risk factors. It has been suggested that the association between smoking and PAD may be stronger than that of smoking and coronary artery disease (CAD). The number of pack years is associated with disease severity, an increased risk of amputation, peripheral graft occlusion and mortality. Given these associations, smoking cessation has been the
cornerstone of PAD management. However, due to low smoking cessation rates achieved with medical therapy, modification of this risk factor may be particularly challenging.

Multiple randomized controlled trials have supported the use of an antidepressant, bupropion, in establishing improved smoking cessation rates. Jorenby et al (*Figure 2*) have shown that bupropion, when combined with nicotine replacement therapy, is more effective than either therapy alone.\(^{[25]}\) This should be combined with non-pharmacological strategies, including physician advice at every patient visit and behavioural modification therapy, in order to achieve the best cessation rates.

Recently, substance abuse has been implicated in the processes of accelerated and precocious atherosclerosis as well as Thromboangiitis obliterans. Some of the finer pathological implications of tobacco use and other substances will be discussed in the section on aetio-pathology.

*Figure 2: Comparative abstinence rates for bupropion, nicotine replacement therapy or both versus placebo (as reported by Jorenby et al)\(^{[25]}\)*
3.1.2) Diabetes mellitus

Many studies have shown an association between diabetes mellitus and the development of PAD. In patients with diabetes, for every 1% increase in haemoglobin A1c, there is a corresponding 26% increased risk of developing PAD. Over the last decade, mounting evidence has suggested that insulin resistance plays a key role in the clustering of cardiometabolic risk factors (also referred to as Metabolic syndrome or Syndrome X) which include hyperglycaemia, dyslipidaemia, hypertension, deep venous thrombosis and obesity.

3.1.3) Dyslipidaemia

In the Framingham study, a fasting total cholesterol > 7 mmol/L was associated with a doubling in the incidence of intermittent lower limb claudication. However, the ratio of total to high-density lipoprotein (HDL) cholesterol was the best predictor of risk for PAD. Although some studies have shown total cholesterol to be a powerful independent risk factor for PAD, others have failed to confirm this association.

Good quality evidence supporting the use of statins to lower LDL cholesterol in PAD patients, were obtained from the Heart Protection Study. Over 20 500 subjects at high risk for cardiovascular events (including 6748 patients with PAD), were enrolled. Patients were randomized to simvastatin 40 mg, antioxidant vitamins, a combination of treatments or placebo, with a 5-year follow up period. Simvastatin 40 mg was associated with a 12% reduction in total mortality, 17% reduction in vascular mortality, 24% reduction in CAD events, 27% reduction in cerebrovascular events and a 16% reduction in non-coronary revascularizations. Similar results were obtained in the PAD subgroup, whether they had
evidence of coronary artery disease at baseline or not. Importantly, there was no threshold cholesterol value below which statin therapy was not associated with benefit. A limitation of this study was that the evidence in PAD was derived from a subgroup analysis of symptomatic PAD patients.

A more recent meta-analysis of 14 randomized trials pertaining to statin therapy, concluded that a 1 mmol/L reduction in the level of LDL cholesterol, was associated with a 20% decrease in the risk of major cardiovascular events.\textsuperscript{[28]} This benefit was also not dependent on the initial lipid levels.

3.1.4) \textit{Hypertension}

Hypertension is associated with all forms of cardiovascular disease, including a two- to three- fold increased risk of developing PAD. However, the relative risk for developing PAD is less than for diabetes or smoking. Current hypertension guidelines support the aggressive treatment of blood pressure in patients with atherosclerotic occlusive disease, targeting a blood pressure of 140/90 mmHg. In the subgroup of patients with diabetes or renal insufficiency, a blood pressure of 130/80 mmHg should be targeted.\textsuperscript{[29,31]}

3.1.5) \textit{Hyperhomocysteinemia}

The prevalence of hyperhomocysteinaemia in the PAD population, is significantly higher than in the general population (prevalence of 1%). It is reported that hyperhomocysteinaemia is detected in about 30% of young patients (aged 55 or below) with PAD. The suggestion that this condition may be an independent risk factor for atherosclerosis, has now been substantiated by several studies. As with cigarette smoking,
it may be a stronger risk factor for PAD than for CAD. While B-vitamin and / or folate supplementation can lower homocysteine levels, this does not reduce the incidence of cardiovascular events. Two studies investigating this supplementation regime in patients with CAD, demonstrated no benefit and even a suggestion of harm.[31,32]

3.1.6) Chronic renal insufficiency

A strong association of renal insufficiency with PAD has been reported, with some recent evidence suggesting it may be causal. The HERS study (Heart and Estrogen / Progestin Replacement Study) reported an independent association of renal insufficiency with future PAD development in postmenopausal women.[33]

4) AETIO-PATHOLOGY

Multiple approaches to the classification of upper limb ischaemic conditions have been described. None are more clinically relevant than categorizing patients into acute or chronic ischaemia, according to the duration of their symptoms. This approach assists the clinician in deliberating the most appropriate management pathway, while honing in on the most common underlying aetiologies. Although essential in the clinical setting, this classification does not lend itself to an in depth discussion of different aetiological factors. A more appropriate classification system for discussion purposes is illustrated below (Table 2). Causes of ULI are divided into two broad categories, namely Upper Extremity Occlusive Disease (UEOD) and Thrombo-Embolic Disease (TED). The limited nature of this dissertation does not allow for in depth discussion of each and every aetio-pathological factor. Therefore, the most common and interesting aetio-pathologies in each category, will be discussed in more detail.
### Table 2: A proposed aetio-pathological classification of upper limb ischaemia

<table>
<thead>
<tr>
<th>UEOD</th>
<th>TED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atherosclerosis (UEAOD)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Thromboangiitis obliterans</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Vasculitides</strong></td>
<td></td>
</tr>
<tr>
<td>Small vessels:</td>
<td>Non-valvular:</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>- Atrial fibrillation</td>
</tr>
<tr>
<td>- Systemic sclerosis (Scleroderma)</td>
<td>- Ischaemic cardiomyopathy</td>
</tr>
<tr>
<td>- Mixed connective tissue disease</td>
<td>- Myocardial infarction</td>
</tr>
<tr>
<td>- Systemic Lupus Erythematosus</td>
<td>- Ventricular aneurysm</td>
</tr>
<tr>
<td>- Polymyositis / Dermatomyositis</td>
<td>- Atrial myxoma</td>
</tr>
<tr>
<td>- Sjögren’s syndrome</td>
<td>- Paradoxical emboli via PFO</td>
</tr>
<tr>
<td>- Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Large vessels:</td>
<td>Valvular:</td>
</tr>
<tr>
<td>- Giant cell arteritis</td>
<td>- Rheumatic heart disease</td>
</tr>
<tr>
<td>- Takayasu’s disease</td>
<td>- Bacterial endocarditis</td>
</tr>
<tr>
<td>- Radiation arteritis</td>
<td>- Sequelae of cardiac valve replacement</td>
</tr>
<tr>
<td><strong>Secondary vasospastic disorders</strong></td>
<td><strong>Extra-cardiac source</strong></td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Aortic:</td>
</tr>
<tr>
<td>- Iatrogenic</td>
<td>- Ascending aortic aneurysm</td>
</tr>
<tr>
<td>- Recreational</td>
<td>- Non-specific / atypical</td>
</tr>
<tr>
<td>- Occupational</td>
<td>- Complicated atheromatous plaque</td>
</tr>
<tr>
<td>- Ammunition workers</td>
<td>- Pseudo-aneurysm</td>
</tr>
<tr>
<td>- Cold exposure</td>
<td>- Post-traumatic / iatrogenic</td>
</tr>
<tr>
<td><strong>Fibromuscular dysplasia</strong></td>
<td>- Aortic dissection</td>
</tr>
<tr>
<td></td>
<td>- Congenital anomaly</td>
</tr>
<tr>
<td></td>
<td>- Aberrant right subclavian artery</td>
</tr>
<tr>
<td></td>
<td>- Kommerrell’s diverticulum</td>
</tr>
<tr>
<td></td>
<td><strong>Peripheral:</strong></td>
</tr>
<tr>
<td></td>
<td>- Subclavian aneurysm</td>
</tr>
<tr>
<td></td>
<td>- Atherosclerotic / atypical</td>
</tr>
<tr>
<td></td>
<td>- Pseudo-aneurysm</td>
</tr>
<tr>
<td></td>
<td>- Post-traumatic / iatrogenic</td>
</tr>
<tr>
<td></td>
<td>- Entrapment syndromes</td>
</tr>
<tr>
<td></td>
<td>- Arterial thoracic outlet syndrome</td>
</tr>
<tr>
<td></td>
<td>- Quadrilateral space syndrome</td>
</tr>
<tr>
<td></td>
<td>- Brachial artery entrapment</td>
</tr>
<tr>
<td></td>
<td>- Arterio-venous fistula / graft</td>
</tr>
<tr>
<td></td>
<td>- Occupational</td>
</tr>
<tr>
<td></td>
<td>- Hypothenar Hammer Syndrome</td>
</tr>
</tbody>
</table>
4.1) Upper extremity occlusive disease (UEOD)

4.1.1) Upper extremity atherosclerotic occlusive disease (UEAOD)

Most series identify embolic disease, trauma and Thromboangiitis obliterans as the most common causes of upper limb ischaemia, followed by UEAOD.\textsuperscript{[1,9,10]} However, Spinelli et al\textsuperscript{[23]} identified atherosclerosis as the most common aetiology (74%) in their upper extremity bypass population. This disproportionately high number might be explained by the unusually high number of patients with dialysis-dependant renal failure (39%) in their study group.

Atherosclerosis may have a variable effect on different arterial segments, both with regards to the morphological pattern of disease (ostial, mono- or multi-segmental) as well as the degree to which the segment is affected. Despite this variability, it should still be regarded as a diffuse disease process affecting multiple vascular beds. Unfortunately, no substantial reports (outside of case reports), could be identified to elucidate and help differentiate the morphological pattern in UEAOD from other anatomical segments prone to the development of atherosclerotic arterial disease.

Atherosclerosis of the upper extremity may manifest in a number of ways. Atheroma formation may progress to occlusion or stenosis of the affected segment. These lesions develop slowly. Often, several decades will pass before a critical narrowing is evident and arterial flow is impaired. This slow progression, as well as the rather robust collateralization response, are possible reasons why upper extremity arterial disease is frequently asymptomatic.
Atheromatous plaque may ulcerate or rupture, resulting in embolization with distal small vessel occlusion, eventually propagating to form extensive arterial occlusion. Thrombosis occurs less commonly. An initial small mural thrombus may evolve to form a major, near-occlusive or occlusive thrombus. Ultimately, lesions progress to form organized, fibrotic thrombus.

UEAOD predominantly affect the proximal vasculature, including the aortic arch, brachiocephalic artery (BCA), subclavian arteries (SCA), axillary and brachial arteries. The most extreme example of this process is aortic arch syndrome, where all branches of the aortic arch are occluded. Usually, only isolated branches occlude or become stenosed, also referred to as partial aortic arch syndrome. Anecdotal evidence suggests that UEAOD frequently involve a single segment of the arterial tree, compared to the predominantly multi-segmental disease encountered in symptomatic lower extremity atherosclerotic occlusive disease.

Less frequently, other more distal segments are affected. These include arteries of the forearm and hand. Obliterative disease of these segments are usually caused by distal embolization from a proximal atheromatous source. The symptomatology may become more severe with coexisting downstream lesions or pre-existing anastomoses.

4.1.2) Thromboangiitis obliterans (TAO)

Thromboangiitis obliterans (also known as Buerger’s disease) is a segmental, occlusive, inflammatory condition of small and medium sized arteries and veins, characterized by
thrombosis and recanalization of the affected vessels.\textsuperscript{[34,35]} It is a non-atherosclerotic inflammatory disease of unknown aetiology, usually affecting young men who are heavy smokers.\textsuperscript{[36]} It differs from other vasculitides in that the serological markers of inflammation and autoantibody formation, are either absent or normal. Pathologically, it differs from other forms of vasculitis in that the vessel wall architecture is relatively well spared and fibrinoid necrosis is absent. Progressive organization of a highly inflammatory thrombus in the vessel lumen, is a consistent finding.\textsuperscript{[37]}

The association between tobacco use and the development of TAO, is incontestable. Use or exposure to tobacco plays a central role in the initiation and progression of the disease. It remains debatable whether cannabis exposure is really implicated in the pathophysiology of distal arteritis in young adults. A recent comprehensive review of the literature\textsuperscript{[38]} collected 70 published cases of the so-called cannabis arteritis. In this review, 97% of cannabis users also smoked tobacco, as cannabis is always consumed mixed with tobacco in Europe. Confounding factors like these add to the difficulty in assessing the effect of cannabis on the initiation and progression of TAO. In a recent retrospective review of 38 consecutive patients with TAO,\textsuperscript{[39]} investigators found that cannabis users were significantly younger at onset of arterial disease despite a similar tobacco exposure. This greater precocity might suggest an accelerating effect of cannabis on TAO pathophysiology. However, a more addictive personality or earlier initiation of tobacco use in cannabis consumers, may have affected this observation. Also, in the absence of toxicological tests, quantification of cannabis exposure cannot be objectively assessed, due to the variability of cannabis concentrations and methods of consumption.
Upper extremity involvement is classic, especially if it presents with Raynaud’s phenomenon of recent onset in a young man. Although TAO most commonly affect the extremities, case reports implicating this disease process in other vascular beds (including cerebral, coronary, intestinal arteries, aorta as well as multi-organ involvement), have been published. [40-43]

A marked decrease in the frequency of the HLA-B12 antigen in patients with TAO (2.2% vs. 28% in controls), was previously reported. [44] Similar to other autoimmune diseases, TAO may have a genetic predisposition without the presence of a direct causative gene mutation. Most investigators agree that TAO is an immune-mediated endarteritis. Recent immunocytochemical studies have demonstrated a linear deposition of immunoglobulins and complement factors along the elastic lamina. [45] The inciting antigen has not been discovered. The role of hyperhomocysteinaemia in the pathogenesis of TAO is controversial. [46] An association between thrombophilic conditions such as antiphospholipid syndrome and TAO, has also been suggested. [47]

4.1.3) Small vessel vasculitides and secondary vasospastic disorders

A host of inflammatory and vasospastic disorders can result in digital ischaemia. Current nomenclature, when describing the clinical manifestation of these disorders, includes the terms phenomenon, syndrome and disease. The inconsistency with which terms are used to describe these conditions, have led to considerable confusion.

In Europe, Raynaud’s phenomenon (RP) is used as a blanket term describing all forms of cold-related vasospasm, with the term Raynaud’s syndrome (RS) being reserved for RP
associated with another (secondary) disease process. Raynaud’s disease (RD) describes the clinical scenario where RP occurs in isolation. American and Australasian researchers use the terms syndrome and phenomenon interchangeably, but differentiate primary from secondary RP. The American nomenclature, as described above, has been adopted and applied to the current text.

In the Framingham Offspring Study, the prevalence of RP was 9.6% in women and 5.8% in men.⁴⁸ A familial predisposition have been described, especially if the onset of RP was under the age of 30 years.⁴⁹ Primary RP has been described in monozygotic twins, but the concordance rate is not currently known.⁵⁰

Vasospasm is the key feature of RP. Maurice Raynaud originally described this phenomenon as “episodic digital ischaemia induced by cold and emotion.”⁵¹ The classical manifestation of pallor, preceding cyanosis and rubor, reflects the initial vasospasm followed by deoxygenation of static blood and reactive hyperaemia. However, the full triphasic colour change is not essential for diagnosis.

