The role of haemodynamic analysis in high flow extracranial to intracranial bypass surgery

A thesis submitted to fulfil the requirements for the degree of

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Abstract

Use of computational haemodynamics technology is well described for a number of diverse conditions in medicine including predicting flows in the Circle of Willis, risk of rupture of aneurysms, and optimum endovascular stent placement in the management of vascular pathology. Saphenous vein or radial artery interposition grafts are often used for high-flow extracranial-intracranial bypass procedures. These bypasses have the potential to supply a considerable volume of cerebral blood flow to the brain. However, long-term patency for specific graft types remains unknown. This is a computation haemodynamic analysis of consecutive interposition bypass cases. The bypasses are between the common carotid artery (CCA) and intracranial Internal carotid artery (ICA) or middle cerebral artery (MCA). Emerging evidence supports a pathogenic role of abnormal wall shear stress (WSS) and pressure turbulence flow as important factors in the development of early graft failure at the anastomotic site. This study aimed to develop a computational fluid dynamics simulator for assessing flow in cerebral high flow revascularisation bypass grafts and to study the impact of variations in the anastomosis angle and pressure gradient across bypass. Also the optimum mean arterial pressure required for maintaining the graft flow was investigated.

Statement of originality

I hereby declare that the work presented in this thesis has not been submitted for a higher degree to any other university or institution. Much of the work presented in this thesis has been published as listed in page xii-List of publications arising from this thesis. Although some of these papers have co-authors, the work appearing in this thesis is entirely my own, with the exception of Chapter 8, which present work jointly carried out by myself and Yu Zhang. Any contribution made to the research by others is explicitly acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis.

This study was approved by the Macquarie University Human Ethics Committee, and performed in accordance with institutional ethics committee guidelines. The protocols are

1. The use of a prospectively collected cerebrovascular database for the purpose of surgical audit (HE26SEP2008-R06107), and

2. Computational haemodynamic evaluation of patient with intracranial aneurysms and cerebrovascular bypass surgery (5201000234)

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List of publications arising from this thesis

Manuscripts:

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Comparative Patency Between Intracranial Arterial Pedicle and Vein Bypass Surgery.
Neurosurgery 2011: 69(2); 308-314

Sheau Fung Sia, Leon Lai, Michael Kerin Morgan.
Measuring competence development for performing high flow extracranial-to-intracranial bypass. *Journal of Clinical Neuroscience* 2013. In press

Sheau Fung Sia, Yi Qian, Wataru Matsuda, Alberto Avolio, Michael Kerin Morgan. Evaluation of Brain Extracranial-to-Intracranial (EC-IC) Bypass Treatment by Using Computational Hemodynamic Technology. *World Congress of Biomechanics* 2010, IFMBE Proceedings 31, 1542-1545

Sheau Fung Sia, Yi Qian, Wataru Matsuda, Yu Zhang, Michael Kerin Morgan
Haemodynamic effects from a common carotid to middle cerebral bypass with varying degrees of proximal internal carotid stenosis.
Submitted and under review

Sheau Fung Sia, Yu Zhang, Yi, Qian, Michael Kerin Morgan
Mean arterial pressure required for maintaining patency of extracranial to intracranial bypass grafts: an investigation with computational haemodynamics models. Case series*.* *Neurosurgery* 2012: 71(4); 826-832

Yu Zhang*, **Sheau Fung Sia***, Michael Kerin Morgan, Yi Qian
Flow resistance analysis of extracranial-to-intracranial (EC-IC) vein bypass. *Journal of Biomechanics* 2012*:* 45(8); 1400-1405

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Sheau Fung Sia, Andrew S Davidson, Michael Kerin Morgan
Comparative patency for intracranial arterial pedicle and vein bypass surgery.
Oral presentation in 9th International Conference on Cerebrovascular Surgery (ICCVS). Nagoya, Japan, 2009

Sheau Fung Sia*, Wataru Matsuda, Yi Qian, Michael Kerin Morgan.
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Other publications arising from during the period of candidature

S. Sheaufung, Taufiq, A; Nawawi, O; M.S.,Naicker; V, Waran.
Neurenteric cyst of cervicothoracic junction: A rare cause of paraparesis in paediatric patient. *Journal of Clinical Neuroscience* 2009; 16: 679-581

Vicknes Waran, Narayanan Vairavan, **Sheau Fung Sia**, Basri Abdullah.
A new expandable cannula system for endoscopic evacuation of intraparenchymal hemorrhages. *J Neurosurgery* 2009; 111: 1127-1130

Sheau Fung Sia, Andrew S Davidson, Judy R Soper, Paul Gerachi, S Fiona Bonar. Protuberant Fibro-osseous Lesion of the Temporal Bone: "Bullough Lesion" *American Journal of Surgical Pathology* 2010; 34(8): 1217-1223

Yu Zhang, Toyoki Furusawa, **Sheau Fung Sia**, Jianmin Liu, Mitsuo Umezu, Yi Qian. Proposition of an outflow boundary approach for carotid artery stenosis CFD simulation. *Computer Methods in Biomechanics and Biomedical Engineering* 2012. Jan 30; PMID 22288780

Declaration of contribution to chapters containing published or submitted work

Chapter 1

Candidate performed all data acquisition, analysis and interpretation of data. Candidate was the major contributor to the manuscript

Chapter 2

Senior author performed data acquisition. Candidate performed all data analysis and interpretation. Candidate was the major contributor to the manuscript

Chapter 3

Senior author performed data acquisition. Candidate performed all data analysis and interpretation. Candidate was the major contributor to the manuscript

Chapter 5

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Wataru Matsuda contributed to the subset of CFD modelling and data acquisition

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Chapter 7

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Yu Zhang contributed to the subset of CFD modelling and data acquisition

Chapter 8

Yu Zhang performed the majority of CFD modelling and data acquisition. Candidate performed a subset of data acquisition and interpretation.

Candidate and Yu Zhang co-wrote the manuscript.

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Abbreviations and definitions

A1	- Anterior cerebral artery segment 1
AAA	- Abdominal aortic aneurysm
BTO	- Balloon test occlusion
CBF	- Cerebral blood flow
CBV	- Cerebral blood volume
CCA	- Common carotid artery
CDU	- Colour Doppler ultrasound
CFD	- Computational fluid dynamics
CI	- Confidence interval
CoW	- Circle of Willis
CT	- Computed tomography
CTA	- Computed tomography angiogram
DICOM	- Digital Imaging and Communications in Medicine
ECA	- External carotid artery
EC-IC	- Extracranial-to-Intracranial
EEG	- Electroencephalography
ELANA	- Excimer Laser Assisted Non-occlusive Anastomosis
HF EC-IC	- High flow Extracranial-to-Intracranial
ICA	- Internal carotid artery
ICG	- Indocyanine green
MAP	- Mean arterial pressure
MCA	- Middle cerebral artery
M1	- segment 1 of MCA
mRS	- Modified Rankin scale
PCA	- Posterior cerebral artery
PComA	- Posterior communicating artery
PET	- Positron emission tomography

rOEF - Regional oxygen extraction fraction

STA-MCA - Superficial temporal artery to middle cerebral artery

SPECT - Single-photon emission computed tomography

SVG - Saphenous vein graft

TIA - Transient ischaemic attack

WSS - Wall shear stress

Nomenclature and Greek Symbols

f_i	- Body forces
p	- Pressure
t	- Time
v	- Velocity
D	- Graft diameter
Q	- Volume flow rate
Re	- Reynolds number
μ	- Viscosity
ρ	- Density
Δp	- Pressure difference
λ	- Resistant number
$\dot{m}$	- Mass flow rate
ξ	- Resistant coefficient

List of units

cm - Centimetre

g - Gram

kg - Kilogram

L - Litre

m - Metre

mg - Milligram

min - Minute

mm - Millimetre

s - Second

Subscripts

i, j - Spatial coordinate indices

$inlet$ - Inlet condition

$outlet$ - Outlet condition

Chapter 1

High flow extracranial-to-intracranial brain bypass surgery. Review

Abstract

Cerebral revascularisation may be necessary in the management of complex skull base tumours and intracranial aneurysms. A variety of vascular reconstruction techniques have been described since the first successful bypass more than 50 years ago. Bypass grafting can be considered high flow when radial artery or saphenous vein is interposed between the extracranial carotids and intracranial vessels. The decision as to whether to use a low or high flow bypass is determined by the anticipated cerebral blood flow needed or the availability of a scalp artery. In this review, we consider the current indications, strategies and techniques of high flow extrcranial to intracranial bypass.

Keywords: Cerebral revascularisation, vein, arterial graft, vessel sacrifice, surgery, EC-IC bypass

Introduction

Bypass vascular anastomosis were first described and established at the turn of the 20th century by Carrel (Carrel 1907) and Guthrie (Guthrie 1907). As a result of extensive study and successful technique they developed in vascular anastomosis, Carrel was awarded the Nobel Prize in Physiology and Medicine 1912. It was not until the early 1950's (with the development of modern surgical and angiographic techniques) that the field of cerebrovascular surgery would begin its explosive growth. In 1951, Miller Fisher postulated the role for bypass surgery to manage carotid disease (Fisher 1951). The early clinical attempts commenced in the 1960's with feasibility established but failure with high flow extracranial to intracranial bypass (HF EC-IC) (Woringer *et al.* 1963) reported in 1963 followed by the establishment of the feasibility of superficial temporal to middle cerebral artery (STA-MCA) bypass first established in the laboratory and then successfully in humans reported by the next decade, Yasargil (Yasargil 1969) and Donaghy (Donaghy 1967). Lougheed succeeded with a case of HF EC-IC bypass to the intracranial ICA at this time (Lougheed *et al.* 1971). However, the complexity of the HF EC-IC bypass in comparison to the STA-MCA bypass led to the wide adoption of the low flow bypass in preference to the HF EC-IC bypass. Until the mid-1980's, the number of neurosurgeons that had performed large case series of superficial temporal to middle cerebral artery bypass was increasing exponentially (Chater *et al.* 1977; Merei *et al.* 1977; Piepgras *et al.* 1977). However, the publication of the EC-IC bypass study called into question the role of all bypass for any category of disease state and the performance decline dramatically.

Intuitively, one would expect that improvement of brain blood flow would reduce the likelihood of stroke. However, defining the appropriate indications has proven to be elusive. The problem of defining this role is due to lack of understanding of the natural history of various intracranial pathologic states and the risks involved in the surgical procedures. With advances in anatomical and functional imaging, greater sophistication in the prediction of the need for bypass has evolved.

In general, there are two major indications for extracranial to intracranial (EC-IC) bypass surgery. These are flow augmentation and flow replacement. Flow augmentation is considered suitable where brain blood flow is borderline. That is when, infarction is considered likely to occur due to low flow but as yet has either not occurred or has occurred but may enlarge. For this borderline blood flow, there exists sufficient flow to maintain neuronal viability despite the threat of infarction in the future. Moyamoya disease and intracranial occlusive disease are typical examples of where bypass is used to augment threatened flow. Such cases may be considered for low flow bypass with superficial temporal or occipital arteries as the graft. A superficial temporal artery initially delivers 30ml/min with a proven capacity to dilate and increase this flow with time. Flow replacement may be indicated when an artery contributing to, or branching from, the Circle of Willis (CoW) needs to be sacrificed in the course of managing complex intracranial vascular pathology or skull base tumours. These high flow extracranial to intracranial (HF EC-IC) bypasses, using saphenous vein or radial artery as the graft, have the potential to supply a considerable volume of blood flow to the brain. In addition, they have greater reach than the arterial grafts.

Despite the seemingly sound basis for low flow bypass in selected cases, as yet there is no class I clinical evidence of support for results of HF EC-IC bypass grafts. Furthermore, with the unfavourable results of published data of the EC-IC Bypass study (Group 1985) and Carotid Occlusion Surgery Study (COSS) (Powers *et al.* 2011) ensure that the current indications for EC-IC bypass remain limited. Since this report, there has been a rapidly diminishing number of procedures performed by neurosurgeons. It also generated great controversy and has been widely criticised (Ausman *et al.* 1986; Awad *et al.* 1986; Goldring *et al.* 1987). Case series support for low flow bypass exists for patients with symptomatic Moyamoya disease and those with occlusive disease leading to reduced blood flow with cerebral haemodynamic insufficiency in which the microcirculation of the region of interest is maximally vasodilated and there is increased oxygen extraction in comparison to normal. This has been termed stage 2 haemodynamic failure [increase oxygen extraction factor (OEF)} by Grubb and colleagues (Grubb *et al.* 1998) and in the presence of internal carotid occlusion has been shown to significantly increase the risk of stroke above that of those with ICA occlusion that do not have an increase in OEF as measured by PET (Table 1.1). These results are consistent with other series that have reported patients with internal carotid artery occlusion and “misery perfusion.” The order relative risk is increase 3-6 fold (Grubb *et al.* 1998; Garrett *et al.* 2008).

Table 1.1 Stages of haemodynamic failure: Positron emission tomography measurement (Powers *et al.* 1987)

Stage	Regional Cerebral Blood Volume **(rCBV)**	The ratio of Regional Cerebral Blood Volume **(rCBV)**/ Regional Cerebral Blood Flow **(rCBF)**	Regional Oxygen Extraction Ratio **(rOEF)**
0	Normal	Normal	Normal
1	↑	↑	Normal
2	↑↑	↑↑	↑
3 (irreversible ischaemia and infarction)	Maximum	Maximum	Decreased

High flow EC-IC bypasses use long saphenous vein or radial artery as the bypass graft conduits. These grafts are interposed between a cervical artery [often the common carotid artery (CCA)] and the intracranial internal carotid artery (ICA), middle cerebral artery (MCA), posterior cerebral artery (PCA), or vertebral artery. HF EC-IC bypass surgery has considerable more risk than low flow bypass. In a recent series of 152 vein bypass cases, the procedure-related complication rate was 8% (half of these complications were fatalities) (Sia *et al.* 2011). Peri operative ischaemia, graft occlusion and haemorrhagic transformation of ischaemic brain account for the most serious of these complications. Long-term, HF EC-IC bypass into the intracranial circulation differs from the experience of peripheral vascular surgery in that long-term graft patency of 93% can be achieved (Sundt *et al.* 1988; Jafar *et al.* 2002; Sekhar *et al.* 2002; Sia *et al.* 2011).

Our purpose is to review the current indications, selection criteria, diagnostic evaluation strategies approach and long-term graft patency for HF EC-IC cerebral revascularisation.

Search strategy

Method: A literature review was performed to review the origins and current uses of high flow bypass procedures in neurosurgery. We searched the Cochrane Neurosurgery, Scopus and Medline. The date of the most recent search was 29 Dec 2011

Two online databases were searched using the following strategies:

1. Ovid Medline (1948 to 2011) was searched using the following MeSH terms and keywords: (cerebral revasculari*ation.mp or cerebral revascularisation) AND (exp saphenous vein) OR (Vascular patency/ or veins/or vascular surgical procedures/ or saphenous vein) OR (artery graft.mp) OR (interpositional graft.mp). The results were limits to humans and English language.
2. Scopus was search using the following Title, Abstract, Keyword terms: ("Cerebral revasculari*ation") OR ("Brain Bypass") AND ("saphenous venous") OR ("arterial graft") OR ("interpos* graft"). Results were limits to articles, reviews, conference papers and English language

History

Brain bypass surgery has been available for treating patients with selective intracranial vascular pathology for more than 50 years (Table 1.2). The introduction of microneurovascular techniques in the early 1960's has made a major advance in the development of cerebral revascularisation. Woringer (Woringer *et al.* 1963) reported the first HF EC-IC bypass surgery in early 1960s. However, this technique remained obscure because of its complexity and high morbidity. Revascularisation failed to gain popularity until Donaghy (Donaghy 1967) and Yasargil (Yasargil 1969) demonstrated in the late 1960s that superficial temporal to middle cerebral artery bypass (STA-MCA) was feasible at a relatively low risk. High flow bypass was attempted again by William Lougheed (Lougheed *et al.* 1971) in Toronto, who reported a case of CCA to intracranial ICA interposition saphenous vein graft (SVG) in 1971. This larger conduit EC-IC bypass technique remained unpopular until described by Sundt (Figure 1.1) and Piepgras, who has helped to pioneer many cerebral revascularisation procedures for the treatment of unclippable large aneurysms (Sundt *et al.* 1982). Since then, a number of authors have reported using venous conduit EC-IC bypass surgical techniques for the treatment of patients with intracranial pathology needing vessel trapping and sacrifice (Sundt *et al.* 1986; Greene *et al.* 1993; Morgan *et al.* 1994; Lawton *et al.* 1996; Lawton *et al.* 1996; Morgan *et al.* 1996; David *et al.* 1997; Kalavakonda *et al.* 2001; Sekhar *et al.* 2001; Morgan *et al.* 2002). Various innovation techniques (Table 1.2.) have been reported, including Spetzler and colleagues' bonnet bypass for the treatment of complex MCA aneurysm (Greene *et al.* 1993), Sekhar and colleagues' direct petrous-to-supraclinoid ICA bypass in the treatment of intracavernous aneurysm (Sekhar *et al.* 1990), Morgan's CCA to intracranial ICA bypass with an end-to-end distal anastomosis on the internal carotid artery at the site between the ophthalmic and posterior communicating arteries (Morgan *et al.* 1996), sutureless (van Doormaal *et al.* 2010) or excimer laser-assisted non-occlusive EC-IC bypass (Bremmer *et al.* 2009) and a novel approach of U clip endoscopic radial artery harvesting for high flow EC-IC bypass to simplify the intracranial microanastomosis and reduce temporary occlusion time (Ferroli *et al.* 2009; Ferroli *et al.* 2009). Unlike the arterial pedicle low flow bypass, which requires a period of maturation to enlarge and supply an adequate blood flow to distal territory, a high flow EC-IC using interposition conduits can produce an immediate substantive increase of flow to hemisphere.

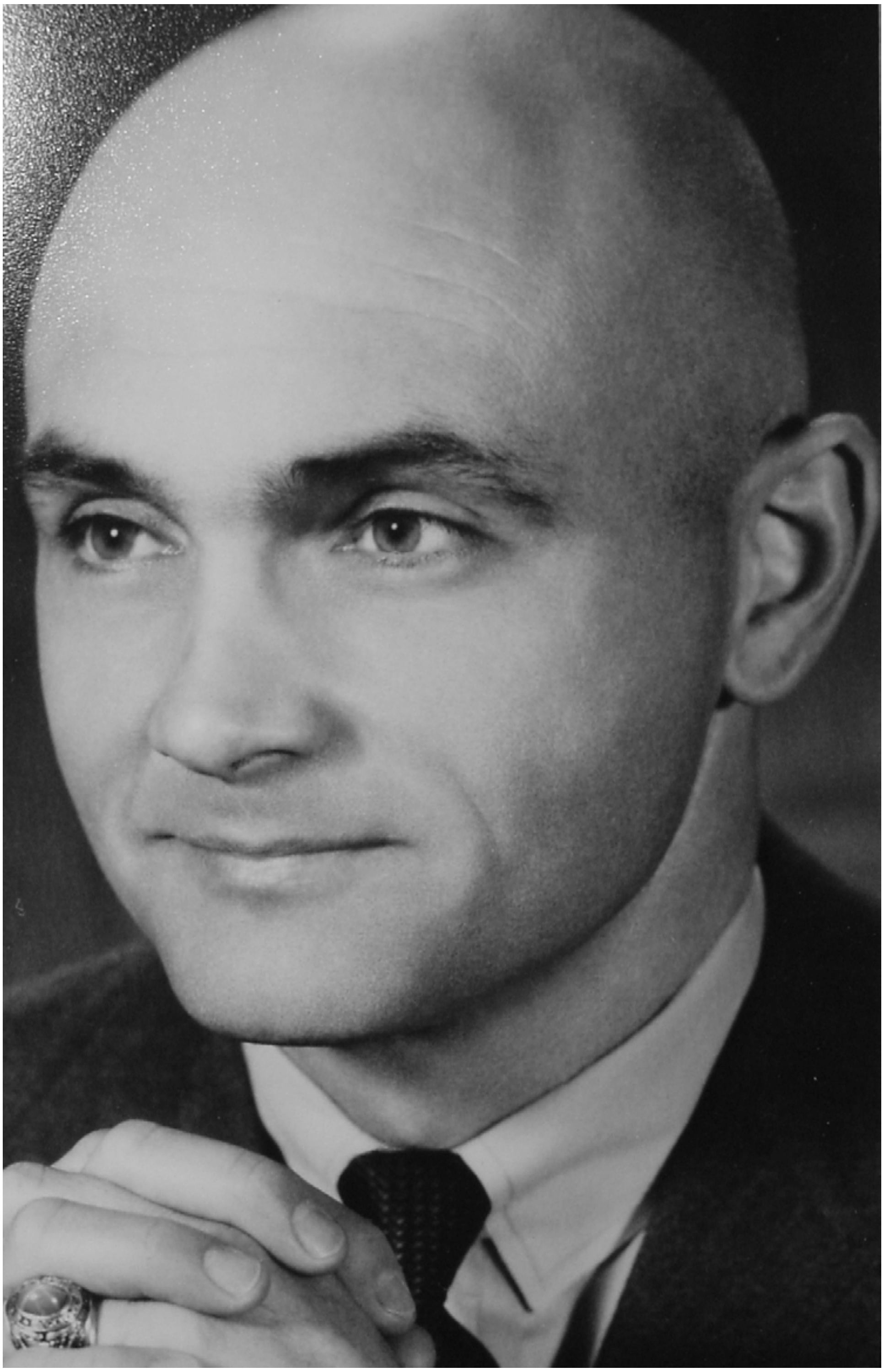

Figure 1.1 Pioneer of microsurgery, Dr Thoralf. M. Sundt, Jr. (1930-1992). Professor and Chairman, Department of Neurosurgery, Mayo Medical School, Mayo Clinic, Rochester, Minnesota.

Table 1.2 Summary of the evolution of high flow cerebral bypass

Authors	Year	Reported event
Woringer & Kunlin	1963	Performance of a CCA to ICA bypass utilising saphenous graft
Lougheed	1971	Venous bypass graft between CCA to intracranial ICA
Story *et al.*	1978	1.ICA to cortical branch of MCA bypass with saphenous vein graft (SVG) 2.ECA to MCA with synthetic tube of polytetrafluoroethylene (PTFE)
Spetzler	1980	Subclavian artery to MCA using saphenous vein. Bonnet bypass
Fisch	1980	Bypass between the cervical and petrous ICA
Sundt *et al.*	1982	Saphenous vein graft for posterior circulation disease
Morgan *et al.*	1985	Treatment of intracranial aneurysms by combined proximal ligation and EC-IC bypass with vein graft
Spetzler	1990	Bypass between the petrous and supraclinoid ICA
Serbinenko	1990	Venous bypass for intracavernous or non-clippable giant aneurysms of ICA
Morgan *et al.*	1996	Interposition saphenous vein bypass graft between the common and intracranial ICA.
Candon *et al.*	1996	Cervical-to-petrous ICA saphenous vein in situ bypass

Tulleken *et al.*	1996	Excimer laser-assisted non-occlusive anastomosis (ELANA) high flow bypass
Ustun *et al.*, Ulku *et al.*	2004	Innovation technique on radial artery graft for bypass of the maxillary artery to MCA and PCA
Ferroli *et al.*	2009	Endoscopic radial artery harvesting for U-clip: A novel bypass technique
Van Doormaal *et al.*	2010	Sutureless excimer laser assisted non-occlusive anastomosis (SELANA)

CCA: Common carotid artery, ECA: External carotid artery, ICA: Internal carotid artery, MCA: Middle cerebral artery, PCA: Posterior cerebral artery

Who should be considered for high flow bypass?

Rationale for bypass surgery:

The basis for bypass surgery is haemodynamic security. Physiological and functional image testing is commonly employed to assess the need for bypass. The volume of flow determines the net volume of brain protected. The brain receives about one fifth of the cardiac output, and consumes 20% of total body resting O_2 consumption (Barrett *et al.* 2009). Quantitative assessment of cerebral blood flow (CBF) reveals an average flow of 50-55 ml/100g/min. This results in a normal vertebral and internal carotid combined flow of blood flow of 700 ml/min. The normal oxygen-extraction ratio is approximate 40% and the glucose extraction ratio is 10-15% (Khurana *et al.* 2004). In vitro studies have shown that protein metabolism is inhibited at a 50% reduction of CBF and is completely suppressed when flow is below 15ml/100g/min. At rate below 10-12 ml/100g/min, irreversible neuronal damage (ionic pump failure and cytotoxic oedema) (Khurana *et al.* 2004) and infarction will occur if sufficient time elapses without restoration of flow. It is becoming apparent that when assessing these patients, not only quantitative evaluation of patient's CBF necessary, but the patient's preoperative radiological evaluation assessing the anticipated physiological state (cerebrovascular reserve) and adequacy of collateral circulation must be assessed by balloon test occlusion (BTO). This technique was first described and used in humans by Serbinenko in 1974 (Serbinenko 1974). BTO has been described with a number of variations both at normal blood pressure and temporarily lowering blood pressure (hypotensive challenge, lowering mean arterial pressure with nitroprusside drip by 20mmHg, or 25% of mean arterial pressure, whichever was greater.) These include neurological examination, angiographic anatomical assessment of collateral circulation from the Circle of Willis or leptomeningeal connections, time delay of angiographic venous filling, EEG, SPECT, stump pressure and CBF determination amongst the more common tests (Herkes *et al.* 1993).

However, the indications for BTO are controversial. One approach favours HF EC-IC bypass in patients who fail BTO (selective approach); Alternatively, some authors advocate revascularisation surgery in all patients who have undergone planned vessels sacrifice for tumour and aneurysms (universal approach) (Lawton *et al.* 1996). BTO techniques, however, have a small but significant risk (e.g. in dissected vessels or where significant thrombus exists within an aneurysm). It has both false positive and negative predictive value in determining stroke risk after occlusion, fail to predict the potential for propagated thrombo-embolic complications from distal stasis in an artery occluded having been deemed sacrificable by the BTO (Heros *et al.* 1983), and cannot estimate the potential risk for accelerating degenerative disease through contralateral arteries as a result of increasing the shear stress through the Circle of Willis (e.g. contralateral or midline aneurysm development after occlusion). What the BTO can likely predict is whether or not a HF EC-IC bypass will have sufficient velocity following anastomosis (as determined by the driving pressure gradient) that graft occlusion is unlikely and it can determine the depth of cerebral protection that is required during cross-clamp in establishing the bypass. There is clearly no reason to perform a bypass if there is no pressure gradient to maintain flow and patency. However, a BTO is not always necessary or desirable due to the associated arterial anatomy or arterial disease (including ipsilateral aneurysmal thrombus, contralateral occlusive disease and aneurysms present on the collateral supply to the artery under consideration for BTO) (Morgan *et al.* 1994; Morgan *et al.* 1996).

Indication for high flow EC-IC bypass

High flow (HF) EC-IC bypass has been employed in four clinical settings:

a. **Planned vessel sacrifice for tumour or aneurysm.**

Strategic surgical or endovascular occlusion of an artery in the management of tumours or aneurysms may be judged on occasions to require the addition of a bypass procedure for the security of brain blood flow (Friedman *et al.* 2003; Liu *et al.* 2003). Creation of an interposition high flow bypass is the typical method of choice when flow requirements are likely to be significantly greater than 30 ml/min. This strategy of Hunterion ligation, which Drake (Drake 1975) has described in the treatment of inoperable intracranial aneurysms, has proven to be effective with high obliteration rate in all the main intracranial arteries.

b. Planned vessels sacrifice for stroke risk reduction in carotid arterial injuries including post-traumatic dissections and pseudoaneurysms.

When vessel replacement or sacrifice is anticipated for the need of stroke risk reduction such as cases of carotid dissection not amenable to conservative or endovascular management (e.g. of persistent pseudoaneurysm for more than three months, symptomatic cerebral ischaemia resulting from high grade stenosis despite maximum anticoagulation, bilateral acute dissection where progression on one side would likely to lead to decompensation of CBF with poor collateral circulation) (Morgan *et al.* 1996). Vishteh and colleagues (Vishteh *et al.* 1998) have shown the role of bypass in the management of persistently symptomatic traumatic ICA dissection with reduction of ischaemia and with excellent long-term outcomes and graft patency rates. Morgan and Sekhon reported that HF EC-IC bypass in the management of carotid or vertebral artery dissection has potential benefits over other treatments because of the maintenance of high flow, the avoidance of abnormal watershed areas of flow, and the elimination of the risk of emboli (Morgan *et al.* 1994). This indication may diminish with the introduction of flow diverting stents.

c. Emergency revascularisation due to stroke in evolution or possible stroke in evolution

In the management of unplanned major arterial loss at surgery, when it is evident or anticipated that stroke is likely to ensue, a saphenous vein bypass graft (SVG) provides higher flow and better approximate physiological conditions than does STA bypass. Morgan performed 23 emergency revascularisation surgeries for stroke in evolution in his vein bypass series (Sia *et al.* 2011). Of these, 20 procedures were performed as a consequence of technical problems encountered during aneurysmal repair, while 3 patients had symptomatic ischaemic symptoms suggesting early infarction due to high grade ICA stenosis from dissection with poor angiographic collaterals. It is important that this surgery proceeds urgently as the surgery is difficult if not impossible with brain swelling associated with ischaemia. Effective relaxation with mannitol and diligent anaesthetic care are critical to the technical success of this surgery.

d. Augmentation of cerebral blood flow in chronic haemodynamic ischaemia where a scalp artery is unavailable or too short.

In a small group of patients with chronic cerebrovascular compromise resulting in TIA's or border zone infarction, who have failed medical therapy (antiplatelet agents and maximising modifiable risks factors) and whose lesions are not amendable to conventional surgical and endovascular therapy may be considered candidates for HF EC-IC bypass. The role of surgical revascularisation with HF EC-IC bypass for patients who have ischaemic disease remains controversial (Group 1985; Grubb *et al.* 1998; Powers *et al.* 2011). The most common indication is symptomatic vertebrobasilar occlusive disease where endovascular stenting is not possible (Friedman *et al.* 2003).

Bypass patency

The short and long-term patency of HF EC-IC bypass grafts has been studied by various authors (Sundt *et al.* 1982; Group 1985; Onesti *et al.* 1989; Regli *et al.* 1995; Sia *et al.* 2011). For the experienced neurovascular surgeon, patencies of 90-95% can be obtained. For smaller vessels and deeper anatomy, slightly lower patencies are expected. Sundt reported that the early graft failure is generally attributable to thrombosis, precipitating factors like intimal desquamation on graft wall with both the loss of its protective fibrinolytic activity and exposure of the underlying thrombogenic collagen fibres, slowed graft flow and the coagulopathy of the patient's blood, has been well documented (Sundt *et al.* 1987). Thus it is crucial that mechanical trauma to the vein be minimised during surgery. The reported long term graft patency ranges from 73% to 100% patent after salvage procedure (Table 1.3) (Diaz *et al.* 1985; Regli *et al.* 1995; Jafar *et al.* 2002; Morgan *et al.* 2002; Sekhar *et al.* 2002; Friedman *et al.* 2003; Evans *et al.* 2004; Bulsara *et al.* 2008; Cantore *et al.* 2008; Sia *et al.* 2011). From our own experience, the surgical outcome for 152 intracranial vein bypass procedures using vein has been good with an acceptable complication rate. The senior author (MKM) has performed vein bypasses on 105, 23 and 24 cases, in the broad categories of planned vessels sacrifice for tumour and aneurysm or stroke risk reduction, augmentation of cerebral blood flow in chronic haemodynamic ischaemia and emergency revascularisation due to stroke in evolution, respectively. The long-term clinical outcome includes a downgrade in function (mRS >1) as a complication of HF EC-IC bypass surgery in 7.9% (95% CI, 4.5-13.4%). This included 6 patients who died (Sia *et al.* 2011). Most graft failures occurred within the first week following surgery. For bypasses that were patent at 1 week after the surgery, the 6 week and 6 months patency was 99% (Sia *et al.* 2011).