The precise mechanism causing RP is poorly understood, but believed to be due to multiple, interdependent factors that interact closely to produce symptoms. These include neurogenic, inflammatory, immunological and genetic factors as well as interactions of blood constituents with the vessel wall.

In approximately half of patients with RP, a significant underlying systemic cause can be identified. Half of these cases are caused by a connective tissue disorders, most
commonly systemic sclerosis or mixed connective tissue disease. Other conditions associated with secondary RP, are listed in Table 3.

Secondary, compared to primary RP, often present with a more severe degree of ischaemia due to the presence of established occlusive disease. Residual symptoms on long term follow-up as well as mortality, is higher in the patient group with systemic disease, compared to local disease associations.

Table 3: Conditions associated with secondary Raynaud’s phenomenon.

<table>
<thead>
<tr>
<th>Category and condition</th>
<th>Incidence of RP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis (Scleroderma)</td>
<td>95%</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>85%</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>40%</td>
</tr>
<tr>
<td>Polymyositis / Dermatomyositis</td>
<td>40%</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>33%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Obstructive</strong></td>
<td></td>
</tr>
<tr>
<td>Distal UEAOD</td>
<td></td>
</tr>
<tr>
<td>Thromboangiitis obliterans</td>
<td></td>
</tr>
<tr>
<td>Micro-emboli (Cardiogenic / Arterio-arterial)</td>
<td></td>
</tr>
<tr>
<td>ATOS (especially when associated with cervical ribs)</td>
<td></td>
</tr>
<tr>
<td><strong>Occupational</strong></td>
<td></td>
</tr>
<tr>
<td>Hypothenar Hammer Syndrome (HHS)</td>
<td></td>
</tr>
<tr>
<td>Vinyl chloride disease</td>
<td></td>
</tr>
<tr>
<td>Ammunition workers</td>
<td></td>
</tr>
<tr>
<td>Frozen food packers</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacological</strong></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Cryoglobinaemia</td>
<td></td>
</tr>
<tr>
<td>Reflex sympathetic dystrophy</td>
<td></td>
</tr>
</tbody>
</table>

Interesting occupation-related causes of secondary RP include Hypothenar hammer syndrome (will be discussed in the section on thrombo-embolic disease), cold exposure, vinyl chloride disease (affecting approximately 3% of exposed workers) and ammunition workers (only manifests once the vasodilatory effects of nitrates are removed, i.e. at home or when on leave).
4.2) Thrombo-embolic disease (TED) of the upper extremity

At this point, the reader is invited to review Table 2 once more (below), as this will be used as a framework to guide discussion on the aetio-pathological aspects of TED.

Table 2: A proposed aetio-pathological classification of upper limb ischaemia

<table>
<thead>
<tr>
<th>UEOD</th>
<th>TED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atherosclerosis</strong> (UEAOD)</td>
<td><strong>Cardiac source</strong></td>
</tr>
<tr>
<td>Thromboangiitis obliterans</td>
<td>Non-valvular:</td>
</tr>
<tr>
<td>Vasculitides</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Small vessels:</td>
<td>Ischaemic cardiomyopathy</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Systemic sclerosis (Scleroderma)</td>
<td>Ventricular aneurysm</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Paradoxical emboli via PFO</td>
</tr>
<tr>
<td>Polymyositis / Dermatomyositis</td>
<td>Valvular:</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Bacterial endocarditis</td>
</tr>
<tr>
<td></td>
<td>Sequelae of cardiac valve replacement</td>
</tr>
<tr>
<td>Large vessels:</td>
<td>Extra-cardiac source</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Aortic:</td>
</tr>
<tr>
<td>Takayasu’s disease</td>
<td>Ascending aortic aneurysm</td>
</tr>
<tr>
<td>Radiation arteritis</td>
<td>Non-specific / atypical</td>
</tr>
<tr>
<td></td>
<td>Complicated atheromatous plaque</td>
</tr>
<tr>
<td>Secondary vasospastic disorders</td>
<td>Pseudo-aneurysm</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Post-traumatic / iatrogenic</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Recreational</td>
<td>Congenital anomaly</td>
</tr>
<tr>
<td>Occupational</td>
<td>Aberrant right subclavian artery</td>
</tr>
<tr>
<td>Ammunition workers</td>
<td>Kommerrell’s diverticulum</td>
</tr>
<tr>
<td>Cold exposure</td>
<td>Peripheral:</td>
</tr>
<tr>
<td></td>
<td>Subclavian aneurysm</td>
</tr>
<tr>
<td></td>
<td>Atherosclerotic / atypical</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
<td>Pseudo-aneurysm</td>
</tr>
<tr>
<td></td>
<td>Post-traumatic / iatrogenic</td>
</tr>
<tr>
<td></td>
<td>Entrapment syndromes</td>
</tr>
<tr>
<td></td>
<td>Arterial thoracic outlet syndrome</td>
</tr>
<tr>
<td></td>
<td>Quadrilateral space syndrome</td>
</tr>
<tr>
<td></td>
<td>Brachial artery entrapment</td>
</tr>
<tr>
<td></td>
<td>Arterio-venous fistula / graft</td>
</tr>
<tr>
<td></td>
<td>Occupational</td>
</tr>
<tr>
<td></td>
<td>Hypothenar Hammer Syndrome</td>
</tr>
</tbody>
</table>

The most common causes of ALI include arterial embolism, thrombosis and trauma. Embolic and thrombotic disease processes will be discussed separately.
4.2.1) Embolic disease: General remarks

Emboli may arise from several possible origins. Traditionally, embolic sources have been classified as either cardiac or extra-cardiac in origin. Consistently, it has been reported that the heart is the most frequent source of emboli followed by the proximal aorta and supra-aortic trunk.\textsuperscript{[12,52-53]} Approximately two-thirds of emboli involving the upper extremities, originate from the heart, with 9–12\% classified as cryptogenic.

The origin of the embolus affect the size and consequently the level at which it occludes the affected vessel. Emboli originating from the heart are usually larger in size and tend to lodge more proximally, often at the bifurcation of the brachial artery. Arterial emboli travel more distally, however exceptions to the rule do exist. Haimovici,\textsuperscript{[13]} reported the subclavian artery to be the site of occlusion in 11.7\%, the axillary artery in 23\%, the brachial artery in 61\%, the radial artery in 23\% and the ulnar artery in 1.6\% of patients with AULI. Comparison between studies is difficult due to different methods used to establish the site of occlusion (clinical, operative and angiographic findings). Despite this confounding factor, multiple reports have confirmed the brachial artery to be the most commonly occluded artery in the upper limb.\textsuperscript{[1,2,54,55]}

Most authors describe a higher incidence of embolism affecting the right arm compared to the left. This phenomenon can probably be explained by the larger diameter of the brachiocephalic artery compared to the left subclavian artery as well as the favourable angle that exists between the aorta and the brachiocephalic artery.\textsuperscript{[4]}
The natural clinical course of a peripheral arterial embolus depends upon the location of the occlusion, the completeness of luminal obliteration, the extent of secondary thrombosis and the degree of spontaneous restoration of the collateral circulation. Occlusion of the subclavian artery is usually well tolerated and compensated for by collateral blood supply. The axillary artery, too, has a rich collateral blood supply from the more proximal subclavian branches (Figure 3). Combined subclavian and axillary occlusion usually cause ischemia of the entire arm.

*Figure 3: Schematic representation of collateral circulation pathways around the right shoulder joint in the setting of SCA occlusion*
Occlusion of the brachial artery has different effects, depending on the site of occlusion, presence of collateral branches as well as the metabolic requirements of tissue distal to the occlusion. The brachial artery is often occluded at the origin of the deep brachial or at the bifurcation into ulnar and radial arteries.\textsuperscript{[52]} If the occlusion occurs proximal to the deep brachial artery origin, the arm usually presents with ischaemic signs and symptoms due to a lack of collateral blood supply. Conversely, the collateral blood supply for an occlusion distal to the deep brachial artery is profuse (including the deep brachial, superior and inferior ulnar collateral arteries as well as the cubital vessels), hence the clinical picture is commonly less severe. Occlusion of either the radial or ulnar arteries is not markedly injurious. However, occlusion of the more distal deep palmar arch can result in tissue necrosis.

4.2.2) Embolic disease: Non-valvular origins of cardio-emboli

Cardio-embolic sources can be of valvular or non-valvular origin. \textit{By far the most common non-valvular cause, is atrial fibrillation}. Due to the erratic, uncoordinated contraction of the atria, a variable amount of static blood occupies the atrial appendage, predisposing to thrombus formation. Part of this thrombus may gain entry to the systemic circulation, resulting in systemic embolization.

\textit{Ischaemic conditions of the myocardium} can manifest with cardio-embolic events. This may present in the acute setting due to an acute myocardial infarction complicated by a dramatic increase in afterload (also referred to as “pump failure”) or in a delayed fashion by presenting with ischaemic cardiomyopathy. In both conditions, pooling of near-static blood within the chambers lead to thrombus formation. A small percentage follows acute
myocardial infarction, be it clinically apparent or occult (also referred to as a silent myocardial infarction or SMI). SMI is not an infrequent event, with an incidence of 1-4% in the non-diabetic population and 10-20% in diabetic patients. The pathogenesis is incompletely understood, but thought to be sequelae of diabetic autonomic neuropathy.\textsuperscript{[56-57]} This condition should always be borne in mind, especially when confronted with diabetic patients.

\textit{Atrial myxoma} is the most common benign tumour of the heart, representing approximately 50% of all cardiac tumours. Clinical manifestations are determined by the location, size and mobility of the tumour. Possible presentations include cardiac obstruction, arrhythmias and peripheral embolization. The embolization of tumour fragments or thrombotic material covered with tumour cells, occur in approximately 30% of myxoma patients.\textsuperscript{[58,60]} Most of these tumours embolize to the central nervous system, resulting in ischaemic cerebrovascular incidents. Secondary embolization to the coronary arteries, kidneys, intestines and peripheral arteries have been described.\textsuperscript{[61]} Among 4396 reports of myxoma in the literature,\textsuperscript{[59]} only 10 cases of atrial myxoma, complicated with AULI, have been reported. Even though rare, an embolizing myxoma should be included in the differential diagnosis of a young, otherwise healthy patient presenting with acute arterial ischaemia.\textsuperscript{[62]}

Various forms of \textit{interatrial communications}, such as patent foramen ovale (PFO) and atrial septal defect (ASD), occur in a significant proportion of the general population. In an autopsy study of 965 hearts from normal people spanning an age range of 10 decades, the overall incidence of PFO was 27%.\textsuperscript{[63]} The earliest documentation of paradoxical
embolism through a PFO, was in the 1877 text of Julius Cohnheim. In more modern times, a group of investigators based in Paris, France first postulated an important role for PFO’s in young patients (younger than 55 years of age) with cryptogenic stroke based on a case-control study.\[^{64}\]

The mechanistic model of systemic embolization caused or facilitated by a PFO, is paradoxical embolism. Venous clots and rarely other particles (such as air, fat, amniotic fluid, tumor emboli or emboli from right heart endocarditis), pass from the systemic venous circulation to the arterial circulation by means of a variable right-to-left shunt. The clinical diagnosis of paradoxical embolism relies on the concurrence of arterial embolism, venous thrombosis, interatrial communication and a gradient favouring right-to-left shunting.\[^{65}\] This gradient occurs transiently in normal individuals during early ventricular systole as well as the strain and release phase of the Valsalva maneuver. During the straining phase the right atrial pressure rises disproportionately, followed by a sudden increase in systemic venous return to the right atrium in the release phase.\[^{66}\]

4.2.3) Embolic disease: Valvular origins of cardio-emobli

Few complications of valvular heart disease can be more devastating than systemic embolism. Causes include rheumatic heart disease, bacterial endocarditis and sequelae of valve replacement surgery.

The incidence of systemic embolism in *rheumatic mitral valve disease* (mitral stenosis and/or mitral regurgitation), is greater than in any other form of valvular heart disease and increases dramatically with the development of atrial fibrillation (AF).\[^{67}\] The risk of
systemic emboli in rheumatic mitral valve disease is also greater in older patients\textsuperscript{[68-71]} and those with lower cardiac indices,\textsuperscript{[68]} but appears to correlate poorly with mitral calcification\textsuperscript{[67]} and mitral valve area.\textsuperscript{[68]}

Clinically detectable systemic emboli in isolated \textit{aortic valve disease}, are uncommon. The small, but consistent frequency of systemic emboli reported in earlier studies of aortic valve disease, may best be explained by unrecognized mitral valve disease, ischemic heart disease or coexisting AF. However, one centre emphasized the thrombo-embolic potential of severe calcific aortic valve disease by histologically demonstrating micro-thrombi in 10 of 19 calcified and stenotic aortic valves.\textsuperscript{[72]} It appears, therefore, that calcific micro-emboli from heavily calcified aortic valves are not as rare as previously thought, but rather difficult to detect due to their small size (unless visualized in the retinal artery).

With the advent of effective antimicrobial therapy, the incidence of systemic emboli in \textit{Infective Endocarditis} (IE), has decreased. In the pre-antibiotic era, clinically detectable emboli occurred in 70 to 97\% of patients with IE.\textsuperscript{[74]} Recent reports suggest figures in the region of 12 to 40\%.\textsuperscript{[75-80]} The use of echocardiography was met with great enthusiasm, in order to identify the patient at risk of embolization. Initial reports proposed a high correlation between echocardiographically demonstrable vegetations and embolism.\textsuperscript{[81-84]} However, in a more recent review of this subject, one centre reported that 80\% of patients with IE had echocardiographic evidence of vegetations, while only one third had features of systemic emboli.\textsuperscript{[85]}
The patient with *prosthetic valve endocarditis* deserves special mention. With the exception of patients with bio-prostheses in normal sinus rhythm, patients with prosthetic valves are at a constant risk of thrombo-embolism, emphasizing the importance of uninterrupted anticoagulation therapy. The risk of thrombo-embolic events in prosthetic valve endocarditis are higher than in native valve endocarditis, approaching 50-88%. [86,87]

**4.2.4) Embolic disease: Extra-cardiac origins**

An extra-cardiac source of emboli is nowadays identified in 5–12% of patients presenting with peripheral embolic disease. *Aneurysms are the most common extra-cardiac source of peripheral emboli*, followed by ulcerated atherosclerotic plaque rupture and disruption, leading to macro-embolization of plaque components (athero-embolism) or micro-embolization of platelet aggregates. Systemic athero-embolism may present in any of three clinical forms:

- The asymptomatic form, not diagnosed during the subject’s lifetime, but recognized at autopsy.
- A benign form, such as blue toe / digit syndrome or cutaneous livedo, with a relatively good prognosis if managed correctly.
- A diffuse multi-systemic form with a poor prognosis.