Conclusion

High flow EC-IC bypass remains an important option in the treatment of intracranial occlusive disease and in flow replacement in the setting of planned vessels sacrifice for intracranial pathology. Cerebral revascularisation constitutes an important treatment modality in the management of complex aneurysm, skull base tumour and stroke prevention. Graft selection and bypass strategy are critical steps in the planning of HF EC-IC bypass surgery. In properly selected patients, HF EC-IC bypass grafting is a viable and effective option treatment for patients. This review demonstrates a reasonable rate of morbidity and mortality with good graft patency rates. To some reports, the end results are striking in term of their originality and clinical outcome. The success of the procedure, however, is critically dependent on patient selection. The ability to perform this surgery is an important adjunct in the armamentarium of cerebrovascular surgery and surgical skills that are needed to perform this procedure should be maintained.

Table 1.3 Summary of results from selected previously reported series of patients (>20) undergoing HF EC-IC bypass.

Author	Year	No of patients	Patient procedures	Indication				Graft patency	Mortality
				Augmentation of CBF	Planned vessels sacrifice for tumour and aneurysm	Planned vessels sacrifice for stroke risk reduction	Emergency revascularisation		
Diaz	1985	27	29	25	4	0	0	83%	7%
Regli	1995	201	202	127	75	0	0	86% (1year) 82% (5 years) 73%(13 years)	NA
Morgan	1996	20	22	3	6	13	0	95%	5%
Santoro	1999	20	20	0	20	0	0	95%	NA
Sekhar	2002	133	137	0	133	0	0	95.6%	4%
Jafar	2002	29	30	0	29	0	0	93.3%	3%
Morgan	2002	55	57	0	25	28	4	95%	7%

Friedman	2003	130	130	47	79	4	0	NA	NA
Evans	2004	19	22	0	22	0	0	100% (after salvage procedure)	5%
Van Doormaal	2006	34	34	0	32	0	0	97%	6%
Bulsara	2008	NA	100	0	100	0	0	99% 98% (6 mths)	0%
Cantore	2008	41	41	0	41	0	0	92.7%	9.8%
Sia	2011	146	152	24	67	38	23	93%	4%

EC-IC: extracranial-to-intracranial, NA: non-available

Thesis objectives

This thesis work aimed

1) To report our experience of long term patency of interpositional vein grafts in patients with high flow (HF) EC-IC brain bypass.
2) To report our experience with competence development in the performance of HF EC-IC bypass surgery by measuring those problems specifically related to the functioning of the bypass graft whether or not they led to adverse clinical outcomes.
3) To demonstrate the feasibility of integrating patient-specific 3D CTA images data and develop a computational fluid dynamics (CFD) simulator for flow in patients who underwent HF EC-IC brain bypass surgery.
4) To study the impact of variations in anastomosis angles, pressure gradient across bypasses and to investigate the degree of stenosis of the ICA required for continuous blood flow in an HF EC-IC interposition vein bypass to the MCA.
5) To study the optimum mean arterial pressure (MAP) required that would maintain the graft flow on bypass anastomosis site, and
6) To propose an innovative approach evaluating EC-IC bypass with SVG on CFD model based on flow resistance analysis and pipe flow theory

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Chapter 2

Comparative patency between intracranial arterial pedicle and vein bypass surgery

Abstract

Background: Long-term patency of extracranial-to-intracranial (EC-IC) vein bypass is poorly understood.

Objective: We report our experience of patency of arterial pedicle grafts and interposition vein grafts for the purpose of EC-IC bypass.

Methods: We analysed 294 consecutive patients who underwent 178 intracranial arterial pedicle bypass procedures and 152 intracranial vein bypass procedures. Bypass patency was assessed by digital subtraction angiography, computed tomographic angiography, and/or Doppler ultrasound. The modified Rankin Scale (mRS) was assigned for clinical grading at the last follow-up consultation.

Results: The main indication for arterial pedicle bypass surgery was internal carotid artery occlusion (79 cases); for vein bypass surgery, it was giant aneurysms (61 cases). Procedure-related complications due to surgery occurred in 3 cases (1.7%; 95% CI: 0.4-5.1%) of arterial pedicle bypass surgery and 12 cases (7.9%; 95% CI: 4.5-13.4%) of vein bypass surgery. The patency rate at 6 weeks was 98% (95% CI: 95.0-99.7%) for arterial pedicle bypass and 93% (95% CI: 87.4-96%) for vein bypass, with almost all graft failures occurring within the first week following surgery. Beyond the first week, bypass patency was similar for both groups, with both arterial pedicle grafts and vein bypass grafts that were patent at 1 week having a long-term patency of 99%. There was no statistically significant difference in early, late, and overall patency between the 2 bypass groups.

Conclusions: The surgical complication rate was greater for vein bypass. Both arterial pedicle and vein bypass have good long-term patency.

Keywords: Arterial pedicle, cerebrovascular surgery, EC-IC bypass, graft patency, haemodynamic insufficiency, STA-MCA, vein bypass

Introduction

The role of extracranial-to-intracranial (EC-IC) bypass surgery has not been established by class 1 or 2 evidence for any broad category of adult intracranial vascular pathological states (The EC/IC Bypass Study Group 1985). However, supporting evidence for bypass surgery can be found in case series in the treatment of selected patients (Sundt 1990; Schmiedek *et al*. 1994; Grubb *et al.* 1998; Thanvi *et al.* 2007). Once it has been determined that intracranial bypass surgery is appropriate in an individual case, the choice of procedure is determined by the short-term requirements (e.g. blood flow deemed necessary, available conduits, anticipated period of vessel occlusion during the performance of the surgical anastomosis, anticipated response to the new border zone, technical complexity), the risk of surgery, and the long-term expectations of graft patency (Morgan *et al.* 2000). For aorto-coronary bypass, long-term patency of the internal mammary artery (as a pedicle to the coronary arteries) is superior to that of interposition saphenous vein bypass (Fitzgibbon *et al.* 1996; Goldman *et al.* 2004). However, the vascular haemodynamic environment in coronary artery surgery differs significantly from that of the low-resistance intracranial circulation. Therefore, extrapolation of the superiority of arterial conduit bypass over that of interposition saphenous vein graft, when considering the intracranial circulation, may be erroneous.

The Mayo Clinic series suggests that long-term patency of saphenous vein bypass intracranially exceeded vein graft bypass for aorto-coronary or peripheral vascular surgery grafts (Regli *et al.* 1995). Furthermore, recent innovations, such as excimer laser-assisted non-occlusive EC-IC bypasses, make it timely to review the long-term patency of interposition venous conduits for bypass into the intracranial circulation (Bremmer *et al*. 2009). In this article, we compare vein bypass with that of intracranial arterial pedicle graft to explore the long-term robustness of intracranial venous bypass. We analysed results of our patients who underwent cerebral revascularisation bypass between January 1990 and June 2010 to determine long-term graft patency of interposition saphenous vein bypass graft between the extracranial circulation and the intracranial circulation.

Methods

Between January 1990 and June 2010, we prospectively collected and analysed data on 294 consecutive patients (154 male and 140 female) undergoing cerebrovascular bypass. This study was approved by the Macquarie University Human Research Ethics Committee, and performed in accordance with institutional ethics committee guidelines. We recorded demographics, clinical indications, and radiological and treatment-related information.

Bypass Technique

The technique and early results have been reported in previous publications (Morgan *et al.* 1994; Morgan *et al.* 1996; Brennan *et al.* 1999; Morgan *et al.* 2002; Jeffree *et al.* 2009). In brief, all patients were given 150 mg aspirin on the morning of surgery. The superficial temporal artery (STA) was prepared and harvested with a standard operative procedure for STA-to-middle cerebral artery (MCA) bypass.

Vein bypass between the common carotid artery (CCA) and intracranial internal carotid artery (ICA) or MCA was carried out via an exposure of the CCA, ICA, and external carotid artery (ECA) via an anterior sternomastoid approach (this was contralateral to the targeted distal anastomosis in one case of CCA occlusion), followed by an orbitozygomatic craniotomy. The roof and lateral wall of the orbit were removed, and the dura was opened and reflected on the superior orbital fissure. The Sylvian fissure was widely split, the basal cisterns were opened, and the intracranial ICA (or MCA) exposed. Great care was taken when splitting the Sylvian fissure to avoid damaging the pia, because the patient had been given aspirin and heparin was to be used at the time of the proximal anastomosis. If retraction of the frontal or temporal lobe was necessary, the retraction was gently continued during the early part of the surgery when mannitol (1 g/kg) was producing its effective relaxation. A subcutaneous tunnel anterior to the ear was created with a large-bore tunneller. The vein, selected for its even calibre by preoperative venous duplex ultrasound, usually was harvested from the long saphenous vein below the knee. The vein was harvested and distended immediately before it was needed for distal anastomosis to ensure that ischaemia of the venous endothelium lasted for the minimum length of time. The vein was then positioned between the CCA and the intended distal anastomotic site via the large-bore subcutaneous tunnel. The vein was distended again within the tunneller to ensure it was not twisted. The calibre of the tunneller had to be large enough not to impede the rotation of the vein during this inflation and thus prevent any twisting of the vein in it subcutaneous site. The distal anastomosis was performed before the proximal anastomosis, because the distal anastomosis was more difficult. This ensured that the vein would be slack enough to allow it to be manoeuvred as required during the difficult suturing. The length of the vein was determined when performing the proximal anastomosis on the CCA. The vein for the distal anastomosis was prepared by a straight, sharp cut and removal of the loose adventitia for the end-to-end anastomosis if intended for the intracranial ICA or at 45 degrees with a long fish-mouth if an end-to-side anastomosis on the MCA was planned. For anastomosis to the intracranial ICA, a permanent aneurysm clip was placed immediately distal to the ophthalmic artery, and a temporary clip was placed on the ICA immediately proximal to the posterior communicating artery (PComA) to allow for some collateral flow during cross-clamping. When there was insufficient room for the temporary clip to permit the ICA to splay open to allow for anastomosis, the temporary clip was placed more distally on the ICA (proximal to the anterior choroidal artery) and also crossing the PCA. It often became necessary to move the site of ICA division more distally from the distal dural ring of the ICA, because the senior author (MKM) has found that the ICA wall appears to dissect more easily close to the distal dural ring. When this arterial wall separation occurs, it is more difficult to achieve accurate suture placement. Division of the ICA was performed with straight scissors. When the distal anastomosis was intended for the MCA, the MCA site was selected on a straight segment of artery of sufficient length to accommodate the long fish-mouthed vein. The senior author (MKM) has experienced greater difficulty ensuring a watertight closure when the anastomosis is on the outer convexity of a curve. The MCA arteriotomy was created with a super-knife (Alcon 15° blade, Alcon Inc., Hünenberg, Switzerland) and lengthened with microscissors. Heparin was not used at this point, because the distal anastomosis is thoroughly irrigated free of blood products. Heparin, 2500 units, was administered immediately prior to the reestablishment of flow across the distal anastomosis. The distal end was sutured with interrupted 8-0 sutures on the intracranial ICA and 9-0 sutures for the MCA. Although the senior author used continuous suturing in some cases, the time gained with the running stitch can be lost with correcting errors of tension that allow suture-line leakages following cross-clamp release.

After the distal anastomosis was completed, the proximal anastomosis was performed on the distal CCA with an arteriotomy to accommodate the 45-degree angle cut of the vein and the long fish-mouth. Suturing was performed with a running 7-0 stitch. Before flow was established in the vein bypass, the vein was de-aired with a 25-gauge needle hole at its highest point. Blood flow in the vein bypass and suture line security were checked with Doppler ultrasound and visually. In most cases, following establishment of bypass flow, the ICA was almost completely ligated at its origin. On occasional, ICA was surgically trapped and narrowed. The trapped ICA segment was not completely ligated in order to preserve a minimal flow to the ophthalmic artery to avoid sudden loss of retinal blood flow.

In the case of bypass to the upper posterior circulation, the intracranial exposure was by a subtemporal approach to the posterior cerebral artery (PCA) adhering to the principles already discussed. In most cases, the PCA is not long enough to perform a fish-mouth on the vein at this site. Retractors are necessary for PCA anastomosis. Vertebral artery anastomosis was performed with a far lateral medial transcondylar approach for an end-to-end distal anastomosis. No excimer laser-assisted non-occlusive anastomosis techniques were used in any cases in this series.

Post operatively, bypass patency was established by digital subtraction, computerised tomography angiogram, or Doppler/duplex ultrasound examination at 6 weeks, 1-year, and then at 2-yearly intervals thereafter. The clinical status of each of the 294 surgical patients was documented at 6 weeks following surgery. A good outcome was defined as a modified Rankin Scale (mRS) (van Swieten *et al* 1988) (Table 2.1) score of 0 or 1; adverse outcomes were considered relevant if they produced a change in mRS of more than 1 as a result of surgery. The clinical condition assigned at last follow-up was used to determine the mRS for those assessed as having sustained an adverse outcome at 6 weeks.

Patients were divided into 2 groups for analysis based on graft selection: (1) arterial pedicle bypass STA conduit; and (2) saphenous vein interposition bypass from an extracranial to an intracranial artery. Patients who had undergone bypass using radial artery as the graft and occipital-to-posterior inferior cerebellar artery anastomosis were excluded from this study, because these procedures were performed on only 6 occasions and do not fit well into either of the 2 categories. Indirect anastomoses also were excluded.

Table 2.1 The Modified Rankin Scale (van Swienten *et al*. 1988)

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disabilities: Unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disabilities: Requiring some help, but able to walk without assistance
4	Moderately severe disability Unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	Severe disability: Bedridden, incontinent, and requiring constant nursing care and attention

Statistics

Continuous variables are expressed as mean 6 standard deviation and categorical variables as percentages. Comparisons were made between arterial pedicle bypass and vein bypass with regard to overall patency and occlusion rates. Survival curves were created to evaluate patency rates over time using GraphPad Prism 5 for Mac OS X (GraphPad Software, Inc, LaJolla, California). Because the a priori assumption of proportional hazards could not be met, comparisons were made using the Wilcoxon test. A value of $P< 0.05$ was considered statistically significant. The modified Wald method (Newcombe 1998) was used to calculate the 95% confidence intervals for a surgical risk proportion for downgrading following surgery.

Results

In the 20 years covered by this study, a total of 294 patients with 330 cerebrovascular bypasses were analysed. The mean age was 49 ± 20 years (range, 5-87 years) for the arterial pedicle graft and 45 ± 16 years (range, 9-74 years) for vein graft. This difference was not significant. There were 166 males and 128 females. Thirty-six patients had bilateral procedures; of these, 2 patients underwent 3 procedures apiece. Patients were followed for an average of 23 ± 32 months (range, 0-196 months) in the case of arterial pedicle grafts and 38 ± 48 months (range, 0-186 months) in the case of vein grafts. There were 178 and 152 patient procedures in the arterial pedicle and vein bypass groups, respectively. The bypass type, surgical indications, clinical characteristics, and outcomes are summarized in Table 2.2.

Table 2.2 Characteristic of 330 Cerebrovascular bypasses by different clinical indication for surgery

	Bypass type	Arterial pedicle bypass for augmentation of cerebral blood flow in chronic haemodynamic ischaemia	Arterial pedicle bypass for planned vessel sacrifice for tumour and aneurysm	Vein bypass for augmentation of cerebral blood flow in chronic haemodynamic ischaemia	Vein bypass for planned vessel sacrifice for tumour and aneurysm or stroke risk reduction	Vein bypass for emergency revascularisation due to stroke in evolution or where possible stroke in evolution present*	Total
	CCA-intracranial ICA	NA	NA	2	78	6	86
	CCA-MCA	NA	NA	4	20	13	37
	CCA-PCA	NA	NA	10	1	3	14
	CCA- intracranial VA	NA	NA	8	6	1	15
Total vein bypass		NA	NA	24	105	23	152
	STA-MCA	163	14	NA	NA	NA	177
	STA-PCA	1	0	NA	NA	NA	1
Total arterial pedicle bypass		164	14	NA	NA	NA	178

	Chronic ICA occlusion with ongoing clinical haemodynamic insufficiency	79	NA	4	NA	NA	
	Moyamoya	58	NA	1	NA	NA	
	MCA occlusion or stenosis	26	NA	1	NA	NA	
	Aneurysm	NA	13	NA	61	9	
	Tumour	NA	1	NA	6	NA	
Indications for bypass	Vertebrobasilar occlusive disease	1	NA	18	3	NA	
	ICA dissecting aneurysm	NA	NA	NA	35	3	
	ICA occlusion with stroke in evolution resulting from attempted aneurysm repair	NA	NA	NA	NA	8	
	Arterial injury during aneurysm repair	NA	NA	NA	NA	3	
Total		164	14	24	105	23	330

	Bypass type	Arterial pedicle bypass for augmentation of cerebral blood flow in chronic haemodynamic ischaemia	Arterial pedicle bypass for planned vessel sacrifice for tumour and aneurysm	Vein bypass for augmentation of cerebral blood flow in chronic haemodynamic ischaemia	Vein bypass for planned vessel sacrifice for tumour and aneurysm or stroke risk reduction	Vein bypass for emergency revascularisation due to stroke in evolution or where possible stroke in evolution present*	Total
Adverse outcome due to progressive nature of disease and underlying condition	Ischaemia	7	1	1	0	3	12
	Haemorrhagic transformation	0	0	0	0	0	0
	Graft rupture	0	0	0	0	0	0
	Distal artery occlusion/embolus	0	0	0	0	0	0
	Weakness/ paresis	1	1	3	1	1	7
	Cavernous sinus syndrome	0	0	0	1	0	1
	Hydrocephalus	0	0	0	1	0	1
Adverse outcome resulting in a downgrade in mRS to 2-5 due to surgery	hemiparesis	1	0	0	2	1	4
	dysphasia	0	0	0	0	1	1
	Homonymous hemianopsia	0	0	0	2	0	2
	Cerebellar infarct	0	1	0	0	0	1

Mortality (%)	Graft thrombosis	0	0	0	3	2	5
	Anastomosis rupture	0	0	0	1	0	1
	Remote territory infarction	0	1	0	0	0	1
Total							7(2.1)

* Possible stroke in evolution is assessed to be the case during the course on an operation where a vessel needs to be sacrificed (e.g. during a repair of an aneurysm the vessel requires sacrifice) and it is suspected that the native collaterals would be insufficient to prevent infarction (e.g. a failed test balloon occlusion or poor radiological collaterals).

Selected abbreviations and Acronyms
CCA = common carotid artery
ICA = internal carotid artery
MCA = middle cerebral artery
PCA = posterior cerebral artery
VA = vertebral artery
STA = superficial temporal artery
mRS = modified Rankin Scale

The main indication for surgery in the 178 patients in the arterial pedicle bypass group was to augment cerebral blood flow by STA-MCA bypass for chronic haemodynamic ischaemia such as ICA occlusion (79 patients), Moyamoya disease (58 patients), and MCA occlusion or stenosis (26 patients). Other arterial pedicle bypasses were performed in conjunction with planned vessel sacrifice for aneurysm and tumour in 14 patients. In addition, 1 STA-PCA bypass was performed for chronic haemodynamic ischaemia due to vertebral artery occlusion. In the vein bypass group, 152 saphenous vein graft (SVG) conduits were created, as follows:

-86 (57%) CCA-to-intracranial ICA bypasses;

-37 (24%) CCA-to-MCA bypasses;

-15 (9.9%) CCA-to-intracranial vertebral artery bypasses;

-14 (9.2%) CCA-to-PCA bypasses.

Broadly defined, the indications for surgery were to allow planned vessel sacrifice (n = 105), augmentation of cerebral blood flow in the presence of chronic haemodynamic ischaemia (n = 24), and emergency revascularisation surgery for stroke in evolution (n = 23).

For the 105 surgeries that fell into the broad category of planned vessel sacrifice, the specific indications were as follows:

-to facilitate the exclusion of an aneurysm: 61 procedures;

-to facilitate the exclusion of a diseased artery identified as presenting a risk of stroke, e.g., arterial dissecting aneurysm: 38 procedures;

-to facilitate resection of tumour: 6 procedures.

Of the 38 vein bypasses performed for the purpose of excluding a diseased artery identified as presenting a risk of stroke, 35 were performed in cases of dissecting aneurysms, and 3 were performed in cases with bilateral vertebrobasilar occlusive disease and recurrent transient ischaemic attacks.

Vein bypass for augmentation of cerebral blood flow was performed in 24 patients with chronic haemodynamic ischaemia. Eighteen patients in this category were suffering from crescendo vertebrobasilar insufficiency symptoms despite maximal medical therapy. Four patients underwent vein bypass with symptomatic chronic ICA occlusion because they were unsuitable candidates for STA-MCA surgery due to previous loss of CCA or ECA. None of the 24 patients with chronic haemodynamic ischaemia developed stroke, either radiological or clinical, as a consequence of inadequate blood flow to the revascularised territory. All patients remained neurologically intact following surgery.

In addition to planned vessel sacrifice, emergency revascularisation surgery for stroke in evolution was performed in 23 patients. Among these, 20 procedures were performed as a consequence of technical problems encountered during aneurysm clipping. The other 3 cases presented with symptomatic ischaemic symptoms suggesting early infarction due to high-grade stenosis from ICA dissections and poor angiographic collaterals. Four of the 23 patients progressed to completed stroke despite an angiographically successful revascularisation procedure. None of the patients developed haemorrhagic transformation following the procedure. No patients from these cohorts were lost to follow-up.

Overall Patency

The graft patency rate at 6 weeks was 98% (95% CI; 95.0- 99.7%) for arterial pedicle bypass and 93% (95% CI; 87.4-96.0%) for vein bypass (Figure 2.1). Most graft failures occurred within the first week following surgery. Bypass patency was similar for the 2 groups beyond the first week. For arterial pedicle bypasses that were patent at 1 week, the 6-week and 6-month patency was 99%. Two arterial pedicle STA grafts were found to be occluded in a patient with Moyamoya disease 4 years after the surgery. For cases where a vein bypass was patent at 1 week, the 6-week and 6-month patency rate was 99% (Figure 2.1). There was no significant statistical difference between the 2 procedures in early, late, and overall patency (Table 2.3).

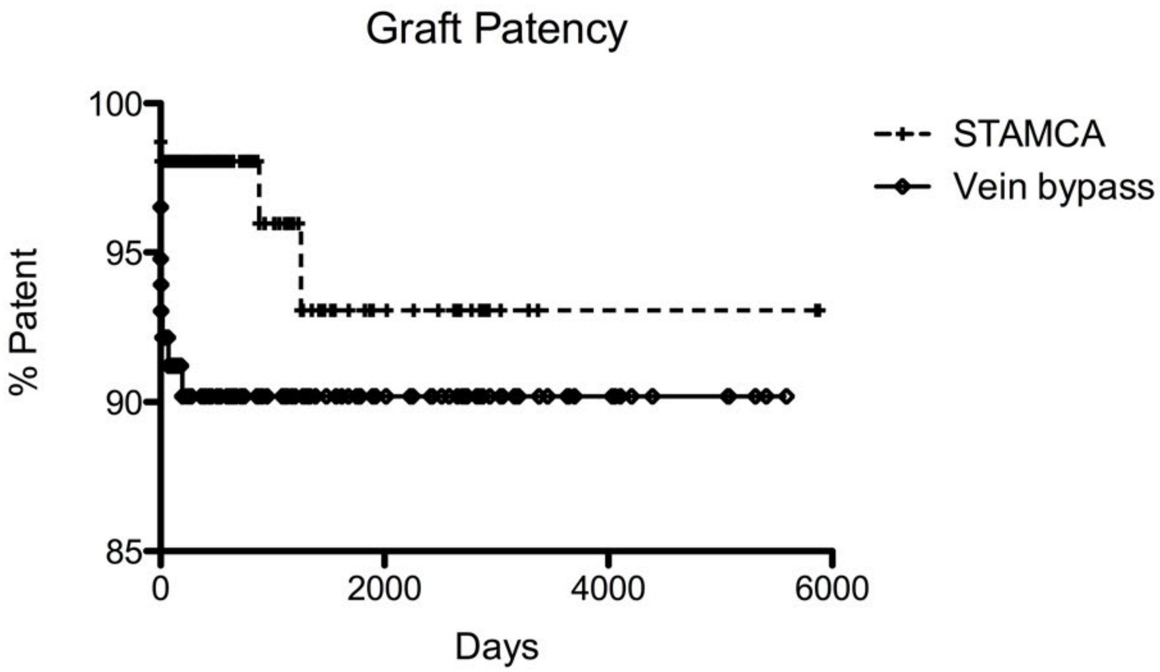

Figure 2.1 Arterial pedicle (178) and vein (152) anastomosis with an average 30 months (range 0-196 months) and long term patency rate.

Table 2.3 Overall graft patency

	Arterial pedicle graft (n=178)		Vein graft (n=152)		p*
	n (%)	95%CI	n (%)	95%CI	
Early graft a occlusion	3(2)	0-5%	9(6)	3-11%	0.07
Delayed graft b occlusion	2(1)	0-4%	2(1)	0-5%	>.99
Overall patency	173(97)	93-99%	141(93)	88-96%	0.06

a ≤ 6 weeks

b ≥ 6 weeks

*Fisher's exact test

Neurological outcome post-bypass surgery

Three patients (1.7%; 95% CI, 0.4-5.1%) suffered a downgrade in function (mRS >1) as a complication of arterial pedicle bypass surgery (Table 2.2). This included 1 patient who died. Twelve patients (7.9%; 95% CI, 4.5-13.4%) suffered a downgrade in function (mRS >1) as a complication of vein bypass surgery (Table 2.2). This included 6 patients who died. The mechanism for the perioperative death in the case of the arterial pedicle graft was pontine infarction in a patient undergoing STA-MCA bypass for ICA occlusion; this patient also had pre-existing basilar artery occlusion. The mechanism for the perioperative morbidity leading to a downgrade to a mRS of 2 in the case of the arterial pedicle graft was ischaemic infarction within the territory of intended graft protection.

The mechanisms for early postoperative deaths in the vein bypass group were occlusion of the bypass and hemispheric infarction in 5 patients and a delayed rupture of the ICA at the anastomosis site in 1 patient. The case of perioperative morbidity leading to a downgrade to a mRS of 3 was a patient treated for a giant MCA aneurysm who developed infarction in the distribution of the lenticulostriate artery territory from MCA thrombosis proximal to the aneurysm trapping. Five patients experienced a downgrade to a mRS of 2 due to surgery: 1 case each of an embolus to the MCA; vasospasm; infarction from embolus to the posterior cerebral artery (via a foetal posterior communicating artery); and border zone infarction related to the cross-clamp period of 38 minutes. No patient suffered an adverse outcome due to haemorrhagic conversion.

Discussion

The present study of 294 patients with 330 bypasses constitutes a series of patients with cerebrovascular bypass grafts. Although our primary interest in this report is long-term patency, we included our early postoperative periods for comparison. However, the variation in indications for surgery makes comparison of early postoperative outcomes problematic, in that it rarely arises that a patient is considered equally suitable for either procedure. Our preference always is to perform arterial pedicle graft, if deemed appropriate. When we have used an interposition venous conduit, it usually is because no arterial pedicle was suitable (e.g., previously occluded CCA and ECA, or insufficient length of the STA for bypass to the PCA). The present results are in significant contrast to the widespread belief that saphenous vein grafts have a poor long-term patency (Fitzgibbon *et al.* 1996; Goldman *et al.* 2004). For patients in the arterial pedicle bypass group, the patency is 99%. Furthermore, if the arterial pedicle graft was patent at 1 week after surgery, the graft was patent in 99% of cases at 6 weeks and 6 months after surgery. For the vein bypass group, the patency was 93%. However, if the vein bypass was patent at 1 week, the graft was patent in 99% of cases at 6 weeks and 6 months after surgery. The venous bypass with longest follow-up remains patent at more than 16 years. With respect to long-term patency, our series results are favourable compared with those of other series using both the traditional approach to vein bypass surgery and the new innovative non-occlusive bypass surgeries. Sekhar and colleagues (Sekhar *et al.* 1999) reported early and late graft patency of 95% and 94%, respectively, with traditionally performed vein bypass surgery. The new innovative procedures of excimer laser assisted non-occlusive extracranial-to-intracranial bypasses have been reported to have a 92% early patency rate and 77% patency rate at 1 month (Bremmer *et al*. 2009). However, these differences may be related to patient selection rather than differences in technique. Variation in long-term outcomes between our results and other institutional experiences may reflect differences in case selection. Case selection influences the pressure gradients across the anastomosis sites, and these pressure gradients determine the velocity of flow. A sufficient velocity of flow within the venous conduit is required to prevent thrombosis.

The relatively low procedure-related complication rate for arterial pedicle bypass surgery reinforces this graft's suitability for patients with evidence of chronic cerebral haemodynamic insufficiency in cases where blood flow can be incrementally augmented over time with the arterial pedicle graft enlargement. Our results are in keeping with the international EC/IC Bypass Study Group (The EC/IC Bypass study Group 1985).

The relatively high procedure-related complication rate of 8% in vein bypass cases (half of whom died) suggests this bypass should be reserved for those patients with ominous natural pathological history, failed medical therapy, no viable endovascular option, and no other alternative strategies that deliver a high blood flow. We believe that the low haemorrhagic transformation rate that we report for vein bypass surgery is due to the avoidance of retraction during the cross-clamp period as well as careful attention to blood pressure management as soon as flow is established through the bypass.

Changes in approach over the years of this analysis in our unit have been the greater use of endovascular means for managing stenotic disease and a greater reluctance to attempt bypass in the presence of stroke in evolution. Endovascular techniques have become the first-line treatment option for stenotic (either atheromatous or dissection related) of the ICA and the vertebrobasilar system. However, for stenotic disease of the MCA or occluded symptomatic arteries, I will continue to consider bypass surgery a reasonable option. The patient with acute stroke seldom is considered for bypass surgery with large-calibre bypass because of the almost certain need for the use of a retractor on the already ischaemic brain.

Conclusion

We report arterial pedicle grafts and vein bypass with large conduit patency for an average 30 months after surgery showing favourable results in long-term patency in both intracranial arterial pedicle grafts and intracranial vein bypass. The long-term patency for saphenous vein grafts is much better than previously reported.

Disclosure

Chapter was co-author with Andrew S Davidson, Nazih N Assaad, Marcus A Stoodley and Michael K Morgan

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Chapter 3

Measuring competence development for performing high flow extracranial-to-intracranial bypass

Abstract

Objective: A challenge for surgeons performing extracranial-to-intracranial bypass procedures is the development and maintenance of competency because of the infrequency with which such surgery is necessary. We report our experience with competence development in the performance of high flow extracranial-to-intracranial bypass surgery by measuring those problems specifically related to the functioning of the bypass graft whether or not they led to adverse clinical outcomes.

Method: We reviewed the National Hospital Morbidity Database for the years 1999 (June) to 2011 (July) for both low flow and high flow extracranial-to-intracranial bypass to identify the frequency with which such surgery is performed. We also interrogated a prospectively collected database retrospectively to evaluate indicators of technical problems of high flow extracranial-to-intracranial bypass (graft occlusion, stenosis, disruption, or distal ischaemia), surgical complications of the bypass leading to a modified Rankin Score >2 and intraoperative cross-clamp time. Cross-clamp time was considered the total time that circulation may have been impaired including both the distal and proximal cross-clamp periods. Other complications regarded as unrelated to the technical performance of the bypass were not included. The cumulative risk was calculated for each case.

Results: The extracranial-to-intracranial bypass rate averaged 39 cases per year for an estimated annual rate of 1.9 cases per 1,000,000 head of population. With regards the series database, the technical complication rate (graft occlusion, stenosis, disruption, distal ischaemia or surgical complications of the bypass leading to a modified Rankin Score >2) was 14.7% (95%CI 10.1-20.9%). Graft specific complications leading to a modified Rankin Score >2 was 5.9% (95%CI 3.1-10.6). Cross-clamp data was unknown for the first 32 cases. For cases with cross-clamp time recorded (83 cases) intraoperative cross-clamp time (± standard deviation) was 44 $\pm$ 14 min. There was no significant improvement in cross-clamp time over the period recorded. The surgical performance related complications appeared to have peaked at around case 120 (approximately 5,000 days after the first high flow extracranial-to-intracranial bypass).

Conclusion: High flow extracranial-to-intracranial bypasses are rarely performed procedures that challenge the development of surgical competence.

***Keywords**:* Competency; complication; high flow; EC-IC bypass; surgery; vein

Introduction

High flow extracranial-to-intracranial (HF EC-IC) bypass is occasionally necessary in the management of aneurysms and skull base tumours (Sundt *et al.* 1987). These complex and rarely performed surgeries pose many challenges including selection of procedure and technical performance. Selection of cases has been well described but limited to evidence from case series due to the infrequency of the surgery. We have previously reported our selection criteria and outcomes (Morgan *et al.* 1994; Morgan *et al.* 1996; Morgan *et al.* 2000; Morgan *et al.* 2002; Sia *et al.* 2011). However, an analysis of the development and maintenance of competent performance has not been previously reported. We report our experience with competence development in the performance of surgery for HF EC-IC bypass.