Although less commonly encountered, a few interesting disease processes may manifest with peripheral arterial embolism. These include entrapment syndromes of the peripheral arteries, congenital anomalies of the aortic arch as well as occupational / recreational diseases.
4.2.4.1) Arterial thoracic outlet syndrome (ATOS)

Historically, when Adson first described his manoeuvre in 1927,[89] thoracic outlet syndrome was called scalenus anticus syndrome. The underlying abnormality was thought to be compression of the subclavian artery (SCA) by the anterior scalene muscle (ASM). Approximately 30 years later, it was recognized that in addition to the SCA, the subclavian vein or brachial plexus can also be compressed and that structures other than the ASM, were also implicated in compression. In 1956, Peet et al renamed the condition by coining the all-inclusive label, thoracic outlet syndrome (TOS).[90]

Throughout the course of medical history, TOS has developed a reputation as a condition based on convoluted neurological and vascular symptoms. Physicians have continually disagreed about the relevance and pathogenesis of TOS, leading to a wide spectrum of opinions and research directions. This disagreement is augmented by the presence of anatomic anomalies and abnormal diagnostic tests observed in an asymptomatic population, resulting in further dispute about the specificity and sensitivity of commonly used diagnostic tests.[91]

Thoracic outlet syndrome describes a variety of symptoms caused by compression of the brachial plexus or subclavian vessels, at the thoracic outlet. In the majority of cases, symptoms are neurological in nature, with pain and weakness resulting from C8 or T1 nerve root compression. Arterial or venous symptoms resulting from compression are uncommon, accounting for 5% of cases in a large published series by Roos et al.[88] Anatomically, the thoracic outlet and corresponding area of neurovascular compression, is considered to incorporate 3 areas, namely the interscalene triangle, costoclavicular triangle
Typically, the left and right SCA ascend into the neck before arcing laterally towards the medial border of the ASM. They descend laterally from the lateral margin of the ASM towards the outer border of the first rib, at which point they become the axillary arteries.\cite{94} There are many variations described in the literature concerning the course of the SCA relative to the ASM. These include the right subclavian artery passing anterior, within, or posterior to the ASM.\cite{94-98} These variations may occur because of a hypertrophied muscle, muscle strain or accompanying soft tissue abnormalities such as fibrosis or congenital bands.\cite{99} Cervical ribs occur in 1–6% of the general population and in approximately 10% of patients with TOS.\cite{93,100-102}

*Figure 4: Schematic representation illustrating the anatomical relations of structures to the 3 areas of entrapment (interscalene and costoclavicular triangle, subcoracoid space)*
The list of causative mechanisms in TOS is extensive (Table 4), yet one of the earliest and most consistently described, is the presence of a cervical rib. Galen first documented the presence of cervical ribs in 2 AD and further elaboration by the anatomist Vesalius during the first dissections of human bodies in 1543, provided additional insight.\textsuperscript{[103-104]}

**Table 4: Causative mechanisms described in TOS**

<table>
<thead>
<tr>
<th>Soft tissue lesions</th>
<th>Bony lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalene muscles + fibro-muscular bands</td>
<td>Cervical rib (Complete / Partial)</td>
</tr>
<tr>
<td>Subclavian muscle + costo-clavicular ligament</td>
<td>First rib anomalies (Synostosis / Bifid)</td>
</tr>
<tr>
<td>Pectoralis minor muscle + fibro-muscular band</td>
<td>Long C7 transverse process</td>
</tr>
<tr>
<td></td>
<td>Clavicular abnormalities</td>
</tr>
</tbody>
</table>

In a review of their experience with ATOS, the University of Natal reported the largest South African series to date.\textsuperscript{[105]} The most common bony lesion identified, was that of a compressed SCA between a cervical rib and the insertion of the anterior scalene muscle (See Table 5 for summary of findings).

**Table 5: Summary of underlying bony pathology encountered in ATOS.\textsuperscript{[105]}**

<table>
<thead>
<tr>
<th>Bony lesion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cervical rib, articulated on scalene tubercle of 1\textsuperscript{st} rib</td>
<td>15</td>
</tr>
<tr>
<td>Partial cervical rib with fibrous band to scalene tubercle</td>
<td>7 (+2 declined surgery)</td>
</tr>
<tr>
<td>Osseous anomaly of 1\textsuperscript{st} rib, articulated on 2\textsuperscript{nd} rib</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>26</td>
</tr>
</tbody>
</table>

The sequelae of a chronically compressed SCA represent the end stage of an undiagnosed condition. Compressive stenosis (postural or fixed) at the thoracic outlet develops with fibrous cuffing of the affected vessel, followed by post-stenotic dilatation (PSD) and
aneurysm formation. Aneurysmal degeneration leads to mural thrombus formation and with it, risk of serial distal embolization (Figure 5). Most emboli are small and localized to the palmar and digital vessels, commonly presenting with Raynaud’s phenomenon. If unrecognized, severe digital ischaemia with digital ulceration or gangrene may occur. Although the genesis of PSD by wall vibration secondary to turbulent flow dynamics has been well studied, the natural history and clinical outcome of this chronic process is poorly understood, but certainly not benign. Experimental evidence suggests that PSD is a reversible phenomenon after release of the stenotic or compressive lesion.\textsuperscript{106-107}

Figure 5: Schematic representation illustrating the anatomical relations and sequelae of a chronically compressed SCA (As depicted by Clagett)\textsuperscript{108}

The axillary artery is vulnerable to compression as it passes beneath the tendon of the pectoralis minor muscle, where it is fixed at the origin of the circumflex humoral arteries. Repetitive vessel injury can lead to intimal hyperplasia and stenosis, aneurysmal degeneration of the arterial wall with distal thrombo-embolism, pseudoaneurysm formation or propagating dissection.\textsuperscript{109}
By means of a retrospective analysis of 41 patients with objective findings of ATOS, Criado et al identified a spectrum of underlying arterial pathologies associated with this condition.\cite{110}

**Table 6: Spectrum of arterial pathologies associated with ATOS (adapted from Criado et al)\cite{110}**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclavian artery aneurysm</td>
<td>12</td>
</tr>
<tr>
<td>Postural stenosis with post-stenotic dilatation</td>
<td>10</td>
</tr>
<tr>
<td>Postural stenosis with post-stenotic dilatation</td>
<td></td>
</tr>
<tr>
<td>Subclavian artery</td>
<td>5</td>
</tr>
<tr>
<td>Axillary artery</td>
<td>2</td>
</tr>
<tr>
<td>Fixed subclavian stenosis</td>
<td>5</td>
</tr>
<tr>
<td>Fixed stenosis with post-stenotic dilatation</td>
<td>4</td>
</tr>
<tr>
<td>Luminal filling defect</td>
<td>2</td>
</tr>
<tr>
<td>Subclavian artery occlusion</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td><strong>41</strong></td>
</tr>
</tbody>
</table>

Muscular hypertrophy (particularly of the scalene muscles) in athletes performing repetitive overhead activities (including weight lifters, swimmers and baseball players),\cite{108} may put these athletes at risk of ATOS. Baseball pitchers and volleyball players are at particular risk of axillary artery injury due to repetitive and forceful arm elevation and extension. Male athletes appear to be at greater risk of axillary artery injury, with no gender-specific difference related to subclavian artery injury.\cite{111}

4.2.4.2) Quadrilateral space syndrome

This syndrome usually affects athletes performing repetitive, strenuous shoulder activity, such as baseball pitchers and volleyball players.
The quadrilateral space is formed by the teres minor (superiorly) and major (inferiorly), the long head of the triceps (medially) and the humerus (laterally) (Figure 6). After arising from the third part of the axillary artery, the posterior circumflex humeral artery (which can reach up to 8mm in size among major league baseball players) joins the axillary nerve as it traverses the quadrilateral space. At this point, structures are vulnerable to compression, particularly in the setting of hypertrophied surrounding muscles.

Figure 6: Schematic representation illustrating the anatomical relations of the quadrilateral space, with particular reference to the posterior circumflex humeral artery and axillary nerve.

Clinical presentation may include poorly localized discomfort within the shoulder girdle, paresthesia or numbness within the axillary nerve distribution or fatigue and weakness on
extreme abduction and external rotation. Distal ischaemic symptoms may occur as a result of serial arterial embolization in association with aneurysm formation.

Definitive diagnosis is made at arteriography by establishing position-dependant (abduction and external rotation of the shoulder joint) occlusion of the posterior circumflex humeral artery.

4.2.4.3) Brachial artery entrapment

Rarely, position-dependant ischaemia may occur during hyperextension of the elbow joint. Associated anatomical anomalies include the presence of a supracondylar spur with anomalous insertion of the pronator teres muscle, responsible for compression of the brachial artery.\textsuperscript{[113]} A case study of brachial artery entrapment exclusively due to muscular hypertrophy, have been reported.\textsuperscript{[114]} Although exceedingly rare, these conditions should be considered in patients presenting with atypical symptoms of ATOS.

4.2.4.4) Hypothenar Hammer Syndrome (HHS)

HHS is often overlooked in the absence of a thorough occupational and recreational history. Importantly, this condition is usually reversible through cessation of the offending activity, but can lead to morbidity and even amputation if not timeously recognized.

Other terminology used to refer to an occupational disease triggered by continuous use of vibrating hand-held machinery, include hand-arm vibration syndrome (HAVS) and vibration white finger (now largely superseded by the broader concept of HAVS). HAVS refers to a disorder that affects the blood vessels, nerves, muscles and joints of the hand,
wrist and arm. Injury can occur at frequencies between 5 and 2000 Hz, but the greatest risk exists between 50 and 150 Hz. HHS refers to the vascular component of HAVS.

The concept of HHS was first described in 1934,[115-116] but the term ‘Hypothenar Hammer Syndrome’ was coined by Conn, after recognizing the mechanism of injury.[117] The incidence of HHS is remarkably low when one considers the relatively large segment of population exposed to the relevant occupational hazards. Possible explanations include anatomical variability of the vasculature in this region as well as the presence of subclinical disease. These factors may also explain the variable presentation of patients, ranging from asymptomatic disease to tissue necrosis.

Although most commonly encountered within the work place (including carpentry,[117] motor mechanics and metal workers), HHS is not restricted to this environment. Recent case reports and case series have confirmed the presence of HHS in recreational and professional sport activities, including volleyball,[115] hockey,[115] mountain biking,[118] tennis,[119] badminton,[120] weight lifting and baseball.

The underlying pathogenesis of HHS is based on repetitive blunt trauma to a relatively unprotected terminal ulnar artery. After emerging from Guyon’s canal (between the pisiform and hook of the hamate), the distal ulnar artery becomes somewhat fixed as it runs superficially across the hypothenar musculature.[117] Between its deep palmar branch and the origin of the superficial palmar arch, it is particularly vulnerable as it is only protected by skin, subcutaneous tissue, palmaris brevis muscle and superficial aponeurosis.[117,121] Repetitive blunt trauma to the hypothenar eminence (Figure 8)
compresses the ulnar artery against the hook of the hamate (the so called “hammer and anvil effect”), triggering vasospasm. Trauma to the adventitial layer may cause thickening and fibrosis, ultimately leading to extrinsic scarring with post-stenotic dilatation / aneurysm formation or arterial occlusion. Distal embolization of the digital arteries may exacerbate ischaemia.

Figure 7: DSA of a 49-year-old recreational baseball player’s right hand

Previously repaired ulnar artery aneurysm

Distal digital artery occlusion of 3rd, 4th and 5th digits.
4.2.4.5) Congenital anomalies

Anatomical anomalies of the aortic arch and upper limb vasculature are rare occurrences (estimated frequency of 3%) that have been implicated in the pathogenesis and development of ischaemic conditions. These congenital anomalies may create stenoses, aneurysms (often manifesting as thrombo-embolism) and occlusive disease of the upper extremities, but are usually fortuitous radiological findings as it frequently follows an asymptomatic course.

The most common aortic arch anomaly (as described by Hunauld in 1735) is the occurrence of a left aortic arch with an aberrant right SCA, seen in 0.5% of the population. The vessel originates distal to the left subclavian origin (typically posterior and inferior on the arch) and crosses the midline between the oesophagus and vertebral
In 1794, Bayford described the first case of symptomatic compression of the oesophagus by the posteriorly positioned aberrant right SCA, known as dysphagia lusoria. These patients may also have associated anomalies, such as a common carotid trunk and right vertebral artery originating directly from the right common carotid artery.

*Figure 9: Anatomic relations of an aberrant right SCA.*

Other, less common anomalies include the occurrence of a *right aortic arch with an aberrant left SCA*. Degenerative aneurysmal changes at its aortic origin may occur in up to 60% of patients, known as Kommerell’s diverticulum.
Variations in the arterial anatomy of the upper extremities, are uncommon and rarely cause ischaemia of the upper extremity in isolation. Most of these variants occur in either the radial or ulnar artery; brachial artery variations are less common. Variability in the path or source of the radial artery is reported in up to 30% of patients. The most common variation is a high radial artery origin, arising from the brachial or axillary artery proximal to the antecubital fossa. This is estimated to occur in between 2% and 14% of extremities. Substantially less common variations include absence of the radial artery, duplication of the radial artery and superficial passage of the radial artery above the tendons of the snuffbox (adductor pollicis longus and extensor pollicis brevis). Variation in the ulnar artery pathway or position is much less commonly seen (3% to 5%).

The blood vessels in the hand communicate via 3 major arches—2 palmar and one dorsal arch. A great number of studies have elucidated the extreme anatomic variance in this network of vessels, particularly on the radial aspect of the hand. Studies demonstrate the superficial palmar arch to be complete in more than 80% of patients, with the deep palmar arch complete in more than 90%. A clinically relevant anatomic variant is the presence of a communication between a persistent median artery (an embryologic remnant that normally undergoes apoptosis during upper limb development) and the superficial palmar arch, which serves to complete the arch. This was seen in 15.5% of specimens in a well-performed cadaveric study.
4.2.5) Thrombotic disease

Atherosclerosis of the upper extremity arteries is a relatively rare occurrence, leading some investigators to label all non-traumatic cases of AULI, as embolic. While this may hold true for a large proportion of cases, it fails to distinguish the rarer causes of arterial occlusion, such as native arterial thrombosis. The true incidence of thrombosis as a cause of AULI is difficult to determine. Reports suggest that 5% of AULI cases in population studies and 9–35% in surgical series are due to native artery thrombosis. Establishing the correct diagnosis is essential in order to offer appropriate management options. Treatment usually requires bypass surgery or thrombolytic therapy, with inappropriate embolectomy or thrombectomy associated with higher morbidity and mortality rates.

Most of the proximal arterial lesions that cause emboli, can also result in thrombosis (including atherosclerotic plaques, aneurysms and arteritis). As Virchow suggested in 1856, thrombus formation is the result of an interaction between an injured vascular surface, stasis and hypercoagulability of blood. Arterial thrombosis most often develops at the points of severe stenosis. However, a thrombus can form in the absence of significant pre-existing stenosis, particularly when the surface of the plaque is ulcerated or after intra-plaque haemorrhage has occurred (vulnerable / unstable plaque). Low-flow haemodynamic states, such as congestive heart failure, hypovolaemia or hypotension of any cause may predispose to arterial thrombosis. Hypercoagulable states, such as myeloproliferative disorders, hyperviscosity syndromes and coagulation disorders, may also contribute to thrombosis of the diseased artery.
5) THE ANATOMICAL BASIS OF DISEASE

On initial evaluation of this condition, it may be difficult to establish the precise aetio-pathological process involved. Therefore, making use of a structured approach will be of benefit to the clinician. Some authors prefer classifying causes according to local, regional and systemic disease processes. Others categorize patients into two main groups, namely Upper Extremity Occlusive Disease and Thrombo-embolic Disease (refer to section on Aetio-pathology).

As surgeons, an attractive approach to the myriad of underlying aetiologies, is the implementation of an anatomical framework. A differential diagnosis for each arterial segment can be compiled (*Figure 10* below), but should be interpreted in terms of the relevant clinical information.
Figure 10: A proposed anatomical approach to the aetiology of upper limb ischaemia

Axillary artery:
- Atherosclerotic stenosis / occlusion / degenerative aneurysm
- Arterial TOS (Postural / fixed stenosis +/- PSD or aneurysm formation)
- Radiation induced vascular injury
- Thrombosed axilo-femoral bypass graft

Brachial artery:
- Embolic occlusion (usually macro-emboli from proximal source)
- Atherosclerotic stenosis / occlusion
- Thrombosed haemodialysis AV fistula / graft
- Congenital anomalies

Ulnar and radial arteries:
- Buerger’s disease
- Embolic occlusion
- Atherosclerotic stenosis / occlusion
- Congenital anomalies (usually absent radial artery)

Palmar arches:
- Buerger’s disease
- Embolization from proximal source (usually micro-emboli)
- Occupational (HHS)
- Congenital anomalies (incomplete superficial and/or deep palmar arch)

Digital arteries:
- Buerger’s disease
- Embolization from proximal source (micro-emboli)
- Connective tissue disorders
- Vasculitis
- Occupational (HHS)

Systemic venous circulation / right heart:
- Paradoxical embolism via PFO / ASD originating from:
  - DVT
  - Air-/fat-/amniotic- or tumour emboli
  - Right heart infective endocarditis

Brachiocephalic / subclavian arteries:
- Atherosclerotic stenosis / occlusion / degenerative aneurysm
- Arterial TOS (Postural / fixed stenosis +/- PSD or aneurysm formation)
- Takayasu’s arteritis (Type I, II or IV)
- Fibromuscular dysplasia
- Congenital anomalies (absent proximal left SCA)

Ascending aorta / aortic arch:
- Atherosclerotic stenosis / occlusion / degenerative aneurysm
- Aortic dissection (Stanford A)
- Takayasu’s arteritis (Type I, II or IV)

Cardiac:
- Non-valvular
  - Atrial fibrillation
  - Myocardial infarction
  - Ischaemic CMO
  - Left ventricular aneurysm
  - Left atrial myxoma
- Valvular
  - Rheumatic mitral valve disease
  - Left heart infective endocarditis
  - Sequelae of cardiac valve replacement

Systemic venous circulation / right heart:
- Paradoxical embolism via PFO / ASD originating from:
  - DVT
  - Air-/fat-/amniotic- or tumour emboli
  - Right heart infective endocarditis

Radiation induced vascular injury
- Thrombosed axillo-femoral bypass graft

Brachial artery:
- Embolic occlusion (usually macro-emboli from proximal source)
- Atherosclerotic stenosis / occlusion
- Thrombosed haemodialysis AV fistula / graft
- Congenital anomalies

Ulnar and radial arteries:
- Buerger’s disease
- Embolic occlusion
- Atherosclerotic stenosis / occlusion
- Congenital anomalies (usually absent radial artery)

Palmar arches:
- Buerger’s disease
- Embolization from proximal source (usually micro-emboli)
- Occupational (HHS)
- Congenital anomalies (incomplete superficial and/or deep palmar arch)

Digital arteries:
- Buerger’s disease
- Embolization from proximal source (micro-emboli)
- Connective tissue disorders
- Vasculitis
- Occupational (HHS)
6) CLINICAL PRESENTATION AND MANAGEMENT PATHWAYS

Clinicians prefer categorizing presenting patients into acute or chronic ischaemia, according to the duration of their symptoms. Acute ischaemia should be immediately assessed and the severity of ischaemia used to guide early management decisions.

6.1) Acute upper limb ischaemia

According to the TASC II consensus document,[11] acute limb ischemia (ALI) is defined as any sudden decrease in limb perfusion posing a potential threat to limb viability. Patients usually present within 2 weeks following the acute event, but time to presentation may be influenced by the severity of ischaemia and access to healthcare.[24] Clinical decision-making hinges upon a focused, but thorough history and clinical examination. Essential questions need to be answered pertaining to limb viability, the severity of ischaemia, suspected underlying aetiology, the presence of serious concurrent systemic diseases and conditions mimicking AULI.

Limb viability

An inappropriate attempt at revascularization of an irreversibly ischaemic limb, may result in preventable mortality. Signs that preclude limb salvage include the presence of compartmental rigidity and fixed skin staining (Table 6 – Rutherford category III). A small number of patients present in a moribund state with signs of irreversible limb ischaemia. Terminal care may be the kindest and most appropriate management option in these patients. Primary amputation, after adequate resuscitation and stabilization, should be offered to candidates deemed fit for a general or loco-regional anaesthetic.
Severity of ischaemia

The severity of ischaemia can be accurately established by a systematic clinical examination and bedside doppler investigation. The duration, location and intensity (including change in the severity over time) of pain as well as the presence of motor or sensory deficiencies, guide early management decisions regarding the urgency of revascularization. Immediately threatened extremities should undergo an emergent attempt at revascularization, while a period of further investigation, observation and non-operative treatment may be appropriate in managing the marginally threatened limb. Rutherford et al\cite{131} suggested a classification system (\textit{Table 7}) in an attempt to standardize reports dealing with ALI.

\textit{Table 7: Suggested classification of acute limb ischaemia\cite{131}}

<table>
<thead>
<tr>
<th>Category</th>
<th>Description/prognosis</th>
<th>Sensory loss</th>
<th>Muscle weakness</th>
<th>Doppler signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Viable</td>
<td>Not immediately threatened</td>
<td>None</td>
<td>None</td>
<td>Arterial Audible, Venous Audible</td>
</tr>
<tr>
<td>II Threatened</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Marginal</td>
<td>Salvageable if promptly treated</td>
<td>Minimal/none</td>
<td>None</td>
<td>Often inaudible, Usually audible, Audible</td>
</tr>
<tr>
<td>b) Immediate</td>
<td>Salvageable if immediately treated</td>
<td>Pain at rest</td>
<td>Mild/moderate</td>
<td>Audible</td>
</tr>
<tr>
<td>III Irreversible</td>
<td>Major tissue necrosis or permanent nerve damage</td>
<td>Profound, insensate</td>
<td>Profound, paralysis</td>
<td>Inaudible</td>
</tr>
</tbody>
</table>

Suspected underlying aetiology

Importantly, the clinician should attempt to distinguish embolic from thrombotic occlusions, considering that management pathways differ considerably. Typically, the patient that presents with an embolic occlusion will do so early (usually within 24 hours) due to a lack of arterial collateralization and often present with a more severe grade of ischaemia.
Thrombotic occlusions present later, usually within days of the acute event. One particularly important implication, is the relative ineffectiveness of thrombolysis in the management of thrombosis present for more than 2 weeks duration (as per post-hoc analysis of the STILE trial data). It is important to enquire about a history of arm claudication and previous revascularization procedures. Signs of atherosclerotic occlusive disease of the contralateral upper extremity, favour the diagnosis of thrombosis.

*Serious concurrent diseases*

The identification of serious systemic illnesses in patients with AULI, is important for several reasons. Poorly optimized systemic diseases (including hypertension, diabetes, ischaemic heart disease / recent cardiac events and renal dysfunction), can influence the patient’s fitness for a general or loco-regional anaesthetic, contribute to the underlying disease process and drastically affect the patient’s prognosis. This can be best appreciated in the subgroup of patients presenting with embolic disease of the upper extremities. Deguara et al\(^\text{[1]}\) reported, in a subgroup of patients that underwent embolectomy, that all early (30 day) mortalities were attributable to cardiopulmonary incidents, none being a consequence of arm ischemia or gangrene. The majority of patients (84%) with embolic disease had associated ischaemic heart disease or a recent myocardial infarction and between 51 - 63% was diagnosed with atrial fibrillation. The higher mortality rate of patients undergoing a seemingly small surgical procedure under general anaesthesia compared with loco-regional anaesthesia, may also reflect an increased risk of cardiovascular events.
**Conditions mimicking AULI**

Though AULI may often be an easy diagnosis to make, one has to consider certain conditions that may mimic or influence patient presentation. These include systemic shock / low flow states (especially if associated with chronic occlusive disease), subclavian-axillary vein thrombosis presenting with phlegmasia cerulea dolens, acute cervical compressive neuropathy and exertional forearm compartment syndrome.

**Non-operative vs operative management**

Individual events of AULI, are not usually as limb-threatening as those in the lower extremity and thrombo-embolectomy is not always required for limb salvage. AULI may be managed by implementing various treatment modalities, but no real guidelines exist to clarify when a conservative approach is warranted. Previous publications suggest that conservative management of patients with AULI results in functional limb impairment in 50 – 75% of cases and is therefore not advocated.\[^{52,133}\] Recent publications have challenged this view by highlighting several case series reporting successful conservative management in a selected subgroup of patients, with excellent functional outcome. Conservative management takes advantage of the superior collateral arterial supply in the arm, compared with the lower extremities.

The best level of evidence on this topic, takes the form of a recently performed systematic review.\[^{134}\] Conservative therapies included anticoagulation, rehydration and treatment of contributing medical conditions. A total of 34 retrospective studies and 3 review articles were recovered. Operative management was performed most commonly (86%), followed by conservative management (11%) and interventional radiological approaches (3%).
Catheter-directed embolectomy procedures, when performed as the primary treatment modality, revealed an overall success rate of 85%–90%. Significant selection bias and treatment inconsistencies in the subgroup of patients receiving conservative management, hampered the interpretation of results. The perused literature only reported the use of conservative management in patients deemed to be unfit for surgical management or those with symptomatically mild disease, not considered worth treating. On worsening of symptoms, patients initially treated conservatively, were crossed over to the surgical intervention group. Furthermore, some patients were managed supportively without the initiation of anticoagulants. In those studies where anticoagulants were initiated, long-term anticoagulation rates were poor with some authors reporting a 22% effective anticoagulation rate in patients representing with recurrent embolism.\textsuperscript{135}

When considering the evidence, it is clear that inherent challenges do exist. Significant numerical and ethical dilemmas may arise when attempting to perform a randomized controlled clinical trial to attain level-one evidence. The tendency to treat “fit” and “unfit” patients differently, is deeply ingrained in clinical practice and it may be viewed unethical to deny a “fit” patient operative therapy in view of the current literature.

Some authors believe that an initial conservative approach in suitable patients, are practiced more commonly than is reported. This underreporting limits the literature’s ability to report progress and when combined with selection bias, leads to poor quality data. Therefore, units regularly practising a non-operative approach to the acutely ischaemic upper limb, has a responsibility to audit and publish their results.
7) OUTCOME

Series that combine both acute and chronic ischaemia are rare.\textsuperscript{[1,5-7]} The largest of these, included 172 patients undergoing revascularization procedures for upper limb ischaemia over a 20 year period.\textsuperscript{[1]} About two-thirds of the procedures were performed for acute ischaemia, with embolic disease being the most common underlying pathology in this subgroup, closely followed by trauma. More than half of the patients presenting with chronic ischaemia had an intrinsic atherosclerotic stenosis or occlusion of the subclavian or axillary artery, with the rest made up by thoracic outlet syndrome and iatrogenic injuries.

7.1) Acute upper limb ischaemia: Embolic disease

Numerous reports have been published with regard to outcome after lower extremity embolectomy. In contrast, few reports have focused on upper extremity embolic disease\textsuperscript{[53,136-141]} with most of these only presenting early (30 day) outcome.\textsuperscript{[53,136-139]} Generally, the functional outcome after upper extremity embolectomy is excellent, provided that there was minimal delay in presentation and severe ischaemia was not present at the time. However, early (30 day) mortality remains high, mostly as a result of severe comorbid disease.

The concept that mortality following embolectomy is a consequence of the patient’s comorbidity rather than the embolus itself, is well supported.\textsuperscript{[1,52]} Throughout the literature, it is generally agreed that patients who present with acute embolic episodes, have a high early (30 day) mortality rate ranging between 9 – 19%.\textsuperscript{[1,138,142,143]} Deguara et al\textsuperscript{[1]} reported a 30-day mortality rate of 18.2% in patients undergoing upper extremity
embolectomy (n = 10). All deaths were attributable to cardiopulmonary events. A further
11 patients died within a year of surgery, resulting in a 12-month mortality rate of 38.2%
(n = 21). In a retrospective single centre study of 148 patients admitted with acute upper
limb ischaemia, Licht et al reported that the cause of death was mostly due to
cardiovascular (32%) and cerebrovascular (22%) incidents with 8% of patients dying from
malignancy during the 5 year follow-up period.\textsuperscript{142}

These high mortality rates are convincing of poor short-term outcome, however, the
relative paucity of long-term follow-up data led some authors to question whether this
phenomenon persist after discharge from hospital. This was addressed by a National
Cohort Study in Denmark, published in 2010, that followed 1 377 patients after thrombo-
embolectomy for a period of 5 to 17 years. Age- and sex-specific risk of stroke was 2 to
16 times higher and risk of death 3 to 11 times higher than that of the general
population.\textsuperscript{143}

Specific populations have been described, where the outcome is even worse than
mentioned above. Javid et al\textsuperscript{144} reported on the outcome of 20 patients with an
underlying malignancy and arterial thrombosis. The outcome was generally poor. Two
patients underwent major amputations. The mortality rate from the time of presentation
was 50% at 3 months and 83% at 12 months. Therefore, arterial thrombosis should
probably be viewed as an agonal event in many of these patients and palliative treatment
may be the most appropriate management option.
Authors generally agree that prompt operative intervention is the single most important determinant of a successful functional outcome. Be that as it may, some reports claim that the duration of symptoms before embolectomy does not significantly impact on functional outcome.\textsuperscript{[136,142]} Licht et al\textsuperscript{[142]} disclosed that 26\% of patients in their series were treated more than 24 hours after the onset of symptoms and that the time interval between symptom onset and revascularization, did not significantly influence long-term result as measured by arm-function (Table 8; Chi-square = 3.9 with $p = 0.42$ between the three time intervals).

\textit{Table 8: Relationship between arm-function and duration of ischaemia (Licht et al)\textsuperscript{[142]} }

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Normal arm-function</th>
<th>Slightly decreased arm-function</th>
<th>Severely decreased arm-function</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 12h</td>
<td>33 (87%)</td>
<td>4 (11%)</td>
<td>1 (2%)</td>
<td>38</td>
</tr>
<tr>
<td>12-24h</td>
<td>13 (93%)</td>
<td>1 (7%)</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>More than 24h</td>
<td>11 (69%)</td>
<td>4 (25%)</td>
<td>1 (6%)</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>57 (84%)</td>
<td>9 (13%)</td>
<td>2 (3%)</td>
<td>68</td>
</tr>
</tbody>
</table>

It may be argued that analysis of the length of ischaemia and arm function does not take into account the severity of ischaemia. Thus, patients who presented after 24 hours may have had less severe ischaemia than those who presented earlier because of pain. Even though one should aim to operate promptly in these patients in order to minimise potential functional compromise, the time interval per se should not be seen as a contra-indication to surgery. The extremity should only be regarded as being out of therapeutic reach if the patient presents with a rigid limb, indicating irreversible ischemia.
7.2) Acute upper limb ischaemia: Thrombotic disease

Few studies report the use of thrombolytic therapy in AULI, even though its role in the lower extremities has been well established.\textsuperscript{[145]} When studies commenting on the use of thrombolytics in AULI are considered, thrombolysis and surgery have equal efficacy, but small numbers mitigate this conclusion.\textsuperscript{[146-148]} Cejna et al\textsuperscript{[147]} also found thrombolysis to have equivalent results to surgery, with the exception of distal occlusions, where results were found to be inferior. Concerns regarding the use of thrombolytics in AULI revolve around the risk of haemorrhagic cerebro-vascular incidents. Some authors suggest that this risk may be higher with upper than lower extremity thrombolytic therapies.