Materials and methods

A retrospective study examined a prospectively collected database of a single surgeon (MKM) of cerebral HF EC-IC bypass operated between Sept 1990 and Jan 2012. This study was approved by the Macquarie University Human Research Ethics Committee, and performed in accordance with institutional ethics committee guideline. The database recorded demographic, clinical, anatomical, cross-clamp time and outcome data. For the purpose of analysis, surrogate measures of failure of competent performance for HF EC-IC bypasses included those specifically related to technical complications (graft occlusion within 7 days, graft stenosis within 7 days, graft disruption, distal ischaemia detected on postoperative CT scan of the brain within 1 week of surgery) and surgical complications of the bypass leading to a modified Rankin Score >2. These complications are referred to Graft Complications. Adverse outcomes unrelated to the surgery of HF EC-IC bypass were not considered to be Graft Complications. Cross-clamp time was analysed for trend.

For the purpose of placing the surgery in context, hospitalisation for EC-IC bypass were identified from the National Hospital Morbidity Database (NHMD) for the year 1993 to 2011. However, only the years between 1999 and 2010 have complete data. There was insufficient information to select the subset of HF EC-IC bypass cases. The NHMD is a collective of records for hospital admitted patients from public and private hospitals in Australia, and is governed by the Australian Institute of Health and Welfare (AIHW) ((AIHW) 2010). This database has been detailed in a previous publication (Lai *et al.* 2012). The procedure for EC-IC bypasses was defined by the procedure codes for either low flow EC-IC bypass (39818) (e.g. STAMCA) or HF EC-IC bypass (39821).

Operative technique of high flow bypass

Pre-operative preparation

The long saphenous vein is usually selected for the graft conduit because of ease of harvest, greater assurance of tributary (branch) security at time of harvest and its resilience against vasospasm. If the long saphenous vein is unsuitable (due to size mismatch, thickened walls, thrombosis, uneven calibre along a 23 cm length or numerous tributaries) radial artery is selected. The course of the long saphenous vein is marked preoperatively with venous duplex ultrasound and selected for both even calibre and a length of 23 cm with a minimal number of tributaries. If radial artery is to be used, the anaesthetist needs to be aware to avoid placing a radial arterial line in the selected conduit. The potential ischaemic threat to the hand is assessed with an Allen's test and CTA examining the ulnar artery and the collateral cascade in the hand. Aspirin (150 mg) is commenced preoperatively and continued in the postoperative period.

Operative technique

Cervical and cranial preparation

The most common site for proximal anastomosis in our experience is the common carotid artery (CCA) due to the convenience and limited cross-clamp time. The initial stage of surgery is the CCA exposure via the standard anterior sternocleidomastoid approach that is performed for carotid endarterectomy. For distal anastomosis to the internal carotid artery (ICA) or middle cerebral artery (MCA), the CCA exposure is followed by an orbitozygomatic craniotomy. The roof and lateral wall of the orbit are removed and the dura is opened and reflected on the superior orbital fissure. The Sylvian fissure is widely split, the basal cisterns opened and the intracranial ICA or MCA exposed. Care is taken during the Sylvian fissure split to minimise the damage caused to the pia as the patient has suboptimal platelet activity and it is anticipated that heparin will be used during the surgery. For bypass to the posterior cerebral artery (PCA) either a subtemporal craniotomy or a large Sylvian fissure dissection is employed to expose the P2 segment. For subtemporal exposure it is imperative that the middle fossa floor is drilled flat. Effective brain relaxation is critical and it is our practice to use Mannitol (1 gm/kg) at the commencement of the intracranial surgery. A subcutaneous tunnel anterior to the ear is created with a large bore tunneller.

Preparing the conduit

The vein or artery is harvested after the exposure of the planned distal anastomosis. These conduits are harvested as close to the anastomosis time to minimise endothelial ischaemia of the conduit that may predispose to thrombus formation. Careful attention to the technical aspects of vein harvesting and preparation are crucial to the long-term success of saphenous vein bypass grafts (Sundt *et al.* 1987). Appropriate distension using a Shiley catheter with heparinised solution is applied to the conduit after harvesting to look for constricting bands and leaks from overlooked tributaries. The vein is worked between the index finger and thumb until the spasm in the vein has been overcome. At this time unligated branches will be secured and reinforced. A calcium blocker (e.g. verapamil 5mg in 3 cc of Ringer's solution) is useful to add to the infusate in the case of radial artery conduits. The distended conduit must measure at least 5 mm in diameter. The conduit is then positioned between the CCA and the intended distal anastomotic site through the large bore subcutaneous tunnel. The conduit is again distended within the tunneller to ensure that it is untwisted. The tunneller needs to be of sufficient calibre so as not to impede rotation of the conduit during this inflation. Care must be taken to grasp only the adventitia when possible, during the harvesting and anastomosis. The vein should be handled with care to prevent mechanical trauma and vasospasm. Venous spasm can cause protrusion of endothelial cells into the lumen and the formation of subendothelial extension of medial smooth muscle cells, which lifts the overlying endothelial cells and exposed the thrombogenic subendothelium (Sundt *et al.* 1987).

Distal anastomosis

The distal anastomosis is performed before the proximal anastomosis, as the distal anastomosis is the more difficult. This ensures enough slackness of the conduit to facilitate its manoeuvrability. The length of the conduit is determined when performing the proximal anastomosis to the CCA. The distal conduit requires meticulous removal of the loose adventitia tissue to ensure good visualisation of suture placement. For end-to-end anastomoses (ICA) or end-to-side on smaller calibre arteries (e.g. PCA), the end is prepared with a straight sharp cut and for other end-to-side anastomoses (MCA) the cut is at 45 degrees with a long fish-mouth. For anastomosis to the intracranial ICA, a permanent aneurysm clip is placed immediately distal to the ophthalmic artery and a temporary clip is placed on the ICA immediately proximal to the posterior communication artery (to allow for some collateral flow during cross-clamping). When there is insufficient room for the temporary clip to allow for the ICA to splay open to allow for anastomosis, the temporary clip is placed more distally on the ICA (but must be applied proximal to anterior choroidal artery) and the posterior communication artery is also cross-clamped. During the cross-clamp time appropriate anaesthetic brain protection is required (both anaesthesia – including EEG inactivity, hypertension and cooling - and minimal or no brain retraction). A systolic blood pressure of 160mmHg is maintained by the anaesthetists. Thiopentone (aiming for temporary burst suppression) is administered prior to cross-clamp application. For anastomosis to the ICA the division is performed with straight scissors. For distal anastomoses to the MCA, a site is selected on a straight segment of artery of sufficient length to accommodate the long fish-mouthed vein. For end-to-side arteriotomies, the opening can be initiated with a super knife (Alcon 15° blade, Alcon Inc., Hünenberg, Switzerland) and lengthened with micro-scissors. Systemic heparin is not used at this point (although used with the irrigation) as the distal anastomosis is thoroughly irrigated free of blood products. A heparin 2,500 unit is administered immediately prior to the re-establishment of flow across the distal anastomosis (at the time when the circulating blood first comes into contact with the suture line). The distal end is sutured with interrupted 8-0 sutures on the intracranial ICA and 9-0 sutures for MCA or PCA. Although continuous suturing has been used, the senior author preferred interrupted method as the time gained with the running stitch can be lost with correcting errors of tension and suture line leakage that can occur following cross-clamp release if a running suture is used. Following the distal anastomosis, the temporary clips can be released on the recipient artery of an end-to-side anastomosis. A temporary clip is placed upon the conduit to protect against air entering when the proximal flow is initially established.

Proximal anastomosis

The proximal anastomosis is performed on the distal CCA (as an example) with an arteriotomy to accommodate the 45 degree angle cut of the vein and the long fish mouth. Suturing is performed with a running 7-0 stitch. Prior to establishing flow in the vein bypass, the vein is de-aired with a 25G needle hole at its highest point after which the temporary clip on the graft, establishing flow, can be removed. Blood flow in the vein bypass and suture line security can be checked with Doppler and Indocyanide Green.

Statistics analysis

Continuous variables are expressed as mean $\pm$ standard deviation or 95% confidence interval. The 95% confidence intervals were calculated by the modified Wald method for a proportion. Analyses were carried out in Prism 5 for Mac OS X (GraphPad Software, Inc). Linear regression was use to check correlation between cases and the cross-clamp time as well as cases and days since first surgery.

Results

During the 11-year period, June 1999 to July 2010, 434 hospital discharges for low flow and high flow EC-IC bypasses in Australia were recorded. The distribution of cases per 1,000,000 head of population is demonstrated in Figure 3.1. This produces an average of 1.9 cases per 1,000,000 Australians per year.

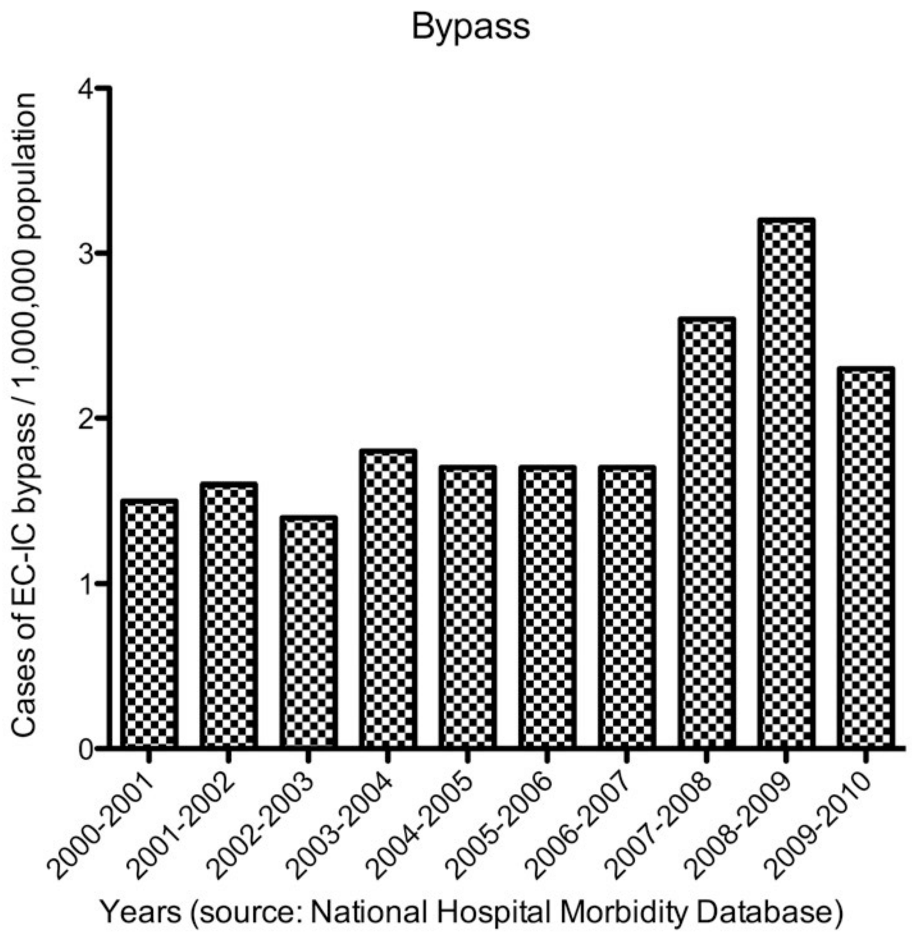

Figure 3.1: The National Hospital Morbidity Database of Australian cases of EC-IC bypass (both low flow and high flow) between July 2000 and June 2010 adjusted for population.

In the clinical study, 170 HF EC-IC bypasses were performed by the senior author (MKM) during a 22-year period between June 1990 and January 2012. The indications for surgery and early results have been reported in previous publications (Morgan *et al.* 1994; Morgan *et al.* 1996; Morgan *et al.* 2002; Sia *et al.* 2011). Cases of Graft Complications are recorded in Table 3.1. Outcomes with the cumulative sum of these complications are illustrated in Figure 3.2. The rate of Graft Complications varied throughout the series from a maximum of 18.5% (95% CI 12.5-26.5%) at case 119 to 14.7% (95% CI 10.1-20.9%) at case 170. These Graft Complications were associated with a mRS>2 in 5.9% (10 of 170) cases. Graft Complications were due to: problems with the conduit in 20 cases (17 occlusion, 1 stenosis, 1 rupture of distal anastomosis, 1 leak from branch of conduit); distal ischaemia in 4 cases; and retrograde thrombosis of a lenticulostriate artery in 1 case (Table 3.1).

Of these 170 patients, 83 cross-clamp times for both the proximal and distal anastomosis were available for analysis. No cross-clamp time was recorded in the first 35 cases. Cross-clamp times were known for 61% (of 135) of cases beyond case 35. The mean cross-clamp time was 44 ± 14 min. Analysing the change in cross-clamp time with case number (Figure 3.2B) by linear regression found no significant improvement ($P=0.55$) with further experience beyond case 35 ($R^2 = 0.0043$).

The distribution of all cases over time is illustrated in Figure 3.2C. The incidence of cases in this series was evenly distributed with an average 8 cases per year. The linear regression of this relationship was highly significant ($P<0.0001$) with a tight correlation (R^2 of 0.9951).

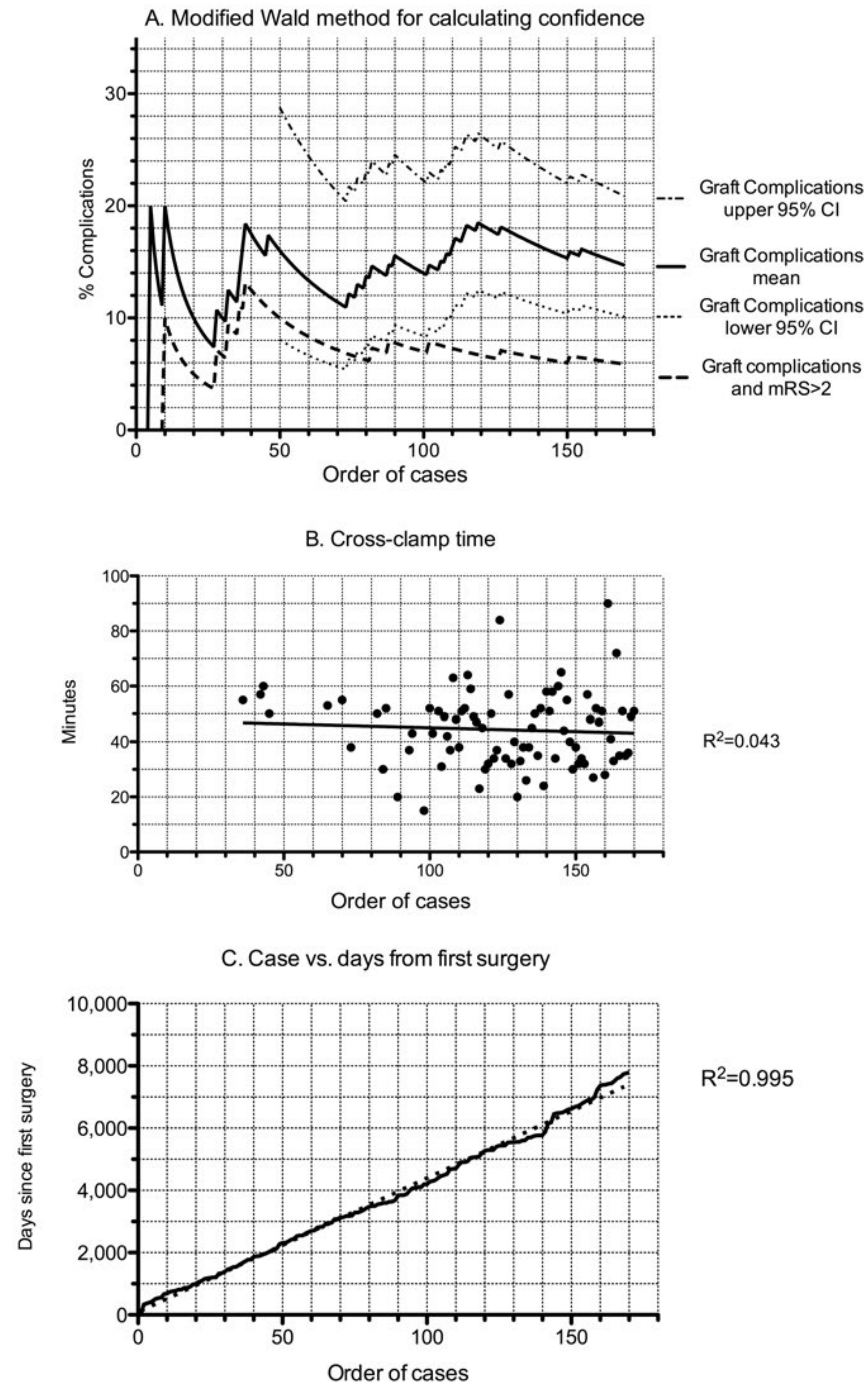

Figure 3.2: Case experience of High Flow EC-IC bypass in cumulative case order of A: Graft Complications (with 95% confidence interval) and Graft Complications leading to mRS>2. B: Cross-clamp time with linear regression. C: Relationship between case order and time since first case performed (with linear regression).

Table 3.1: Adverse outcomes from bypass surgery and technical complications of bypass

Case	Pathology	Presentation	Bypass (cross-clamp time)	Adverse outcome of bypass leading to mRS>2	Graft Complications	Clinical outcome
33F	Ruptured giant ICA cavernous aneurysm	Subarachnoid haemorrhage	CCA-ICA vein bypass	Distal border zone infarction	Stenosis distal anastomosis	mRS2
58M	Giant MCA aneurysm	Intraoperative unscheduled occlusion of MCA	CCA-MCA vein bypass	MCA infarction	Thrombosed graft	Dead
54M	ICA dissection with inadequate collaterals	Horner's syndrome	CCA-ICA vein bypass	MCA infarction	Thrombosed graft	Dead
38F	ICA dissecting aneurysm progressing	Headache	CCA-ICA vein bypass	MCA infarction	Thrombosed graft	Dead
38M	ICA dissection with inadequate collaterals	Border zone infarction	CCA-ICA vein bypass	MCA infarction	Thrombosed graft	Dead
39F	Bilateral ICA dissection	TIA	CCA-ICA vein bypass (55min)	Nil	Thrombosed graft	Normal
21M	Post irradiation Moyamoya syndrome with no scalp artery	Global cognitive decline	CCA-MCA radial bypass	Extradural haemorrhage	Delayed leak from radial artery branch	mRS5
46F	ICA stenosis and M1 occlusion	TIAs	CCA-MCA radial bypass (50min)	Nil	Thrombosed graft	Normal
41F	Bilateral giant ICA cavernous aneurysms	Left abducens palsy	CCA-MCA vein bypass (38min)	Nil	Thrombosed graft	mRS1
61M	Bilateral ICA dissection	TIAs	CCA-ICA vein bypass	Nil	Cross-clamp period	mRS2

Case	Pathology	Presentation	Bypass (cross-clamp time)	Adverse outcome of bypass leading to mRS>2	Graft Complications	Clinical outcome
74M	VA and BASA stenosis previously stented	VBIs from VA stent	CCA-VA vein	Nil	Thrombosed graft	mRS2
42F	Bilateral giant ICA cavernous aneurysms	Abducens palsy	CCA-ICA vein bypass	MCA infarction	Thrombosed graft	Dead
44F	Giant ICA cavernous aneurysm	Pain and abducens palsy	CCA-ICA vein bypass	Subarachnoid haemorrhage	Delayed rupture distal anastomosis	Dead
60M	MCA occlusion	Orthostatically precipitated TIAs	CCA-MCA vein bypass (20 min)	Distal border zone infarction	Cross-clamp period	mRS2
66M	Occlusion Bilateral VA	VBIs	CCA-PCA vein bypass (43min)	MCA infarction	Cross-clamp period	mRS3
61F	Chondrosarcoma C3 requiring VA sacrifice	Nil	CCA-VA vein (49min)	Nil	Thrombosed graft	Normal
54F	Giant ICA subarachnoid aneurysm failed GDC and neck tore at surgery	Emergency revascularisation	CCA-MCA vein bypass (37min)	Distal border zone infarction	Thrombosed graft	mRS2
56F	Giant ICA cavernous aneurysm progress growth	Cavernous sinus syndrome	CCA-ICA vein bypass (48min)	MCA infarction	Thrombosed graft	mRS1
55F	Large ICA aneurysm	Blind eye	CCA-MCA vein bypass (38min)	Nil	Thrombosed graft	mRS2
57M	Giant ICA cavernous aneurysm with inadequate collaterals	Blind eye	CCA-ICA vein bypass (64min)	PCA infarction (foetal)	Cross-clamp period	mRS2
44F	ICA dissection with inadequate collaterals	Mild dysphasia and hemiparesis	CCA-ICA vein bypass (59min)	Distal border zone infarction	Thrombosed graft	mRS2

39F	Large ICA subarachnoid aneurysm	Headache	CCA-ICA vein bypass (45min)	Nil	Thrombosed graft	Normal
62F	Giant MCA aneurysm	Small stroke right MCA	CCA-MCA vein bypass (34min)	Retrograde thrombosis in M1 with lenticulostriate occlusion	Nil	mRS3
54M	Giant ICA terminal aneurysm	Intraoperative unscheduled occlusion of terminal ICA and branches	CCA-MCA vein bypass (38min)	MCA infarction	Thrombosed graft	Dead
22F	Giant ICA cavernous aneurysm	Right 6th nerve palsy, embolus thrombolysed after aphasic hemiplegia	CCA-ICA vein bypass (57min)	Nil	Thrombosed graft	Normal

CCA: common carotid artery, ICA: internal carotid artery, MCA: middle cerebral artery, M1: proximal horizontal segment of middle cerebral artery, mRS: modified Rankin Scale, PCA: posterior cerebral artery, TIA: transient ischaemic attack, VA: vertebral artery, VBI: vertebrobasilar insufficiency.

Discussion

There have been descriptions of the improvement in performance for laparoscopic and robotic assisted surgery with time and experience (Miskovic *et al.* 2011; Ou *et al.* 2011; Ou *et al.* 2011; Ramart *et al.* 2011). This series is the first detailed report of a case study of a single surgeon's performance development for HF EC-IC bypass surgery. Most learning of surgical skills occurs in the operating room on patients. However, there are some rare surgical procedures in which learning in the operating room is not possible. This is particularly so where the most challenging part of the performance may be time critical, may have profound adverse consequences if performed inexpertly, is so infrequently performed that reinforcement of learnt skills is not possible, and is paradigm specific. One such example is HF EC-IC bypass surgery. While the technical skill to perform this surgery is required of a cerebrovascular surgeon, the number of procedures performed each year is small. In Australia, there are only 1.9 cases of both low flow and high flow EC-IC bypass per 1,000,000 annually. It is unknown as to the total number of HF EC-IC cases performed in Australia annually. However, it is known that the vast majority of EC-IC bypasses in Australia are superficial temporal to middle cerebral artery bypasses.

Cerebral revascularisation with HF EC-IC bypass constitutes an important treatment modality in the management of a broad array of complex aneurysms, skull base tumours and stroke prevention. Graft selection and bypass strategy is a critical. In properly selected patients, HF EC-IC bypass grafting is a viable and effective option for the treatment of selected patients. However, these reconstructive procedures pose substantial risks. Therefore, the time to reach a competent performance in this rarely executed surgery is of critical importance. This study represents a single surgeons experience and it is unknown whether this is representative of other neurosurgeons experience due to lack of similar reports. From the visual analysis of Graft Complications (Figure 3.2A), it would appear that a consistent level of performance was seen to occur at case 120 and beyond. However, the cross-clamp times did not significantly differ in the cases where this was measured. Of importance is that not all Graft Complications resulted in a major adverse clinical outcome (5.9% of 170 cases) and the distribution of the peak in the cumulative outcome curve differed from that of all Graft Complications (Figure 3.2A). The peak rate on mRS>2 due to Graft Complications was at case 36 with 11% at this time. For this case series the development of improving competence is evident beyond 120 cases, representing more than 14 years of experience.

In a US population based cohort study between 1992 and 2001, 558 low flow EC-IC bypass operations were performed at 158 hospitals by 115 identified surgeons (Amin-Hanjani *et al.* 2005). For 29% of patients, their bypass procedure was the only one recorded at their particular hospital during that year. And in 42% of patients, their particular surgeons performed no other bypass procedure during that year. In a multivariate analysis in which adjustment was made for age, sex, race, diagnosis, admission type, geographical region, medical co-morbidity, and year of surgery, high volume hospitals demonstrated less frequently, had an adverse discharge disposition (OR 0.54, $p = 0.03$) (Amin-Hanjani *et al.* 2005). This US study has demonstrated that surgical expertise in EC-IC has been linked with both institutional and surgeon volumes.

Although the need for HF EC-IC bypass is rare, this surgical technique is necessary to be performed by at least some cerebrovascular neurosurgeons. How this can be achieved will remain challenging. There is a need for specific demonstrable competence amongst neurosurgeons performing vascular anastomosis and a requirement for continuing demonstration that competence is maintained in cerebrovascular-neurosurgical workforce in Australia.

Because of the small number of cases, it will inevitably have a significant impact upon both the maintenance of competence in those already performing HF EC-IC bypass surgery on a regular basis as well as an impact on new generations of neurosurgeons who may wish to pursue cerebrovascular surgery as a subspecialty. Consideration needs to be given to prolonged mentorship when learning this technique.

This analysis is limited in several significant areas. It represents a single surgeon's experience, and is a retrospective analysis of data that was maintained and collected in a prospective fashion with the inherent risk of bias. With regards the analysis of national hospital databases, there are potential limitations in sampling, errors in coding, and lack of specific information about the indication of HF EC-IC bypasses.

Conclusion

HF EC-IC bypass is technically demanding. Improvement of surgical performance over a considerable time is evident in this series. To facilitate improved performance for these techniques requires strategies of learning that need to consider the rarity of these cases as well as ensuring reduction in complications and optimising patient outcome.

Disclosure

Chapter was co-author with Leon Lai and Michael Kerin Morgan (senior author)

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Chapter 4

Computational haemodynamic fluid analysis in high flow extracranial to intracranial bypass surgery

Abstract

Extracranial-to-intracranial circulation high flow brain bypass using interposition saphenous vein is well described for a number of diverse conditions to provide cerebral perfusion where the natural circulation is dramatically threatened such as sacrifice of an artery for treatment of giant cerebral aneurysms. One of the challenges with this procedure is maintaining a patent graft. It has been shown that early graft failure may be precipitated by various factors including low flow rates through the graft, low wall shear stress in the areas of disturbed flow and inadequate pressure gradient between the proximal and distal anastomosis. Recent data generated from computational fluid dynamics models suggest that in a newly established vein bypass, local wall shear stress could be altered and this is associated with endothelial dysfunction, platelet activation and subsequent graft thrombosis.

A non-invasive three-dimensional computational fluid dynamics technique was employed in this study to examine, quantify and characterize the local haemodynamic parameters and, in particular, the wall shear stress and pressure gradient across high flow extra cranial to intracranial bypass grafts. This was done with the help of numerical simulations, patient-specific geometries and physiologically realistic flow rates.

In this chapter, the principles of image processing, image segmentation algorithms, surface model with three-dimensional grid generations, volume and numerical methods for Navier-Stokes equations involved in the creation of bypass models are described.

***Keywords**:* Computational haemodynamic, high flow, venous conduit, brain bypass, extracranial to intracranial bypass

Introduction

Computational fluid dynamics (CFD) technology is being increasingly used as a tool for studying patient-specific haemodynamic characteristics. It has been well described in diverse conditions, including studies of the Circle of Willis (Alnaes *et al.* 2007), predicting risk of cerebral aneurysmal rupture (Cebral *et al.* 2011; Cebral *et al.* 2011; Xiang *et al.* 2011), endovascular in-stent thrombosis mechanism (Jou *et al.* 2011), arteriovenous fistula haemodynamic alteration in dialysis patients (Longest *et al.* 2000; Caroll *et al.* 2011) and drag forces in stent-graft migration of patient-specific abdominal aortic aneurysm (Molony *et al.* 2010). Studies using those models have the potential to replicate the exact anatomy of patient-specific haemodynamic factors related to clinical events. Numerical models have proven to be a more efficient way to predict blood flow behaviour inside complex domains (Steinman *et al.* 2003). Haemodynamic changes such as arterial wall shear stress (WSS) and blood flow velocities, following high flow cerebral bypass surgery, are not well understood. The haemodynamics at the anastomotic sites are influenced by the local flow patterns that have been altered in the creation of the bypass, such as flow separation and reattachment, vortices, and stagnation points. Little is known about the haemodynamic alteration after bypass surgery and its effects on graft patency. Only a few studies have directly examined the relationship between the post procedural haemodynamic features in the vicinity of the brain bypass (Sia *et al.* 2010; Eicker *et al.* 2011).

In the treatment of complex intracranial arterial diseases, various interposition conduit bypass operative strategies to replace the intracranial artery and maintain brain blood flow have been described (Morgan *et al.* 1994; Morgan *et al.* 2000; Nussbaum *et al.* 2000; Eguchi 2002; Morgan *et al.* 2002). The preferred conduits for the graft are saphenous vein graft (SVG) or radial artery. These bypasses can supply a large volume of cerebral blood flow. The development of clinical imaging such as magnetic resonance and computed tomography now provide a detailed patient-specific description of the actual haemodynamic of living tissue. However, analysis of the bypass vascular structure in patients and experimental animal models has proven to be difficult. The combination of mathematical modelling of blood flow and biomechanical interactions within the vasculature can be very complex and challenging. Simulation models from patient-specific imaging data with CFD using realistic boundary conditions may provide detailed information and contribute to the understanding of the underlying pathophysiology. Flow charts of the computational modelling procedure and sequencing are summarized in Figure 4.1.