7.3) Chronic upper limb ischaemia – Bypass procedures in general

Upper limb arterial bypass procedures were first described by Garret in 1965. Since then, only a few small surgical series have reported their single centre experience with this procedure (Table 9).

<table>
<thead>
<tr>
<th>Publication</th>
<th>Study group</th>
<th>Tissue loss as indication</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinelli F et al\textsuperscript{[23]} Eur J Vasc Endovasc Surg (2010) Retrospective (Italy)</td>
<td>23 patients (1998-2008)</td>
<td>35%</td>
<td>Primary patency 82.6%, Secondary patency 91.3%, Limb salvage 100%</td>
</tr>
<tr>
<td>Hughes K et al\textsuperscript{[9]} J Vasc Surg (2007) Retrospective (USA)</td>
<td>20 patients (1990-2003)</td>
<td>15%</td>
<td>Primary patency 85%, Secondary patency 85%, Limb salvage 100%</td>
</tr>
<tr>
<td>Chang BB et al\textsuperscript{[149]} J Vasc Surg (2003) Retrospective (USA)</td>
<td>15 patients (1992-2002)</td>
<td>83%</td>
<td>Primary patency 88.8%, Secondary patency 88.8%, Limb salvage 88.8%</td>
</tr>
<tr>
<td>Roddy SP et al\textsuperscript{[10]} J Vasc Surg (2001) Retrospective (USA)</td>
<td>56 patients (1986-1998)</td>
<td>13%</td>
<td>Primary patency 87%, Secondary patency 98%, Limb salvage 100%</td>
</tr>
</tbody>
</table>
In general, the results achieved with upper limb arterial bypass procedures are satisfying, with reported graft patency rates of between 85-98% at 2 years. Multiple factors influence surgical outcome. Certainly the most important factor, the indication for surgical intervention, varied significantly between trials. Spinelli et al reported tissue loss as the indication in 83% of patients compared to 13% reported by Roddy et al. Other indications included exertional arm pain (Roddy et al 30%; Hughes et al 55%) and rest pain (Roddy et al 57%; Hughes et al 30%). Units, implementing a more aggressive approach to the management of relatively minor symptoms, may reflect better surgical outcomes, especially superior limb salvage rates.

In stark contrast with the subgroup of patients presenting with embolic upper limb disease, none of the recent surgical bypass series (Spinelli et al 2010, Hughes et al 2007) reported any perioperative deaths, cardiac complications, wound infection, pulmonary complications or renal failure. The mean length of post-operative hospitalisation was 3-6 days.

7.4) Chronic upper limb ischaemia – Distal bypass procedures

A systematic review of 16 publications reporting on distal (infra-brachial) upper extremity bypass procedures, was recently performed. At an average follow-up of 37 months, the overall autologous vein graft patency rate was 85% and autologous arterial (including deep inferior epigastric artery; lateral femoral circumflex artery and thoraco-dorsal artery) graft patency rate 100%. All studies reported an improvement of ischemic symptoms including a reduction in cold sensitivity, pain and digital ulceration.
7.5) Chronic upper limb ischaemia – Endovascular procedures

The endovascular management of upper extremity atherosclerotic occlusive lesions, are being progressively explored. Current evidence seems to favour the use of percutaneous techniques in the management of occlusive disease of the supra-aortic trunks, while the treatment of infra-brachial lesions are still controversial.

The technical success rate of open surgical BCA/SCA revascularization is high, but major complications may occur (13-19% incidence) with an expected 30 day mortality rate of 2–3%. Multiple publications suggest similar success rates with less morbidity and mortality, when implementing percutaneous revascularization techniques to address occlusive lesions of this arterial segment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Arterial lesions</th>
<th>Technical success</th>
<th>Mean follow-up</th>
<th>Restenosis</th>
<th>1\text{st} patency</th>
<th>2\text{nd} patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez-Lopez et al. 1999</td>
<td>69</td>
<td>70 SCA</td>
<td>95.7%</td>
<td>13mo</td>
<td>10%</td>
<td>92% at 18mo</td>
<td>96% at 18mo</td>
</tr>
<tr>
<td>Henry et al. 1999</td>
<td>113</td>
<td>113 SCA</td>
<td>91.2%</td>
<td>51.6mo</td>
<td>15.5%</td>
<td>87% at 30mo</td>
<td>94% at 30mo</td>
</tr>
<tr>
<td>De Vries et al. 2005</td>
<td>110</td>
<td>110 SCA</td>
<td>93%</td>
<td>34mo</td>
<td>7.8%</td>
<td>89% at 60mo</td>
<td>-</td>
</tr>
<tr>
<td>Przewlocki et al. 2006</td>
<td>75</td>
<td>73 SCA, 2 BCA</td>
<td>93.3%</td>
<td>24.4mo</td>
<td>15.6%</td>
<td>77% at 60mo</td>
<td>95% at 36mo</td>
</tr>
<tr>
<td>Patel et al. 2007</td>
<td>170</td>
<td>166 SCA, 1 BCA</td>
<td>98.3%</td>
<td>35.2mo</td>
<td>15.9%</td>
<td>83% at 66mo</td>
<td>96% at 54mo</td>
</tr>
</tbody>
</table>

Table 10: Summary of studies reporting on SCA / BCA stent placement

Patel et al.\textsuperscript{[155]} recently published their experience with primary percutaneous revascularization of symptomatic BCA/SCA atherosclerotic lesions. This series is the largest to date, with 170 consecutive patients treated over a 13 year period. The technical
success and patency rates were comparable to previously published reports, however, technical success in recanalizing occlusions (90.5%) were significantly higher than reported by prior studies. The author attributes this to the evolution of recanalization techniques, with 62% of patients with occlusions undergoing a retrograde brachial approach or combined femoral/brachial approach. Complications were reported in 5.9% (n=10) of patients with no procedure-related deaths recorded. This compares favourably with surgical series.\textsuperscript{[151-154]}

Literature on the endovascular management of radial and ulnar occlusive disease, are currently limited to case reports and small case series.\textsuperscript{[156-157]} From this limited pool of data, it is clear that further investigation is required before firm recommendations can be made.
The objective of this study was to comprehensively review the Vascular Surgery Unit’s experience with upper limb ischaemia over a 12 year period by defining the pattern and distribution of disease and pathological profile, describing key demographic and clinical features and reporting on conventional clinical outcomes (including mortality, morbidity, limb salvage and re-intervention rates). These findings were interpreted in context of the current literature in order to identify potential areas of interest, perhaps paving the way for further (more focused) research on a variety of related topics.
CHAPTER FOUR: METHODS

1) STUDY DESIGN

Retrospective descriptive study

All patients that underwent a surgical intervention for upper limb ischaemia at Groote Schuur Hospital’s Vascular Unit between January 2000 and December 2011, were included in the audit. Approval from the Department of Surgery Research Committee and Faculty of Health Sciences Human Research Ethics Committee was obtained prior to accessing data (Appendix 1 & 2). A research folder was compiled for each patient and numeric codes assigned in order to maintain patient confidentiality. On completion of the data collection process, both qualitative and quantitative data were analyzed and comparisons made to the current literature. Interesting observations were highlighted and discussed in monograph form.

2) STUDY PARTICIPANTS

Sample selection

All patients that underwent a surgical intervention for upper limb ischaemia from 2000 to 2011, were retrospectively selected from the Groote Schuur Hospital Vascular Unit’s operative database.

Inclusion criteria

- Patients that underwent revascularization and ablative procedure(s) for upper limb ischaemia at Groote Schuur Hospital’s Vascular Unit
- Procedure(s) performed from January 2000 to December 2011
- Primary as well as secondary procedures
Exclusion criteria

- Penetrating and / or blunt traumatic vascular injuries

The Trauma Unit at our facility published extensively on this topic (including brachial, axillary and subclavian artery injuries[^160-162] – a total of 242 patients) between 2003 and 2011. In order to guard against the duplication of data, this subgroup of patients were excluded from the current series.

- Primary Raynaud’s phenomenon

3) OUTCOME MEASUREMENTS

Patient hospital records, in the form of a hospital folder or microfilms, were obtained from Medical Records Department and data electronically captured by means of a data collection sheet in Microsoft™ Word (*Appendix 3*). Referral letters, clinical notes, treatment charts and special investigations (including laboratory results sheets in the folder) were perused. The NHLS Disa electronic results system was accessed for each patient to confirm that no laboratory investigations of significance, were overlooked. This process was performed by the researcher, under the following headings:

- **Demographic details**
  - Age, gender and ethnic group

- **Contact details**
  - Address and telephone number of patient or relative

- **Clinical presentation**
  - Acute limb ischaemia
    - Rutherford grade I, IIa, IIb or III, with or without the presence of compartment syndrome
- Chronic limb ischaemia
  - Digital ulceration (active or healed), Raynauds phenomenon, claudication symptoms or neuro-vascular symptoms

- Risk factor(s) for atherosclerosis
  - Hypertension, hypercholesterolaemia, Diabetes mellitus (Type I/II) and cigarette smoking (including estimated pack years)
  - Other substances (including cannabis and TIK)

- Other systemic diseases

- Appropriate medical therapy
  - Pre-event as well as post-event

- Underlying aetio-pathology
  - Embolic source
    - Cardiac or extra-cardiac (including site of occlusion)
  - Thrombotic source
    - Associated with atherosclerosis or thrombophilia (including site of occlusion)

- Special investigations performed
  - Upper limb dopplers, upper limb duplex arteriogram, digital doppler pressure with caloric stimulation
  - Angiogram (Arch or select run)
  - MD-CTA, MRA
  - CXR / C-spine X ray
  - Echo / ERNA
o Laboratory investigations
  • S-fibrinogen, CRP and ESR, fasting homocysteine level, S-creatinine, HIV status

• Procedure(s) performed
  o Date and length of procedure, time started (within day time or after hours)

• Open surgical procedure
  o Embolectomy, bypass graft (including type), fasciotomy performed, ablation performed (including before or after attempt at revascularization and level of amputation)

• Endovascular procedure
  o PTA, stentgraft placement (including type and site), thrombolysis (alone or as combination therapy)

• Peri-operative (30 day) and follow-up (6 months, long term) data
  o Died / Alive (including reason for death)
  o Systemic complications
  o Procedure related complications
    • Wound complications, bypass graft complications, neuropraxia / nerve injuries and ablation
  o Pulse status / Doppler pressures / Duplex arteriogram
    • Improved, same or deteriorated
  o Function
    • Normal, weakness, contracture, claudication
A clinical research folder was compiled for each patient and numeric codes assigned in order to maintain patient confidentiality. The research folder included the afore mentioned Microsoft™ Word data collection sheet, copies of referral letters, results from special investigations performed as well as operation sheets.

4) DATA ANALYSIS
On completion of the data collection process, data was transferred from the patient research folders and consolidated in a Microsoft™ Excel data collection sheet. The data was appropriately coded to assist data analysis. Data analysis was performed using STATA® statistics / data analysis program by StataCorp, Texas, USA. Frequencies and percentages were calculated for categorical data. Means and standard deviations or medians and percentiles were calculated for continuous data.
CHAPTER FIVE:

RESULTS

1) INTRODUCTION

When dealing with a broad topic and, in the absence of a specific question being asked, presenting findings in an isolated fashion may be less informative to the reader. Therefore, although slightly unconventional, the results of this study will include concise, relevant discussion of the literature in the interest of capturing the true context of these findings. The “discussion” section (chapter 6) will focus on future research perspectives.

2) INCIDENCE AND DEMOGRAPHICS

Sixty-four patients presenting with upper limb ischaemia, were evaluated and managed surgically during the 12 year study period (from 01 January 2000 to 31 December 2011). As previously mentioned, referrals managed non-surgically, were excluded from this series. Therefore, Figure 11 should not be interpreted as the total number of referrals received, but as the number of referrals warranting surgical intervention.

Figure 11: Patients receiving surgical intervention
A clear escalating trend was observed, with 56% of surgically managed patients, referred within the last 4 years of the study period (2008-2011). Seeing that subjects were retrospectively selected from an operative database, no data pertaining to the total number of referrals were captured. Therefore, no correlation can be made between the number of referrals received and the number of patients managed surgically. Regardless, an increase in the absolute number of referrals is still the most conceivable explanation to rationalize the observed trend. This finding, however, needs to be interpreted in context of the population growth within the Western Cape during the study period and does not necessarily represent a true increase in disease incidence (Figure 12).

Figure 12: Western Cape population growth according to recent Census statistics

Another, less likely explanation may be that a more aggressive surgical approach (or more guarded approach to non-operative management) was followed during the last 4 years of the study period. Anecdotally though, the indications for surgical intervention has remained unchanged during this period.
**Age and gender**

Forty females (62.5%) with a mean age of 51 years (range 15 – 84 years) and 24 males (37.5%) with a mean age of 46 years (range 15 – 76 years), were included in the study, reflecting a male to female ratio of 0.60. Comparatively, the 2011 Western Cape Census figures reported a male to female ratio of 0.96, drastically higher than that of the study group. However, one has to be mindful of the fact that demographic variables may be strongly influenced by the underlying cause of ischaemia (*Table 11*).

*Table 11: Comparative demographic details according to prevailing aetiologies*

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>N of patients</th>
<th>Mean age (range)</th>
<th>M:F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombo-embolic disease</td>
<td>30</td>
<td>55 (37 – 80)</td>
<td>0.43</td>
</tr>
<tr>
<td>Atherosclerotic occlusive disease</td>
<td>12</td>
<td>57 (39 – 84)</td>
<td>0.71</td>
</tr>
<tr>
<td>Thoracic outlet obstruction</td>
<td>8</td>
<td>28 (15 – 59)</td>
<td>1.67</td>
</tr>
<tr>
<td>Takayasu’s disease</td>
<td>4</td>
<td>27 (20 – 36)</td>
<td>0.33</td>
</tr>
<tr>
<td>Thromboangiitis obliterans</td>
<td>4</td>
<td>46 (36 – 53)</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Considering that we are dealing with an aetiologically heterogeneous group of patients, significant demographic findings should rather be discussed in context of the underlying cause of ischaemia.

**Embolic versus UEAOD**

Multiple publications support the view that patients with thrombo-embolic ULI, when compared to UEAOD, present at a more advanced age.[1,163] One of these series included 172 patients undergoing revascularization procedures for ULI over a 20 year period.[1] The mean age of presentation in the thrombo-embolic subgroup (n=61) was appreciably older (72.4 years) than those presenting with UEAOD (n=29, mean age 62.5 years). Interestingly, this finding was not observed in our series, with the thrombo-embolic
subgroup (n=30) notably younger than expected (mean age of 55 years) compared to the subgroup presenting with UEAOD (n=12, mean age of 57 years). A larger proportion of females were affected by thrombo-embolic disease in our series, than reported by Deguara et al\textsuperscript{[1]}. The reasons for these findings are still unclear and further investigation is warranted.

\textit{Table 12: Demographic comparison of TED versus UEAOD subgroups}

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>Mean age</th>
<th>M:F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombo-embolic</td>
<td>30</td>
<td>55 years</td>
<td>1:2.3</td>
</tr>
<tr>
<td>UEAOD</td>
<td>12</td>
<td>57 years</td>
<td>1:1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Deguara et al</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean age</td>
<td>M:F ratio</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>72.4 years</td>
<td>1:1.1</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>62.5 years</td>
<td>1:1.9</td>
</tr>
</tbody>
</table>

\textbf{Race}

Patients of mixed-race heritage contributed 48\% to the study group, followed by Caucasians (27\%), Blacks (23\%) and Indians (2\%). Once again, it is important to interpret these findings in terms of the 2001/11 Western Cape Census figures (\textit{Figure 13}). Unfortunately, due to multiple confounding factors being present, no firm conclusions can be drawn regarding the race-specific incidence of ULI. One such factor is the unknown number a patients seeking medical attention from private health care facilities.

\textit{Figure 13: Race prevalence}
Referral patterns

As expected, the majority of cases (84%) were referred from health care facilities located within the Cape Metropole. Approximately 8% of patients were referred from centres outside of the Cape Metropole, but within the borders of the Western Cape with 2 patients referred from the Eastern Cape.

Table 13: Source of referral according to province

<table>
<thead>
<tr>
<th>Province</th>
<th>n</th>
<th>Percentage</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Cape</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cape Metropole</td>
<td>54</td>
<td>84.4</td>
<td></td>
</tr>
<tr>
<td>Outside Cape Metropole</td>
<td>5</td>
<td>7.8</td>
<td>92.2</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>2</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>4.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Most referrals were received from Secondary Hospitals (52%), with Community Health Centres (16%), Tertiary Hospitals (13%), Private facilities (13%) and Primary Hospitals (3%) contributing to the rest of the referrals.

Table 14: Level of referring facility

<table>
<thead>
<tr>
<th>Level of facility</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Health Centre</td>
<td>10</td>
<td>15.6</td>
</tr>
<tr>
<td>Primary Hospital</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>Secondary Hospital</td>
<td>33</td>
<td>51.6</td>
</tr>
<tr>
<td>Tertiary Hospital</td>
<td>8</td>
<td>12.5</td>
</tr>
<tr>
<td>Private sector</td>
<td>8</td>
<td>12.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>4.7</td>
</tr>
</tbody>
</table>
### Table 15: Specific referring facility

<table>
<thead>
<tr>
<th>Facility</th>
<th>n</th>
<th>Percentage</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community Health Centres</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khayalitsha CHC</td>
<td>2</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Mitchell’s Plane CHC</td>
<td>2</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Retreat CHC</td>
<td>3</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Hanover Park CHC</td>
<td>3</td>
<td>4.7</td>
<td>15.7</td>
</tr>
<tr>
<td><strong>Primary Hospitals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Bay Hospital</td>
<td>2</td>
<td>3.1</td>
<td>18.8</td>
</tr>
<tr>
<td><strong>Secondary Hospitals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conradie Hospital</td>
<td>2</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Victoria Hospital</td>
<td>9</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>New Somerset Hospital</td>
<td>9</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>GF Jooste Hospital</td>
<td>6</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>George Hospital</td>
<td>5</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>Frere Hospital</td>
<td>1</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Livingstone Hospital</td>
<td>1</td>
<td>1.6</td>
<td>70.3</td>
</tr>
<tr>
<td><strong>Tertiary Hospitals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groote Schuur Hospital</td>
<td>8</td>
<td>12.5</td>
<td>82.9</td>
</tr>
<tr>
<td><strong>Private Sector</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private GP</td>
<td>4</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Private Casualty</td>
<td>1</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Private Surgeon</td>
<td>2</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Private Physician</td>
<td>1</td>
<td>1.6</td>
<td>95.3</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>3</td>
<td>4.7</td>
<td>100.0</td>
</tr>
</tbody>
</table>

3) RISK FACTORS

**Risk factors for atherosclerosis and the development of UEAOD**

Compared to previous publications reporting on the incidence of atherosclerotic risk factors in UEAOD,\textsuperscript{[9,23]} our series reflected small numbers (n=12).

The most striking feature recognized was the disproportionately high prevalence of cigarette smoking (83%), almost double that reported by Spinelli et al\textsuperscript{[23]} (Table 16).
Smoking history could be quantified from the clinical records in 8 out of 10 patients, with an average of 31 pack years.

As previously mentioned, tobacco use is particularly prevalent in patients with upper extremity atherosclerotic occlusive disease (UEAOD) and seems to have a stronger causative association than diabetes, hypertension and dyslipidaemia. The above figures reaffirm the undeniable role played by cigarette smoking in the different manifestations of peripheral arterial disease as well as the importance of addressing this modifiable risk factor.

Recently, substance abuse has been implicated in the process of accelerated and precocious atherosclerosis as well as Thromboangiitis obliterans (TAO). A history of substance abuse were present in 9% of subjects with 5 patients reporting regular cannabis use and 1 patient presenting with a complication of intra-arterial heroin injection.

Hypertension was present in 50% of patients in the UEAOD subgroup, which compared well with the 2007 report by Hughes et al[9] (Table 16). Numerous authors (including Roddy[10] and Hughes et al[9]) have reported on the significantly lower incidence of diabetes mellitus in upper extremity bypass patients, compared to the lower extremity bypass population from the same centres. Nonetheless, our series estimated the incidence of diabetes mellitus to be 17%, much lower than suggested by preceding reports. In addition, 33% of patients were previously diagnosed with dyslipidaemia.
The most recently published surgical series reporting on procedures performed for UEAOD, quote the following risk factor incidences:

Table 16: Studies evaluating incidence of risk factors in atherosclerotic occlusive disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Smoking(%)</th>
<th>HPT(%)</th>
<th>DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes et al, 2013 [9]</td>
<td>55</td>
<td>35</td>
<td>Not reported</td>
<td>29</td>
</tr>
<tr>
<td>Spinelli et al, 2009 [23]</td>
<td>23</td>
<td>43</td>
<td>26</td>
<td>48</td>
</tr>
<tr>
<td>Hughes et al, 2007 [9]</td>
<td>20</td>
<td>Not reported</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Current series</td>
<td>12</td>
<td>83</td>
<td>50</td>
<td>17</td>
</tr>
</tbody>
</table>

Pharmacological modification of atherosclerotic risk factors

After an in-depth evaluation of clinical records (including referral letters, prescription charts and clinical admission notes), it was estimated that as many as 16 out of 60 patients (27%) were not receiving adequate pharmacological therapies aimed at addressing pre-existing risk factors. The TASC II document (section B1.2)[24] was used as a guideline to assess the appropriateness of pre-referral therapy. In 4 patients, clinical information regarding pre-referral treatment was insufficient in order to assess the appropriateness of medical therapy.

Systemic comorbidities in the Thrombo-embolic subgroup

The presence of serious concurrent illness in this specific patient group, impact greatly on clinical outcomes. Deguara et al[11] attributed all early (30 day) mortalities to cardiopulmonary incidents, none being a consequence of arm ischemia or gangrene. The majority of patients (84%) with embolic disease, had associated ischemic heart disease or
a recent myocardial infarction and between 51 - 63% was diagnosed with atrial fibrillation.

In the current series, 8 of the 30 patients (27%) had recent clinical, electrocardiographic, echocardiographic and / or angiographic signs of ischaemic heart disease. Four patients (13%) were in atrial fibrillation at the time of initial presentation. Intra-cardiac thrombus could be identified in one patient. These figures suggest that concurrent cardiac conditions might be underdiagnosed in our setting, however this needs to be interpreted in context of the demographic profile. One such demographic consideration is the difference in mean age of 17 years (current series 55 years; Deguara[1] 72 years) in the TED subgroup of patients, perhaps indicating a younger population with a lower risk of developing CAD.

Other associated systemic diseases were pulmonary tuberculosis (5 patients), previous cerebro-vascular incidents (3 patients) and underlying carcinoma (3 patients – lung, breast and cervix cancer respectively).

4) AETIO-PATHOLOGY

The largest surgical series investigating patients undergoing revascularization procedures for ULI, was published by Deguara et al[1] in 2005. A total of 172 patients were included over a 20 year period, with 53 cases related to upper extremity trauma (excluded in the current series). Comparison of data between the two series (Table 17 and 18), makes for interesting discussion. Some similarities and differences have been highlighted and will be discussed subsequently.
Table 17: Summary of current series according to underlying aetio-pathology

<table>
<thead>
<tr>
<th>Aetio-pathology</th>
<th>N of patients (%)</th>
<th>N of procedures</th>
<th>Mean age</th>
<th>M:F ratio</th>
<th>30-Day mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombo-embolic</td>
<td>30 (47%)</td>
<td>47</td>
<td>55</td>
<td>1:2.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Arterial thoracic outlet syndrome</td>
<td>2 (3%)</td>
<td>5</td>
<td></td>
<td>1:2.3</td>
<td>-</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>2 (3%)</td>
<td>4</td>
<td></td>
<td>1:2.3</td>
<td>-</td>
</tr>
<tr>
<td>Polymyositis compartment syndrome</td>
<td>1 (2%)</td>
<td>1</td>
<td></td>
<td>1:2.3</td>
<td>-</td>
</tr>
<tr>
<td>Chronic</td>
<td>29 (45%)</td>
<td>33</td>
<td>44</td>
<td>1:1.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Atherosclerotic disease</td>
<td>12 (19%)</td>
<td>16</td>
<td>57</td>
<td>1:1.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Arterial thoracic outlet syndrome</td>
<td>6 (9%)</td>
<td>6</td>
<td>28</td>
<td>5:1</td>
<td>-</td>
</tr>
<tr>
<td>Takayasu’s disease</td>
<td>4 (6%)</td>
<td>4</td>
<td>27</td>
<td>1:1.3</td>
<td>-</td>
</tr>
<tr>
<td>Thromboangiitis obliterans</td>
<td>4 (6%)</td>
<td>4</td>
<td>46</td>
<td>3:1</td>
<td>-</td>
</tr>
<tr>
<td>Occupational small vessel disease</td>
<td>3 (5%)</td>
<td>3</td>
<td>32</td>
<td>1:2</td>
<td>-</td>
</tr>
</tbody>
</table>

Ratio of acute to chronic presentations

Despite the apparent disproportion of acute to chronic presentations in the Deguara group, the ratios are similar to the current series after exclusion of the trauma subgroup. The

Table 18: Summary of cases according to underlying aetio-pathology, by Deguara et al[1]

<table>
<thead>
<tr>
<th>Aetio-pathology</th>
<th>N of patients (%)</th>
<th>N of procedures</th>
<th>Mean age</th>
<th>M:F ratio</th>
<th>30-Day mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombo-embolic</td>
<td>61 (35%)</td>
<td>68</td>
<td>72</td>
<td>1:1.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Trauma</td>
<td>53 (31%)</td>
<td>54</td>
<td>33</td>
<td>5:1:1</td>
<td>3.8</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>2 (1%)</td>
<td>2</td>
<td>46</td>
<td>0:2</td>
<td>-</td>
</tr>
<tr>
<td>Chronic</td>
<td>56 (33%)</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic disease</td>
<td>29 (17%)</td>
<td>32</td>
<td>63</td>
<td>1:1.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Subclavian steal syndrome</td>
<td>15 (9%)</td>
<td>15</td>
<td>63</td>
<td>2:3</td>
<td>-</td>
</tr>
<tr>
<td>Arterial thoracic outlet syndrome</td>
<td>8 (5%)</td>
<td>8</td>
<td>47</td>
<td>1:1.7</td>
<td>-</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>4 (3%)</td>
<td>4</td>
<td>51</td>
<td>1:1</td>
<td>-</td>
</tr>
</tbody>
</table>
percentage of patients presenting with TED (current series 45%; Deguara et al 51%) and UEAOD (current series 18%; Deguara et al 24%) were similar in both series.

**Thrombo-embolic disease**

As expected, the majority of thrombo-embolic events resulted in occlusion at the level of the brachial artery (17 patients in total). Nine patients presented with higher occlusions (2 subclavian artery, 7 axillary artery). Three patients had thrombo-embolic occlusions distal to the elbow (2 radial artery, 1 ulnar artery) and one patient presented with blue finger syndrome. Eyers et al\(^{[2]}\), in an excellent review of this subject, collected data from multiple series in order to establish the most common level of arterial occlusion. Our series compare well with these figures (*Figure 14*).

*Figure 14: Comparative diagram (Eyers et al\(^{[2]}\) vs Current series) translating the incidence of arterial occlusion within relevant arterial segments.*

<table>
<thead>
<tr>
<th>Eyers et al(^{[2]})</th>
<th>Current series</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.5%</td>
<td>56.6%</td>
</tr>
<tr>
<td>25.6%</td>
<td>23.3%</td>
</tr>
<tr>
<td>7.2%</td>
<td>6.7%</td>
</tr>
<tr>
<td>8.6%</td>
<td>13.3%</td>
</tr>
</tbody>
</table>
In the current series, a left-sided predominance was noted across all levels of obstruction with a right to left sided ratio of 1:2. This is exceedingly unusual, as most authors describe a higher incidence of embolism affecting the right arm, probably due to the larger diameter of the BCA compared to the left SCA as well as the favourable angle that exists between the aorta and BCA.\textsuperscript{[4]}

**Atherosclerotic lesions**

The subclavian artery was predominantly involved (8 patients), the axillary artery in 1 patient and the brachial artery affected in 3 patients. Therefore, a clear proximal pattern was observed in this subgroup of patients. Once again, as observed in the thromboembolic subgroup, clear left sided predominance was noted with a right to left ratio of 1:5. All subclavian lesions were left sided. Morphologically, 6 lesions were described as stenotic, 5 as occlusions and 1 patient presented with thrombosis of a degenerative aneurysm. Unfortunately, it was not possible to accurately ascertain from clinical notes whether predominantly ostial, mono- or multi-segmental disease was present.

**Table 19: Summary of underlying arterial lesions in UEAOD subgroup**

<table>
<thead>
<tr>
<th>Morphological lesion</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis</td>
<td>6</td>
</tr>
<tr>
<td>Occlusion</td>
<td>5</td>
</tr>
<tr>
<td>Degenerative aneurysm</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>
Arterial thoracic outlet syndrome (ATOS)

Eight patients developed upper limb ischaemia as a consequence of ATOS, of which 7 (88%) presented with underlying bony pathology. This subgroup of patients was generally younger than patients presenting with thrombo-embolic or UEAOD, with a mean age of 28 years (Table 1). Interestingly, two of these patients presented with AULI (Rutherford I and IIa), with 6 patients presenting with chronic symptomatology.