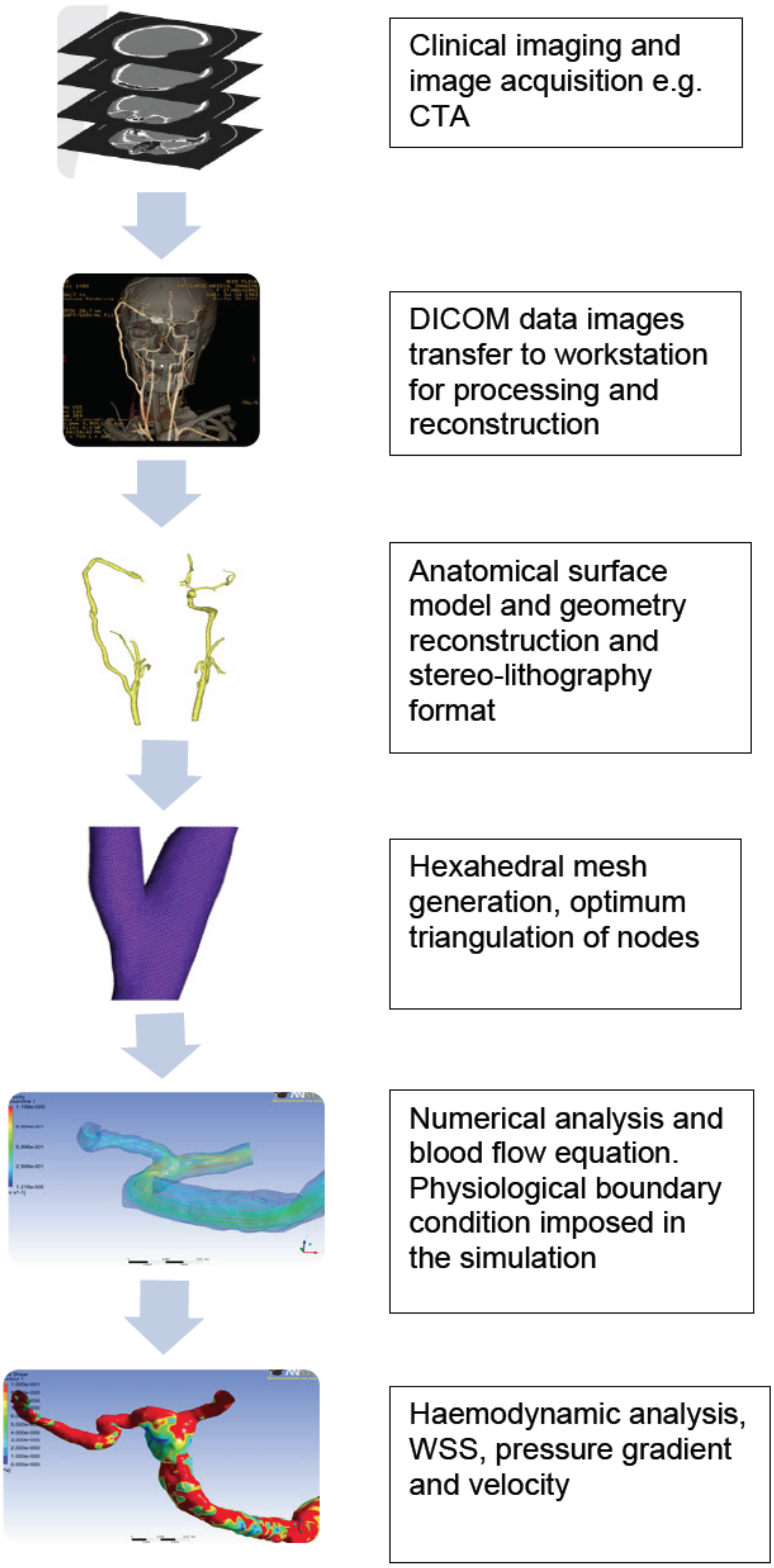

Figure 4.1 An overview of the Computational fluid dynamic (CFD) analysis algorithm-based on a patient case

Clinical Imaging and image acquisition

To construct a patient-specific high flow extrcranial to intracranial (HF EC-IC) bypass model, it is necessary to create a realistic anatomical model. Computed tomography angiography (CTA) is the preferred modality for defining accurate geometry and was used to obtain patient- specific images of the cerebrovascular bypass. The CTA was done according to standard protocols, using a helical CT scanner (General Electric Medical Systems, Discovery™ CT750HD) with multidetector-row capability. A section thickness of 0.625mm and a table speed of 9mm/s. Zero-degree table and gantry tilt were used. Sections in digital imaging and communication in medicine (DICOM) format were acquired with a 512 x 512 matrix. Scanning was started from the arch of the aorta and continued parallel to the orbito-meatal line to the level of Circle of Willis (CoW) during the intravenous injection of contrast material at the rate of 5.0 ml/s. The contrast data images were transferred to Advantage 4.5 workstation (General Electric Medical Systems) for post processing. Reconstructed images including surface display models were obtained. We did not perform additional injections for the purpose of this data acquisition.

Anatomical model and reconstruction

The main steps in obtaining an anatomical model of a HF EC-IC bypass model included, segmentation of region of interest (i.e. bypass construct including the proximal and distal anastomosis), the construct of a surface triangulation and the generation of a 3D grid of tetrahedral. The luminal surface of the vascular anastomosis of the bypass was extracted in the format suitable for volume mesh generation used for fluid dynamic calculation. The current 3D reconstruction of CTA images used a technique that was superior to 2D methods in clarifying relationships between proximal and distal anastomosis of the HF EC-IC bypass from adjacent vessels and bony structures.

Surface model and mesh generation

In the current study, a validated thresholding technique for region segmentation and lumen cross-section contour was conducted in Materialise Interactive Medical Images control System (MIMICS) (V14.0; Materialise, Leuven, Belgium) allowing for the creation of a 3D bypass geometry and volume rendering. The process was semiautomatic and it ran in a common graphical interface producing image and geometry. Minimum density threshold processing was applied to optimize visualization of the bypass construct. Images were refined in order to increase the resolution and avoid intersection between close bony structure and vessels. Images were then smoothed to reduce noise interference. This software allowed us to display baseline axial, coronal and sagittal views and to create reformatted orientations with 3D volume. This construct would form the basis for initialization of a geometry deformable model, which allows the optimum triangulation of nodes placement on the surface of the edge of vasculature structures. The final model was smoothed and interactively cut and extruded, and saved into stereo lithography (STL) format. The model was visualized on top of the image in order to visually verify that it realistically represents the desired bypass construct. Figure 4.2 shows an example of a computational grid bypass construct at the distal anastomosis. This surface triangulation mesh is used as a support surface to define the computational domain during haemodynamic analysis. For the numerical simulation, a 3D computational hexahedral grid was generated.

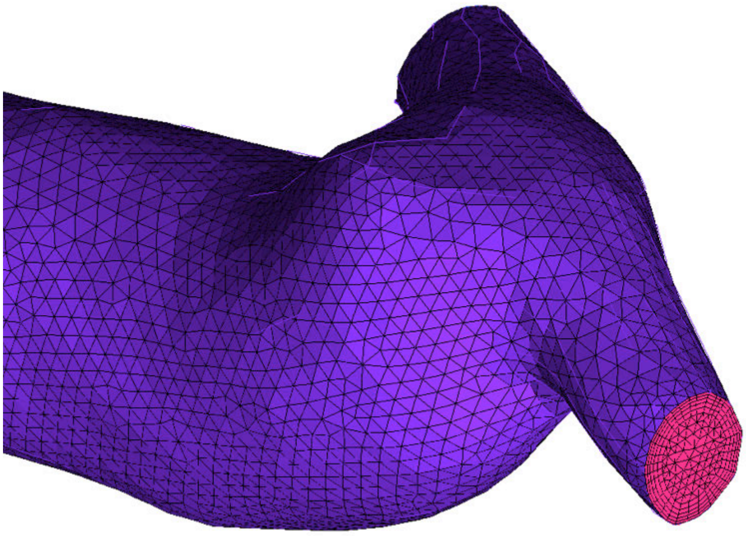

Figure 4.2 An example of distal anastomosis of computational grids bypass construct

A study of patient-specific data obtained by radiological imaging showed that simulations incorporating parent vessels geometry proximal to the region of interest are preferable (Castro *et al.* 2006). The importance of producing a laminar flow pattern in the model to minimize the influence of the upstream parent artery geometry on the haemodynamics of an anastomosis is of critical importance, as failure to properly model the inflow stream contributed by the upstream parent vessel may significantly impact the results of brain bypass haemodynamic models (Castro *et al.* 2006). For this reason, we have included 100mm of modelling at the upstream of parent artery geometry in our bypass model. This will help the simulated blood flow achieve a steady state and minimize the margin of computed analysis error.

Blood flow equations and numerical analysis. To solve the Navier-Stroke equations, we used the software package ANSYS (V 13.0, ANSYS, Inc., USA). ANSYS uses the mixed finite-element method to solve the nonlinearities equation with an efficient geometry multi-grid algorithm. It was important to optimise the accuracy of analysis at the arterial bifurcation or anastomosis. The optimum number of grid nodes with best accuracy and optimum computing time were carried out on cluster desktop computers.

Blood was mathematically modelled with the Navier-Stokes (N-S) formula for a time-dependent viscous incompressible Newtonian fluid and continuity equation that describes the most general movement of fluid medium. These equations are defined below.

$$\frac{\partial}{\partial t}(\rho v_i) + \frac{\partial}{\partial x_j}(\rho v_i v_j) = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j}[\mu\,(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i})] + f_i$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x_j}(\rho v_j) = 0$$

Where $i, j = 1,2,3,$ x_1, x_2, x_3 means coordinate axes v_i, v_j and p are the velocity vector and the pressure in the point of the fluid domain, ρ and μ are blood density and viscosity, t is time. The term f_i expresses the action of body forces.

The energy loss (EL), between inlet and outlet used to evaluate the cardiac workloads was calculated by the equation, which is expressed as below:

$$\text{EL}=\sum_{inlet}(P_{inlet} + \frac{1}{2}\rho v_{inlet}^2)Q_{inlet} - \sum_{outlet}(P_{outlet} + \frac{1}{2}\rho v_{outlet}^2)Q_{outlet}$$

It is known that Navier-Stokes equations are sensitive to pressure gradients only and not to absolute values. Hence, the absolute values of the prescribed pressure led to no error, but not the pressure gradient (Alnaes *et al.* 2007). Kinetic energy, including the pressure gradient and energy dissipation, impacting on the vascular graft were similarly computed across the same cut plane by deriving the positive inbound velocities. From the computed velocity field, WSS and pressure on the boundary of the geometric model were visualised with colour-coded magnitudes according to ANSYS software.

Physiological conditions imposed in the simulation and boundary condition

The rheological properties of blood are mainly dependent on the, volume fraction of red cells in blood (haematocrit). Although seemingly a logical assumption that blood can be thought of as a suspension of particles in an aqueous medium and is neither homogenous nor Newtonian (i.e. water), defining this with appropriate modelling has proven to be difficult (Castro *et al.* 2006). To complete the Navier-Stokes equations, we imposed physical conditions on blood flow at the boundary of the computational domain. Due to the relative large size of the vessels compared to individual blood cells and typically large shear rates in arteries, the non-Newtonian effects are typically neglected for large arteries in this modelling process, and blood flows were assumed to be a Newtonian fluid, with constant viscosity (μ=4.0×10-3 Pa·s) and density (ρ=1060 kg/m^3). CFD was performed with an assumption of a laminar, homogenous, incompressible blood flow with solid vessels vein graft, non-slip and non-penetration constraints at the wall. The body forces of blood were omitted. An average Reynolds number of 200 - 300 was used as it was within the range of normal blood flow in human flow conditions.

The range of Reynold number (Re),

$$Re = \frac{vD}{v}$$

Where v is the mean volume velocity in an instant of period, D is the diameter of the carotid artery, and v is the kinematic viscosity of blood

$$v = \frac{\mu}{\rho}$$

In this study, physiological in flow boundary condition for patient was derived from real-time mean pulsatile velocities flow rate (halve of peak velocity) carotid Doppler ultrasound examination of common carotid, external and internal carotid artery. Since flow rate was not available at distal anastomosis (i.e. intracranial anastomosis), traction free boundary conditions were applied in all the outlet boundaries. This approach assumes that all the distal vascular beds have similar total resistance to flow and flow division among the arteries which is determined by the geometry of the bypass construct. In this finite element calculation modelling, therefore, flow rate is imposed at the inlets and null pressure was set at the out flow of the bypass construct.

Carotid Doppler ultrasound

For examination of extracranial arteries [CCA, external carotid artery (ECA) and internal carotid arteries (ICA)] of both sides, patient had an initial 10 minutes of rest in a supine position with head slightly elevated and turned to the contralateral side by ≈10-30° before ultrasound with a 9MHz linear array transducer of a computed sonography system (General Electric LogiQ E9). Flow volume measurements were generally taken at 1-2 cm below the carotid bulb in the CCA, and 1-2 cm above the carotid bulb in the ECA and ICA or bypass anastomosis junction. The luminal diameter was determined on the B-mode image of the vessels as the distance between the internal layers of the parallel walls. The mean of 3 measurements was evaluated. At the same site, we aimed to keep the angle of insonation of 60 ° to determine time-average flow velocity (TAV) in each extracranial vessel. These values were set as the inflow boundaries condition in CFD modelling. Pulse Colour Doppler ultrasound provides an estimate of the mean velocity within a selected gate by colour coding the information. Red and blue colours are arbitrarily assigned to the directions toward or away from the probe transducer (Figure 4.3). Evidence has suggested that average flow rate were sufficient for accurate simulations, so long as enough geometry was included in the model (Ford *et al.* 2005). The intravascular flow volume (FV) in each vessel or bypass graft was then calculated as the product of TAV and the cross-sectional area (A) of the circular vessels according to the formula FV=TAV x A ml/min.

With the inlet and outlet flow boundary conditions, the results of blood flow pattern, distribution and pressure gradient across the patient-specific brain bypass model were evaluated.

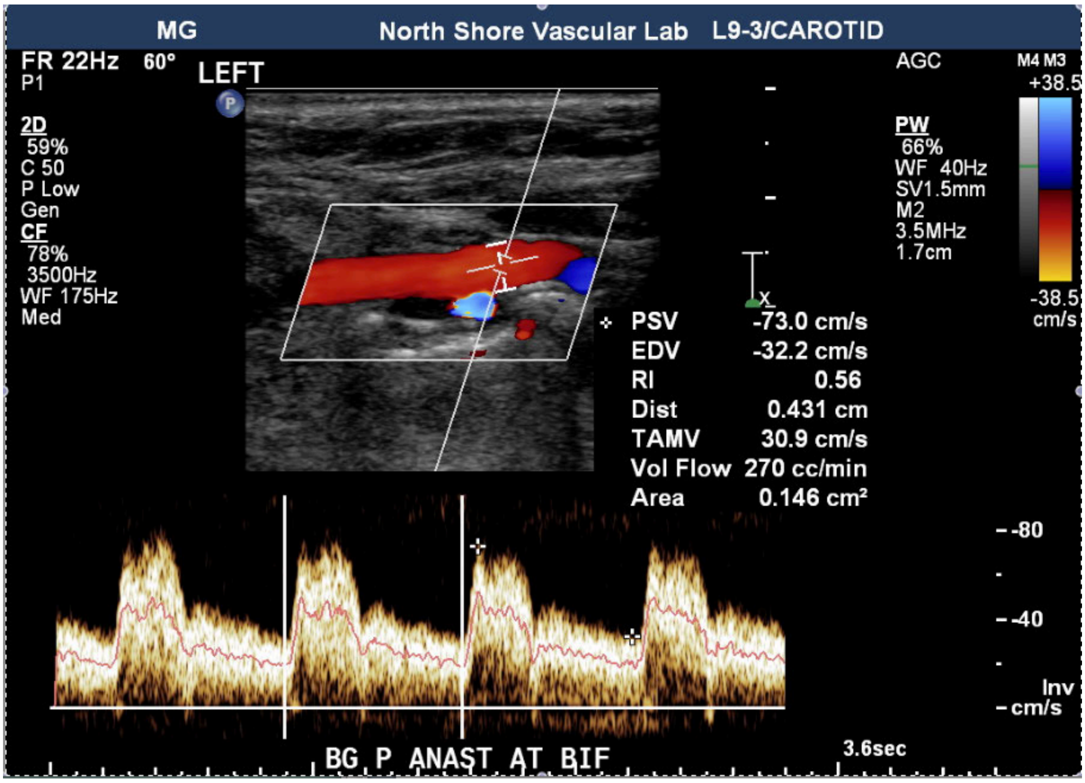

Figure 4.3 Carotid Doppler ultrasound examination

Conclusion

The main purpose of this chapter was to describe the method used in patient-specific image to study the haemodynamic in HF EC-IC bypass. These included image processing, segmentation algorithm, 3D grid generations, finite volume method for Navier-Stoke fluid equation and rheological models. Assuming laminar incompressible flow in planar, smooth, rigid anastomosis, the transient 3D haemodynamic has been simulated numerically. This method of CFD analysis based on patient-specific CTA data was feasible producing qualitative and quantitative information on pressure gradient and WSS. It has been shown that the most important parameter for an accurate determination of the blood flow pattern is the geometry of the vessels. Other parameters including blood rheology, wall motion, non-Newtonian effects of blood and blood flow rates were found to be of “second-order” effects with respect to the geometry. These simulations can be a powerful tool for computer assisted surgery and therapeutic decision making in the management of cerebrovascular disease. It may provide quantitative recommendation in bypass technique and contribute to increased patency rates. In this work, the possible association between haemodynamic factors and graft failure after HF EC-IC bypass surgery could also be determined.

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Chapter 5

Evaluation of brain extracranial-to-intracranial (EC-IC) bypass treatments by using computational haemodynamic technology

Abstract

Computational fluid dynamics (CFD) techniques were used to investigate the haemodynamic effect on EC-IC brain bypass. Local haemodynamic factors at the vascular anastomosis sites have long been thought to play an important role in the platelet activation, growth of intimal hyperplasia and thrombosis of brain bypass anastomosis and hence, affecting graft longevity.

In this study, the medical imaging data computed tomography (CT) angiography were collected in DICOM format and processed by using commercial visualisation and mesh generation software, which allowed extraction of the luminal surface of the vascular anastomosis in brain bypass surgery. 3D geometries were reconstructed for the purpose of numerical analysis. With the real-time velocities derived from Doppler ultrasound measurements as boundary conditions, the results of blood flow pattern across the patient-specific brain bypass was evaluated.

On the computational simulation, we observed there was almost a constant blood flow rate in the graft and internal carotid artery (ICA), and energy loss between proximal and distal also appeared constantly up to 60 % ICA stenosis. Beyond this point with further narrowing of the ICA, the blood flow shunting started to occur. There was also a significant energy loss and pressure gradient different at the bypass segment. We found there was no significant wall shear stress (WSS) different at the border zone of middle cerebral artery (MCA) against the different angle of distal bypass anastomosis. The results indicated that haemodynamic characteristics were not sensitive to the anastomosis angle.

Image-based patient-specific computational models can be used in an efficient manner that allows clinical studies of brain bypass haemodynamics. This modelling not only help us to quantify the WSS, velocity and pressure gradient in brain bypass surgery, it may also help guide future therapeutic strategies to reduce graft failure and preserve the perfusion at the border zone area.

Keywords: Cerebral revascularisation, extracranial-to-Intracranial (EC-IC) bypass, computational fluid dynamic, brain bypass surgery, haemodynamics.

Introduction

The cerebral revascularisation surgery has been available as a potential treatment for stroke or intracranial vascular disease. However, the role of cerebrovascular bypass has not been established as the first line treatment of choice in any adult intracranial vascular disease (Group 1985). However, in the treatment of selected patients for an individual reasons, a case can occasionally be made for brain bypass surgery (Sundt 1990; Schmiedek *et al.* 1994; Grubb *et al.* 1998; Thanvi *et al*. 2007). Having determined the requirement that intracranial bypass surgery is appropriate in an individual case, the choice of procedure is determined by both the short-term requirements (including risks of surgery, volume of blood flow deemed necessary, available conduits, anticipated period of vessel occlusion during the performance of the anastomosis surgery, the expectations of the circulation unprotected by the region of supply from the bypass as well as technical complexity) together with long-term concerns of the longevity of graft patency (Morgan *et al.* 2000). From in vitro fluid dynamic studies, it is known that vascular geometry plays a key role in determining local flow field. Surgically created anastomosis or abnormal geometry in vessel like stenosis and dilatation will induce flow disturbances and alter the velocity profiles (Staalsen *et al.* 1995). Furthermore, the presence of different shear rate following the changing of vasculature shape and the spatial gradient of the blood flow velocity field across the vascular bypass has shown to lead to a disturbed flow pattern in time and space that favouring abnormal activation of platelets within the anastomosis and subsequently graft failure (Ruggeri *et al.* 1999; Ruggeri 2002; Haruguchi *et al.* 2003; Schirmer *et al.* 2007). However, the understanding of vascular haemodynamic environment in middle cerebral artery (MCA) perfusion border zone areas with low resistance intracranial circulation and fluid dynamic induced in thrombosis after cerebrovascular bypass surgery remain poorly understood. The objective of this study is to demonstrate the feasibility of integrating patient-specific three-dimensional (3D) computed tomography (CT) angiography image data to construct the patient-specific computational haemodynamic model of brain bypass anastomosis.

Methodology

In the present study, the medical imaging data CT angiography (CTA) of a cerebrovascular bypass patient were collected in DICOM format and processed by using commercial visualisation and mesh generation software, which allowed extraction of the luminal surface of the vascular anastomosis in brain bypass surgery. The computational haemodynamic analysis system, validated in-vivo and in-vitro in Qian's studies (Qian *et al.* 2007), was also used to obtain the information of blood flow at the reconstructed brain bypass in detail. 3-D geometries were reconstructed for the purpose of numerical analysis. With the real-time velocities derived from Doppler ultrasound measurements as inlet and outlet flow boundary conditions, the results of blood flow pattern, various type of anastomosis morphology and wall stress across the patient-specific brain bypass was evaluated. Kinetic energy including the pressure gradient and energy dissipation impacting into the vascular graft was similarly computed across the same cut plane by deriving the positive inbound velocities.

The blood flow performed by the computational analysis system of equations is the Navier-Stokes (N-S) equation and continuity equation that describe the most general movement of fluid medium. These equations are defined below.

$$\frac{\partial}{\partial t}(\rho v_i) + \frac{\partial}{\partial x_j}(\rho v_i v_j) = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j}[\mu\,(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i})] + f_i$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x_j}\left(\rho v_j\right) = 0$$

Where $i, j = 1,2,3,\ \ x_1, x_2, x_3$ means coordinate axes, v_i, v_j and p is the velocity vector and the pressure in the point of the fluid domain, ρ and μ is blood density and viscosity, t is time. The term f_i expresses the action of body forces. Due to the relative large size of the vessels compared to individual blood cells and typically large shear rates in arteries, the blood flows were assumed to be a Newtonian fluid, with constant viscosity (μ =4.0×10-3 Pa·s) and density (ρ = 1060 kg/m^3). The body forces of blood were omitted. The typical Reynolds number is approximate 200 - 300 in the ICA. Therefore, laminar calculation would be used in the study. The energy loss (EL) between inlet and outlet used to evaluate the cardiac workloads was calculated by the equation, which is expressed as below:

$$EL=\sum_{inlet}(P_{inlet} + \frac{1}{2}\rho v_{inlet}^2)Q_{inlet} - \sum_{outlet}(P_{outlet} + \frac{1}{2}\rho v_{outlet}^2)Q_{outlet}$$

The haemodynamic characteristics of brain bypass blood flow patterns were also quantified and their possible association to peri-operative clinical decision, clinical outcome and long term graft patency were explored. The anastomosis angle and the stenotic ratio of internal carotid artery (ICA) were modified by using image software. The haemodynamic characteristics, i.e. wall shear stress (WSS) distribution around of anastomosis, and blood flow rate through the graft, were simulated under the various anastomosis angle and ICA stenosis.

Results

A tall 13-year-old boy presented with progressive left visual loss over past one year. He had a strong family of Marfan's syndrome, a type of systemic connective tissue disease which might potentially weaken the arterial wall. He was diagnosed to have a fusiform type of left internal carotid artery (ICA) aneurysm (Fig 5.1a). He subsequently underwent inter-positional saphenous venous grafting (IPSVG) brain bypass from left common carotid artery (CCA) to middle cerebral artery (MCA) with trapping of the ICA fusiform aneurysm (Fig 5.1b). The intended trap ICA segment was partially occluded in hoping that the thrombosis could occur with time should the blood flow slow down. At the same time, it would be perfused adequately to the ICA distal run off ophthalmic artery while awaiting collateral to develop from extracranial ICA circulation.

Based on the patient CTA extraction vascular configuration data with partially ligated ICA (Figure 5.2), various bypass model were simulated by reconstructing the ICA with different degree of "computational induced stenosis" looking at how the changes of the stenosis affecting blood flow indices in the bypass graft.

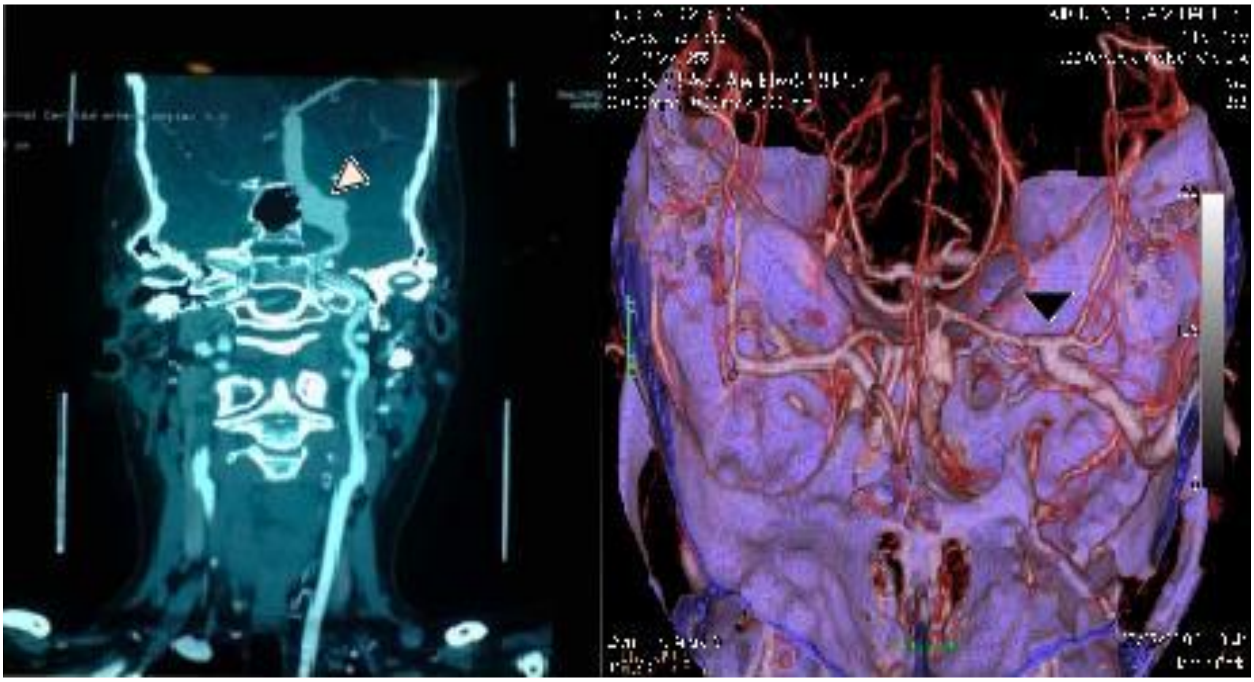

Fig.5.1a (left) Coronal CTA brain scan shows a left diffuse ectactic ICA aneurysm (white arrow) b (right) 3D CTA after EC-IC bypass surgery. The black arrow indicates the distal anastomosis bypass

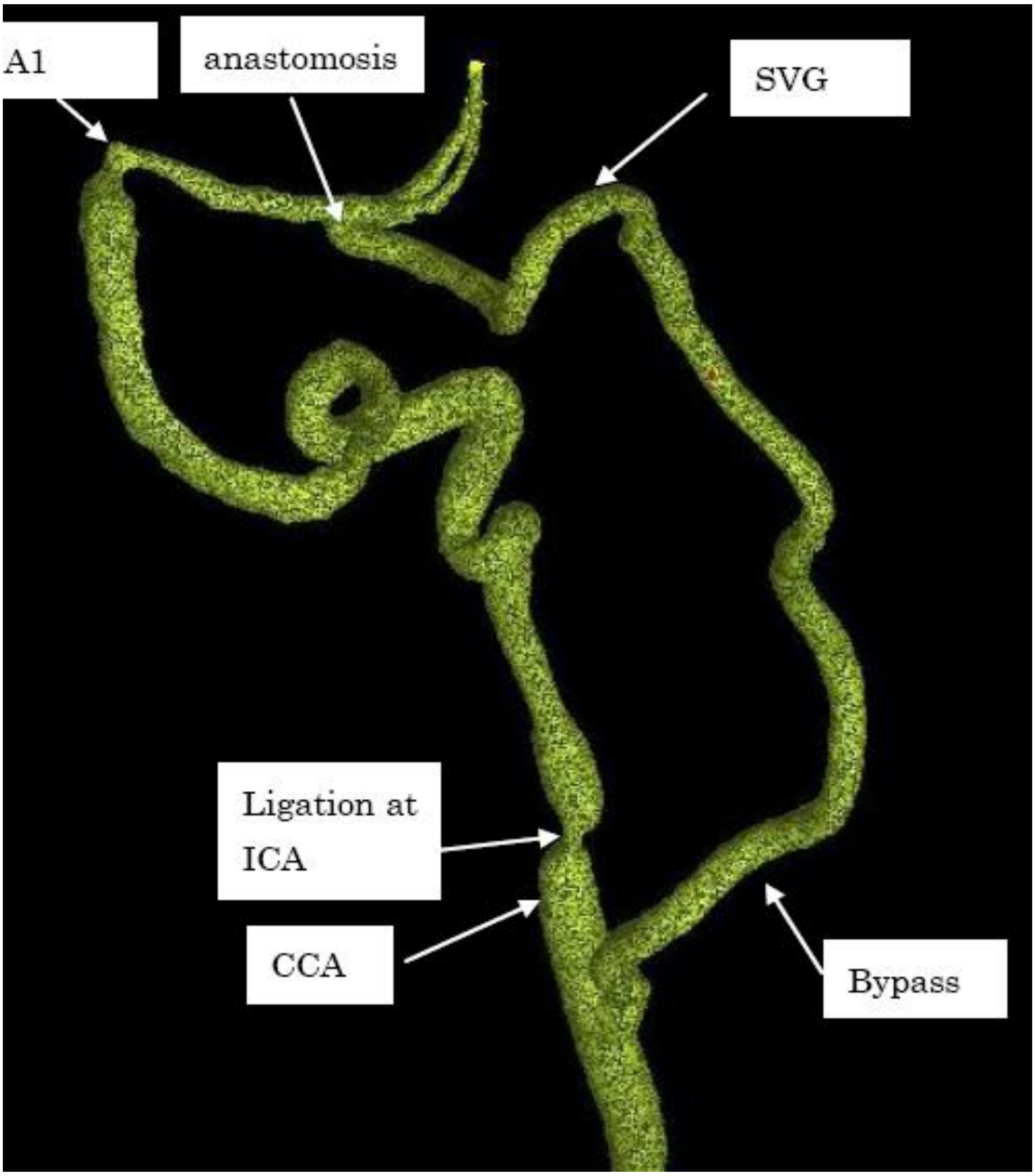

Figure 5.2 Parent vessel model dimensions were based on CTA DICOM images.

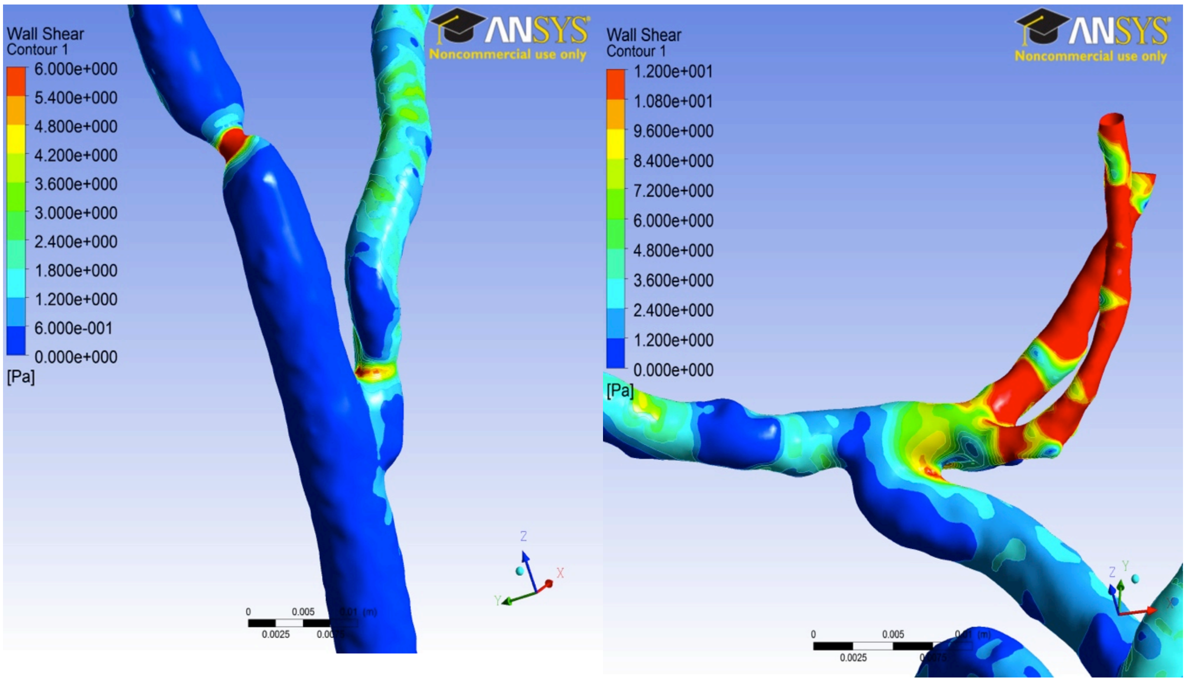

Figure 5.3a and b showed WSS distribution proximal and distal anastomosis.

On the computational simulation, we observed there was almost a constant blood flow rate in the graft and ICA, and energy loss between proximal and distal also appeared constantly up to 60 % ICA stenosis. Beyond this point with further narrowing of the ICA, the blood flow shunting started to occur (Figure 5.4).

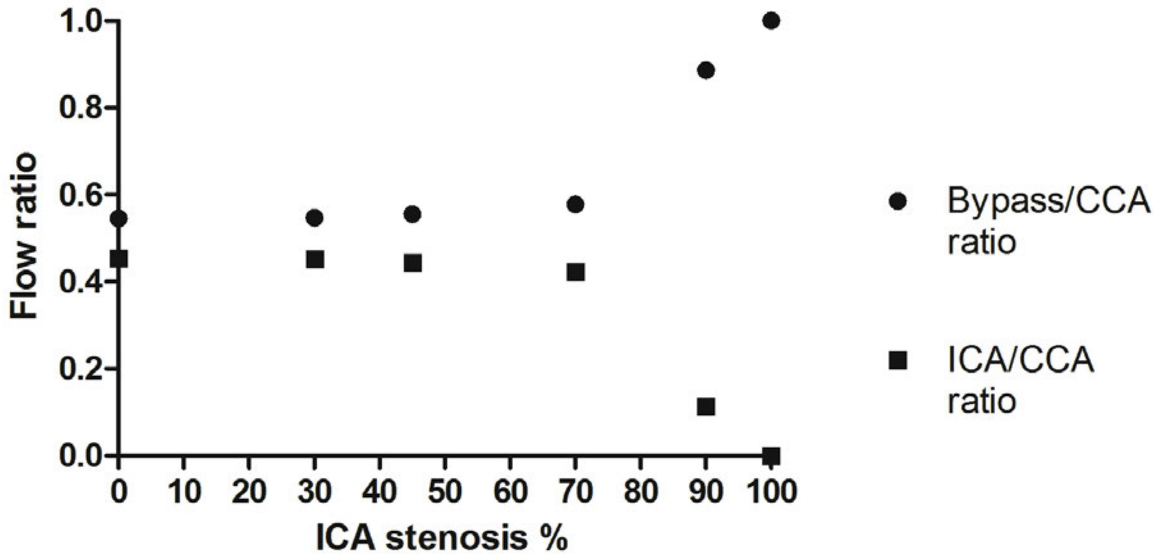

Figure 5.4 Blood flow distribution in ICA and bypass graft with various degree of ICA stenosis

There was also a significant energy loss (Figure 5.5) at the bypass segment. We found there was no significant WSS or flow change at the middle cerebral artery (MCA) border zone against the different angle of distal anastomosis bypass. The results indicated that haemodynamic characteristics were not sensitive enough influenced by the flow and energy loss across the vascular bypass. Figure 5.6 was the results of maximum WSS at proximal and distal location. The maximum WSS increased against ICA stenosis.

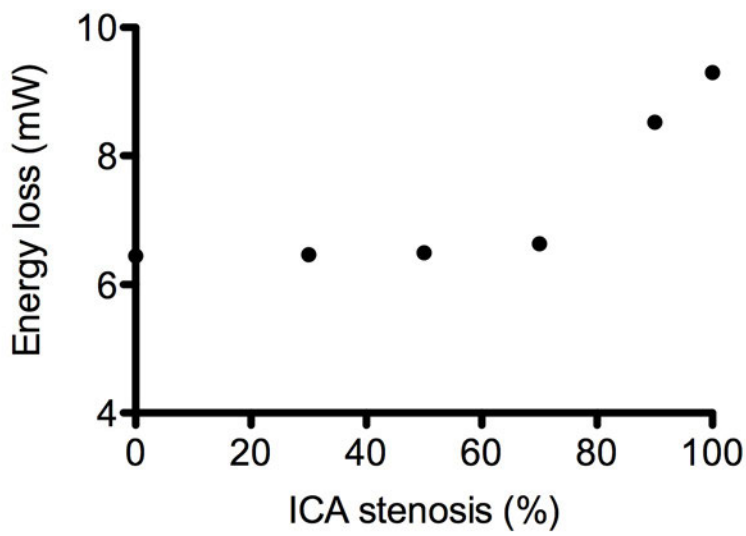

Figure 5.5 Energy loss dissipation across the bypass graft with various degree of ICA stenosis.

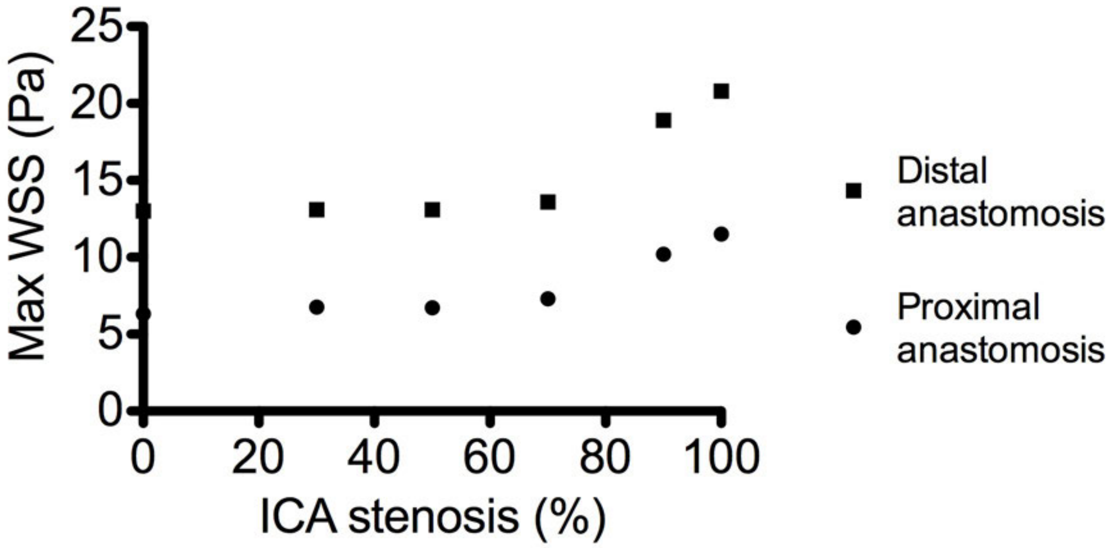

Figure 5.6 Maximum WSS at proximal and distal location at various degree of ICA stenosis.

Discussion

Computational fluid dynamic analysis can be applied to the complex flow related pathophysiology in cerebrovascular bypass. In the human blood circulation, shear stress and local flow field play a critical role in determining where most vascular pathology originates (Glagov *et al.* 1988; Davies 2009), in particularly at the surgical created anastomosis bypass area. Schirmer and Malek employed a modelling strategy to investigate the interaction between haemodynamic insufficiency thromboembolism and complex blood flow patterns in intracranial atherosclerotic disease (Schirmer *et al.* 2007). It appears that abnormal stenosis or narrowing would harbour a haemodynamically pathological environment that favours platelet activation and abnormal shear stress. The method presented here enabled the estimation of optimum degree of parent vessel stenosis that allows minimum blood flow velocity to bypass graft and hence theoretical advantages in term of lowering the risk of thrombosis causing graft occlusion or embolus. With this, improved modelling approaches may help elucidate the mechanism for the observed risk of graft thrombosis and failure after brain bypass surgery.

Conclusion

Image based patient specific computational fluid dynamic study provides additional insights into the haemodynamics of interposition vein graft in HF EC-IC bypass surgery which might prove to be of great value in aiding the therapeutic decision making process. This modelling not only help us to quantify the WSS, velocity and pressure gradient in brain bypass surgery, it would also provide a foundation helping us to plan our peri-operative surgical strategies that we might need to do to reduce graft failure and preserve the perfusion at the border zone area.

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Chapter 6

Haemodynamic effects resulting from a common carotid to middle cerebral bypass with varying degrees of proximal internal carotid stenosis

Abstract

Object: To investigate the degree of stenosis of the internal carotid artery required for continuous blood flow in an interposition high flow extracranial to intracranial bypass graft to the middle cerebral artery.

Methods: Computational fluid dynamics techniques were used to investigate a case of common carotid to middle cerebral artery brain bypass with varying degrees of internal carotid artery stenosis. Blood flow patterns across the patient-specific brain bypass were evaluated.

Results: Simulation found that for cross section stenosis of less than 60%, no flow occurred in the bypass graft. Further narrowing of the internal carotid artery increased flow linearly within the bypass graft. There was significant energy loss and pressure gradient difference between the proximal and distal anastomosis sites of the bypass.

Conclusion: Computational fluid dynamics helps us to quantify the flow distribution, wall shear stress and pressure gradient in brain bypass surgery. The angle of the distal anastomosis had no effect on haemodynamic indices, allowing this consideration to be ignored in modelling. This modelling technique is useful to estimate the required degree of stenosis in the artery that is to be occluded to ensure sustained flow in the bypass. This will be of importance where there is staged surgery with a time interval between the bypass and the definitive internal carotid artery occlusion.

Keywords: Cerebral revascularisation, extracranial-to-Intracranial bypass, computational fluid dynamics, brain bypass surgery, haemodynamic, Internal border zone

Introduction

Extracranial to intracranial (EC-IC) bypass surgery can be performed to either augment or replace cerebral blood flow (Sia *et al.* 2011). The choice of intracranial revascularisation procedures are not standardized and depend on available conduits (arterial pedicle or venous graft), blood flow adequacy to the intended bypass territories, surgical technique complexity (end-to-side, end-to-end or side-to-side anastomosis), and the long-term expectations of graft patency (Sundt *et al.* 1987; Morgan *et al.* 1994; Morgan *et al.* 1996; Morgan *et al.* 2000; Morgan *et al.* 2002; Jeffree *et al.* 2009; Sia *et al.* 2011). In cases where vessel occlusion is anticipated to treat a tumour or aneurysm, it may be decided to stage the procedures, with a time interval between establishing the bypass and the definitive occlusion or sacrifice of the vessel. However, the potential for the competition of flow by the original native circulation may negatively impact upon the sustainability of the newly established bypass graft. More precisely, presence of abnormally high or low shear rates through the bypass favours abnormal platelets activation, thrombus formation and graft failure (Ruggeri *et al.* 1999; Ruggeri 2002; Haruguchi *et al.* 2003; Schirmer *et al.* 2007).

A strategy that can be used to induce and maintain the flow in the bypass graft is, at the time of the EC-IC bypass procedure, to surgically narrow (but not occlude) the artery that will be sacrificed or occluded at the next procedure. However, the degree of narrowing necessary to optimise patency of the graft is poorly understood.

A second concern is the prediction of the consequences for the sharing of downstream flow between the bypass and the native collaterals (compensating the loss of normal blood supply). Surgically created anastomoses will induce local flow disturbances, alter velocity profiles (Staalsen *et al.* 1995), and alter the internal border zone between native collateral flow and bypass flow. At the boundaries between these territories, there will be a point with no or low flow. Where the bypass is established to the middle cerebral artery (MCA), such points of low flow may occur in the region of the lenticulostriate arteries (Morgan *et al.* 2000). Internal border zone infarctions may result from branch occlusion due to these haemodynamic changes.

The objective of this study was to demonstrate the feasibility of integrating patient-specific three-dimensional (3D) computed tomography angiography (CTA) image data to construct the patient-specific computational fluid dynamic (CFD) model of high flow extracranial to intracranial (HF EC-IC) bypass anastomosis. A common carotid artery (CCA) to middle cerebral artery (MCA) bypass was modelled with varying degrees of internal carotid artery (ICA) stenosis. The modelling was used to predict the minimal degree of stenosis necessary to ensure sustained continuous flow in the bypass. This model was tested with varying angles of the distal anastomosis to see how this might affect the prediction. This was thought to be important, as the angle of the distal anastomosis cannot be easily predicted prior to surgery.

Methodology

A tall 13-year-old marfanoid male presented with progressive left visual field loss over one year. He was diagnosed with a fusiform left ICA aneurysm. He underwent HF EC-IC bypass from the left CCA to MCA using a saphenous vein graft (SVG). At the same surgical procedure the intracranial ICA proximal to the aneurysm was surgically trapped and narrowed. The trapped ICA segment was not completely ligated in order to preserve a minimal flow to the ophthalmic artery to avoid sudden loss of retinal blood flow.

Our methods, and the computational haemodynamic analysis system, have been described in detail and validated in-vivo and in-vitro in previous studies (Qian *et al.* 2010; Sia *et al.* 2010). In summary, the medical imaging data CTA was performed using a helical CT scanner (GE Medical Systems) with multidetector-row capability. Section thickness of 0.625mm, and a table speed of 9mm/s and zero-degree table (and gantry tilt) were used. Sections in DICOM format were acquired with a 512 x 512 matrix. Scanning was started from the arch of the aorta and continued parallel to the orbito-meatal line to the level just beyond the Circle of Willis during the intravenous injection of contrast material at the rate of 3.5mls/s. All the images were immediately transferred to a workstation (Real-Intage®) for volume rendering. Contour interpolation was used to generate 2-D contours based on gray scales pixels with a thresholding value of 226 to 3071. Following this, a 3-D geometry was built by interpolating those 2-D contours in normal direction. The luminal surface of the vascular anastomosis in the HF EC-IC bypass surgery was extracted in the format suitable for import by grid generators, with each grid size maximum of 0.3mm. This method avoids surface noise that would result in inaccuracy of 3D geometry. Instead of using the global smoothing, we used manual local smoothing to keep the 3D geometry as realistic as possible. This method gave an average error of one third of original pixel size in 3D geometry (Jamali *et al.* 2007). Three-dimensional geometries were reconstructed for the purpose of flow simulation. Optimum number of grid nodes, with best accuracy and optimum computing time, were established using ANSYS workbench (V 12.1, ANSYS, Inc., USA) on cluster desktop computers. CFD was performed assuming a solid vessels vein graft wall and non-slip and non-penetration constraints at the wall. With the real-time velocities derived from pulse-Doppler ultrasound displaying the spectrum of blood velocities, the mean arterial velocity was used as inlet boundary criteria. The simulation was performed under steady flow condition. Based on the patient CTA extraction of the vascular configuration data from the 90% stenosis of the ICA, various morphology bypass models were simulated looking at blood flow indices and wall shear stress (WSS) changes at the proximal and distal anastomoses following computer model reconstruction of the ICA with variations in the degree of stenosis (Figure 6.1) and anastomosis angles (150 °, 135 °, 90 ° and 75 °) (Figure 6.5 and Figure 6.6).

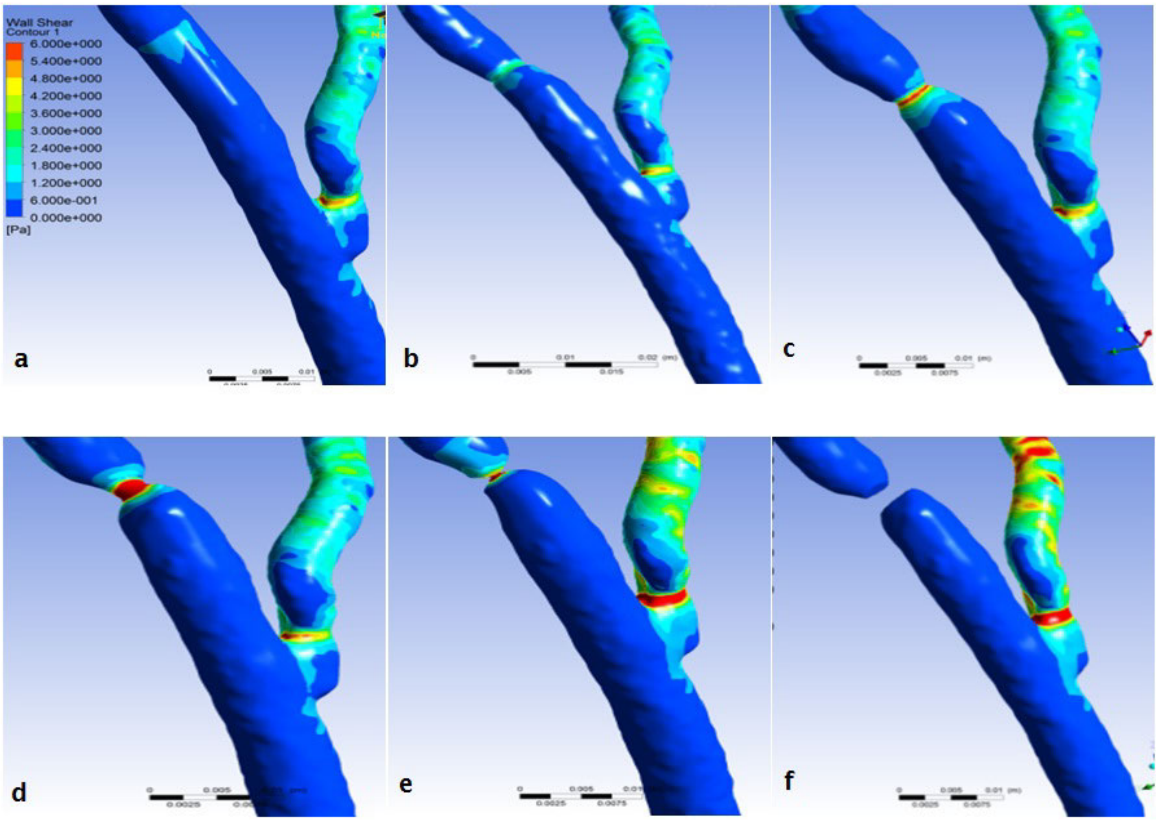

Figure 6.1 Wall shear stress distribution at proximal end-to-side anastomosis CCA to vein graft with various degrees of ICA stenosis, a) no stenosis, b) 30%, c) 50%, d) 70%, e)90% and f) total occlusion.

The blood flow calculations performed by the computational analysis system of equations utilized the Navier-Stokes (N-S) equation and continuity equation that describe the most general movement of fluid medium. These equations are defined below.

$$\frac{\partial}{\partial t}(\rho v_i) + \frac{\partial}{\partial x_j}(\rho v_i v_j) = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j}[\mu (\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i})] + f_i$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x_j}(\rho v_j) = 0$$

where $i, j = 1,2,3,$ x_1, x_2, x_3 means coordinate axes, v_i, v_j and p are the velocity vector and the pressure in the point of the fluid domain, ρ and μ are blood density and viscosity. Due to the relative large size of the vessels compared to individual blood cells and typically large shear rates in arteries, the blood flows were assumed to be a Newtonian fluid, with constant viscosity (μ =4.0×10-3 Pa s) and density (ρ = 1060 kg/m^3). The Reynolds number in the normal ICA is 200 – 300, which is comparatively less than typical laminar flow of 1000 in any tubular structure. Therefore, laminar calculation was used in the study. The energy loss (EL), kinetic energy between inlet and outlet (including the pressure gradient and energy dissipation impacting into the vascular graft) were calculated by the equation, which is expressed below:

$$\text{EL}= \sum_{inlet}(P_{inlet} + \frac{1}{2}\rho v_{inlet}^2)Q_{inlet} - \sum_{outlet}(P_{outlet} + \frac{1}{2}\rho v_{outlet}^2)Q_{outlet}$$

The haemodynamic characteristics of HF EC-IC bypass blood flow patterns were also quantified and their relationships with clinical decisions were explored. The anastomosis angle and the stenotic ratio of ICA were modified by using image software. The haemodynamic characteristics of WSS distribution of proximal and distal anastomosis, and blood flow rate, through the graft and MCA border zone, were simulated under the various anastomosis angles and ICA stenosis.

Results

On the computational simulation, when the ICA had less than 60% area stenosis (Fig 6.2), there was normal volume of flow in the ICA and no flow in the bypass. Beyond 60% stenosis, the blood flow within the bypass linearly increased with the degree of ICA stenosis and the flow in the ICA linearly decreased. With an increase in bypass flow, there was a significant increase in WSS at the heel region of the bypass. Similar patterns of energy loss and WSS at the proximal and distal vein graft anastomosis were also observed as the degree of ICA stenosis increased.

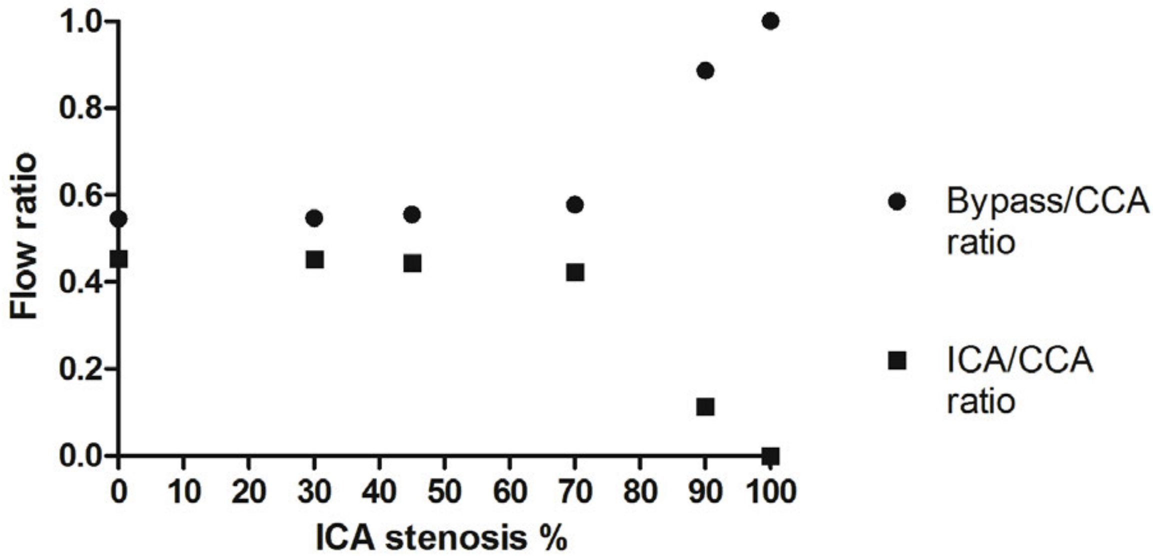

Figure 6.2 Blood flow distribution in ICA and bypass graft with various degrees of ICA stenosis.

Further analysis of the angle of anastomosis was performed. We used the 90% ICA stenosis on which we based our model, as this was the degree of stenosis that is used clinically for this bypass procedure. Various angles were simulated at the proximal and distal anastomosis. For proximal anastomosis (CCA to vein graft), anastomosis angles of 30, 45 and 90 degrees were modelled for WSS distribution (Fig 6.3). These anastomoses were characterized by flow acceleration into the proximal anastomosis marked by a moderate rise in WSS magnitude. This was most profoundly evident at the heel region of the proximal anastomosis. The peak WSS, energy loss and flow ratio between the CCA and bypass segment were, however, relatively constant and were not related to the angle of the anastomosis (Fig 6.4). At the intracranial distal anastomosis (vein graft to MCA), angles were varied over 150, 135, 90 and 45 degrees to evaluate the effect on the distal anastomosis haemodynamics (Figure 6.5 and Figure 6.6). There was evidence of flow separation with development of a retrograde shear vector, particularly evident in the anastomosis segment that was vein graft. Despite the inflow separation with retrograde shear vector, we observed there was no major influence on peak WSS or flow changes in the middle cerebral artery border zone region with these varying angles of the distal anastomosis. Normalized shear rate along the upstream of the middle cerebral arterial wall were relatively constant throughout various angles of distal anastomosis in 90% ICA stenosis, as well as in the model of complete ICA occlusion (Figure 6.7).

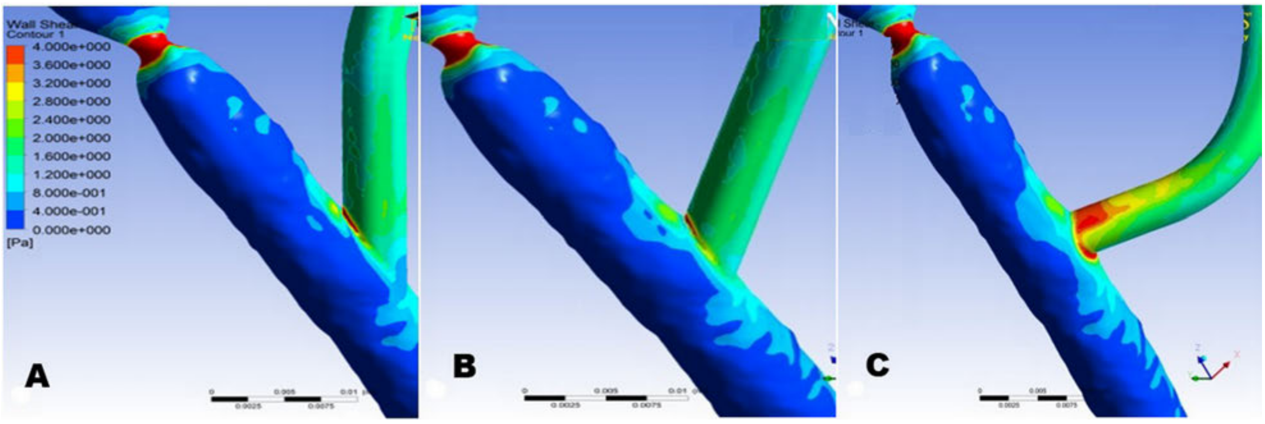

Figure 6.3 Wall shear stress distribution at the proximal anastomosis (CCA to vein) with various degrees of anastomosis angle, A) 30, B) 45 and C) 90.

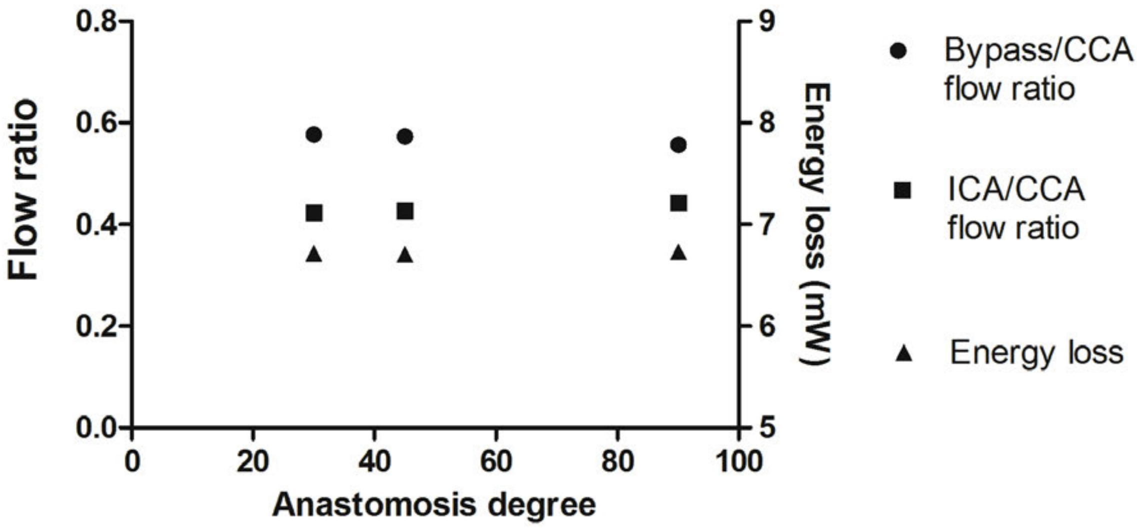

Figure 6.4 Energy loss, flow distribution at ICA and vein bypass segment at proximal anastomosis with various anastomosis angles.

Table 6.1 WSS (Pa) distribution at distal anastomosis and M1 borderzone at 150, 135, 90 and 45 degrees end to side anastomosis with 90% stenosis and complete ICA occlusion.

Internal carotid artery (ICA)	Anastomosis degree (°)			
	45	90	135	150
90% stenosis	7.7	9.6	14.8	12.7
Complete Occlusion	0.574	0.573	0.569	0.566

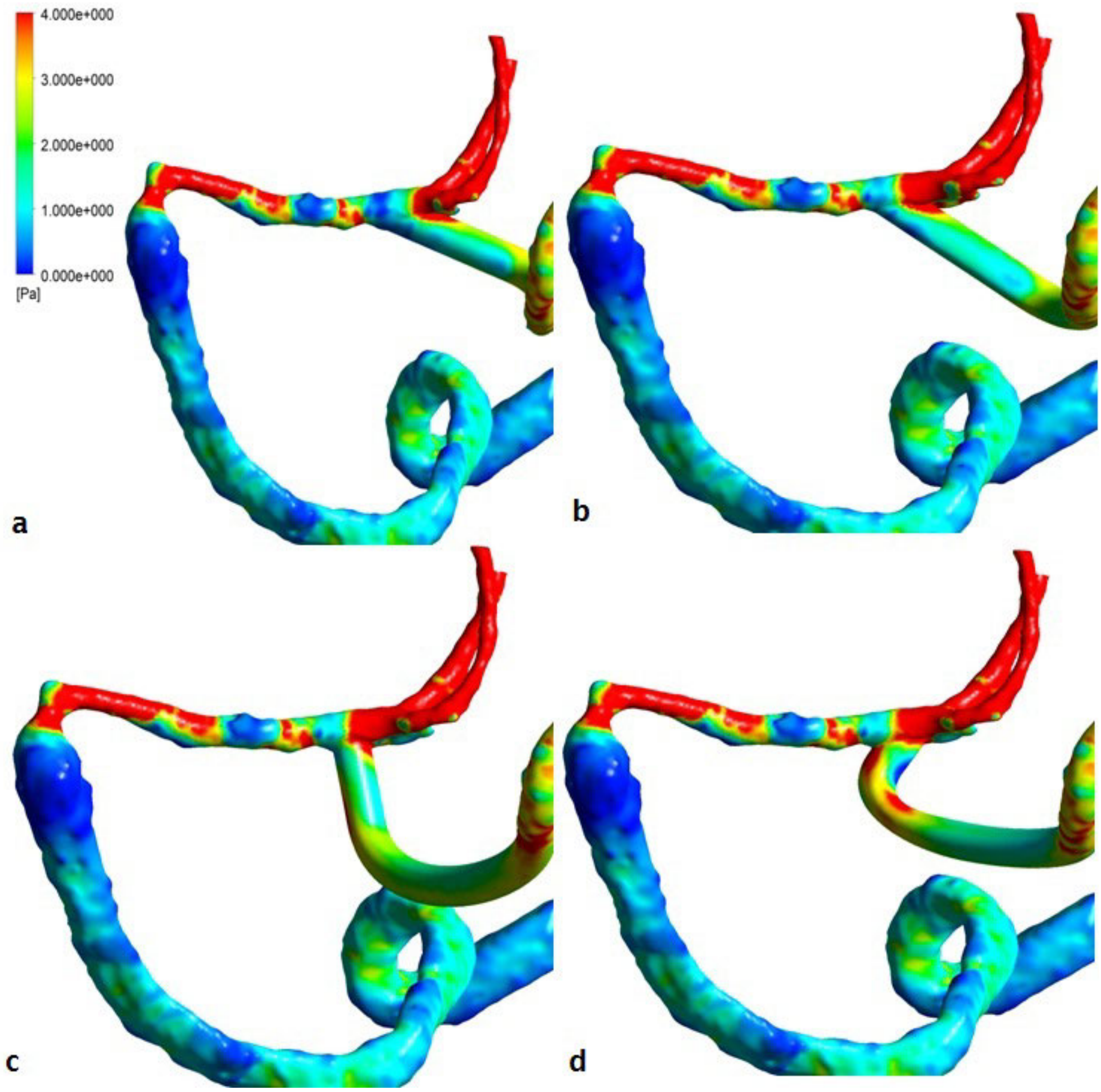

Figure 6.5 WSS distribution at distal anastomosis and M1 border zone at a) 150, b) 135, c) 90 and d) 45 degrees end to side anastomosis with 90% ICA stenosis.

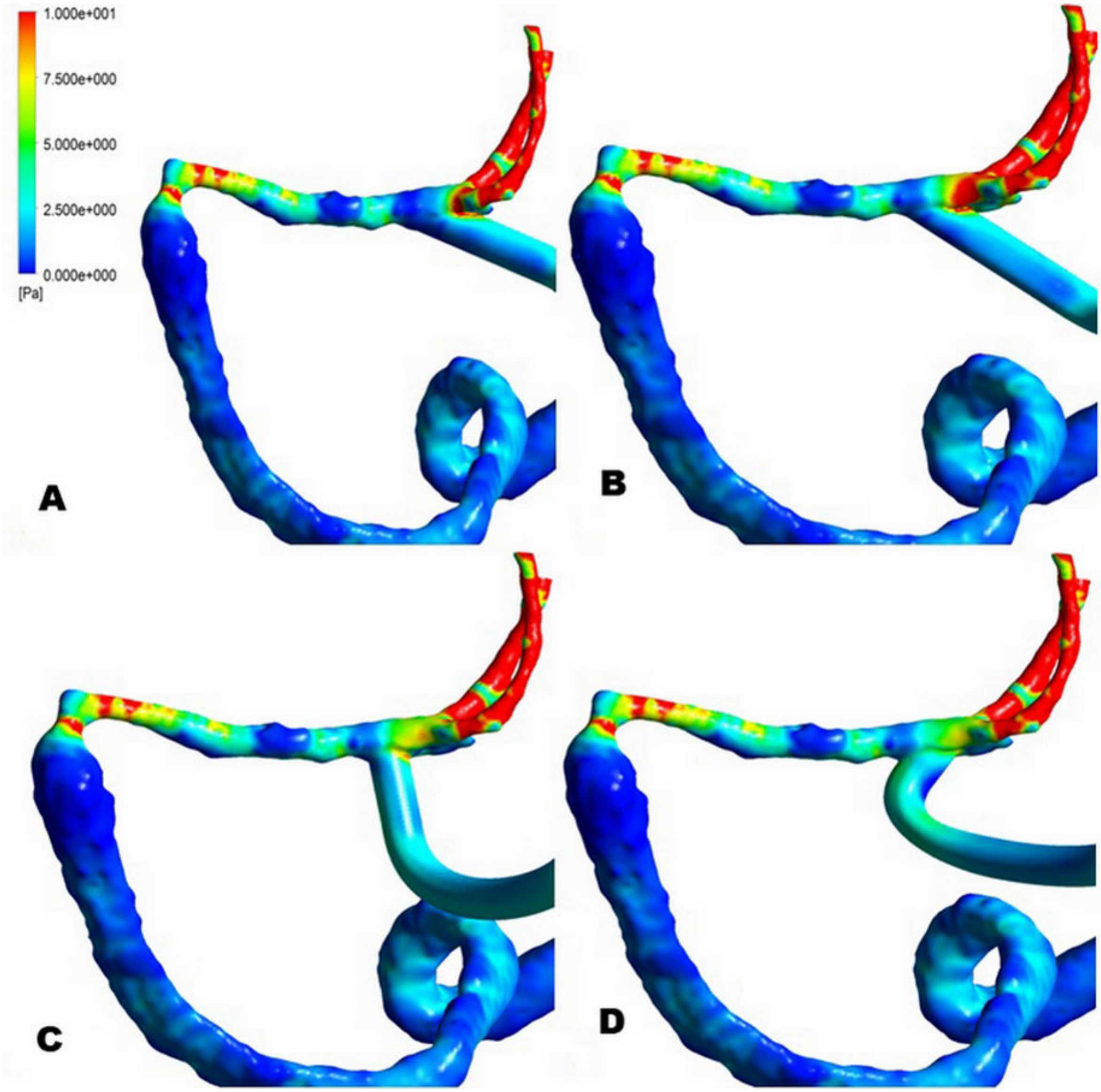

Figure 6.6 WSS distribution at distal anastomosis and M1 border zone at A) 150, B) 135, C) 90 and D) 45 degrees end to side anastomosis with complete ICA occlusion.

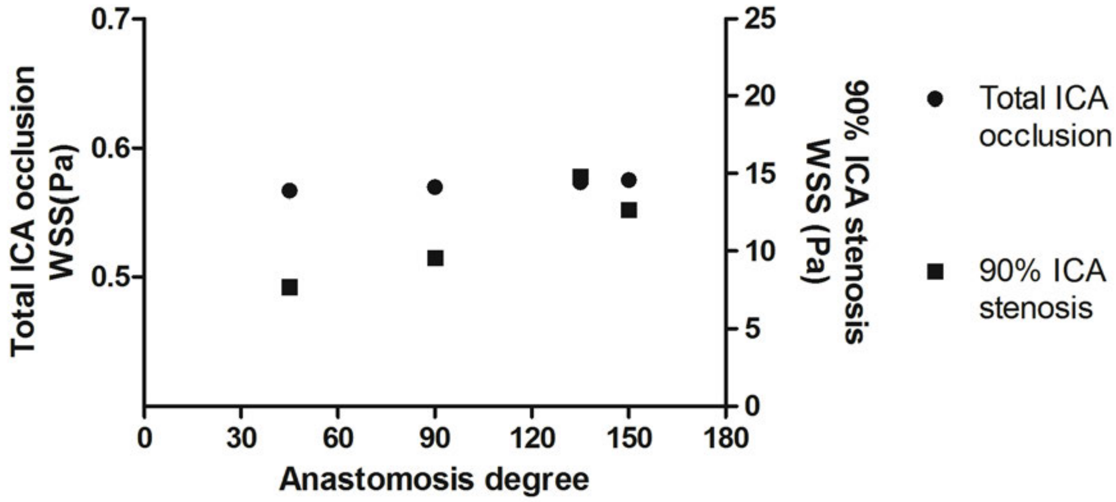

Figure 6.7 WSS distribution at distal anastomosis and M1 border zone at 150, 135, 90 and 45 degrees end to side anastomosis with 90% stenosis and complete ICA occlusion.

Discussion

Application of CFD as a tool for studying patient-specific haemodynamics is gaining in popularity. Numerous CFD clinical applications, particularly predicting the thrombosis rate in endovascular treatment of aneurysm and risk of rupture of cerebral aneurysms, have been described (Cebral *et al.* 2005; Shojima *et al.* 2005; Bai-Nan *et al.* 2011). Since the blood flow distribution and velocity profiles near the vascular bifurcation depend strongly on the geometry, it has been suggested that certain geometries (e.g. high curvature, obtuse and large angle of anastomosis) would alter the velocity profile, leading to more flow separation and low WSS. These geometric configurations, therefore, might be predisposed to early graft failure due to thrombosis, in the short-term, and to atherosclerosis and intimal hyperplasia, in the long-term. We set out to use high-resolution data sets obtained from CTA combined with a robust computational fluid approach to study anastomosis angles in HF EC-IC brain bypass and perfusion at the border zone area.

Flow dynamics and distribution

On the carotid artery computational simulation, we showed the outflow ratio changes in the carotid bifurcation from CCA to the ICA, ECA and vein bypass graft when the area of stenosis exceeds 60% (Fig 6.1 and Fig 6.2). Beyond 60%, further narrowing of ICA will result in increasing flow within the bypass. This increase was linearly related to the degree of stenosis beyond 60%. This is to be expected from both the theoretical and the experimental evidence but has yet to be investigated by CFD modelling (Nichols *et al.* 2005). Clinically, this degree of stenosis in the ICA has been found to be necessary before a benefit can be obtained by carotid endarterectomy (NASCET Collaborators 1991; ECST Collaborative Group 1991; NASCET 1991; NASCET 1991). This supports the likelihood that the benefits from carotid endarterectomy relate to a mechanical alteration in flow dynamics rather than removing the lesion generating the source of emboli.

Schirmer and Malek (Schirmer *et al.* 2007) employed similar modelling strategies to investigate the interaction between haemodynamic insufficiency, thromboembolism and complex blood flow patterns in intracranial atherosclerotic disease. They reported that intracranial arterial narrowing creates a haemodynamically pathological environment that favours platelet activation with embolus formation due, in part, to alterations in WSS. Flow rate of at least 40 cc/min are required to maintain a good patency rate (Sundt *et al.* 1987). The reasons for this relates to WSS. WSS is a flow-induced stress that can be described as the frictional force of viscous blood. Shear stress and local flow field play a critical role in determining where most vascular pathology originates (Glagov *et al.* 1988; Davies 2009). This is particularly the case at the surgically created anastomosis bypass sites. Schirmer and Malek (Schirmer *et al.* 2007) revealed that abnormal stenosis or narrowing would create a haemodynamically pathological environment that favours platelet activation and abnormal shear stress. Recent studies have indicated the WSS changes, in space and time, affect endothelial cell function and alter local vascular tone, including nitrous oxide (NO) elaboration, monocytes adhesion, and smooth muscle cell proliferation and migration (Davies *et al*. 1995; White *et al*. 2001). Low and oscillatory WSS is regarded as a major factor in the development and growth of atherosclerotic and intimal hyperplasia in bypass grafts (Westerhof *et al.* 2005). Intimal hyperplasia in vein grafts is sensitive to wall shear. Dobrin and colleagues (Dobrin *et al.* 1989) examined the haemodynamic mechanical factors, radial pressure extension and WSS on intimal hyperplasia in autogenous vein grafts on a canine's femoral artery. They observed intimal hyperplasia was less evident on the side with high flow (obtained by complete femoral artery ligation) as compared to the side where the femoral artery was left partially patent with low flow in the vein graft. Similar in-vitro findings were found in Kohler and Jawien's study (Kohler *et al.* 1992) where intimal hyperplasia was significantly greater in rat CCA with a low flow group as compared with a high flow group. This is particularly pertinent in the case of bypass to the MCA where a point of low flow may occur in the region of the lenticulostriate arteries, at the point of border zone between the bypass flow and the native collaterals for the planned occluded artery (Morgan *et al.* 2000). Internal border zone infarctions may result from occlusion due to these haemodynamic changes.

Based on the computational modelling, we observed there was no major influence on WSS or flow changes in the MCA border zone (between the native circulation and that of the bypass) with differing angles of the distal anastomosis. This was the case despite the inflow separation with retrograde shear vector. CFD result revealed haemodynamic indices at the border zone were not sensitive to various anastomosis angles. In this case, the absence of any WSS difference with varying angles of the distal bypass anastomosis may be due to lack of inflow influence from both the ipsilateral hypoplastic anterior cerebral artery segment 1 (A1) and posterior communicating artery (PCA).

Limitations

Our current modelling technique has limitations as it assumes a rigid congruent bypass conduit and does not take into account vessel wall thickness, elastic properties, pulsatility, or complex temporal flow pattern changes in the Circle of Willis. Included in this complex temporal flow pattern is flow from the posterior circulation that may have a phase difference, and retrograde flow during parts of the cardiac cycle. In order to decrease computational time, our simulation study is based on a number of simplifying assumptions including considering blood as a Newtonian fluid as well as neglecting the effect of wall movement, gravity and position. However, the fluid solid interface model from cardiac gated images is more realistic than the rigid model. We used a mean velocity waveform derived from carotid Doppler that may not represent the pulsatile waveform in patients with HF EC-IC bypass. Although it would be desirable to obtain in-vivo velocity data that can be coupled with the patient's bypass geometry, such data were not feasible. Furthermore, study of the distribution of haemodynamic forces in bypass graft has always been hampered by the complexity of intracranial vasculature, particularly at the carotid siphon area. Meticulous skeletonising of the extraluminal ICA surface for computational modelling at the carotid siphon is mandatory.

Conclusion

Image-based patient-specific computational models combined with information from other imaging modalities can be used in an efficient manner that allows clinical studies of HF EC-IC bypass haemodynamics. Improved modelling approaches may help elucidate the mechanism for graft thrombosis and graft failure after HF EC-IC bypass surgery. This modelling not only assists the quantification of the flow distribution, WSS and pressure gradient in HF EC-IC bypass surgery, it may also provide a foundation in the understanding of haemodynamic stress and the pathophysiology of brain vascular disease. This technique may prove to be of value when planning surgery to assist the prediction of graft failure.

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Chapter 7

Mean arterial pressure required for maintaining patency of high flow extracranial to intracranial bypass grafts: an investigation with computational haemodynamic models. Case series

Abstract

Background: Maintaining flow in a newly established high flow bypass into the intracranial circulation may be threatened by low blood pressure. The purpose of this study was to identify mean arterial blood pressures below which early graft failure may ensue.

Methods: Computational fluid dynamic blood flow simulation and Doppler ultrasound derived velocities were combined to study twelve patients with high flow extracranial to intracranial brain bypass with interposition saphenous vein. Each patient underwent carotid duplex and high-resolution CTA examination to source the necessary data. The proximal anastomosis for all twelve was the common carotid artery. The distal anastomosis was the intracranial internal carotid artery in nine and middle cerebral artery in three. A mean time-averaged pressure gradient across both anastomosis of the graft was then calculated. This formed the basis for calculating the mean arterial pressure above which would maintain graft flows of greater than 40 ml/min.

Results: The bypass graft mean blood flow ± standard deviation was 180.3±76.2 ml/min (95% CI: 131-229). The mean time-averaged pressure gradient across the bypass graft was 10.2±8.7 mmHg (95% CI: 4.6-15.7). This compared with a mean pressure gradient on the contralateral carotid of 21.7±13.8 mmHg. From this data, the minimum mean systemic pressure necessary to maintain graft flow of at least 40ml/min was calculated to be 61.6 ± 2.31 mmHg and the mean peak WSS at proximal anastomosis was 0.8±0.7 Pa (95% CI: 0.3-1.2)

Conclusion: Mean arterial pressure below approximately 60 mmHg in the early post operative period, may induce the haemodynamic environment to precipitate thrombosis and bypass failure after high flow extracranial to intracranial bypass surgery. Blood flow below 40ml/min in the immediate postoperative period, thus wall shear stress, may have deleterious effect on endothelial function and predispose to early graft occlusion.

Keywords: Cerebral revascularisation, extracranial to intracranial (EC-IC) bypass, computational fluid dynamic, brain bypass surgery, haemodynamics, optimum pressure, graft thrombosis

Introduction

Early graft failure in high flow extracranial to intracranial bypass (HF EC-IC) with interpositional saphenous venous grafts (SVG) may be precipitated by low flow rates through the bypass graft (Sundt *et al.* 1987; Morgan *et al.* 1994; Nussbaum *et al.* 2000; Eguchi 2002; Morgan *et al.* 2002). Sundt estimated that vein grafts require a minimum flow rate of 40 ml/min to maintain a good patency rate (Sundt *et al.* 1987). This flow rate will be dependent upon both the radius of the graft and the pressure gradient through which the blood flow passes across both anastomoses. Because of anaesthesia and intensive care management, the pressure gradient can vary considerably during the early life of the graft when suture lines are most thrombogenic. The aim of this study was to utilize a combination of data derived from computational fluid dynamic (CFD) studies and carotid duplex ultrasound from clinical cases of high flow common carotid to intracranial arterial bypass with interposition SVG to estimate the minimum mean arterial pressure (MAP) that would maintain graft flows of at least 40 ml/min.

Patients and methods

We retrospectively reviewed the pre-procedural and post-procedural three-dimensional (3D) CT angiography (CTA) data. Twelve patients with HF EC-IC bypasses with SVG were analysed. Nine patients had common carotid artery (CCA) to intracranial internal carotid artery (ICA) bypass and 3 had CCA to middle cerebral artery (MCA) bypass. We recorded demographics, clinical indications, diagnosis and treatment-related information. This study was approved by the university human research ethics committee, and performed in accordance with institutional ethics committee guidelines. The medical imaging data of colour coded duplex sonography and CTA of the twelve patients were collected. Postoperatively, bypass patency was established by CTA and Doppler/duplex ultrasound examination. Coloured coded duplex was performed at the same time as the postoperative CTA. Our methods and the computational haemodynamic analysis system have been described in detail in our previous studies (Qian *et al.* 2010; Sia *et al.* 2010). In brief, bilateral CCA, external carotid artery (ECA) and internal carotid arteries (ICA) along with the bypass conduit were examined with a 9MHz linear array transducer of a computed sonography system (GE LogiQ E9) to determine time-average flow velocity (TAV).

This was performed after an initial 10 minutes of rest with subjects in a supine position with head slightly elevated and turned to the contralateral side by 10 to 30 degrees. Flow volume measurements were taken at 1-2 cm below the carotid bulb in the CCA, and 1-2 cm above the carotid bulb in the ECA and ICA or bypass anastomosis junction. The luminal diameter was determined on the B-mode image of the vessels as the distance between the internal layers of the parallel walls. The mean of 3 measurements was evaluated at the same site. The angle of insonation was 60°.

The TAV values were set as inflow boundaries condition in CFD modelling. The intravascular flow volume (FV) in each vessel or bypass graft was then calculated as the product of TAV and the cross-sectional area (A) of the circular vessels according to the formula FV=TAV x A ml/min. For computed tomography scanning, the medical imaging data CTA for the cerebrovascular bypass patients was performed with a helical CT scanner (GE Medical Systems) with multidetector-row capability. The data was obtained using a section thickness of 0.625mm and a table speed of 9mm/s. Zero-degree table and gantry tilt were used. Sections in DICOM format were acquired with a 512 x 512 matrix. Scanning was started from the arch of the aorta and continued parallel to the orbito-meatal line to the level of Circle of Willis during the intravenous injection of contrast material at the rate of 3.5ml/s. To allow for the creation of a 3D bypass geometry and volume rendering, a validated thresholding technique for regional segmentation and lumen cross-sectional contour was conducted in Materialise Interactive Medical Images Control System (MIMICS)(V 14.0; Materialise, Leuven, Belgium). The luminal surface of the vascular anastomosis in HF EC-IC was extracted in the format suitable for volume mesh generation used for fluid dynamic calculations. The optimum number of grid nodes, with best accuracy and optimum computing time, were carried out using ANSYS workbench (V 13.0, ANSYS, Inc., USA) on cluster desktop computers. CFD was performed with an assumption of a laminar, homogenous, incompressible blood flow with solid vessels vein graft, non-slip and non-penetration constraints at the wall. With the addition of real-time mean pulsatile velocities derived from Doppler ultrasound it was possible to evaluate the inlet and outlet flow boundary conditions, the results of blood flow pattern and distribution and pressure gradient across the patient-specific brain bypass. Kinetic energy, including the pressure gradient and energy dissipation impacting into the vascular graft, was similarly computed across the same cut plane by deriving the positive inbound velocities.

The blood flow performed by the computational analysis system of equations is the Navier-Stokes (N-S) equation and continuity equation that describe the most general movement of fluid medium (Qian *et al.* 2010; Sia *et al.* 2010). Due to the relative large size of the vessels examined (in comparison to individual blood cells) and the large shear rates in arteries, the blood flows were assumed to be Newtonian with constant viscosity (μ =4.0×10-3 Pa·s) and density (ρ = 1060 kg/m^3). The body forces of blood were omitted. An average Reynolds number of 200 - 300 was used as this is within the range of normal blood flow in humans. The energy loss (EL) between inlet and outlet used to evaluate the cardiac workloads was calculated by the equation, which is expressed as:

$$EL = \sum_{inlet}(P_{inlet} + \frac{1}{2}\rho v_{inlet}^2)Q_{inlet} - \sum_{outlet}(P_{outlet} + \frac{1}{2}\rho v_{outlet}^2)Q_{outlet}$$

For our patients, assumptions were made regarding the pressure distal to the anastomosis from data collected from the literature regarding normal capillary flow (Castro *et al*. 2008). A distal mean systemic pressure at the arterio-capillary junction of 45 mmHg (Castro *et al*. 2008) were chosen based on pressure modelling work in human circulatory system. The haemodynamic characteristics of HF EC-IC bypass blood flow patterns were also quantified along with their possible association to peri-operative clinical decisions. The general information of the patients and the characteristics of the HF EC-IC bypass were summarized in Table 7.1.

Statistic studies

The program GraphPad Prism (version 5.03) was used for statistical analysis. All the measured values are expressed as the mean ± standard deviation. Student's t test was used to reveal any difference in blood flow between the pre- and post- bypass surgery in both the ipsilateral and contralateral carotid arterial systems. Vessel cross sectional area correlation of flow volume parameters was evaluated with Spearman's rank correlation coefficient. The level of statistical significance was set at p<0.05 for all tests.

Table 7.1 Demographic features and location of intracranial pathology treated with extracranial-intracranial (EC-IC) inter positional saphenous venous grafting brain bypass

Pt	Age/ Sex	Treated pathology	Proximal Anastomosis	Distal Anastomosis	Bypass flow volume (ml/min)	Mean Velocity (PSV) cm/s	Max WSS (Pa)		Pressure gradient difference (mmHg)		Mean Blood flow velocity at 40 ml/min on bypass segment (cm/s)	Max WSS at 40ml/min BF (Pa)	Minimum MAP requires to deliver BF of 40ml/min on bypass segment (mmHg)
							Bypass ipsi-lateral	Normal contra-lateral	Bypass ipsi lateral	Normal contra-lateral			
1 JB	63/F	Left Intracavernous aneurysm	CCA	Intracranial ICA	250.6	45.1	26.5	NA	12.33	16.80	3.6	0.9	53.3
2 PH	62/M	Left Cavernous sinus meningioma	CCA	M1 segment of MCA	41.0	6.4	49.8	NA	30.58	35.80	3.1	0.62	52.6
3 RA	56/F	Left paraclinoid aneurysm	CCA	Intracranial ICA	159.7	36.6	19.5	NA	7.52	11.26	4.6	0.28	52.3
4 NR	36/F	Left ICA traumatic pseudoaneurysm	CCA	Intracranial ICA	238.3	28.1	18.2	21.0	2.11	1.52	2.4	0.46	51.2
5 RB	35/M	Right ICA false and dissecting aneurysm	CCA	Intracranial ICA	170.4	37.4	12.8	17.0	3.70	14.44	2.1	0.30	48.5
6 AB	47/M	Right ICA dissecting aneurysm	CCA	Intracranial ICA	146.6	29.4	25.4	17.5	20.42	38.38	4.0	0.47	53.4
7 DM	45/F	Right cavernous meningioma	CCA	MCA	98.8	49.9	2.3	15.5	14.53	47.38	10.1	2.98	56.1
8 ND	63/F	Left ICA aneurysm	CCA	Intracranial CCA	222	55.5	5.0	6.38	2.13	15.21	5.0	0.78	49.1

9 FR	28/F	Right ICA giant aneurysm	CCA	M1 segment of MCA	324.2	90.5	17.5	28.9	3.23	9.96	5.6	1.27	51.8
10 MH	32/M	Left traumatic dissecting ICA aneurysm	CCA	Intracranial ICA	126.3	24.3	22.0	15.2	9.04	34.66	3.8	0.56	49.5
11 GJ	46/M	Left intracavernous aneurysm	CCA	Intracranial ICA	225.5	59.9	7.2	18.7	2.77	18.10	5.3	0.80	49.4
12 PA	55/M	Left traumatic dissecting ICA aneurysm	CCA	Intracranial ICA	160.5	28.4	9.6	13.1	13.54	17.6	3.5	0.10	52.5

BF, Blood flow; ICA, internal carotid artery; CCA, common carotid artery; M1, M1 segment of middle cerebral artery; PSV, peak systolic velocity; WSS, wall shear stress; MAP, mean arterial pressure; NA, not available

Results

Blood flow volume and cross sectional area of bypass graft

In all 12 patients the ipsilateral and contralateral extracranial vessels were examined post operatively (24 vessels). Only 4 patients had pre-operative extracranial imaging available for analysis (8 vessels). Carotid Doppler volumetric examination revealed a mean bypass blood flow to deliver an average of bypass blood flow of 180.3 ± 76.2 ml/min was at 20.5 ± 10.8 cm/s (95% CI: 13.7-27.3). Mean ± standard deviation values for volumetric assessment for bilateral extracranial vessels of CCA, ICA, ECA and bypass grafts are summarized in Table 7.2. No statistical difference was found in each carotid vessel group between the pre-operative and post-operative period.

Table 7.2 Bilateral flow volumes in extracranial arteries before and after the bypass procedures

Vessels	Ipsilateral diseased side (ml/min ± SD)		Contralateral normal side (ml/min ±SD)	
	Pre op	After op	Pre op	After op
CCA	244.6± 123	308.4±99.7	279.6±56	343±66.9
ICA	178.4± 112	NA	211.8±70	242.1±92.9
ECA	90.3±31	101±50.2	86.5±42	106.1±48.3
Bypass graft	NA	180.3±76.2	NA	NA

Values are mean ± SD, expressed in millilitres per minutes.

Mean vein grafts diameter were 4.5 ± 0.8 mm. There was a positive correlation ratio of volumetric flow with cross-sectional area assessment of bypass graft and ECA (Qbypass/QECA *vs* Abypass/AECA) (Spearman's rank correlation coefficient r =2.0 p < 0.05). There was an average doubling of flow volume after surgery at any given cross sectional area (Figure 7.1). Following bypass surgery, there was a coefficient of volumetric per cross sectional area of ICA/ECA decrease within the contralateral carotid system of from 1.2 to 0.9. However, there were no statistical differences in these changes (Figure 7.2).

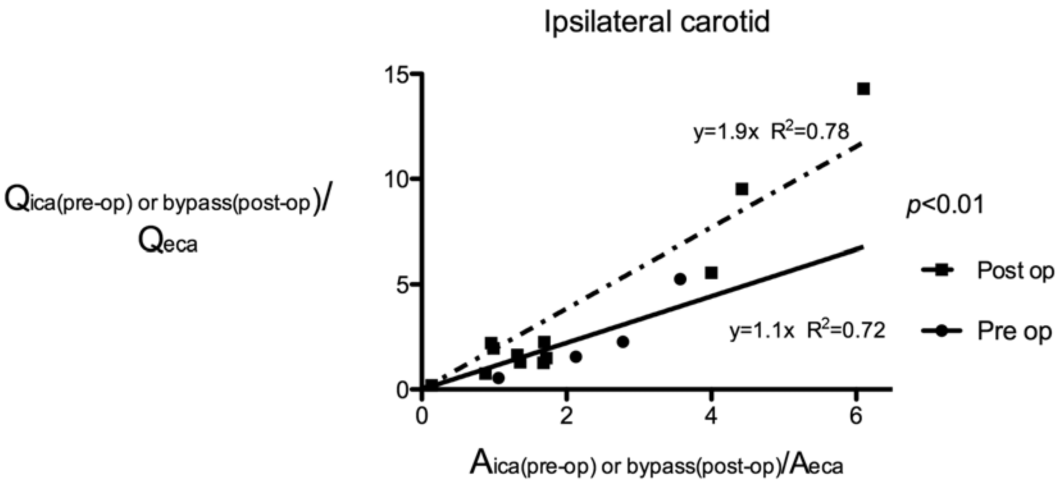

Figure 7.1 Volumetric flow with cross sectional assessment of diseased ICA(pre op), bypass graft(post op) with ECA

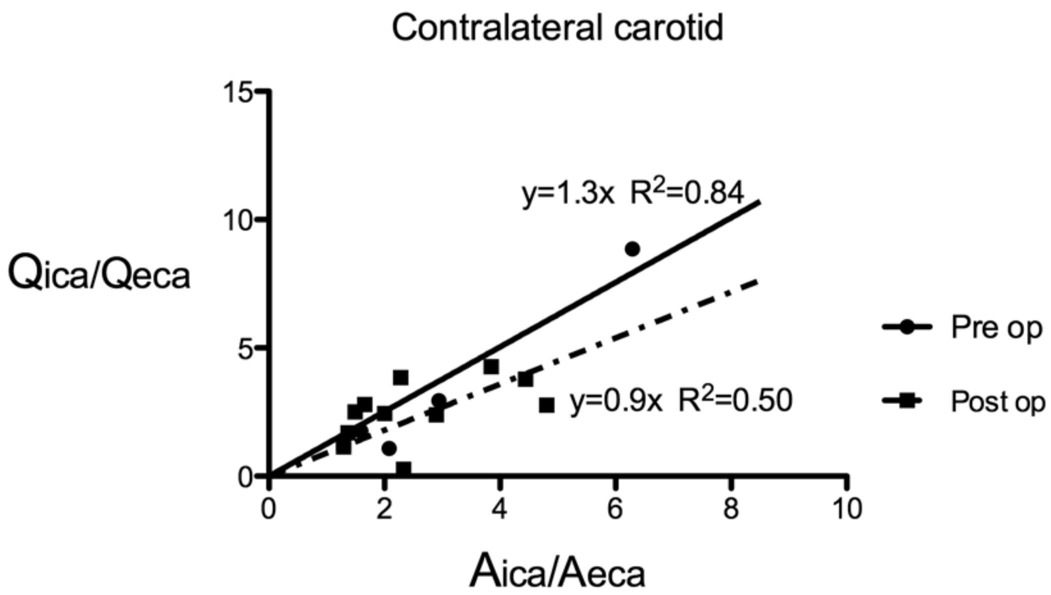

Figure 7.2 Volumetric flow with cross sectional assessment of contralateral ICA with ECA

Pressure gradient, WSS of the bypass graft

CFD derived time-averaged pressure gradient across the ipsilateral (to the bypass) ICA was 28.2 ± 6.9 mmHg prior to the bypass decreasing to 10.2 ± 8.7 mmHg (95% CI: 4.6-15.7) after bypass. This difference was significant. And also, there was significant pressure gradient difference between ipsilateral and contralateral carotid system after surgery (Figure 7.3). Mean max WSS at the heel region of proximal anastomosis (CCA to vein graft) was 17.9 ± 12.7 N/m2 (Pa) (95% CI: 9.8-26.1). There was no statistically significant difference in WSS between ipsilateral and contralateral carotid system after bypass surgery (Figure 7.4).

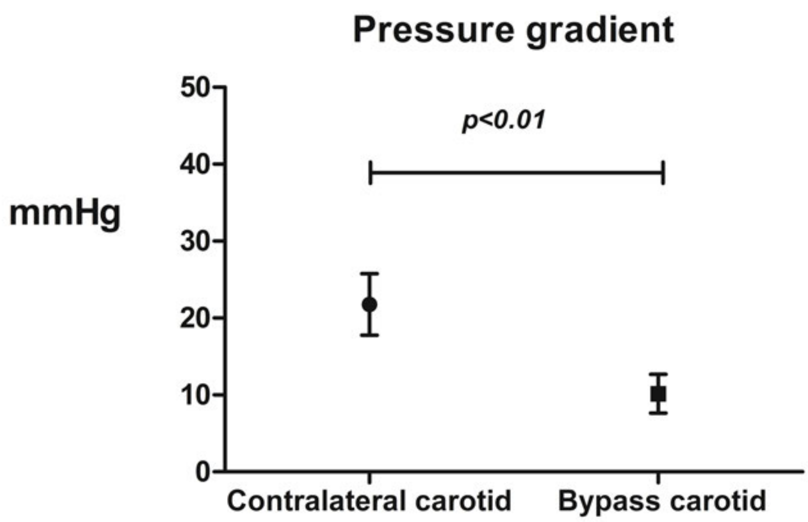

Figure 7.3 Pressure gradient between contralateral and bypass carotid system.

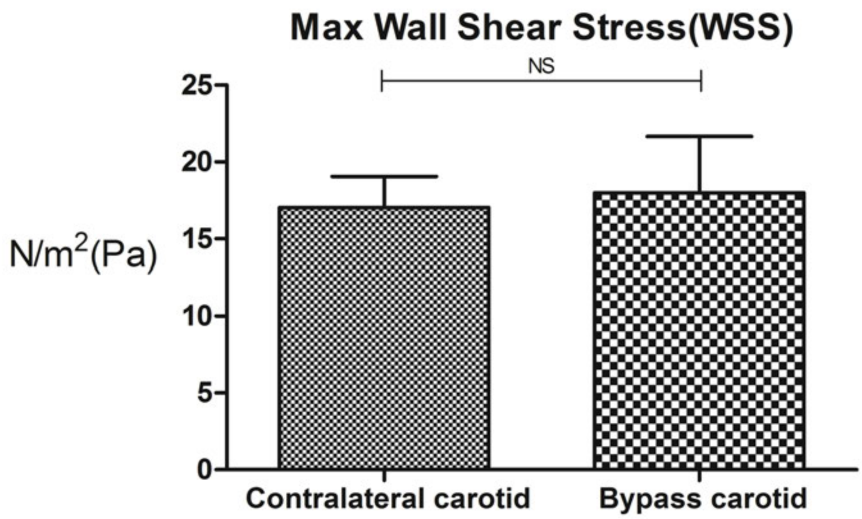

Figure 7.4 Max WSS between contralateral and bypass carotid system post surgery

Maximum WSS, blood flow velocity and mean arterial pressure in simulation bypass model at blood flow of 40ml/min

At blood flow of 40ml/min bypass model simulation, we observed mean max WSS at the heel region of proximal anastomosis (CCA to vein graft) were 0.8 ± 0.7 N/m2 (Pa) (95% CI: 0.3-1.2) (Figure 7.5) with a mean blood flow velocity across vein graft were at 4.4 cm/s (95% CI: 3.1-5.8). On computational haemodynamic simulation, the minimum MAP required to deliver a 40ml/min on bypass graft from the CCA donor site was 51.6 ± 2.31 mmHg (n=12).

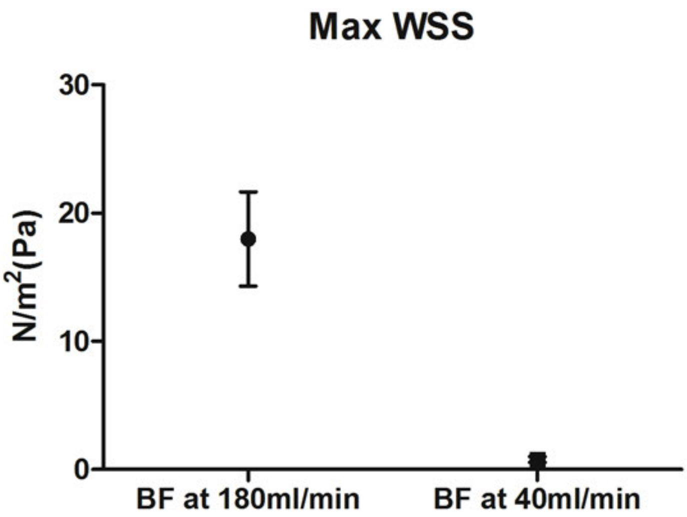

Figure 7.5 Maximum WSS of ipsilateral proximal anastomosis at blood flow of 180ml/min and 40 ml/min.

Discussion

Computational fluid dynamics technology (CFD) as a tool for studying patient-specific haemodynamic characteristic has increased in popularity. CFD has also been used for predicting cerebral aneurysmal rupture risk (Cebral *et al.* 2011; Cebral *et al.* 2011; Xiang *et al.* 2011), in-stent thrombosis mechanism (Jou *et al.* 2011) and arteriovenous fistula haemodynamic alteration in dialysis patients (Caroll *et al.* 2011). We have used this technique for the evaluation of HF EC-IC bypass (Sia *et al.* 2010). In the treatment of complex intracranial arterial disease, various interposition bypass operative strategies, techniques and approaches, have been described to replace the diseased intracranial artery and maintain brain blood flow (Morgan *et al.* 1994; Morgan *et al.* 2000; Nussbaum *et al.* 2000; Eguchi 2002; Morgan *et al.* 2002). The intraoperative parameters such as graft diameter and length are of important in surgical planning to ensure a good clinical outcome. Both the radius and the length of graft are critical to the impedance of graft flow and graft maintenance. Our approach to deliver the appropriate flow with the least amount of energy loss (encouraging the selection of interposition SVG with large diameters) along with graft sustainability must include consideration of the flow velocity that minimizes thrombogenicity at vulnerable locations (e.g. suture lines) as well as minimizing diameter changes at the proximal and distal anastomosis so as to reduce flow turbulence (David *et al.* 1997). In addition to the long-term goal of graft viability and sustainability, there is the short-term hurdle immediately after surgery of the critical importance of the pressure gradient upon flow. In our study, we set out to investigate the minimum MAP for EC-IC bypass surgery with interposition saphenous graft by using patient specific CFD models. We have chosen EC-IC bypass with use of vein as the graft in anterior circulation as they have a greater risk of failure than superficial temporal middle cerebral artery bypass grafts (Regli *et al.* 1995; Sia *et al.* 2011).

Blood flow volume velocity and cross sectional area of bypass graft

Our data suggested that a positive correlation ratio of volumetric with cross-sectional area assessment of bypass graft to ECA (Qbypass/QECA *vs* Abypass/AECA) (Spearman 's rank correlation coefficient $r = 1.9$ $p < 0.05$) with an average of flow volume double after the surgery at any given cross sectional area. With a greater bypass conduit wall distensibility and capacitance, larger blood flow volume would be expected to be deliver via bypass into ipsilateral hemisphere compared to pre-operative diseased artery (in cases in which there is an unhealthy arterial wall to be excluded). Carotid Doppler volumetric examination revealed a blood flow of the bypass graft was 180.3 ± 76.2 ml/min at mean velocity of 20.5 ± 10.8 cm/s. However, there is a great variation in results of similar studies and a great variation in graft patency (include study with ELANA). Our flow results are high compared to Eguchi's vein bypass series (Eguchi 2002) where mean bypass flow was 109ml/min (n=59) when measured with a magnetic flow meter intra-operatively. In the Mayo clinic series (Regli *et al.* 1995), mean graft flow rates at surgery were 100ml/min for anterior circulation saphenous vein bypass grafts, and 110 ml/min for posterior circulation grafts. This increased to greater than 200 ml/min in some grafts at follow-up. Jafar and colleagues, for some cases, reported intraoperative blood flow measurement in saphenous vein bypass grafts in excess of 250ml/min (Jafar *et al.* 2002). Such variations may be explained by patient selection, the circumstances in which measurements were recorded and differences in techniques used to measure the blood flow.

On the contralateral carotid system, coefficient of volumetric per cross sectional area of ICA/ECA was noted to decrease from 1.2 to 0.9 following bypass surgery. This result is not entirely unexpected where bypass flow is substantially greater than normal ICA flow. The interpretation of this result is that the average bypass flow in our series contributed to the contralateral circulation.

Pressure gradient and WSS at bypass graft

Case selection influences the pressure gradient across the anastomosis sites. These pressure gradients determine the blood flow rate and velocity of flow. This velocity of flow has a direct bearing upon the WSS within the vein graft conduit. WSS must fall within a critical range, outside which occlusion will occur. It has been documented that intimal hyperplasia or atherosclerotic plaque usually arises at the arterial bifurcation, the "toe" and the "heel" of the anastomosis, and in area where flow separation is evident with low oscillatory shear stress (WSS), typically less than 0.4 Pa (Westerhof *et al.* 2005). The amount of WSS depends on the geometry of anastomosis (recipient vessels radii), blood flow velocity and pressure gradient across the bypass construct. Areas of normal or above shear (> 1 Pa) induce an atheroprotective endothelial phenotype (Davies *et al*. 1995; Malek *et al.* 1999). In our study, the estimated peak value for WSS at the heel junction of donor CCA proximal anastomosis was 17.9 ± 12.7 Pa (95% CI: 9.8-26.1), which is considered sufficient to prevent disruption of the endothelium dysfunction and atherosclerosis formation (Westerhof *et al.* 2005).

In addition, the significant pressure gradient difference between ipsilateral and contralateral carotid system after surgery (Figure 7.3), with least flow resistance on the bypass venous conduit, would help explained the increase in bypass blood flow to cerebral hemisphere post-operatively. This finding also support the previous interpretation of that the average bypass flow in our series contributed to the contralateral circulation.

Maximum WSS and optimum mean arterial pressure (MAP) in bypass model simulation at blood flow of 40ml/min

Sundt estimated that vein grafts require a minimum flow rate of 40 ml/min to maintain a good patency rate (Sundt *et al.* 1987). Our data suggested that at a blood flow rate of 40ml/min the bypass model predicts an estimated peak values for WSS at the proximal anastomosis of 0.8 ± 0.7 Pa. At these values, there is an atheroprotective endothelial and non-thrombogenic environment predicted to prevent atherogenesis and restenosis from intimal hyperplasia. At lower flow rate or no flow, low oscillatory shear stress (<0.4 Pa) may lead to endothelial dysfunction, inhibition of NO-synthase, greater endothelial cell cycling and increase in apoptosis (Davies *et al.* 1995; Malek *et al.* 1999; Westerhof *et al.* 2005).

We also investigated the MAP requirement to maintain the patency of the graft. While the focus is often upon the long-term patient outcome, the maintenance of flow in the immediate post-operative period is critical to prevent occlusion at the potential sites of thrombosis (such as the suture line). Sundt reported that graft flow of 40ml/min was the minimum required to prevent early post-operative occlusion (Sundt *et al.* 1987). This is supported by our CFD analysis. If we assume that the mean systemic pressure at arterio-capillary junction is 45mmHg (Castro *et al.* 2008), our computational modelling suggests that a graft flow of 40 ml/min requires a mean common carotid arterial pressure of 51.6 ± 2.31mmHg. Data also suggested that common carotid arterial pressure is approximately 10mmHg lower than the radial arterial pressure on the supine position during the surgery (Kono 1990). Therefore, our model predicts a MAP below 60mmHg in the immediate postoperative period may predispose to early occlusion.

This study concluded that postoperative MAP below 60mmHg may lead to a negative outcome (bypass flow< 40ML/min and early occlusion). This work provides proof and verification, based on fluid mechanics, of the existing literature (Sundt et al 1987), on the use of CFD in patient-specific models with personalised flow boundary conditions, something that has tremendous potential in terms of treatment planning and outcome.

The careful attention to MAP during operation not only ensures good flow for graft patency, it also helps guide in postoperative blood pressure management to reduce the incidence of haemorrhagic transformation when flow is established through the bypass (Sia *et al.* 2011). Therefore, MAP between 60-80mmHg will continue to be considered a reasonable protocol in our unit.

Limitations

For computational simplicity, the assumptions that the vessels are rigid tubes have been applied. However, Bergel (Bergel 1961) has demonstrated that for an artery under approximately 100mmHg, the elastic modulus of the carotid artery would be 0.65MPa. This value is consistent with Troii"s study (Troii *et al* 2006) where for a similar blood pressure and arterial elastic module, the impact upon the arterial radius was minimal and may not be of significance. Furthermore, the present study was to compare the pressure gradient between the ipsilateral and contralateral carotid systems to determine mean arterial blood pressures below which early graft failure may ensue. Therefore, it is reasonable to assume the effect of vessels elasticity would have minimal impact upon the analysis of our findings.

Conclusion

Maintaining adequate MAP during HF EC-IC bypass surgery is an essential part of the procedure and will assist in achieving a high rate of graft patency and adequate cerebral blood flow. The present study shows that simulation CFD can be applied to studies of haemodynamics in cerebral revascularisation surgery. CFD analysis enables us to predict blood flow influence, WSS changes, and pressure gradient onto a saphenous vein graft as well as the contralateral carotid arteries. CFD may help in surgical planning and estimate the outcomes of EC-IC bypass surgery.

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Chapter 8

Flow resistance analysis of high flow extracranial-to-intracranial bypass

Abstract

Though high flow extracranial to intracranial bypass surgery has often been used in the treatment of diseased internal carotid arteries, its evaluation is still empirical. The purpose of this study was to propose an innovative approach for the evaluation of extracranial to intracranial bypass surgery based on the analysis of flow resistance in the vein bypass graft and in the contralateral carotid arteries using computational fluid dynamics. Seven patients who underwent high flow extracranial to intracranial bypass surgery were examined with high-resolution computed tomography angiogram (CTA). The reconstructed three-dimensional geometries were segmented to create computational fluid dynamics calculation domains. Colour Doppler ultrasound was used to measure blood flow velocities at the common carotid artery, to determine inflow conditions. Based on the pipe flow theory, drops in pressure are described as $\Delta p = A\dot{m}^2 + B\dot{m}$ where A and B are flow resistance coefficients $\dot{m}$ is blood mass flow rate. Computational fluid dynamics results revealed that, for a healthy internal carotid artery, an average value of A and B were 0.013088 Pa/(ml/min)^2 and 3.105 Pa/(ml/min), respectively. For a vein bypass graft, an average value of A was 0.0143 Pa/(ml/min)^2 and B 3.402Pa(ml/min), which were close to that of healthy internal carotid artery. However, if a bypass utilising a vein as the conduit possesses valves or has a smaller diameter than usual, the flow resistance in that bypass will increase. An imbalance of flow resistances may impose conditions predisposing to haemodynamic failure or aneurysm development distally.

Keywords: Extracranial-to-intracranial (EC-IC) bypass, computational fluid dynamics, flow resistance, venous bypass

Introduction

Extracranial-to-Intracranial (EC-IC) bypass surgery is a surgical procedure to augment or replace cerebral blood flow. For high flow EC-IC (HF EC-IC) bypass, the long saphenous vein is used as the conduit and is interposed between the common carotid artery (CCA) and the intracranial internal carotid artery (ICA), the middle cerebral artery (MCA) or the posterior cerebral artery (PCA). EC-IC bypass surgery has been available for treating selective intracranial vascular pathology for more than 50 years. Woringer reported the first HF EC-IC bypass surgery in early 1960s (Woringer *et al.* 1963). Since then neuroradiologic studies have demonstrated the beneficial effects of bypass surgery on cerebral haemodynamic status (Anderson DE *et al*. 1992).

However the evaluation of HF EC-IC bypass surgery is still empirical (Sia SF *et al.* 2010) and the more common, but low flow, superficial temporal artery to middle cerebral artery (STA-MCA) has failed to improve clinical outcomes in a randomized trial (Group 1985; Powers *et al.* 2011). As a result, EC-IC bypass surgery is not the first line treatment of choice in any category of intracranial vascular disease (Thanvi B *et al.* 2007). In a recent meta-analysis, in a subset of haemodynamic failure patient who underwent EC-IC bypass surgery, 10% of patients sustained cerebral infarction despite optimum surgical intervention (Garrett MC *et al.* 2009). Eguchi reported 70 HF EC-IC bypass procedures in 61 patients, performed over 25 years, and indicated that a failure of EC-IC bypass surgery is best avoided by: untwisting the interposed venous conduit; careful blood pressure control following surgery; and attention paid to maintaining euvolaemia (Eguchi T 2002). Eguchi's results contributed to our postulation that quantitative description of flow resistance is helpful to evaluate bypass surgery. Our aim for this study was to understand the impacts upon cerebral haemodynamic status of HF EC-IC bypass.

By using pipe flow theory (Brater FE *et al.* 1976), for laminar flow, pressure drop within a tube can be described as $\Delta p = A\dot{m}^2 + B\dot{m}$. A and B are flow resistance coefficients and $\dot{m}$ represents mass flow rate. It had already been demonstrated that blood flow obeys the pipe flow theory (Allan CR 1976; Klanchar M *et al.* 1989), and thus, by calculation A and B the quantitative relation between flow rates and pressure drop can be obtained.

Though flow resistance coefficients (A and B) in bypass could be summarised from experimental work, in-vivo measurement of intravascular haemodynamic is always a challenging task. Colour Doppler Ultrasound (CDU) could provide flow rates in CCA, ICA, external carotid artery (ECA) and the interposition venous conduit bypass. However, operator dependent probe handling and artery wall deformation due to probe placement may lead to inaccuracy of measurement (William JZ *et al*. 1981; Morin JF *et al.* 1988; Zhang Y 2006). Kodoma and colleagues used phase contrast MRI to evaluate EC-IC bypass patency rate. Despite these useful techniques, patency rate itself is not sufficient to describe flow regularity in a bypass (Kodoma T *et al.* 1995).

Invasive intra-aneurysm sac pressure measurements method has been used to assess the effectiveness of endovascular repair in the management of abdominal aortic aneurysm (AAA) (Dias NV *et al.* 2004); it has not, however, been able to apply to aneurysms that occur intracranially. In addition to in-vivo measurements, computational fluid dynamic (CFD) is an alternative approach to the analysis of blood flow within aneurysms and carotid arteries (Qian Y *et al.* 2007). Previous publications reported that CFD has been used to evaluate blood mass flow pattern, pressure drop, and wall shear stress (WSS) within aneurysms and the arteries of origin (Carallo C *et al.* 2006). Advanced CFD methods such as direct numerical simulation, lattice Boltzsmann method, and smoothed particle hydrodynamics method were also used to analyse haemodynamic changes in aneurysms (Boyd J *et al.* 2008; Lee SG 2008; Chui YP *et al.* 2010). To date, few CFD publications have directly examined the relationship between flow resistance and outcomes of HF EC-IC bypass surgeries.

The objective of this study was to propose an innovative approach based on the pipe flow theory and to evaluate HF EC-IC bypass surgery using CFD analysis on flow resistance in vein bypass grafts. In order to perform a meaningful CFD analysis, comparison were then made with the contralateral carotid arteries of the patient.

Method

Patient information

Seven patients (4 females and 3 males), age ranged from 28 to 63 years old, were examined by computerised tomographic angiography (CTA) after having HF EC-IC vein bypass surgery. Demographic feature of patient's age, gender, graft diameter and graft anastomosis were listed in Table 8.1.

Table 8.1 Demographic features, graft diameter and position of distal graft anastomosis

Case	Gender	Age	Distal graft anastomosis	Graft internal Diameter (mm)
1	F	28	CCA-MCA	3.63
2	M	32	CCA-ICA	4.20
3	M	62	CCA-MCA	4.75
4	F	56	CCA-ICA	5.90
5	M	35	CCA-ICA	4.90
6	F	45	CCA-MCA	2.65
7	F	63	CCA-MCA	3.37

All proximal anastomoses were end-to-side anastomosis to the common carotid artery (CCA) and distal anastomoses were either an end-to-end anastomosis to the intracranial internal carotid artery (ICA) or an end-to-side anastomosis to the middle cerebral artery (MCA) (dependent upon intracranial vascular pathology and the requirement for surgical arterial trapping). In order to compare with contralateral ICA, all bypass simulations were calculated from the CCA to the MCA. Three-dimensional (3D) geometries of the bypass grafts and the contralateral carotid arteries were reconstructed and segmented using a commercial software package- Materialise Interactive Medical Image Control System (MIMICS) for CFD calculation domain.

Pipe flow resistance

The Darcy–Weisbach equation (Brater FE *et al.* 1976), which is widely used for pipe flow calculation, is an equation that relates the pressure loss due to friction along a given length of pipe to the average velocity of the fluid flow. This equation can approximate blood flow in larger vessels under defined conditions (see below) (Bergel DH 1961). If the flow is laminar, the pressure drop can be described as follows:

$$\Delta p = \frac{1}{2}\lambda(\frac{L}{D})\rho v^2$$

Where Δp is the pressure gradient,$\lambda = \frac{64}{Re} = \frac{64\mu}{\rho v D}$ μ is the viscosity of fluid, L is the length of the tube and D is the diameter of the tube. Equation above can be re-written as:

$$\Delta p = 32\frac{\mu}{\rho}(\frac{L}{D^2})\rho v$$

If the tube has elbows and other bends, then the pressure gradient for those specific elements need to be calculated using the following equation:

$$\Delta p = \frac{1}{2}\xi\rho v^2$$

where ξ is a constant value for a specific shape of bend.

As with other fluids, blood is incompressible. The pressure drop with blood flow in an irregular conduit like a bypass or ICA, can be described as:

$$\Delta p = A\dot{m}^2 + B\dot{m}$$

where $\dot{m}$ is the mass flow rate inside the tube. A and B are coefficients that are only defined by structures. A and B are constant values for a specific artery. Thus, if the same amount of blood passes through different arteries, higher values of A and B will result in a higher pressure drops.

It should be pointed out that equation above is accurate only under the assumption that vessels are rigid tubes. Bergel's work demonstrated that for an artery under approximately pressure of 160 mmHg, the relation between pressure and blood flow rate still satisfies a parabolic function. However, for a pressure greater than 160mmHg, the pressure drop will increase at a slower rate compared to that as calculated by the parabolic function (Bergel DH 1961). As the average pressure within the CCA is 90 mmHg, the rigid wall assumption is acceptable.

CFD modelling

Segmented diseased ICA, bypass, and contralateral ICA are shown in Figure 8.1a. 3D geometry was built based on the "contour interpolation" to generate 2D contours from grey scales of pixels, with 3D geometry segmented by interpolation of those 2D contours in the normal direction. This method prevents the intrusion of surface noises. Instead of using "global smoothing", we used manual "local smoothing" to keep the 3D geometry as realistic as possible. This method sets an average error to be one-third of a pixel in size (Jamali AA *et al.* 2007).

The grid arrangement at the bypass outlet is shown in Figure 8.1b. More than 300,000 elements were used for the whole bypass calculation. Among them were over 100,000 prism boundary elements, which help to calculate wall shear stress (WSS) at boundary layers that cause friction and lead to pressure drops in arteries. It should be noted that 100 mesh layers were extruded in the outer normal direction for all boundaries (not shown in the figure), which helps to minimise the error resulting from uncertain inlet and outlet positions secondary to image processing.

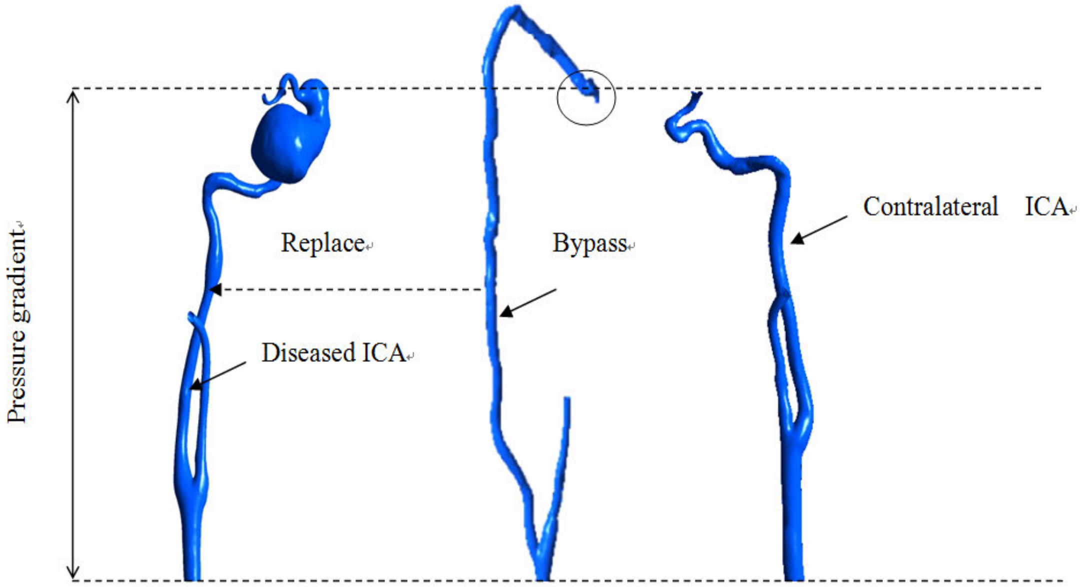


Figure 8.1a Segmented diseased ICA, bypass, and contralateral ICA

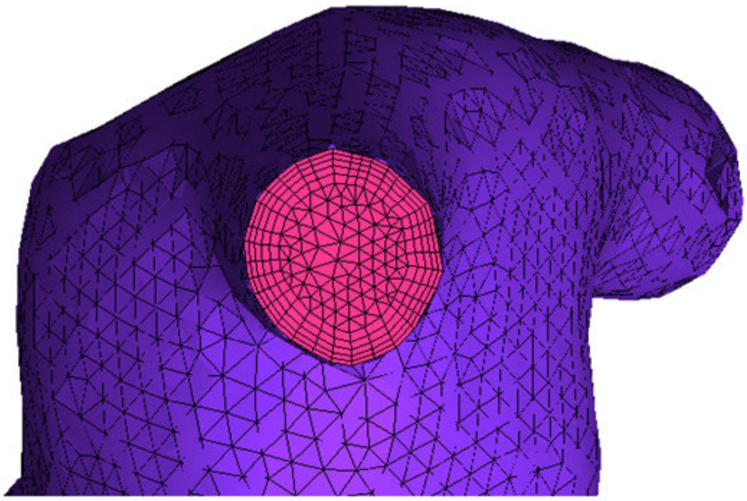


Figure 8.1b Mesh generation model

The Navier-Stokes equations for 3D steady flow with rigid walls were solved using the CFX finite-volume-based CFD solver in ANSYS 12.1 package. Blood was assumed to be a Newtonian fluid with density of 1050 [kg/m^3], and dynamic viscosity of 0.0036 [Pa・s]. The flow reached steady state, and the flow pattern was considered to remain laminar.

Following bypass surgery, CCA inflow velocities measured by CDU were used as inflow conditions for CFD simulations. Diseased ICAs were occluded after surgery. Distal graft anastomoses were either to the MCA or the intracranial ICA. Currently, CDU is unable to be used on intracranial vessels. The Circle of Willis is the anastomotic ring linking the major intracranial vessels at the base of the brain. This anastomotic ring consists of the internal carotid arteries between the posterior communicating artery and the anterior cerebral artery, the anterior cerebral arteries from their origin to and including the interconnecting anterior communicating artery, and the terminal basilar artery with its two posterior cerebral arteries to each of the posterior communicating arteries that anastomose with the internal carotid artery. Because of this anastomosis blood flow pressure gradients and the distribution of oxygen-rich arterial blood is equalized throughout the cerebrum (Cieslicki K *et al.* 2005). Therefore, in the normal cerebral circulation, common pressure points could be assumed at corresponding outlet boundaries during CFD simulation. Hence, simulation inaccuracy is minimised. The purpose of this study was to calculate the pressure gradient from the CCA to the Circle of Willis.

In flow resistance assessment, by adjusting the inlet mass flow rate of the CCA, different mass flow rates of the bypass and ICA were obtained. Based on pressure drop regression curve at different mass flow rates, flow resistance coefficients (A and B) were determined.

Results

Pressure drops and mass flow rates after bypass surgery

Following HF EC-IC bypass surgery, the pressure drops were comparable and similar in both bypass and contralateral ICA (Fig 8.2a). With the exception of cases 6 and 7, the pressure drops for other cases were less than 3000Pa (25 mm Hg). The distribution of mass flow rates at both the bypass and ICA (Fig 8.2b) showed that the mass flow rates of both sides were statistically balanced after surgery.

Comparisons of flow resistance, before and after bypass surgery

In order to compare the flow resistance before and after bypass surgery, Case 1 was selected for simulation. As shown in Figure 8.3, prior to bypass surgery, the flow resistance in diseased ICA [A = 0.0979Pa/(ml/min)^2 and B = 6.153/(ml/min)] was 3 times higher than that of contralateral ICA [A =0.027Pa/(ml/min)^2 and B =2.828 Pa/(ml/min)]. After bypass surgery, the flow resistance in the bypass [A =0.0107Pa/(ml/min)^2 and B =2.874 Pa/(ml/min)] was closer or lower than that of contralateral ICA. This comparison clearly indicated that the high flow bypass successfully improved flow resistance by replacing the diseased ICA.

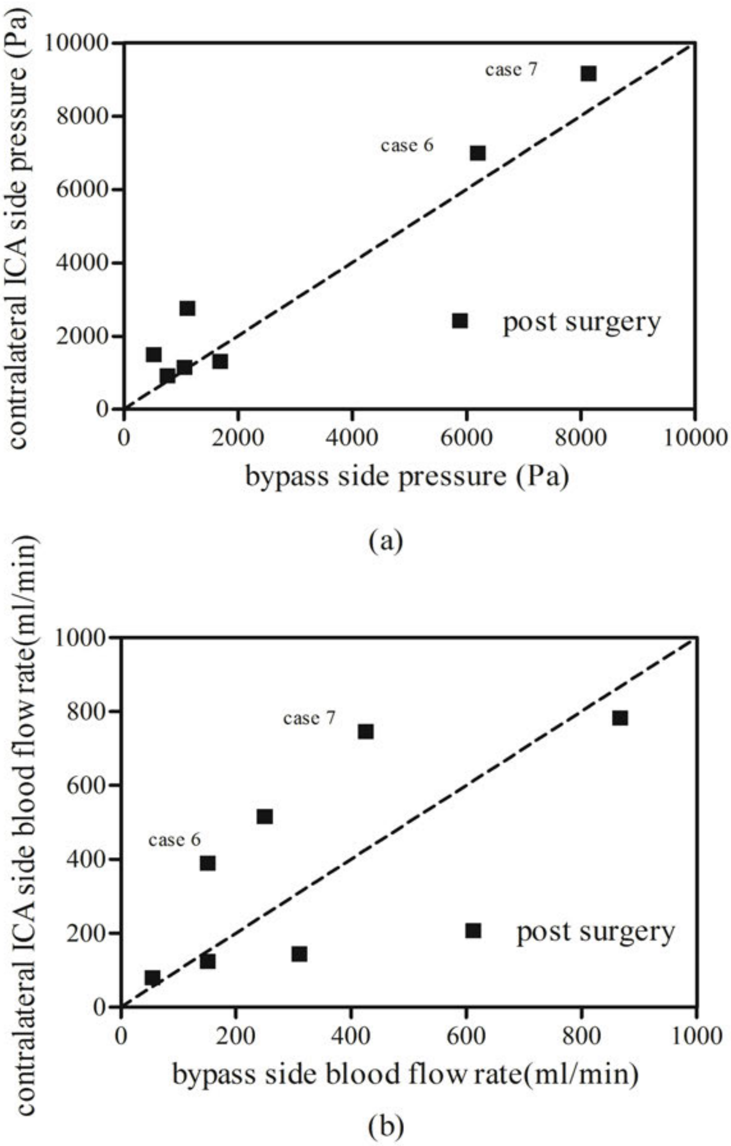


Figure 8.2a Pressure drop at contralateral ICA VS bypass. b Mass flow rate at contralateral ICA *VS* bypass.

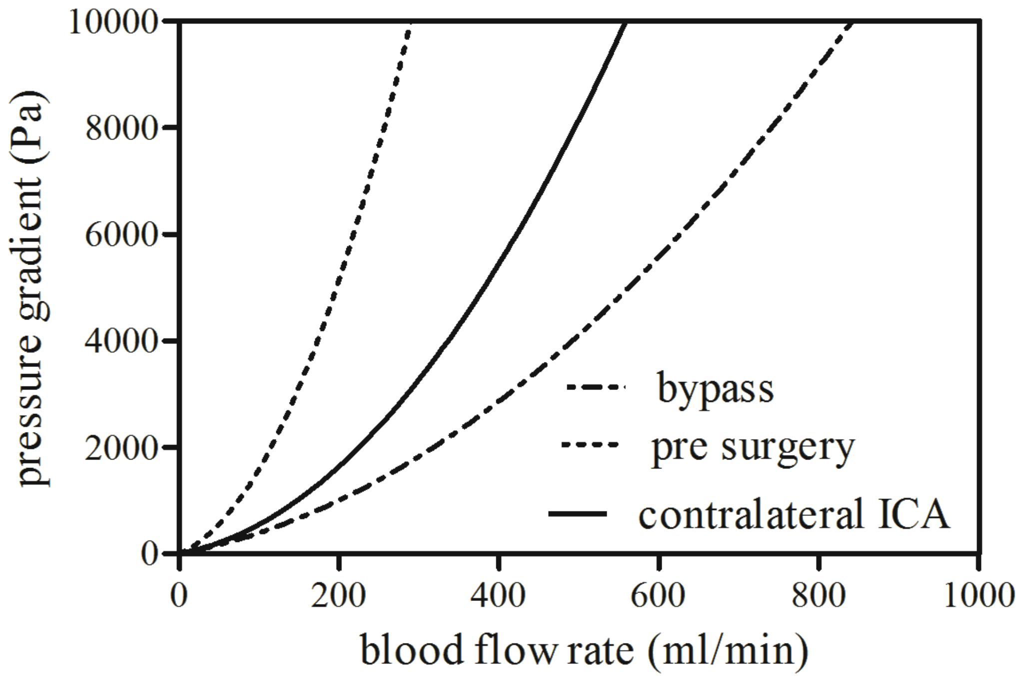


Figure 8.3 Flow resistances before and after a bypass surgery (case 1)

Flow resistances of bypasses and their contralateral ICA.

Comparison of flow resistance in bypasses and their contralateral ICA were made after surgery. As shown in Figure 8.4a and 8.4b cases 2,3,4 and 5 demonstrated similar flow resistances comparing the bypass with the contralateral ICA. For these cases, the presence of a bypass made a significant contribution to haemodynamic balance between the left and right CCA. However, in cases 6 and 7 (Figure 8.4c), the flow resistances in the bypass were higher than that of the contralateral ICA. Table 8.1 showed an average diameter (D) for each graft used. For case 6, the bypass diameter was 2.65mm, which was much smaller than an average bypass diameter 4.2mm. As a result, the flow resistance within the bypass increased. For case 7, the bypass diameter was 3.37mm, which was also smaller than an average bypass diameter. Furthermore, as shown in Figure 8.5, the presence of a point of narrowing of the interposition vein graft, at the site of a valve, has resulted in an increase of local flow resistance.

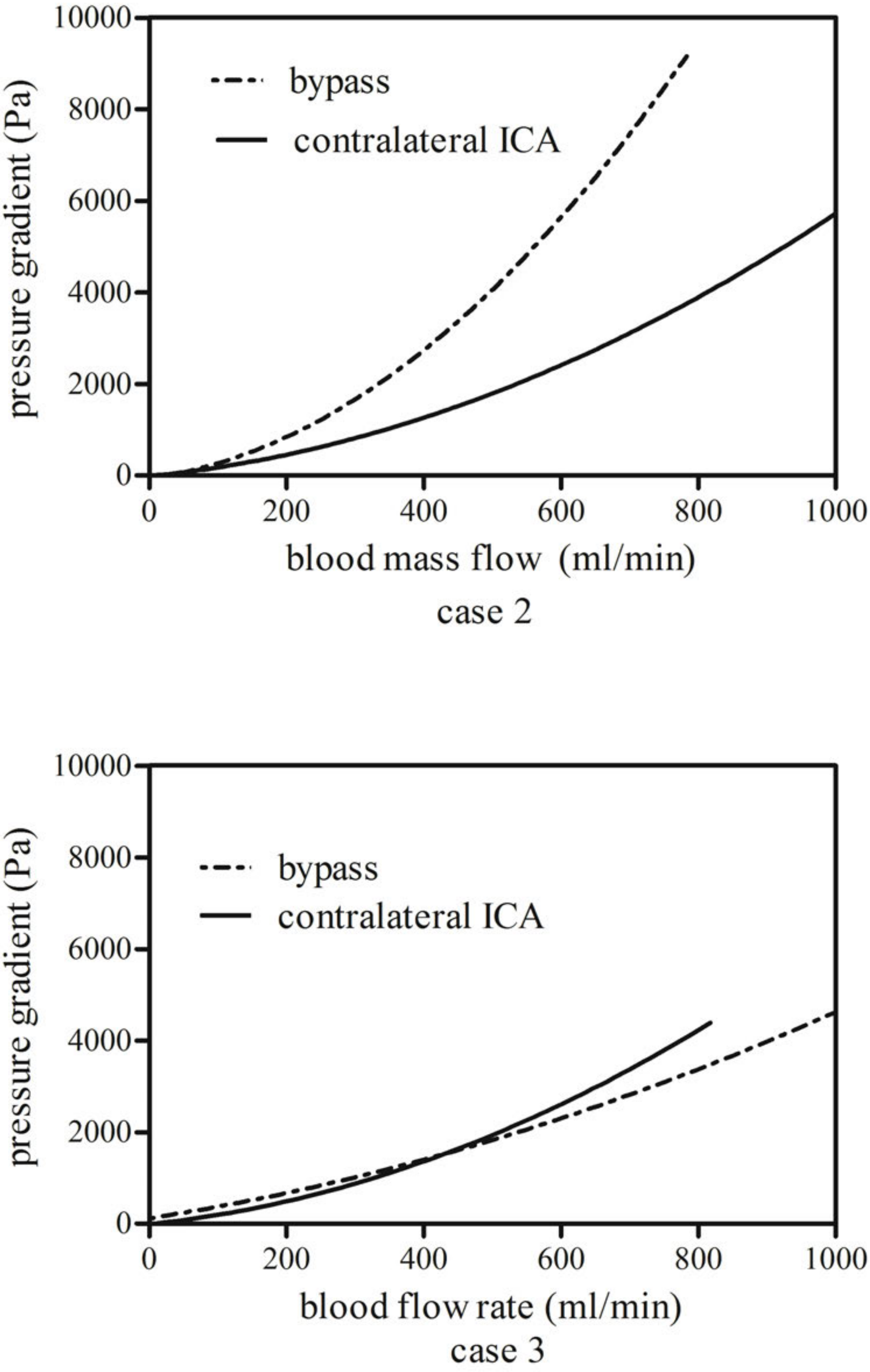
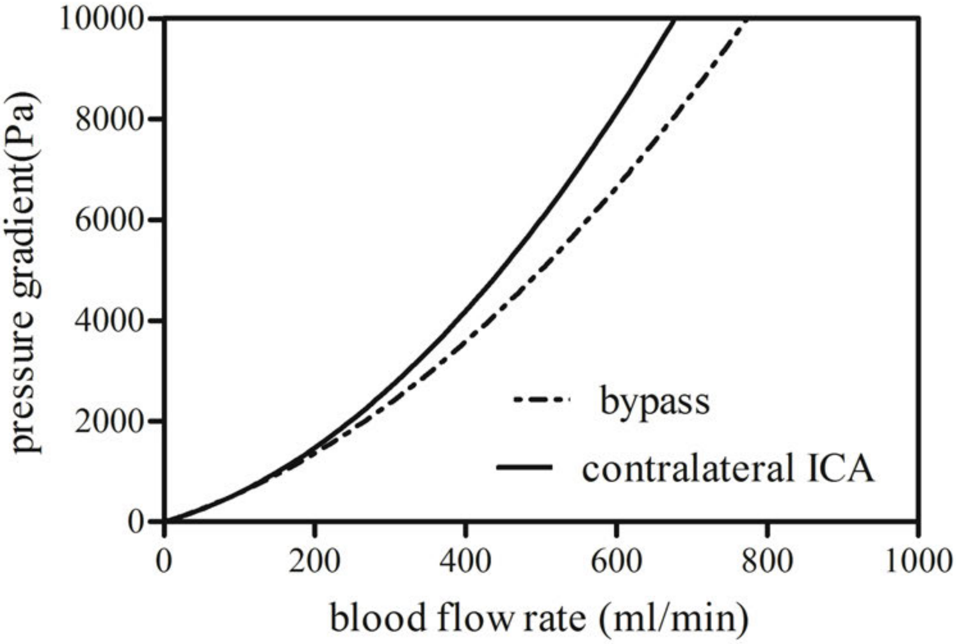
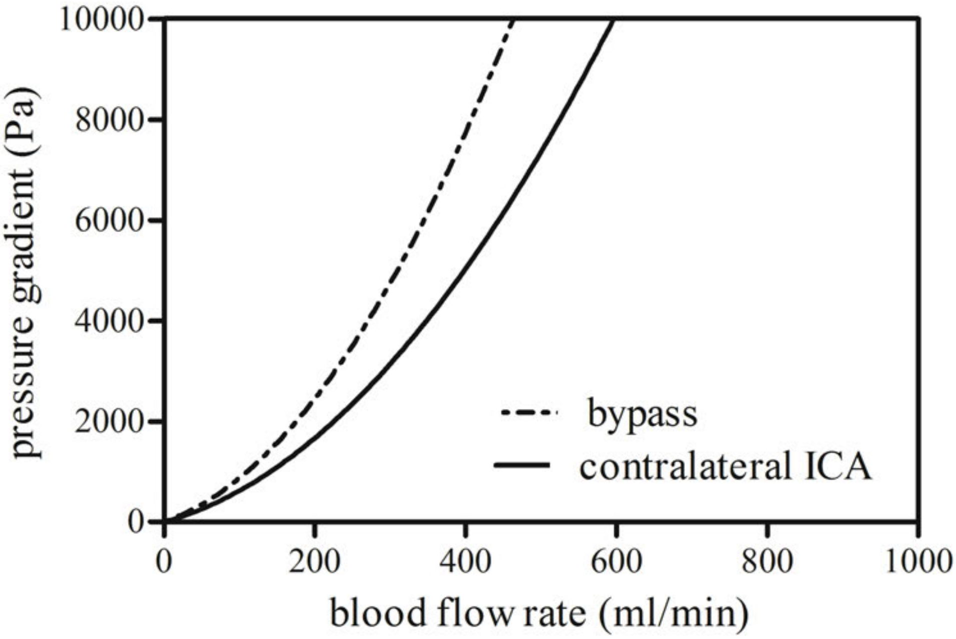


Figure 8.4a Flow resistance: bypass vs. ICA for case 2 and 3

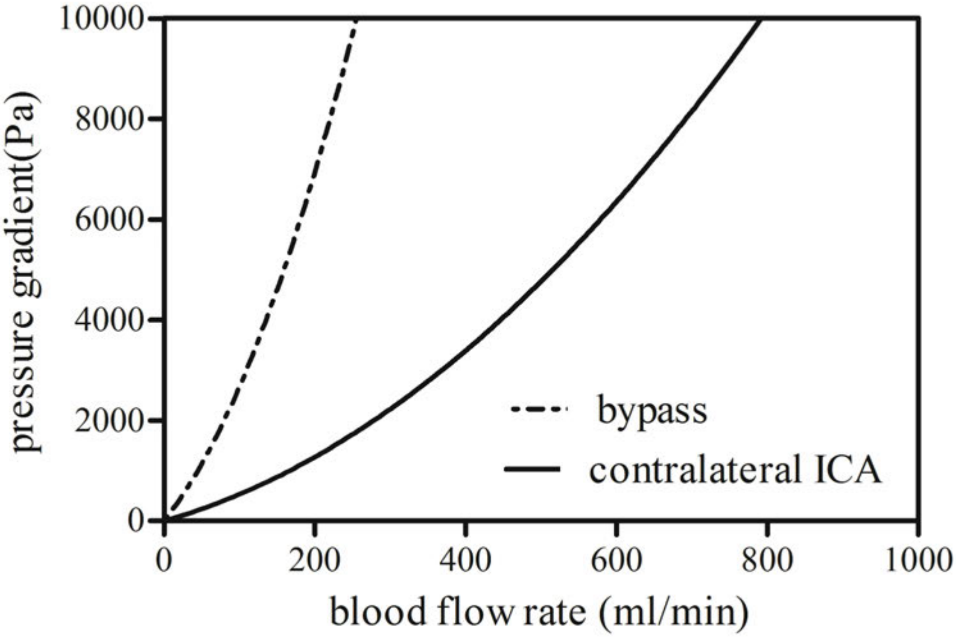


case 4

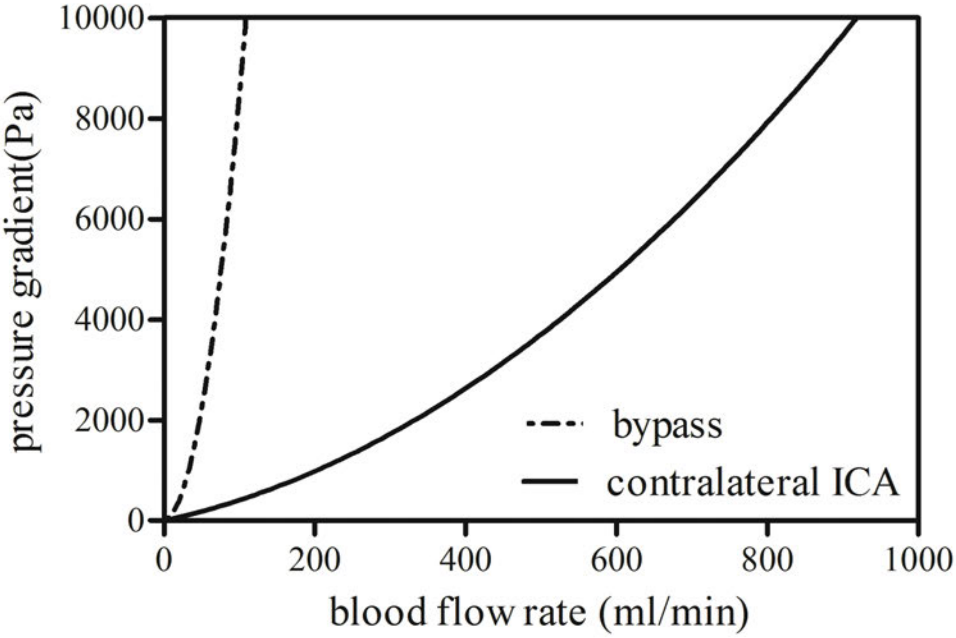


case 5

Figure 8.4b Flow resistance: bypass vs. ICA for case 4 and 5



case 6



case 7

Figure 8.4c Flow resistance: bypass VS ICA for case 6 and 7

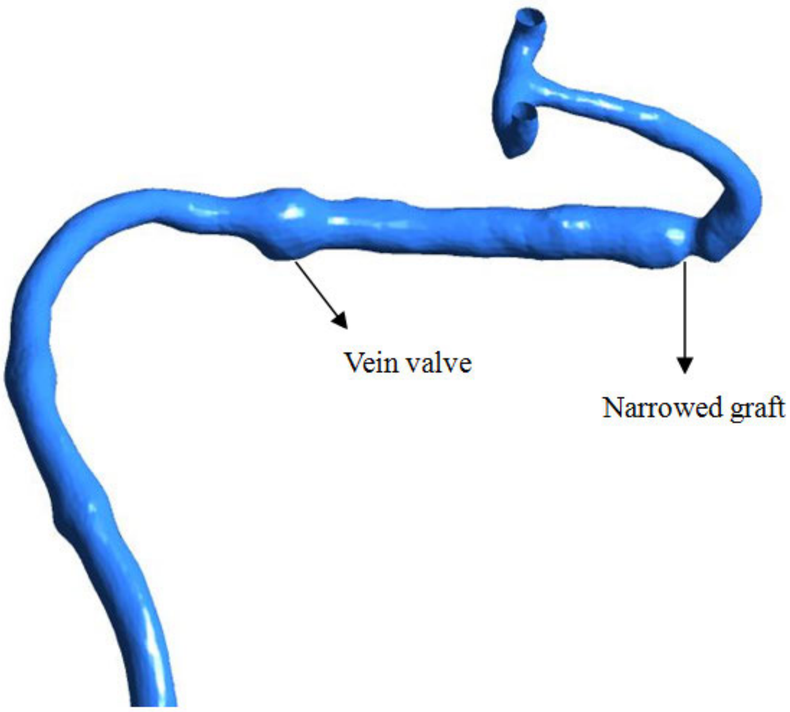


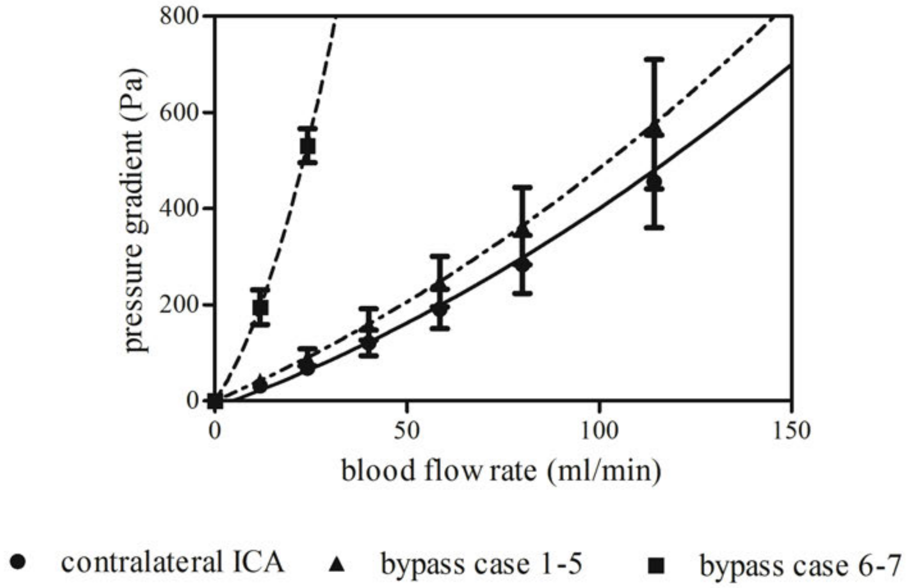
Figure 8.5 CFD bypass model of case 7.

Modelling flow resistance in bypass and ICA

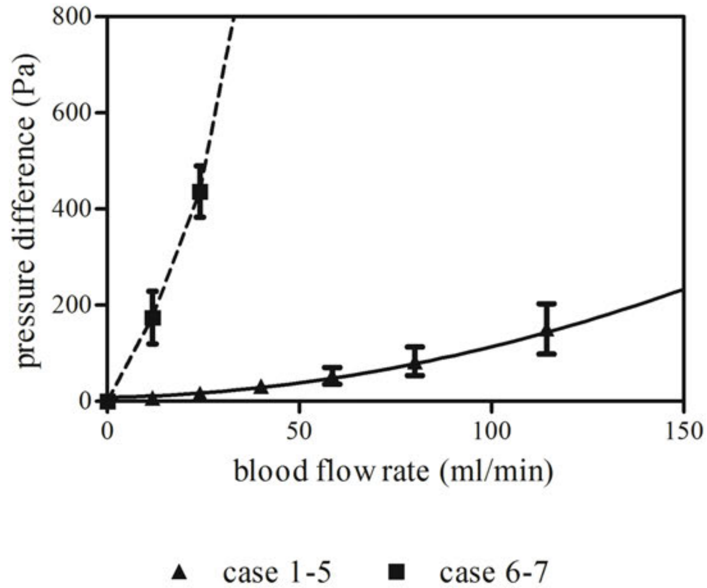
The blood flow modelling through the bypass in this study was for velocities between 0 and 150 ml/min. This was based upon the clinical demonstration of an average bypass flow rate of 109 ml/min (Eguchi, 2002). Pressure gradients simulation between proximal and distal bypass, under various flow conditions, were shown in Figure 8.6a. The calculated average for the resistant value of A of the contralateral ICA was 0.013088 Pa/(ml/min)^2 and B was 3.105Pa/(ml/min) with standard derivations (SD) of less than 25% of calculated pressure gradient. Excluding cases 6 and 7, the average resistance A and B values of the bypass graft was 0.0143 Pa/(ml/min)^2 and 3.402Pa/(ml/min), respectively. These flow resistance, following bypass surgery, were similar to the contralateral ICA. In contrast, flow resistances of A and B in cases 6 and 7 were 0.444 and 11.25 respectively. These results are considerably greater than that of the contralateral ICA.

The differences in pressure gradients between the bypass and the contralateral ICA are shown in Figure 8.6b. In cases 1-5, the pressure difference was less than 200Pa (1.5mmHg) at blood flow rate of 109ml/min. However, in cases 6 and 7, simulating flow rates within the bypass at the minimum of 40 ml/min resulted in a pressure difference between the bypass and the contralateral ICA of 800 Pa (6 mmHg). Furthermore, if the flow in the bypass is simulated at 109 ml/min, the pressure difference between the bypass and contralateral ICA and would exceed 5,000 Pa (38 mmHg). This is physiological impossible. An imbalance between flow resistance of each side results in an imbalance in their pressure gradients, which in turn, will influence flow equilibrium within the Circle of Willis.

In this series, saphenous vein graft lengths of 25-28 cm were chosen for all cases. Our results confirm that with a graft length of 25-28cm, a balance in flow resistance between the bypass and the contralateral ICA could be achieved. We also observed from case 6 and 7 where segmental narrowing existed (due to valves in these cases) flow resistance was influenced and resulted in an imbalance flow between the bypass graft and the contralateral ICA.



(a)



(b)

Figure 8.6a Flow resistance in bypass and ICA. b Pressure gradient difference between bypass and ICA.

Discussion

The haemodynamic changes after HF EC-IC bypass surgery are poorly understood. Based on clinical data, most patients (> 90%) (Garrett MC *et al.* 2009) will recover without clinical evidence of haemodynamic insufficiency. However, blood flow in the bypass for some patients would be small, resulting in cerebral infarction.

This study proposed a new methodology that uses CFD calculation to measure the flow resistance coefficients (A and B) at the bypass and its contralateral ICA. Simulation results showed that in most cases, the flow resistance on the bypass was improved and to be closer to that of the contralateral ICA. It indicated that the haemodynamic conditions were improved with balance between the left and right contributions to the Circle of Willis. However, if the bypass graft has segmental narrowing (e.g. due to venous valves) flow resistance in that bypass will increase. An imbalanced flow resistance between the left and right contributors to the Circle of Willis will result in asymmetrical blood flow rates, as well as asymmetrical shear stress magnitude and spatial distribution within the Circle of Willis. This may predispose to haemodynamic failure in the short term or increase the risk of aneurysm development in the long term (Alnaes *et al.* 2007). We also suggested that further follow-up observations will be required, due to potential change of bypass graft geometries over time (Eguchi T 2002).

Conclusion

CFD can be used to predict flow resistance for both bypass grafts and the contralateral ICA. These results may be of use in predicting the outcome of HF EC-IC bypass surgery using interposition saphenous vein. In cases where the flow resistance within the bypass is similar to that of its contralateral ICA, there is a tendency for the haemodynamic parameters of each side to balance. However, if the flow resistance of a bypass is significant greater than that of contralateral ICA, the haemodynamic condition at the Circle of Willis will lose this balance. Imbalanced flow resistance may result in further development of intracranial cerebrovascular diseases.

Conflict of interest statement

None of the authors have any financial interests to disclose

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Chapter 9

Thesis discussion and conclusion

Summation of thesis results

High flow extracranial-to-intracranial (HF EC-IC) cerebral revascularisation may be necessary in the treatment of complex aneurysms, cranial base tumours that require flow replacement in the setting of planned vessels sacrifice (Sundt *et al.* 1988; Lawton *et al.* 1996; Morgan *et al.* 2000; Sekhar *et al.* 2008; Sia *et al.* 2011). These bypass techniques using the saphenous vein are well established. A variety of vascular reconstruction techniques, in addition to that of direct clip reconstruction, have been described since the first successful bypass more than 50 years ago (Woringer *et al.* 1963; Donaghy 1967; Yasargil 1969; Lougheed *et al.* 1971). These rare surgical procedures are technically demanding. The ability to perform this surgery is an important adjunct in the armamentarium of cerebrovascular surgery. The success of the procedure is critically dependent on patient selection and surgeon's ability to perform microsurgery and detail in care during surgery and in the post-operative period.

Firstly, we reported the patency of HF EC-IC bypass at an average 30 months after surgery. The patency rate at 6 weeks was 93% (95% CI: 87.4-96%), with almost all graft failures occurring within the first week following surgery. Beyond the first week, bypass grafts that were patent at 1 week had a long-term patency of 99% (Sia *et al.* 2011). This result of long-term graft patency for large vein conduit is better than previously reported.

Secondly, during the 11-year period, June 1999 to July 2010, 434 hospital discharges for low flow and high flow EC-IC bypasses in Australia were recorded. This produces an average of 1.9 cases of EC-IC bypass per 1,000,000 Australians per year ((AIHW) 2010). These complex and rarely performed surgeries pose many challenges including learning both selection of procedure and technical performance. An even greater challenge rests with surgeons performing HF EC-IC bypass procedures (a very small proportion of all EC-IC bypasses performed). Surrogate measures of competency performing HF EC-IC bypass include a reduction in problems specifically related to the functioning of the bypass graft. Graft Complications were evident in 14.7% (95%CI 10.1-20.9%) of 170 surgical cases. Graft specific complications leading to a modified Rankin Score >2 occurred in 5.9% (95%CI 3.1-10.6). Improvement of surgical performance over a considerable time is evident in this series. How this can be improved will remain challenging. Because of the small number of cases perform each year in Australia, it will inevitably have a significant impact upon both the maintenance of competence in those already performing HF EC-IC bypass surgery on a regular basis as well as an impact on new generations of neurosurgeons who may wish to pursue cerebrovascular surgery as a subspecialty. Consideration needs to be given to prolonged mentorship when learning this technique or alternative source of training device (e.g. high fidelity microsurgery simulation station) could help minimise and eliminating learning curve-related morbidity.

Apart from microsurgical competency development to ensure graft longevity with fewer graft related complications, there was evidence that graft patency, blood flow distribution and flow velocity profile are dependent on the geometry of newly established anastomoses (Haruguchi *et al.* 2003). Certain geometries (e.g. high curvature, obtuse and large angle of anastomosis) and post-operative physiologic parameters (e.g. arterial haemodynamics, vessels wall elasticity, vessel wall thickness and the intra-arterial pressure waveform) predispose to early and late graft failure. However, little is known about the relative importance of these factors. In my work, possible associations between haemodynamic factors to maintain a patent graft were investigated with CFD and carotid duplex ultrasound.

Application of CFD methods to studies of the cerebral circulation is gaining in popularity. It was shown that the numerical results closely matched the analytical flow solver solution (Castro *et al.* 2006). A few studies have attempted to simulate haemodynamics in the intracranial circulation. This include analysis of the complete Circle of Willis (Alnaes *et al.* 2007), predicting the thrombosis rate in endovascular treatment of aneurysm, rupture risk of cerebral aneurysm (Cebral *et al.* 2005; Bai-Nan *et al.* 2011) and to investigate the impact of vessels radii and bifurcation angles on haemodynamic variations (Alnaes *et al.* 2007). In this work, I set out to use an image-based patient specific methodology to study the haemodynamic changes in patients who have undergone HF EC-IC cerebral revascularisation. The methodology includes image processing, segmentation and 3D grid generation algorithms and finite element solver for Navier-Stokes equation.

It was shown that more than 60% degree of stenosis in the ICA has been found to be necessary before a benefit can be obtained by carotid endarterectomy. This methodology yields results that are in good qualitative agreement with NASCET (Investigators 1991) and ECST (Group 1991) study and support that the benefits from carotid endarterectomy relate to a mechanical alteration in flow dynamics rather than removing the lesion generating the source of emboli. The simulation also showed the technique is useful to estimate the required degree of stenosis in the artery that is to be occluded to ensure sustained flow in the bypass. This will be of importance where there is staged surgery with a time interval between the bypass and the definitive internal carotid artery occlusion.

Furthermore, it was also observed that there was no major influence on WSS or flow changes in the MCA border zone (between the native circulation and that of the bypass) with differing angles of proximal and distal anastomosis. CFD result revealed haemodynamic characteristic at the border zone were relatively unaffected by the physiologic flow conditions to various anastomosis angles, allowing this consideration to be ignored in modelling and hence, cerebrovascular bypass surgery.

In a subsequent study, the mean arterial blood pressure (MAP) below which early graft failure may ensue was also interrogated. Maintaining the flow in a newly established HF EC-IC bypass may be threatened by low blood pressure. Maintenance of acute post-operative flow is critical to prevent occlusion at the potential sites of thrombosis (such as the suture line). In this work, an average bypass graft flow rate of 180 ml/min was reported. In 1987, Sundt documented that graft flow of 40ml/min was the minimum required to prevent early post-operative occlusion (Sundt *et al.* 1987). This is also supported by our CFD analysis. Our data suggested that at 180 ml/min, there is an atheroprotective endothelial and non-thrombogenic environment predicted to prevent atherogenesis and restenosis from intimal hyperplasia. At lower flow rate or no flow, low oscillatory shear stress (< 0.4 Pa) may lead to endothelial dysfunction and create a thrombogenic prone environment, which may lead to graft thrombosis. Our computational modelling also suggested that MAP below 60mmHg in the immediate post operative period may predispose to early graft occlusion. With this approach, a diligent monitoring of MAP during the post operative period, not only ensures good flow to maintain graft patency, but also helps guide management to reduce the incidence of haemorrhagic transformation when flow is established through the bypass graft (Sia *et al.* 2011).

Finally, the flow resistance coefficients of seven bypass grafts and their contralateral ICA have been analysed using patient-specific CFD based on 3D CTA data (Zhang *et al.* 2012). The intra-operative parameters such as graft diameter and length are of utmost relevance in surgical planning to ensure a good clinical outcome. Both the radius and the length of graft are critical to the impedance of graft flow and graft maintenance. I aimed to select saphenous veins with diameters appropriate to provide flow with the least amount of energy loss and minimal flow disturbance. In this study, the effect of flow resistances and impedance on the bypass with various graft diameters were investigated. Simulation results revealed that, in most cases, the flow resistance on the bypass resembled the contralateral ICA. The haemodynamic conditions were improved with balance between the left and right contributors to the Circle of Willis (CoW). However, if the vein bypass has segmental narrowing (e.g. due to venous valves), flow resistance in that bypass will increase. An imbalanced flow resistance between the ipsilateral and contralateral ICA contributor to the CoW will result in asymmetrical blood flow rates, shear stress magnitude and spatial distribution within the CoW. It was found that this haemodynamic imbalance could destabilise the CoW flow pattern. This may predispose to an increased risk of aneurysm development (Alnaes *et al.* 2007). To the best of our knowledge, this was the first time that the flow coefficient resistance has been explored or proposed in HF EC-IC bypasses.

Future direction

Following from the above works, the future work is now focussed on deciphering the influence physiological condition on vascular remodelling and potential change of vein bypass geometries following HF EC-IC bypass surgery. In order to find more significant haemodynamic factors, a unique database is being built at the CFD laboratory, Australian School of Advanced Medicine, Macquarie University. This database will capture patients' demographic, medical images, segmentations, surface models, volume grids, physiological boundaries condition imposed onto simulations and characterisation of the most significant features of the bypass flow. In addition, a longitudinal study has commenced that aims to investigate the effects of spontaneous vascular graft remodelling and flow resistance coefficient of the bypass graft. Although the current patient sample is not large enough to achieve statistical significance, an interesting trend in the association between haemodynamic factors and potential vascular graft remodelling and change of vein bypass geometries over a period of time has been observed. Therefore, bypass vascular graft undergoes a constant remodelling (e.g. changing of diameter) to achieve haemodynamic balance between the left and right contributors to the CoW. Furthermore, the increasing speed of supercomputer makes it possible to run simultaneously many 3D finite element CFD simulations in domains containing millions of elements in short periods of time. This technique could potentially be used to better assess the haemodynamic indices in patients with HF EC-IC bypass surgery in future.

Thesis conclusion

The marriage of CFD and medicine with engineering technology, especially computing, has opened up new frontiers in biomedical research, allowing us to address issues, which were previously considered impossible. CFD analysis can be applied to the complex flow related pathophysiology in cerebrovascular bypass. CFD study provides additional insights into the haemodynamics of interposition vein graft in HF EC-IC bypass surgery which may be of great value in aiding the therapeutic decision making process.

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Zhang, Y., Sia, S. F., Morgan, M. K. and Qian, Y. (2012). "Flow resistance analysis of extracranial-to-intracranial (EC-IC) vein bypass." J Biomech: **45**; 1400-1405

Appendix 1: Publications contributing to thesis

Pages 165-193 of this thesis have been removed as they contain published material. Please refer to the following citation for details of the articles contained in these pages.

Sia, S. F., & Morgan, M. K. (2013). High flow extracranial-to-intracranial brain bypass surgery. *Journal of Clinical Neuroscience*, 20(1), p. 1-5.
doi: 10.1016/j.jocn.2012.02.007

Sia, S. F., Davidson, A. S., Assaad, N. N., Stoodley, M., & Morgan, M. K. (2011). Comparative patency between intracranial arterial pedicle and vein bypass surgery. *Neurosurgery,* 69(2), p. 308-314.
doi: 10.1227/NEU.0b013e318214b300

Sia, S. F., Qian, Y., Matsuda, W., Avolio, A., & Morgan, M. K. (2010) Evaluation of Brain Extracranial-to-Intracranial (EC-IC) Bypass Treatments by Using Computational Hemodynamic Technology. In: Lim C.T., Goh J.C.H. (eds) *6th World Congress of Biomechanics (WCB 2010). August 1-6, 2010 Singapore. IFMBE Proceedings, vol 31. Springer, Berlin, Heidelberg*.
doi: 10.1007/978-3-642-14515-5_393

Sia, S. F., Qian, Y., Zhang, Y., & Morgan, M. K. (2012) Mean arterial pressure required for maintaining patency of extracranial-to-intracranial bypass grafts: an investigation with computational hemodynamic models — case series. *Neurosurgery,* 71(4), 826-832.
doi:10.1227/NEU.0b013e318266e6c2

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doi: 10.1016/j.jbiomech.2012.02.025

Appendix 2: Publications arising from during the period of candidature

Pages 195-216 of this thesis have been removed as they contain published material. Please refer to the following citation for details of the articles contained in these pages.

Sheaufung, S., Taufiq, A., Nawawi, O., Naicker, M. S. & Waran, V. (2009). Neurenteric cyst of the cervicothoracic junction: a rare cause of paraparesis in a paediatric patient. *Journal of Clinical Neuroscience*, 16(4), p. 579-581.
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Sia, S. F., Davidson, A. S., Soper, J. R., Gerarchi, P., & Bonar, S. F. (2010) Protuberant Fibro-osseous Lesion of the Temporal Bone: “Bullough Lesion”. *The American Journal of Surgical Pathology*, 34(8), p. 1217-1223.
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doi: 10.1080/10255842.2011.625358

Appendix 3: Ethic approval letters

Appendix 3 of this thesis has been removed as it may contain sensitive/confidential content

Appendix 4: CD-ROM