Table 20: Summary of ATOS presentations

<table>
<thead>
<tr>
<th>Underlying lesion</th>
<th>Acute presentation</th>
<th>Chronic presentation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical rib</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Muscular band</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Anomalous 1st rib</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clavicle fracture (old)</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Takayasu’s disease

Four patients with Takayasu’s disease presented with chronic upper limb ischaemic symptoms. The mean age of the patients was 27 years with a male to female ratio of 1:3 (Table 1). Three patients complained of upper limb claudication symptoms with one suffering two ischaemic cerebro-vascular incidents prior to presentation. Level of disease ranged from stenosis of the BCA with occlusion of its outflow (one patient) to proximal left CCA stenosis with associated left SCA occlusion (two patients). One patient presented with prosthetic graft sepsis complicated by an acute bleed from the right CCA anastomosis after previous aortic arch reconstruction for aneurysmal disease.
Thromboangiitis obliterans

Four patients with active digital ulceration due to Buerger’s disease, were evaluated and surgically managed during the study period. The mean age at presentation was 46 years and a male to female ratio of 3:1 was noted. The average smoking history was 36 pack years in this subgroup of patients. One patient acknowledged the regular use of cannabis in conjunction with cigarettes.

Small vessel disease

Two patients presented with active digital ulceration in combination with cold-related vasospasm and one with cold-related vasospasm alone. The mean age at presentation was 32 years and the male to female ratio 1:2. The secondary associations were connective tissue disease (SLE), occupational (HHS) and atherosclerotic small vessel disease.

Iatrogenic

The unfortunate occurrence of iatrogenic compartment syndrome was diagnosed in two patients. One patient presented with ALI after tissue infiltration of a peripheral venous catheter (Rutherford IIa) and the other due to acute brachial artery thrombosis after arterial catheterization (Rutherford I).

5) INITIAL CLINICAL PRESENTATION

When considering the timing of symptom onset, 55% of cases were classified as acute ischaemia and 45% as chronic. On comparison of the current series (Table 17) with the Deguara group (Table 18), an apparent disproportion of acute to chronic presentations is noted. However, in order to compare the above data sets reliably, the trauma subgroup of
patents had to be excluded as specified by the current series’ exclusion criteria. After exclusion, the ratio of acute to chronic cases was remarkably similar. (Current series 1.22; Deguara et al[1] 1.13).

Thirty-five patients presented with AULI necessitating surgical intervention during the study period. Table 21 and Figure 15 further reflect relevant detail regarding the clinical presentation of these patients.

**Table 21: Summary of AULI presentations, according to severity of ischaemia**

<table>
<thead>
<tr>
<th>Rutherford grade</th>
<th>n</th>
<th>%</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>9</td>
<td>26</td>
<td>51</td>
</tr>
<tr>
<td>IIa</td>
<td>14</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>IIb</td>
<td>9</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>8</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>100</td>
<td>55</td>
</tr>
</tbody>
</table>

Established compartment syndrome was present in 6 of the 35 AULI cases (17%) and was most prevalent in the Rutherford IIa group (8.6%).

**Figure 15: Incidence of compartment syndrome in AULI subgroup**
The majority of 29 patients with CULI, presented with signs of tissue necrosis (48%), including digital gangrene, active / healed digital ulceration. Other presentations in this group included upper extremity claudication symptoms (31%), rest pain (14%) as well as neuro-vascular symptoms (7%). *Figure 16* compares the above figures with that of other units.

*Figure 16: Summary of CULI presentations*

6) SURGICAL INTERVENTIONS

Overview

Eighty-nine procedures were performed in 64 patients. Of these, 78 were open procedures, 6 were managed via an exclusively endovascular approach and 5 patients underwent a combination of open and endovascular therapy. A distinction should be made between minor procedures (20 in total, average operating time of 49 minutes) and attempts at revascularization (69 in total, average operating time of 136 minutes). In 75 of the 89
cases performed, it was possible to establish whether the procedure was performed in daytime hours (56%) or afterhours (44%).

**Minor and ablative procedures**

Most minor procedures were performed as secondary or tertiary procedures. These included wound debridements, evacuation of haematomas, closure of fasciotomy wounds and excision / ligation of bypass grafts.

*Figure 17: Summary of ablative and minor procedures performed*

![Bar chart showing the number of ablative and minor procedures performed.](chart)

**Procedures performed for TED**

Forty-two procedures for upper limb thrombo-embolism were performed in 26 patients (*Table 22*).
Table 22: Breakdown of procedures performed for thrombo-embolic disease

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary procedures</strong></td>
<td>32</td>
</tr>
<tr>
<td>Thrombo-emolectomy</td>
<td>17</td>
</tr>
<tr>
<td>Thrombo-emolectomy and fasciotomy</td>
<td>7</td>
</tr>
<tr>
<td>Intra-operative thrombolysis (Streptokinase x1, tPA x1)</td>
<td>2</td>
</tr>
<tr>
<td>Brachial-brachial / -distal bypass (Autologous vein graft)</td>
<td>2</td>
</tr>
<tr>
<td>Catheter-directed thrombolysis (Streptokinase x1)</td>
<td>1</td>
</tr>
<tr>
<td>Stentgraft placement (Fluency® 8x40mm)</td>
<td>1</td>
</tr>
<tr>
<td>Aortic arch reconstruction (Gelsoft™ Dacron 8mm graft)</td>
<td>1</td>
</tr>
<tr>
<td>Above-elbow amputation</td>
<td>1</td>
</tr>
<tr>
<td><strong>Secondary procedures</strong></td>
<td>10</td>
</tr>
<tr>
<td>Brachial-distal bypass graft</td>
<td>2</td>
</tr>
<tr>
<td>Re-emolectomy</td>
<td>1</td>
</tr>
<tr>
<td>Fasciotomy</td>
<td>1</td>
</tr>
<tr>
<td>Haematoma evacuation</td>
<td>1</td>
</tr>
<tr>
<td>Veinpatch angioplasty of veingraft</td>
<td>1</td>
</tr>
<tr>
<td>Below-elbow amputation</td>
<td>1</td>
</tr>
<tr>
<td>Digital amputation</td>
<td>3</td>
</tr>
</tbody>
</table>

Procedures performed for UEAOD

Twenty-seven procedures were performed in 16 patients. Twenty-one of these were open surgical interventions and 6 were exclusively endovascular.

Open surgical procedures:

Eleven bypass procedures were performed. These included 4 brachial-distal / -brachial bypass grafts (all performed using autologous reverse vein graft), 2 axillary-brachial bypass grafts (autologous reverse vein graft / autologous SFA graft in patient with previous lower limb ablation), 3 subclavian-axillary / -brachial bypass grafts (2 ePTFE 6mm, 1 Dacron® 6mm) and 2 common carotid-axillary (PTFE 8mm) / -brachial bypass grafts (autologous reverse vein graft).
Endovascular procedures:
Lesions managed by endovascular means, were all located within the subclavian artery. Four lesions were primarily managed with bare metal stent placement (1 x Protégé® 8 x 27mm self-expandable stent, 2 x Omnilink Elite® 8x39mm balloon expandable stent, 1 x Sinus-Flex® 8x40mm self-expandable stent) and one managed with self-expandable bare metal stent placement (Complete® SE 8x60mm) after failed PTA previously. A retrograde brachial approach at cutdown was used to address three of the lesions, with a transfemoral approach implemented in the remaining two cases.

Table 23: Breakdown of procedures performed for UEAOD

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Open procedures</strong></td>
<td></td>
</tr>
<tr>
<td>Bypass procedures</td>
<td></td>
</tr>
<tr>
<td>Brachial-distal / brachial-brachial</td>
<td>4</td>
</tr>
<tr>
<td>Axillary-brachial</td>
<td>2</td>
</tr>
<tr>
<td>Subclavian-axillary / subclavian-brachial</td>
<td>3</td>
</tr>
<tr>
<td>Common carotid-axillary / common carotid-brachial</td>
<td>2</td>
</tr>
<tr>
<td>Primary amputations</td>
<td></td>
</tr>
<tr>
<td>Digital amputations</td>
<td>4</td>
</tr>
<tr>
<td>Secondary amputations</td>
<td></td>
</tr>
<tr>
<td>Above elbow amputations</td>
<td>3</td>
</tr>
<tr>
<td>Graft thrombectomies</td>
<td>2</td>
</tr>
<tr>
<td>Wound haematoma evacuation</td>
<td>1</td>
</tr>
<tr>
<td><strong>Endovascular procedures</strong></td>
<td>6</td>
</tr>
<tr>
<td>Primary procedures</td>
<td></td>
</tr>
<tr>
<td>Subclavian artery balloon angioplasty</td>
<td>1</td>
</tr>
<tr>
<td>Subclavian artery stent placement (Protégé® 8 x 27mm, Sinus-Flex® 8x40mm, 2 x Omnilink Elite® 8x39mm)</td>
<td>4</td>
</tr>
<tr>
<td>Secondary procedure</td>
<td></td>
</tr>
<tr>
<td>Subclavian artery stent placement (Complete® SE 8x60mm)</td>
<td>1</td>
</tr>
</tbody>
</table>
Procedures performed for arterial thoracic outlet syndrome (ATOS)

Eight patients developed upper limb ischaemia as a result of thoracic outlet syndrome.

Table 24: Breakdown of procedures in patients presenting with ATOS

<table>
<thead>
<tr>
<th>Patient</th>
<th>1° procedure</th>
<th>2° procedure</th>
<th>3° procedure</th>
<th>Nr of procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Thrombo-embolectomy, thrombolysis + fasciotomy</td>
<td>TO decompression</td>
<td>Contra-lateral TO decompression</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Thrombo-embolectomy + fasciotomy</td>
<td>TO decompression</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>CCA-brachial RSBG bypass + primary digital amputation</td>
<td>Above elbow amputation</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>SCA-Axillary PTFE bypass + brachial-ulnar RSVG bypass</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>SCA-Axillary PTFE bypass</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>TO decompression</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>TE followed by SCA-Axillary PTFE bypass</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>CCA-brachial Dacron® bypass + brachial-ulnar RSVG bypass + fasciotomy + primary digital amputation</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Two of these patients presented with acute upper limb ischaemia (Rutherford I and IIa), necessitating emergency surgical treatment in the form of thrombo-embolectomy combined with intra-operative thrombolysis (in one patient), followed by fasciotomy. The underlying lesions (muscular band and cervical ribs) were addressed during secondary and tertiary procedures.

Six patients presented with chronic complaints. One patient was managed with primary thoracic outlet decompression and 5 patients underwent arterial bypass procedures combined with primary digital amputation where appropriate. The bypass procedures performed included two CCA-brachial artery bypass grafts (reverse basillic vein graft, 8mm Dacron® prosthetic graft) and three SCA-axillary artery bypass grafts (6mm PTFE...
prosthetic graft). In two of these patients, a further brachial-ulnar artery bypass was performed at the same sitting (reverse saphenous vein graft). One above elbow amputation was performed after failure of a CCA-brachial artery bypass procedure.

**Procedures performed for Takayasu’s disease**

Two patients underwent aortic arch reconstruction (14 x 7mm bifurcated Albograft®) for Takayasu’s disease and one received an axillary-axillary artery bypass graft (6mm PTFE ring-reinforced graft). One patient presented with a stenosis of the brachiocephalic artery at the origin, while two patients had symptomatic (L) SCA occlusion as well as 50% (L) CCA stenosis. One patient presented with graft sepsis that manifested with an acute bleed after previous aortic arch reconstruction (16 x 8mm bifurcated Silvergraft® used for redo-arch reconstruction).

**Thoracoscopic sympathectomies**

Five thoracoscopic sympathectomies were performed for upper limb ischaemia. A standard T2 ganglionectomy was performed with a video-assisted two port technique in all cases. The indications varied and included non-reconstructable small vessel disease (histologically confirmed to be Thromboangiitis obliterans), HHS, SLE vasculitis and atherosclerotic small vessel disease. The average operating time was 55 minutes and included primary digital amputation in two cases.
7) OUTCOME

Surgical outcome measures were reported by quantifying the mortality, morbidity (including systemic and procedural complications) and amputation rates at different time intervals after the initial surgical procedure was performed. These intervals included 30-day outcome, outcome on 6 month follow-up as well as long term follow-up (more than 6 months after initial procedure). Unfortunately, follow-up appointments were poorly attended, especially affecting long term outcome results.

30-Day outcomes

Follow-up data could be accumulated in 53 of the 64 patients (83%). Eighteen amputations were performed in 64 patients, of which 6 were major amputations (above- or below-elbow level). Most amputations (n=10) were performed primarily, in patients presenting with irreversible tissue necrosis not justifying an attempt at revascularization. Eight secondary amputations (4 digital, 3 above-elbow and 1 below-elbow) were performed within 30 days of an initial attempt at revascularization. Two of these were performed following bypass graft occlusion. Therefore, the 30-day amputation rate after initial revascularization, was 12.5%.

At 30-day review, 35 patients were evaluated by clinical palpation, hand-held doppler pressures and/or duplex arteriogram. These findings were compared to corresponding pre-operative assessment, with patients being categorized into 3 groups. Deterioration of pulse status was observed in only one patient.
Table 25: Summary of 30-day outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence to follow-up</strong></td>
<td>53</td>
<td>83</td>
</tr>
<tr>
<td><strong>Mortalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1</td>
<td>7.8%</td>
</tr>
<tr>
<td>Mortalities</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Morbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory insufficiency</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cerebro-vascular incident</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Morbidities</td>
<td>8</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Procedural complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical site haematoma</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Superficial surgical site infection</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bypass graft occlusion</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pseudo-aneurysm post-angiogram</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Delayed fasciotomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neuropraxia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Re-thrombosis of native vessels</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amputation rate</td>
<td>18</td>
<td>23.4%</td>
</tr>
<tr>
<td><strong>Primary amputation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Amputation rate</td>
<td>10</td>
<td>15.6%</td>
</tr>
<tr>
<td><strong>Secondary amputation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Amputation rate</td>
<td>8</td>
<td>12.5%</td>
</tr>
<tr>
<td><strong>Pulse status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>24</td>
<td>68.6%</td>
</tr>
<tr>
<td>Unchanged</td>
<td>10</td>
<td>28.6%</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>Pulse status</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>
6-Month outcomes

Thirty patients attended their 6 month follow-up appointments. No further mortalities or systemic complications were noted in this group. Seven patients (11.9%) presented with procedural complications in the form of bypass graft occlusion (leading to dense hemiplegia in one patient and above-elbow amputation in another), re-occlusion of native vessels post-embolectomy and improving peripheral nerve neuropraxia (thought to have been fasciotomy-related).

Surveillance by clinical examination, hand-held doppler pressures and/or duplex arteriogram, revealed deterioration of pulse status in 5 patients, all of which presented with bypass graft occlusion.

Twenty-three patients were assessed as having a fully functional ipsilateral upper limb (76.7%). Four patients presented with contractures, 1 with motor weakness (affecting activities of daily living) and two with claudication symptoms.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence to follow-up</strong></td>
<td>30</td>
<td>50.8%</td>
</tr>
<tr>
<td><strong>Mortalities</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Morbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic complications</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bypass graft occlusion</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Neuropraxia (improving)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Re-thrombosis of native vessels</td>
<td>7</td>
<td>11.9%</td>
</tr>
</tbody>
</table>
### Amputation rate

*Secondary amputation*

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>1</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

### Pulse status (since 30-day follow-up)

<table>
<thead>
<tr>
<th>Status</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unchanged</td>
<td>25</td>
<td>83.3%</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>5</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

### Functional outcome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>23</td>
<td>76.7%</td>
</tr>
<tr>
<td>Contracture</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Claudication symptoms</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Motor weakness</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Long term outcome

Only 17 patients attended follow-up appointments after the 6 months post-operative period. One patient developed bypass graft occlusion before demising from lung carcinoma 2 months later. No other systemic or procedural complications were noted in this patient group.

Three patients showed signs of pulse status deterioration from the previous 6-month follow-up visit. Thirteen patients reported normal function, 2 patients presented with contractures, 1 patient with motor weakness and 1 patient presenting with claudication symptoms. Due to poor follow-up attendance, these findings have limited interpretational value.
### Table 27: Summary of long term (>6 months) outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to follow-up</td>
<td>17</td>
<td>28.8%</td>
</tr>
<tr>
<td>Mortalities</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic complications</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bypass graft occlusion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amputation rate</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulse status (since 6-month follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>14</td>
<td>82.4%</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>3</td>
<td>17.7%</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Functional outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>13</td>
<td>76.5%</td>
</tr>
<tr>
<td>Contracture</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Claudication symptoms</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

### Special subgroups

When presenting surgical outcome of patients with upper limb ischaemia as a whole, a valuable overall picture of a distinctly heterogeneous disease process, can be obtained. However, comparing different subgroups in an attempt to identify significant discrepancies in outcome, may facilitate correlation with the international literature on these topics. Therefore, relevant subgroup analyses will be discussed next, with specific reference to surgical outcome.
TED vs UEAOD

It is indeed striking that all 5 of the 30-day mortalities, were observed in the subgroup of patients presenting with embolic AULI (see Table 25). The concept that mortality following embolectomy is a consequence of the patient’s comorbidity rather than the embolus itself, is well supported.\textsuperscript{1,52} In our series, the mortalities were attributable to acute coronary syndrome (n=2), acute renal failure (n=2) and acute respiratory failure (n=1). The only death observed in the CULI group, was documented 2 years after initial surgery for UEAOD, when the patient demised from end-stage lung carcinoma.

Table 28: Comparison of TED- and UEAOD- subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>Number of procedures</th>
<th>Mean age</th>
<th>30-Day mortality</th>
<th>Amputation rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>TED</td>
<td>30</td>
<td>47</td>
<td>55</td>
<td>16.7%</td>
<td>13.3%</td>
</tr>
<tr>
<td>UEAOD</td>
<td>12</td>
<td>16</td>
<td>57</td>
<td>0%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

These findings are in keeping with recent international literature on the subject, where the 30-day all-cause mortality rate for patients undergoing upper extremity embolectomy, is estimated to be between 9 – 19\%.\textsuperscript{1,138,142,143} Deguara et al\textsuperscript{1} reported a 30-day mortality rate of 18.2\% in this subgroup of patients and attributed all deaths to cardiopulmonary incidents.

Four patients in the TED group underwent amputations (2 above-elbow and 2 digital amputations) after revascularization was attempted, compared to one above-elbow amputation in the UEAOD group.
Units implementing a more aggressive approach to the management of relatively minor symptoms, may reflect better surgical outcomes, especially superior limb salvage rates. Therefore, when comparing surgical outcome of the UEAOD subgroup to that of international Vascular Units, one has to interpret the results in terms of the indication for surgery. In the current series, 48% of patients with UEAOD, presented with some form of tissue necrosis as opposed to series from Hughes$^9$ (15%) and Roddy$^{10}$ (13%).

**HIV**

Of the 64 patients included in this review, 7 were confirmed to be HIV positive by HIV Ag/Ab Combo (ELISA) testing. However, only 30 patients had documented proof (folder laboratory results sheet or NHLS Disa electronic results system) of a recent HIV test being performed. Only 3 of the 7 patients had documentation of a recent CD4 count or viral load. One patient developed superficial surgical site infection and another demised after prosthetic bypass graft sepsis was complicated by an acute bleed. Due to a low rate of HIV testing and the small number of patients involved, it is not possible to reach firm conclusions regarding clinical outcome in this subgroup of patients.

*Patients managed exclusively by endovascular means*

Six patients, of which one presented with AULI from a proximal embolizing source, were managed by endovascular means alone. All lesions that were addressed, were located in the subclavian artery. Five lesions were managed by primary stent placement, with one lesion stented after failed percutaneous balloon angioplasty. One patient sustained a procedure related complication in the form of an ipsilateral cerebro-vascular incident. No other procedural or systemic complications were noted in this group of patients. All
patients attended follow-up appointments up to 6 months, but only 2 were seen after this period. An improvement in pulse status / perfusion (as evaluated by clinical palpation, hand-held doppler pressures and/or duplex arteriogram) were noted in all patients and normal function of the affected upper limb, were reported.
Vascular surgeons are infrequently confronted with the condition of upper limb ischaemia. Compared to other more common vascular pathologies, clinicians are less familiar with the pattern and distribution of disease, variable aetiologies, diagnostic appraisal and treatment modalities related to this condition. This has generated an innate curiosity regarding several facets of ULI, with particular emphases on identifying key areas fit for further, more focused research.

On review of the literature, it was clear that even though relatively few patients present with this condition, the potential aetiological factors implicated were variable and extensive. Therefore, in the interest of developing a broad perspective, the decision was made to perform a comprehensive, general overview on the topic, rather than to limit oneself to a specific research question.

On evaluation and analysis of the data, certain inherent limitations of the above research method, became clear. Unfortunately, by attempting to discuss distinctly different aetio-pathological processes in unison, important individual characteristics may be obscured. Also, with no specific research question asked or stated, the researchers could only generate multiple, tentative assumptions to base further research on. With this in mind, a few relevant findings will now be discussed.

The true incidence of ULI in the South African context, still remains speculative. A major limiting factor is the paucity of data on the non-operative management of AULI. Units
where an initial conservative approach is often utilized should be encouraged to collect data regarding the incidence and outcomes. A collaborative effort among units may compensate for low numbers and in the process provide adequate data to estimate the true extent of the problem. With the high prevalence of pulmonary tuberculosis, HIV / AIDS and cigarette smoking (83% in the UEAOD subgroup – Table 16) in the study population, it is indeed conceivable that our incidence of ULI may be higher than expected. In the absence of a national registry, a multi-centre trial specifically designed to evaluate these questions, should be performed.

Another interesting phenomenon is the young age at which patients presented with symptomatic disease (Table 12), when compared to international literature. This holds especially true for the TED subgroup of patients (mean age 55 years), usually known for their advanced age at presentation (72.4 years reported by Deguara et al). Possible explanations include the assumed impact that a relatively low life expectancy may have on these figures (57.7 years for males and 61.4 years for females) as well as the suspicion of a different risk factor profile (TB, HIV and cigarette smoking) compared to other research populations.

On review of the referral patterns (Table 14), it is noteworthy that approximately half of AULI referrals were received from surrounding Secondary Level Hospitals, as opposed to the 19.7% collectively referred from Community Health Centres and Primary Level Hospitals. It has incontrovertibly been shown that outcome in patients suffering from ALI is superior if managed in a Vascular Unit with 24 hour consultant cover.[164] Therefore, it is imperative that patients are directly referred from the healthcare facility of first contact,
to the nearest Vascular Unit without unnecessary delay. Although multiple other factors might have influence this pattern, it will be interesting to evaluate the number of “double referrals” within this subgroup of patients in need of urgent revascularization.

Approximately 27% of patients referred were not receiving appropriate pharmacological therapies aimed at addressing pre-existing, modifiable risk factors for atherosclerosis. This is a worrying statistic bordering on a Public Health catastrophe, as these patients are at an increased risk of sustaining adverse cardiovascular events and would benefit from evidence-based best medical therapy. Further inquiry should be made through focused research, in order to ascertain and further define the system failure at hand.

Poor adherence to follow-up has hampered reliable interpretation of conventional clinical outcome. Although variable factors contribute to this phenomenon, the implementation of a computerized ULI database with pre-set, automated follow-up reminders may assist clinicians and administrative staff in contacting patients due for follow-up visits. Compliance to follow-up appointments, as the primary outcome measure, can be evaluated before and after the implementation of such a system.
CHAPTER SEVEN:

CONCLUSION

Although few firm conclusions could be drawn, this review has expanded our overall perspective of ULI, specific to the population we serve. It is anticipated that the publication of our institutional data will create a clinical awareness and facilitate future research projects in this field. A collaborative research effort between South African vascular units will facilitate a comparison of different institutional experiences and enable pooled data analysis, perhaps further defining the pattern of upper limb vascular disease by identifying distinct geographical confounders.
REFERENCES


11) Norgeren L, Hiatt WR, Dormandy JA. Inter-society consensus for the management of peripheral arterial disease. Eur J Vasc Endovasc Surg 2007; 33:S1-75


35) Buerger L: The circulatory disturbance of the extremities: including gangrene, vasomotor and trophic disorders Philadelphia, Saunders; 1924.


75) Cates JE, Christie RV. Subacute bacterial endocarditis: a review of 442 patients treated in 14 centers appointed by the penicillin trials committee of the MRCQ. J Med1951;20,93.


26th March 2012

Dr JM du Toit
Department of Surgery
Division of General Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr du Toit,

RE: PROJECT 2012/021

PROJECT TITLE: Upper limb ischaemia - A twelve year experience

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely,

[Signature]

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE
APPENDIX 2: HUMAN RESEARCH ETHICS COMMITTEE
APPROVAL

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7933
Telephone (021) 406 6338 • Facsimile (021) 406 6411
E-mail: shurett.thomson@uct.ac.za

3 September 2012

HREC REF: 448/2012

Dr J Du Toit
c/o Dr NG Naidoo
General Surgery
OMB

Dear Dr Du Toit

PROJECT TITLE: UPPER LIMB ISCHAEMIA - A TWELVE YEAR EXPERIENCE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year till the 15th September 2013

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

T Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
APPENDIX 3: DATA COLLECTION SHEET

Upper limb ischaemia: Data – collection sheet

Groote Schuur Hospital – Vascular Unit

2000 – 2011

Patient sticker

Demographic details

Name: Hospital number:
Age: Gender:
Ethnic group:

Contact details

Address:

Telephone number: (H) (W)
(C)
Clinical data

Presented with:

- **Acute limb ischaemia**
  - Rutherford grading: □ I □ IIa □ IIb □ III
  - Compartment syndrome: □ Y □ N

- **Chronic limb ischaemia**
  - Digital ulceration
    - Active ulceration □
    - Healed ulceration / digital infarcts □
  - Digits involved:
  - Raynauds symptoms □
  - Claudication symptoms □
  - Neuro – vascular symptoms (specify) □

- **Risk factors for atherosclerosis**
  - Hypertension □
  - Hypercholesterolaemia □
  - DM - Type □
  - Cigarette smoking □
    - Specify packyears:
  - Other substances □
    - Cannabis □
    - TIK □

- **Cardiac disease**
  - IHD □
  - AF □
  - Valvular heart disease □

- **Other systemic disease**
  - Specify:
Relevant medical therapy (indicate class of drug)

Pre-event:
- Anti-HPT
- Insulin
- Anti-platelet agent
- Anti-TB
- Oral hypoglycaemics
- Chol-lowering agent
- Anti-coagulation
- ARV’s

Post-event:
- Anti-HPT
- Insulin
- Anti-platelet agent
- Anti-TB
- Oral hypoglycaemics
- Chol-lowering agent
- Anti-coagulation
- ARV’s

Pathology

Embolic
- Cardiac source
  - Specify:
    - Extra – cardiac source
      - Specify:

Thrombotic
- Atherosclerosis associated
- Thrombophilia
  - Specify:
  - Other
    - Specify:

Site of occlusion:
Abnormal special investigations

- Upper limb dopplers
- Upper limb duplex arteriogram
- Digital doppler with caloric stimulation
- Angiogram
  - Arch
  - Select
- MD – CTA
- MRA
- CXR / C – spine XR
- Echo / ERNA

Laboratory investigations

| Hb | WCC | Platelet count |
| INR | PTT | Fibrinogen |
| ESR | CRP | Homocysteine |
| HIV (CD4= ) | RPR | Lupus a/c |
| AT III | Prot C+S | CardiolipinAb |
| Vit B6 | Vit B12 | RCF |
| ENA | ANF | RF |
| Complement | Chol | LDL |
| HDL | Trig | Creatinine |
Primary procedure

Date of procedure:

Length of procedure:

☐ Started during day time hours    ☐ Started after hours

☐ Open surgical

☐ Embolectomy

☐ Bypass graft

☐ Aortic arch recon    ☐ SCA - Axillary    ☐ Axillary - Brachial

☐ Brachial - Brachial    ☐ Brachial - Distal

☐ Fasciotomy

☐ Amputation

☐ Above elbow    ☐ Below elbow    ☐ Hand - Specify:

☐ Endovascular

☐ On – table angiogram

☐ PTA    ☐ Stent

☐ SCA    ☐ Axillary    ☐ Brachial

☐ Thrombolysis

☐ Alone    ☐ In combination with surgery
Secondary Procedure

Date of procedure:

Length of procedure:

- □ Started during day time hours
- □ Started after hours

- □ Open surgical
  - □ Embolectomy
  - □ Bypass graft
    - □ Aortic arch recon
    - □ SCA - Axillary
    - □ Axillary - Brachial
    - □ Brachial - Brachial
    - □ Brachial - Distal
- □ Fasciotomy
- □ Amputation
  - □ Above elbow
  - □ Below elbow
  - □ Hand - Specify:

- □ Endovascular
  - □ On – table angiogram
  - □ PTA
  - □ Stent
    - □ SCA
    - □ Axillary
    - □ Brachial
  - □ Thrombolysis
    - □ Alone
    - □ In combination with surgery

Describe subsequent procedure(s) if performed:
Follow – up (30 days)

☐ Died

☐ Alive

Specify reason for death:

☐ Systemic complications

Specify:

☐ Procedure related complications

Wound complications

☐ Wound sepsis

☐ Haematoma

Graft complications

☐ Graft occlusion

☐ Graft sepsis

Nerve injuries

☐ Amputation

☐ Upper limb

☐ Arm

☐ Hand

☐ Finger

☐ Pulse status / Doppler pressures

☐ Improved

☐ Same

☐ Deteriorated

☐ Duplex arteriogram

☐ Improved

☐ Same

☐ Deteriorated
Follow – up (30 days to 6 months)

Duration post – procedure:

☐ Died  ☐ Alive

Specify reason for death:

☐ Graft complications
  ☐ Graft occlusion
  ☐ Graft sepsis

☐ Pulse status / Doppler pressures
  ☐ Improved  ☐ Same  ☐ Deteriorated

☐ Duplex arteriogram
  ☐ Improved  ☐ Same  ☐ Deteriorated

☐ Function
  ☐ Normal  ☐ Contracture  ☐ Claudication

☐ Other complications
  Specify:
Follow – up (6 months to longterm)

Duration post – procedure:

- □ Died
- □ Alive
  
  Specify reason for death:

- □ Graft complications
  - □ Graft occlusion
  - □ Graft sepsis

- □ Pulse status / Doppler pressures
  - □ Improved
  - □ Same
  - □ Deteriorated

- □ Duplex arteriogram
  - □ Improved
  - □ Same
  - □ Deteriorated

- □ Function
  - □ Normal
  - □ Contracture
  - □ Claudication

- □ Other complications
  
  Specify: