CEREBRAL HAEMODYNAMIC CONTROL AND CAROTID ENDARTERECTOMY: COMPARISON OF GENERAL AND LOCOREGIONAL ANAESTHESIA

A thesis submitted to the University of Manchester for the degree of

Doctor of Medicine

In the Faculty of Medical and Human Sciences

2011

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SCHOOL OF MEDICINE
Table of contents

LIST OF FIGURES .................................................................................................................. 6

LIST OF TABLES ................................................................................................................... 8

ABSTRACT ............................................................................................................................... 11

DECLARATION ......................................................................................................................... 12

COPYRIGHT STATEMENT ....................................................................................................... 13

ABOUT THE AUTHOR ............................................................................................................ 14

ACKNOWLEDGEMENTS ........................................................................................................ 18

INTRODUCTION ..................................................................................................................... 19

1.1 BACKGROUND TO CEA – HISTORICAL PERSPECTIVE .................................................. 20

1.2 MAKING CAROTID ENDARTERECTOMY SAFER ............................................................. 26

1.2.1 Patient selection and timing of surgery ................................................................... 26

1.2.2 Secondary prevention strategies ............................................................................. 28

1.2.3 Impact of perioperative processes of care .............................................................. 31

1.3 GENERAL VS. LOCOREGIONAL ANAESTHESIA FOR CAROTID ENDARTERECTOMY .......................................................... 35

1.3.1 Background to the choice of anaesthesia for CEA .................................................. 35

1.3.2 General anaesthesia for CEA ................................................................................ 36

1.3.3 Locoregional anaesthesia for CEA ......................................................................... 42

1.3.4 Comparison of GA and LA CEA ............................................................................. 44

1.4 CEREBRAL BLOOD FLOW AND ITS CONTROL ............................................................... 48

1.4.1 Normal control of cerebral blood flow .................................................................... 48

1.4.2 Cerebral autoregulation ........................................................................................ 51

1.4.3 Response of CBF to changes in arterial gases – cerebrovascular reactivity ............. 54

1.4.4 Methods of measurement of cerebral blood flow, autoregulation and vasoreactivity ...... 55

1.4.5 Transcranial Doppler ultrasound ......................................................................... 59

1.4.6 Cerebrovascular autoregulation and vasoreactivity in carotid disease .................... 63
1.4.7 Effect of CEA on cerebrovascular autoregulation and reactivity ........................................... 65
1.4.8 Effect of CEA on cerebral blood flow during and following surgery, and effect of LA vs. GA on these parameters .......................................................................................................................... 72

1.5 CEREBRAL AUTOREGULATION, THE CEREBRAL HYPERPERFUSION SYNDROME AND INTRACEREBRAL HAEMORRHAGE
...................................................................................................................................................... 75
1.5.1 Background ................................................................................................................................... 75
1.5.2 Incidence and predisposing factors ................................................................................................. 76
1.5.3 Clinical features of the cerebral hyperperfusion syndrome ............................................................ 79
1.5.4 Cerebral hyperperfusion and cerebrovascular autoregulation ............................................................ 79
1.5.5 Management of cerebral hyperperfusion ............................................................................................ 81
1.5.6 The cerebral hyperperfusion syndrome and intracerebral haemorrhage ........................................... 82

1.6 PROTEIN S100B AND NEURONE-SPECIFIC ENOLASE IN CAROTID SURGERY .................................................... 84
1.6.1 Biomarkers of cerebral injury ........................................................................................................... 84
1.6.2 Protein S100B .................................................................................................................................... 85
1.6.3 Neurone-Specific Enolase ................................................................................................................ 95
1.6.4 Summary ......................................................................................................................................... 98

1.7 AIMS OF STUDY .................................................................................................................................. 100

METHODOLOGY ...................................................................................................................................... 101

2.1 PATIENT SELECTION AND EXCLUSIONS ......................................................................................... 102
2.1.1 Recruitment ..................................................................................................................................... 102
2.1.2 Collection of baseline characteristics ............................................................................................... 103

2.2 OPERATIVE DETAILS .......................................................................................................................... 104
2.2.1 Anaesthetic technique ....................................................................................................................... 104
2.2.2 Surgical technique ............................................................................................................................ 107
2.2.3 Postoperative care ............................................................................................................................ 108

2.3 TRANSCRANIAL DOPPLER STUDIES .................................................................................................. 109
2.3.1 Pre- and postoperative TCD assessments & intraoperative monitoring .............................................. 109
2.3.2 Tilt-testing ...................................................................................................................................... 113
2.3.3 CO₂ reactivity testing ................................................................. 117

2.4 BLOOD SAMPLING ........................................................................... 120
    2.4.1 Collection and processing of samples ........................................ 120
    2.4.2 Assays ..................................................................................... 122

2.5 STATISTICAL ANALYSES ................................................................. 123
    2.5.1 Power calculations .................................................................... 123
    2.5.2 Analyses of TCD studies ........................................................... 124
    2.5.4 Analysis of biochemical marker data ......................................... 124
    2.5.6 Statistical software .................................................................... 125

EXPERIMENTS & RESULTS ...................................................................... 126

3.1 GENERAL CHARACTERISTICS ............................................................ 127
    3.1.1 Baseline characteristics ............................................................ 127
    3.1.2 Intraoperative characteristics ................................................... 129
    3.1.3 Neurological assessments and outcome data ............................. 131

3.2 BASIC SYSTEMIC AND CEREBRAL HAEMODYNAMIC DATA .................. 132

3.3 CEREBROVASCULAR AUTOREGULATION TESTS ............................... 136

3.4 CEREBROVASCULAR REACTIVITY TESTS ......................................... 146
    3.4.1 Cerebrovascular reactivity ......................................................... 146
    3.4.2 Cerebrovascular resistance ....................................................... 154
    3.4.3 Correlation of indices of cerebrovascular autoregulation and reactivity .............................................. 157

3.5 INTRAOPERATIVE HAEMODYNAMIC DATA ....................................... 159

3.6 BIOCHEMICAL MARKERS OF CEREBRAL INJURY .............................. 165
    3.6.1 Comparison of jugular vs. peripheral blood sampling ............... 165
    3.6.2 Comparison of GA vs. LA for S100β ......................................... 168
    3.6.3 Comparison of GA vs. LA for NSE .......................................... 171
    3.6.4 Cerebral autoregulation and vasoreactivity and biochemical markers of cerebral injury 174

DISCUSSION ......................................................................................... 177

4.1 DISCUSSION OF MAIN FINDINGS .................................................. 178
4.2 LIMITATIONS OF THE PRESENT STUDY ................................................................. 183

4.3 IMPLICATIONS FOR CLINICAL PRACTICE ......................................................... 189

4.4 IMPLICATIONS FOR FURTHER RESEARCH ......................................................... 191

REFERENCES .................................................................................................................. 194
List of figures

FIGURE 1.4.1 ................................................................. 50
COMMON VARIATIONS OF THE CIRCLE OF WILLIS AND THEIR REPORTED PREVALENCE.

FIGURE 1.4.2 ................................................................. 53
RELATIONSHIP OF CEREBRAL BLOOD FLOW AND MEAN ARTERIAL PRESSURE TO ILLUSTRATE NORMAL CEREBRAL AUTOREGULATION.

FIGURE 2.3.1 .................................................................. 112
TYPICAL VELOCITY SPECTRAL WAVEFORMS FROM INSONATION OF THE CAROTID SIPHON AND THE MCA IN RELATION TO THE CIRCLE OF WILLIS.

FIGURE 3.3.1 .................................................................. 145
PREOPERATIVE VS. POSTOPERATIVE IPSILATERAL TILT GRADIENTS DEPENDING ON BASELINE CEREBRAL AUTOREGULATION.

FIGURE 3.4.1 .................................................................. 153
PREOPERATIVE VS. POSTOPERATIVE IPSILATERAL CVRI DEPENDING ON BASELINE CVR.

FIGURE 3.4.2 .................................................................. 158
CORRELATION OF THE TILT-GRADIENT AND CVRI.

FIGURE 3.5.1 .................................................................. 160
COMPARISON OF MEDIAN MAP AT KEY INTRAOPERATIVE TIME POINTS FOR GA VS. LA.

FIGURE 3.5.2 .................................................................. 161
COMPARISON OF MEDIAN MAP AT KEY INTRAOPERATIVE TIME POINTS FOR IMPAIRED VS. INTACT CA.

FIGURE 3.5.3 .................................................................. 161
COMPARISON OF MEDIAN MAP AT KEY INTRAOPERATIVE TIME POINTS FOR IMPAIRED VS. INTACT CVR.

FIGURE 3.5.4 .................................................................. 163
COMPARISON OF MEDIAN % CHANGE IN MCAVm AT KEY INTRAOPERATIVE TIME POINTS FOR GA VS. LA.
FIGURE 3.5.5 ................................................................................................................................. 163

Comparison of median % change in MCAV_m at key intraoperative time points for impaired vs. intact CA.

FIGURE 3.5.6 ................................................................................................................................................ 164

Comparison of median % change in MCAV at key intraoperative time points for impaired vs. preserved CVR.

FIGURE 3.6.1 ............................................................................................................................................... 167

Comparison of jugular and peripheral blood sampling for each time point.

FIGURE 3.6.2 ............................................................................................................................................... 169

Comparison of GA and LA S100b levels for each time point.

FIGURE 3.6.3 ............................................................................................................................................... 170

Comparison of the change in S100b levels for GA and LA at each time point.

FIGURE 3.6.4 ............................................................................................................................................... 172

Comparison of GA and LA NSE levels for each time point.

FIGURE 3.6.5 ............................................................................................................................................... 173

Comparison of the change in NSE levels for GA and LA at each time point.

FIGURE 3.6.6 ............................................................................................................................................... 175

Comparison of jugular and peripheral S100b levels according to (a) baseline CA impairment (b) baseline CVR impairment.

FIGURE 3.6.7 ............................................................................................................................................... 176

Comparison of jugular and peripheral NSE levels according to (a) baseline CA impairment (b) baseline CVR impairment.
List of tables

TABLE 1.5.1 .......................................................... 78
RISK FACTORS FOR THE CEREBRAL HYPERPERFUSION SYNDROME.

TABLE 2.2.1 ........................................................................ 106
ANAESTHESIA PROTOCOLS.

TABLE 3.1.1 ........................................................................ 128
BASELINE CHARACTERISTICS.

TABLE 3.1.2 ........................................................................ 130
INTRAOPERATIVE CHARACTERISTICS.

TABLE 3.2.1 ........................................................................ 133
BASELINE SYSTEMIC AND CEREBRAL HAEMODYNAMIC DATA.

TABLE 3.2.2 ........................................................................ 133
(a) COMPARISON OF PREOPERATIVE VS. POSTOPERATIVE MAP. (b) COMPARISON OF MEAN PER CENT CHANGE IN MAP FOR DAY 1 AND DAY 2 IN GA VS. LA.

TABLE 3.2.3 ........................................................................ 135
(a) COMPARISON OF PREOPERATIVE VS. POSTOPERATIVE IPSILATERAL MCAVm. (b) COMPARISON OF PREOPERATIVE VS. POSTOPERATIVE CONTRALATERAL MCAVm. (c) COMPARISON OF MEAN PER CENT CHANGE IN MCAVm FOR DAY 1 AND DAY 2 IN GA VS. LA.

TABLE 3.3.1 ........................................................................ 137
COMPARISON OF PREOPERATIVE VS. POSTOPERATIVE VALUES OF TILT GRADIENTS FOR ALL PATIENTS, GA GROUP AND LA GROUP.

TABLE 3.3.2 ........................................................................ 138
(a) COMPARISON OF PREOPERATIVE AND POSTOPERATIVE TILT GRADIENTS FOR GA VS. LA BOTH FOR THE IPSILATERAL AND FOR THE CONTRALATERAL SIDES. (b) COMPARISON OF PER CENT CHANGE IN TILT GRADIENT FOR GA VS. LA, BOTH FOR THE IPSILATERAL AND CONTRALATERAL SIDES.
TABLE 3.3.3 .................................................................................................................................................. 140

Comparison of GA vs. LA for preoperative cerebral autoregulation impairment.

TABLE 3.3.4 .................................................................................................................................................. 140

Comparison of GA vs. LA for postoperative cerebral autoregulation impairment.

TABLE 3.3.5 .................................................................................................................................................. 141

Preoperative vs. postoperative impairment of cerebral autoregulation

TABLE 3.3.6 .................................................................................................................................................. 143

Postoperative impairment of autoregulation according to baseline autoregulation status and anaesthetic.

TABLE 3.3.7 .................................................................................................................................................. 143

Change in postoperative autoregulation status compared to baseline.

TABLE 3.4.1 .................................................................................................................................................. 147

Comparison of preoperative vs. postoperative values of CVRI for all patients, GA group and LA group.

TABLE 3.4.2 .................................................................................................................................................. 148

(A) Comparison of preoperative and postoperative CVRI for GA vs. LA both for the ipsilateral and for the contralateral sides. (B) Comparison of per cent change in CVRI for GA vs. LA, both for the ipsilateral and contralateral sides.

TABLE 3.4.3 .................................................................................................................................................. 150

Comparison of GA vs. LA for preoperative CVR impairment.

TABLE 3.4.4 .................................................................................................................................................. 150

Comparison of GA vs. LA for postoperative CVR impairment.

TABLE 3.4.5 .................................................................................................................................................. 151

Preoperative vs. postoperative impairment of cerebral autoregulation.
TABLE 3.4.6 ..................................................................................................................................................151

CHANGE IN POSTOPERATIVE CVR STATUS COMPARED TO BASELINE.

TABLE 3.4.7 ..................................................................................................................................................155

CORRELATION BETWEEN CVRI AND CVRESI.

TABLE 3.4.8 ..................................................................................................................................................155

COMPARISON OF PREOPERATIVE VS. POSTOPERATIVE VALUES OF CVRESI FOR ALL PATIENTS, GA GROUP AND LA GROUP.

TABLE 3.4.9 ..................................................................................................................................................156

(A) COMPARISON OF PREOPERATIVE AND POSTOPERATIVE CVRESI FOR GA VS. LA BOTH FOR THE IPSILATERAL AND FOR THE CONTRALATERAL SIDES. (B) COMPARISON OF PER CENT CHANGE IN CVRESI FOR GA VS. LA, BOTH FOR THE IPSILATERAL AND CONTRALATERAL SIDES.
Abstract

University of Manchester

Name: Demosthenes Dellagrammaticas

Degree title: Doctor of Medicine

Thesis title: Cerebral haemodynamic control and carotid endarterectomy (CEA): comparison of general (GA) and locoregional (LA) anaesthesia.

2011

The role of CEA for stroke prevention in the presence of symptomatic carotid artery stenosis is well established. In order to maximize the benefit of surgery, several perioperative processes of care have been under scrutiny, of which one is the choice of anaesthetic method. The differing effects of GA vs. LA on the cerebral circulation after CEA may be of significance, since changes in the cerebral circulation post-CEA may give rise to cerebral hyperperfusion and intracerebral haemorrhage. This work assessed the effect of GA vs. LA on cerebral haemodynamic control after CEA using transcranial Doppler (TCD) techniques, and correlated these changes with serum markers of cerebral injury.

Subjects undergoing CEA had perioperative TCD monitoring of middle cerebral artery blood flow velocity (MCAV). Pre- and postoperative (within 48 hours of surgery) testing of cerebral autoregulation [CA] (tilt-testing) and cerebral vasoreactivity to CO₂ [CVR] (rebreathing expired air) was conducted. Cerebral haemodynamic parameters and clinical outcome were correlated with changes in jugular venous and peripheral levels of protein S100β and neurone-specific enolase (NSE).

The change in CA and CVR was not different between GA (n=16) and LA (n=20). Overall, CA and CVR improved significantly within 48 hours of CEA for patients with preoperative impairment of these parameters, although some patients with normal baseline CA and CVR exhibited postoperative impairment. Increase of MCAV >100% from baseline after restoration of carotid blood flow was observed in patients with impaired CVR, but resolved by the first postoperative day. Transient elevation in jugular venous (but not peripheral) S100β during surgery was seen. Both jugular and peripheral NSE levels dropped during surgery. Neither anaesthetic method nor CA or CVR status had any effect on changes in serum S100β or NSE.

Cerebral autoregulatory parameters thus improve rapidly after CEA, but appear unaffected by anaesthetic technique. This supports the concept that cerebral hyperperfusion is dependent on factors in addition to impaired CA or CVR. Changes in serum S100β or NSE do not reflect cerebral haemodynamic changes. However, the variability encountered between patients warrants further investigation. The implications for clinical practice and directions for further research are discussed.
Declaration

A subset of the data on tilt-testing in this thesis has been submitted in support of the successful application of Dr Gordon Chapman for the degree of Doctor of Medicine at the University of Leeds (2007), entitled ‘Feasibility of early cerebral haemodynamic testing in patients undergoing carotid endarterectomy’.

However, this thesis includes a greater number of subjects and consists of previously unanalysed CO₂ reactivity and intraoperative data, and Dr Chapman’s work did not include assessment of biomarkers of cerebral injury. In addition, Dr Chapman had no role in the preparation of this thesis.
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Publications – Carotid Disease

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Acknowledgements

This work could not have been undertaken or completed without the supervision and support of Professor Michael Gough. He has remained extremely generous and kind throughout the years during which he has been my mentor, and for this he has my sincere gratitude.

This work also would have been impossible without the collaboration of Dr Gordon Chapman and Dr Simon Howell, both of whom provided limitless support in the design and execution of the experiments in this study. The assistance of Dr Lucy Norcliffe-Kaufmann and Professor Roger Hainsworth was also pivotal in the setup of this study.

No clinical research would be feasible without willing patients and I sincerely thank all the subjects of this study for their participation.

Thanks also go to Professor Charles McCollum. Apart from acting as academic supervisor, he was inspirational in my career choice of vascular surgery.

Thanks also go to Mr Jon Ausobsky and the Higher Surgical Training committee at the Yorkshire and Humber Deanery, whose persistence in considering my training and future career best interests ensured the completion of this work. Professor Ian Chetter deserves particular acknowledgement.

Many surgical trainers along the way supported the preparation of this thesis, and I thank them all for their contributions and forbearance. Particular mention should go to Mr Andrew Mavor, Mr David Russell, Mr Max Troxler, Professor Shervanthi Homer-Vanniasinkam, Mr Brian Johnson, Mr Paul Renwick, Professor Peter McCollum, Mr David Berridge, Professor Julian Scott, Mr Bankole Akomolafe, Mr Patrick Kent and Mr Paxton Dewar. In addition, many of my colleagues-in-training supported and encouraged me along the way, and suffered my periods of absence and distraction during the preparation of this thesis with good grace and for this I am grateful.

I am profoundly grateful to my parents Daphne and Heracles, my brothers Alex and Philip, my stepmother Nicoletta, my grandmother Pothoula and to Julie Oldroyd who, despite the distance, were always there when needed. I could not have completed this work without their unconditional love and support.

I am also indebted to Les Clark without whose support and guidance I would not have written this thesis.

Finally, my heartfelt thanks go to Maria, who helped me complete this work more than she could ever imagine.
Introduction
1.1 Background to CEA – historical perspective

Stroke is the third commonest cause of death and accounts for up to 3% of the disability burden worldwide. It is estimated that the overall mortality following stroke is 30% within the first year, and up to 50% of sufferers are left dependent (Warlow et al., 2003), accounting for up to 6% of National Health Service expenditure (Rothwell, 2001). The majority of strokes are ischaemic and up to 50% of these are caused by thromboembolic complications of extracranial atherosclerosis (Warlow et al., 2003). Many are preceded by a previous non-disabling stroke (Dennis et al., 1989), transient ischaemic attack (TIA) (Dennis et al., 1990) or retinal infarct (Hankey et al., 1991). This is of particular significance, as the risk of stroke due to thromboembolism from carotid stenosis can be dramatically reduced by timely and appropriate surgery in the form of carotid endarterectomy (CEA).

The first successful surgical treatment of symptomatic carotid atherosclerosis by the conventional technique used today was performed by DeBakey in 1953 (DeBakey, 1975), although it was the report of successful treatment of a patient with intermittent attacks of hemiplegia with resection of the atherosclerotic segment of carotid bifurcation in the 1950s by Eastcott (1954) that prompted enthusiasm in the surgical treatment of patients with carotid disease. Despite the inconclusive results of two randomised trials conducted in the 1960s (Fields et al., 1970, Shaw et al., 1984), CEA became the most commonly performed vascular surgical operation in the USA, rising from around 15,000 procedures in 1971 to around 85,000 procedures in 1982, reaching a peak of 107,000 in 1985 (Dyken and Pokras, 1984, Pokras and Dyken, 1988).
By the 1980s however wide variation in indications and patient selection for surgery, with up to 32% of patients undergoing CEA inappropriately (Winslow et al., 1988), together with reports of postoperative stroke and/or death ranging from 2.5% to 24.4% and little robust evidence demonstrating improved long term outlook, led to serious concern regarding the appropriateness of CEA for stroke prevention (Barnett et al., 1984, Warlow, 1984). As a consequence, the number of procedures in the USA had dropped dramatically to 83,000 (Pokras and Dyken, 1988) by 1986. Although the international, multicentre Extracranial Carotid/Intracranial Carotid (EC/IC) Bypass Study, randomising 1377 patients to EC/IC bypass surgery or best medical care, failed to demonstrate any benefit for surgery in terms of stroke and/or death rates (Anonymous, 1985), the feasibility of such a trial for stroke prevention was shown. These considerations led to the inception and execution of the landmark trials of CEA, namely the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET). A third similar trial, the Veterans’ Affairs Trial 309 (VA309) was stopped before recruitment was completed when the results from ECST and NASCET were published.

ECST studied 3024 patients from 100 centres in Europe; NASCET studied 2885 patients in 106 centres mainly from North America, and the VA309 trial 181 patients from 16 Veterans’ Affairs centres in the USA (Rothwell et al., 2003). The trials were broadly similar in design, recruiting patients if they had suffered a recent carotid distribution non-disabling ischaemic stroke, TIA or retinal infarction and had stenosis in the ipsilateral carotid artery. All patients were assessed by a stroke
physician or neurologist to confirm eligibility upon entry, and again at regular intervals subsequently. Assessment of carotid stenosis was by catheter angiography, and the degree of stenosis was determined centrally using different methods; in ECST the approximate diameter of the carotid bulb at the point of stenosis was used as the denominator to express % stenosis, whilst NASCET and VA309 used the diameter of the distal internal carotid. The ECST included patients with any degree of stenosis, whilst in NASCET and VA309 patients with stenosis less than 30% and 50% respectively were excluded. Patients were randomised, by a ratio 2:1 in favour of surgery in ECST and 1:1 in NASCET and VA309, to receive either CEA plus best medical therapy (BMT) or BMT alone, which included aspirin and appropriate antihypertensive therapy.

Both ECST and NASCET reported preliminary results in 1991 (Anonymous, 1991a) (Anonymous, 1991b), identifying definite benefit of CEA for patients with stenosis in the range 70-99% despite a perioperative death and/or stroke risk of 7.5% and 5.8% respectively, and ECST reporting no benefit for stenosis <30%. Recruitment of these patients was thus stopped; VA309 also reported a trend in favour of surgery (Mayberg et al., 1991) but was halted upon the report of results of the former two trials. Recruitment of patients with moderate degrees of stenosis was continued in ECST and NASCET until the trials reported their final results in 1998, ECST identifying benefit only for stenosis of ≥80% in men and ≥90% in women (Anonymous, 1998), and NASCET showing more modest but definite benefit for patients with stenosis in the range 50-69% and durable, definite benefit for stenosis ≥70% (Barnett et al., 1998).

22
The differences in outcomes for these trials were accounted for primarily by the differences in assessment of carotid stenosis on angiography and definition of outcome events. Meta-analysis of the pooled data from ECST, NASCET and VA309 was thus undertaken applying NASCET criteria to angiographic criteria and outcome events, and was reported in 2003 (Rothwell et al., 2003). For patients with stenosis <30% surgery was harmful, for those with stenosis 30-49% or near-occlusion no benefit was demonstrated, for those with stenosis 50-69% a modest benefit (absolute risk reduction (ARR) of any stroke or operative death 7.8%, perioperative stroke and/or death rate 8.4%), and for stenosis 70-99% definite benefit (ARR of any stroke or operative death 15.6%, perioperative stroke and/or death rate 6.2%), based on 5-year follow-up in ECST and NASCET, and 2-year follow-up in VA309.

Whilst ECST, NASCET and VA309 conclusively demonstrated the role of surgery in symptomatic carotid disease, the status of asymptomatic disease remained controversial. Two major studies, the Asymptomatic Carotid Artery Stenosis Study (ACAS) (Anonymous, 1995) and the Veterans’ Affairs Cooperative Study for asymptomatic carotid stenosis (VA) (Hobson et al., 1993) published their results in the mid-1990s, having randomised patients to CEA or BMT. ACAS studied 1662 asymptomatic patients with ≥60% carotid stenosis from 39 North American centres. The death and/or stroke rate in the surgical group was 1.5%, whilst the complication rate attributable to carotid angiography was 1.2%, giving a total periprocedural complication rate of 2.6%. The ARR was 5.9% in favour of surgery for a median
follow-up period of 2.7 years. The authors thus recommended that CEA was beneficial in asymptomatic disease provided a combined surgical and angiographic complication rate was less than 3%. The VA study randomised 444 patients with ≥50% carotid stenosis from 11 Veterans’ Affairs centres in the USA, and found no benefit of surgery in terms of reduction of all stroke and/or death for a follow-up of 47.9 months, although the rate of ipsilateral stroke was significantly reduced by CEA. A meta-analysis of these trials [also including two small similar studies (Clagett et al., 1984) (Anonymous, 1992)] identified an extremely small reduction in ARR (3%) despite a low overall complication rate (including that of angiography) of 3.1% (Chambers et al., 2000). The largest, most current study of asymptomatic carotid disease, the Asymptomatic Carotid Surgery Trial (ACST) recruited 3120 patients with asymptomatic carotid stenosis ≥60% from 126 centres in 30 countries between 1993 and 2003 (Halliday et al., 2004). The perioperative stroke and/or death rate was 3.1%, and an overall ARR at 5 years of 5.4%, representing an almost 50% relative risk reduction. Although this risk reduction is modest, it is statistically significant and consistent with the findings of ACAS. However, it must be borne in mind that based on the results of both ACAS and ACST, the number of patients needed to treat surgically to prevent one disabling or fatal stroke at 5 years is approximately 40, neither study has demonstrated a convincing benefit in women, and there remains doubt whether the excellent surgical results in ACAS could be replicated in routine clinical practice (Rothwell and Goldstein, 2004).

The findings of ECST, NASCET and ACAS has led to a dramatic resurgence in the rates of CEA in the USA (Tu et al., 1998), where up to 150,000 procedures are performed per year and up to 50% of surgeons perform surgery for asymptomatic
stenosis (Masuhr et al., 1998). The enthusiasm for surgery in asymptomatic disease is not mirrored in Northern Europe, where only 7% of surgeons would advocate surgery in the absence of symptoms (Masuhr et al., 1998). The effect of the publication of the results of ACST seems to have had little impact in the practice of UK surgeons, particularly given the increasing recognition that the timing of carotid surgery following a neurological event is crucial given that the highest risk of stroke is within 2 weeks of such an event (Rothwell et al., 2004) – this has resulted in a greater focus on timely identification and surgery for symptomatic patients.
1.2 Making carotid endarterectomy safer

Whilst defining the role of CEA in symptomatic and asymptomatic carotid stenosis, the major trials highlighted the fact that for surgery to be of benefit, the risk of perioperative morbidity and mortality has to be acceptably low. This can be done by (i) appropriate patient selection and timing of surgery, (ii) appropriate secondary prevention strategies, and (iii) improvement in perioperative processes of care.

1.2.1 Patient selection and timing of surgery

As described in the previous section, degree of stenosis on pre-randomisation angiography was a strong predictor of risk in all patients. Subsequent analyses from ECST and NASCET identified groups of patients in whom the perioperative risk of stroke and/or death was influenced by clinical or other angiographic characteristics. In patients randomised to surgery in NASCET, female sex, contralateral carotid occlusion, ipsilateral ischaemic lesion on CT, and irregular or ulcerated plaque on angiography all were associated with worse outcome from surgery, whilst patients with ocular symptoms and a history of coronary artery disease with prior intervention fared better (Ferguson et al., 1999). Other subgroup analyses from NASCET suggested worse outcome for all patients with leukoaraiosis on brain imaging (Streifler et al., 2002) or absence of collateral flow towards the symptomatic cerebral hemisphere (Henderson et al., 2000), and for medically-treated patients with intracranial ICA stenosis (Kappelle et al., 1999).
In ECST, characteristics associated with a worse outcome for surgery were a history of cerebral TIA as opposed to ocular symptoms, female sex, systolic hypertension and peripheral vascular disease (Bond et al., 2002a). Meta-analysis of the results of the two trials with relation to clinical characteristics and timing of surgery (Rothwell et al., 2004) demonstrated that, in patients treated medically, risk of ipsilateral stroke fell with time since the last relevant neurological event, was higher in those with hemispheric events as opposed to retinal ischaemia, and increased with age, presence of diabetes, and presence of irregular or ulcerated plaque on angiography. For the surgical group, the rate of perioperative stroke or death was higher in women, patients with hemispheric rather than ocular events, patients with diabetes or hypertension, and those with ipsilateral ulcerated/irregular plaque or contralateral carotid occlusion. When tested for subgroup treatment effect modification in relative and absolute risk reductions in the risk of the primary outcome with surgery, significant correlation was found with sex, age, and time since last relevant event, and non-significant trends for ipsilateral ulcerated/irregular carotid plaque and nature of primary neurological event. Surgery was thus of most benefit in men, patients aged ≥75, and those randomised within 2 weeks of the last relevant event (Rothwell et al., 2004).

The significance of these observations lies in the acknowledgment that despite the results of the major trials, not all patients benefit to the same extent from CEA. Although no consensus in terms of patient selection exists beyond the broad criteria set by the landmark studies, future meta-analyses of published data may establish guidelines for the most appropriate and cost-effective use of CEA, for example based on scoring systems such as the one suggested by the ECST collaborators (Rothwell et al., 2004).
et al., 1999). In particular, the timing of surgery following relevant symptoms appears to be significant, recent evidence from the Oxford Vascular Study suggesting the risk of completed stroke following TIA being as high as 20% within the first month. Reanalysis of NASCET, ECST and VA309 data showed that 185 strokes per 1000 CEA were prevented if surgery was carried out within 2 weeks of symptoms, with this figure dropping to 85 between 2 and 4 weeks, and further falling to 8 at 12 weeks (Naylor, 2007). Data from the more contemporary GALA Trial highlighted the fact that few patients in the UK underwent endarterectomy within the critical 2-week timeframe (Dellagrammaticas et al., 2007). Current UK (National Collaborating Centre for Chronic Conditions, 2008) and European (Liapis et al., 2009) guidelines now recommend treatment of symptomatic carotid stenosis within 2 weeks of presenting symptoms.

1.2.2 Secondary prevention strategies

Addressing risk factors following successful CEA is important to achieve maximum survival benefit. Although such modification has not been systematically addressed following CEA, the literature regarding secondary prevention strategies for ischaemic stroke is extensive and many findings are applicable post-CEA care.

1) Treatment of Hypertension

Hypertension is the most important yet treatable risk factor for stroke. Treatment of systolic hypertension in those over 60, and lowering diastolic blood pressure by 6
mmHg can achieve a reduction in stroke incidence of 36-42% (Collins et al., 1990) (SHEP Cooperative Research Group, 1991).

(II) LIPID-LOWERING THERAPY

Lipid-lowering therapy has been shown to be of benefit in the prevention of stroke. Both the Scandinavian Simvastatin Survival Study (4S) (Anonymous, 1994) and the Heart Protection Study (HPS) (Heart Protection Study Collaborative Group, 2002) demonstrated a ≈30% relative risk reduction in patients taking simvastatin. Although HPS did not demonstrate a similar reduction in recurrent stroke, patients experiencing cardiac or neurological symptoms within 6 months of enrolment were excluded and the subgroup analysis included patients who had experienced haemorrhagic strokes. For patients following stroke or TIA, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study (Amarenco et al., 2006) showed a modest benefit (2.2% absolute risk reduction for any stroke) of 80 mg atorvastatin vs. placebo in 4731 patients, without any effect in overall survival at 5 years. Nevertheless, even in the absence of firm evidence supporting the use of lipid-lowering therapy for recurrent ischaemic stroke, significant benefit of lipid-lowering therapy in coronary heart disease (CHD) has been demonstrated (Ebrahim et al., 1999) (Heart Protection Study Collaborative Group, 2002) and should be considered for all patients with carotid atherosclerosis, given the high incidence of overt or occult CHD in these patients.
(III) ANTIPLATELET THERAPY

Antiplatelet therapy was routine for all patients participating in the landmark trials of CEA, and has been shown to be beneficial in the treatment of patients with cardiovascular disease. A meta-analysis by the Antiplatelets Trialists’ Collaboration demonstrated a one-quarter reduction in all major vascular events in high-risk patients receiving antiplatelet therapy, low-dose aspirin (75-100 mg) being as effective as higher doses, and clopidogrel being an alternative in those where aspirin was contra-indicated (Antiplatelet Trialists' Collaboration, 1994). In the setting of CEA, a recent Cochrane review suggested a reduction in stroke incidence for patients taking aspirin postoperatively (Peto odds ratio 0.58) without evidence of adverse effect, but no reduction in incidence of other outcomes such as mortality, myocardial infarction (MI) or carotid restenosis (Engelter and Lyrer, 2003). At present anti-platelet therapy is recommended for all patients undergoing CEA (Biller et al., 1998), both perioperatively and postoperatively (Clagett et al., 2004), and, together with dipyridamole, in the setting of ischaemic stroke (Halkes et al., 2006).

(IV) LIFESTYLE MODIFICATIONS

The Royal College of Physicians of London have recommended lifestyle modifications regarding smoking cessation, regular exercise, modification of diet, and reduction in weight, alcohol and salt intake (Intercollegiate Stroke Working Party, 2004), and applying these recommendations to patients post-CEA would seem appropriate.
1.2.3 Impact of perioperative processes of care

Several aspects of perioperative management during CEA have received attention over the last three decades, concerning intraoperative surgical and anaesthetic techniques, perioperative monitoring, and quality control. Despite extensive published reports on the merits of each process of care, little robust evidence exists to support any particular strategy, with few exceptions.

(I) Patch Angioplasty

One such exception is the use of patch angioplasty at completion of the endarterectomy. A Cochrane meta-analysis (Bond et al., 2004a) demonstrated that patch use was associated with a significant reduction in the risk of ipsilateral stroke, stroke of any type and stroke and/or death both during the perioperative period (Peto odds ratio 0.31-0.39), and the risk of stroke and/or death long-term (Peto odds ratio 0.59), although the reviewers acknowledge the data is based on few studies. Furthermore, the risks of perioperative arterial thrombosis and long-term restenosis were also significantly reduced. However there is no evidence to support preference for vein over prosthetic material for patch angioplasty (Bond et al., 2004b).

(II) Heparin and Protamine

It is also generally agreed that systemic anticoagulation with heparin during the time of interruption of flow by arterial cross-clamping is beneficial to prevent perioperative thrombosis; indeed of surgeons participating in ECST and NASCET
over 98% used heparin perioperatively (Bond et al., 2002c, Ferguson et al., 1999), and avoidance of heparin use was associated with significantly increased operative risk in the ECST cohort (hazard ratio 2.33). The role of reversal of anticoagulation with protamine to avoid postoperative haemorrhagic complications remains in doubt, and although some smaller studies have suggested that it may be associated with a higher perioperative stroke rate (Mauney et al., 1995, Fearn et al., 1997, Levison et al., 1999), review of large case series has not confirmed this (Kresowik et al., 2004, Dellagrammaticas et al., 2008).

(III) INTRA-OPERATIVE MONITORING & SHUNTING

In the presence of an incomplete circle of Willis, interruption of carotid blood flow may lead to ipsilateral cerebral ischaemia and stroke due to hypoperfusion. Many surgeons therefore use a temporary shunt to bypass blood from the common carotid artery (CCA) to the internal carotid artery (ICA). Although shunt deployment may preserve cerebral perfusion, its use may make surgery more difficult, and be associated with late carotid restenosis, perioperative atheromatous or air embolisation, intimal flap formation or dissection, and cranial nerve injury (Ott et al., 1980, Green et al., 1985, Ouriel and Green, 1987, Forssell et al., 1995). There is no conclusive evidence that a policy of never, routinely, or selectively shunting (on the basis of monitoring) is associated with better outcome following CEA (Bond et al., 2002b), and no monitoring modality (measurement of stump pressure, electroencephalography [EEG], spontaneous evoked potentials, or transcranial Doppler [TCD]) has been established as the gold standard in detection of critical cerebral ischaemia requiring the use of a shunt. Use of locoregional anaesthesia
(LA) however permits accurate assessment of cerebral perfusion by awake neurological testing, and is associated with a lower rate of shunt use compared to GA (McCleary et al., 2001). Both the use of LA and TCD in CEA are of particular relevance to this thesis and will be discussed in a later section.

(iv) Eversion Carotid Endarterectomy

Conventional CEA is performed using a longitudinal arteriotomy. A method employing a transverse incision and removal of stenotic plaque by eversion of the transected carotid artery was first reported by DeBakey et al. (1959) and later reports by Etheredge (1970) and Jones (1989) served to increase its popularity for atherosclerosis of the ICA. Surgeons employing this technique cite the reported low long-term rate of restenosis owing to the fact that the ICA is closed transversely at its widest part. The main drawback of eversion CEA is the risk of a residual distal intimal flap following endarterectomy. A Cochrane meta-analysis (Cao et al., 2001), whilst confirming the lower incidence of restenosis (Peto odds ratio 0.48) with eversion endarterectomy, did not find significant difference between the two techniques in terms of neurological outcome or local complications, suggesting that choice of technique should depend on surgeon experience.

(v) Quality Control

Since technical imperfection has been identified as an important cause of adverse outcome following CEA (Riles et al., 1994), several methods of assessing the quality of CEA have been proposed. Examples include completion angiography,
angioscopy, duplex ultrasound, and continuous-wave Doppler, to detect intimal flaps requiring correction, kinking of the carotid artery or the presence of intraluminal thrombus (Gaunt et al., 1996). Although all methods have permitted the correction of identified errors and may impact on the rate of intraoperative stroke, there is no evidence that overall postoperative morbidity or mortality is decreased (Lennard et al., 1999) and their routine widespread use has not been adopted.

(vi) Choice of Anaesthetic Technique

Evidence from non-randomised studies suggested an advantage in using LA as opposed to GA for CEA (Tangkanakul et al., 2000). The impact of LA or GA on outcome following CEA was thus studied in the GALA Trial, an international, multicentre, randomised study. The findings of the GALA Trial together with the evidence regarding the advantages and disadvantages of each anaesthetic technique will be considered in the next section of this thesis.
1.3 General vs. Locoregional anaesthesia for carotid endarterectomy

1.3.1 Background to the choice of anaesthesia for CEA

Although Eastcott performed the first reported reconstruction of the carotid arteries under general anaesthesia (GA) (Eastcott et al., 1954), most early carotid endarterectomies were performed under locoregional anaesthesia (LA) (McCleary et al., 2001). Concerns regarding the safety of LA with regards to intraoperative cerebral ischaemia, particularly in restless, uncooperative or semi-conscious patients, together with evidence published in 1963 by Wells (Wells et al., 1963), suggesting that GA may confer protection against intraoperative cerebral ischaemia, led to GA becoming the anaesthetic of choice for most surgeons. Despite revival of interest in LA to allow accurate identification of significant cerebral ischaemia during carotid cross-clamping and thus guide the deployment of a temporary shunt (Imparato et al., 1982, Connolly, 1985), most surgeons continued to use GA for CEA throughout the 1980s and 1990s. Characteristically, the proportion of cases performed under LA in ECST was 3.4% (Bond et al., 2002c). In a survey of practice between 1984 and 1992, only four out of 131 surgeons performing CEA in the UK and Ireland used LA ‘rarely’ or ‘sometimes’ (Murie et al., 1994). Local anaesthesia has enjoyed slightly greater popularity in the USA compared to Europe; LA was used in 7% of cases in NASCET (Ferguson et al., 1999). A more recent survey of processes of care for over 10,000 CEAs in a Medicare population in the USA indicated that LA was being used for only about 10% (Kresowik et al., 2001), whilst a survey of US neuroanaesthetists indicated that 16.7% preferred LA for CEA (Cheng et al., 1997).
LA CEA has increased in popularity in recent years, partly as a result of the GALA Trial (see below), and many surgeons in the UK and Europe are adopting LA CEA as their method of choice. The theoretical advantages of GA and LA and evidence comparing their performance will be summarised below.

1.3.2 General anaesthesia for CEA

General anaesthesia for carotid endarterectomy may have the following potential benefits: (i) The anaesthetic agents used in GA may exert a neuroprotective effect; (ii) GA may permit manipulation of arterial CO$_2$ and arterial blood pressure (ABP); (iii) GA may be associated with less stress for patient and for surgeon, and permit a less hurried operation.

(I) ADVANTAGES OF GENERAL ANAESTHESIA

Perioperative neuroprotection

The potential neuroprotective effect of GA has been widely studied in various settings related to cerebral pathology, in particular the effect of anaesthetic agents on neurological sequelae of carotid surgery, neurosurgery and cardio-pulmonary bypass, and following cardiac arrest or traumatic brain injury. Whilst laboratory and clinical research in this field spans at least 40 years, controversy still remains: the encouraging results seen in vitro or in animal studies have not translated into demonstrable clinical benefit, with the exception of one prospective study of improvement in neurological outcome following cardio-pulmonary bypass with
The anaesthetic agents currently in use for GA can be broadly categorised into the volatile inhalational anaesthetics (for example halothane, isoflurane and sevoflurane), the barbiturates (for example pentobarbital and thiopental) and the intravenous agents etomidate and propofol. The potential for neuroprotection by anaesthetic agents can be explained by their effect on reducing the cerebral metabolic rate for oxygen ($\text{CMRO}_2$); virtually all drugs used in general anaesthesia have this effect to varying degrees. However, at least as important for the potential for neuroprotection are the same mechanisms whereby anaesthetic agents exert their anaesthetic effect, namely reducing excitatory and enhancing inhibitory neurotransmission in the central nervous system.

One of the main mechanisms of ischaemic cerebral injury is the accumulation of toxic concentrations of glutamate and consequent excessive stimulation of postsynaptic glutamate receptors, an effect termed ‘excitotoxicity’ (Kawaguchi et al., 2005). In laboratory studies of brain injury, anaesthetic agents increase tolerance to oxygen-glucose deprivation and glutamate excitotoxicity, and are associated with decreases in intracellular $\text{Ca}^{2+}$ concentration (Sullivan et al., 2002, Kudo et al., 2001, Amorim et al., 1995). The volatile anaesthetics, commonly used in CEA, are weak barbiturate therapy (Nussmeier et al., 1986). The reasons for this are complex; cerebral ischaemia is not a single entity but represents a spectrum of clinical situations with differences in precipitating factors, cause, extent and degree of insult (Warner, 2004). In addition, each anaesthetic agent may have differing effects on the cerebral circulation, metabolism and electrophysiology (Traystman, 2004).
antagonists of glutamate directly at its receptor (Yang and Zorumski, 1991), and may also exert a neuroprotective effect by potentiating of the interaction of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and its receptors (Jenkins et al., 2001) (Hirota and Roth, 1997), thus leading to increased tolerance to ischaemia due to hyperpolarisation of the post-synaptic membrane. Other mechanisms by which anaesthetic agents may exert a neuroprotective effect include redistribution of regional cerebral blood flow (Branston et al., 1979) and free radical scavenging (Wilson and Gelb, 2002).

Further work showing a neuroprotective effect of isoflurane in the early phase but not long term following severe focal cerebral ischaemia (Kawaguchi et al., 2000) suggests that the efficacy of anaesthetics for neuroprotection may be limited by inability to protect against the influence of continued inflammatory reaction or apoptosis induced by the original ischaemic insult.

In the setting of CEA, Wells (1963) suggested improved tolerance to ischaemia during carotid occlusion during GA compared to the awake state, on the basis of EEG changes and neurological signs respectively. Apart from the effect of the anaesthetic agents used (thiopental induction and maintenance of anaesthesia with cyclopropane), the authors acknowledge that other factors may have been responsible for the effect described, namely maintaining an inspired O₂ concentration of 70-80%, hypercapnia and high systolic ABP by infusion of phenylephrine.
Thiopental use during the period of cross-clamping of the carotid arteries to achieve burst-suppression on the electroencephalogram has been described for CEA; although single-centre prospective non-controlled series have reported good outcome from such a technique, the main drawback is the requirement to use relatively large doses of thiopental, resulting in prolonged ventilation and recovery from anaesthesia (Frawley et al., 1994). This would prevent early assessment of neurological status postoperatively and deny the patient early identification of potentially correctable causes for postoperative neurological deficit. Apart from intraoperative neuroprotection, barbiturate therapy for evolving neurological deficit immediately post-CEA has been suggested on the basis of case reports (Markowitz et al., 1984).

Maintenance of anaesthesia is most commonly performed using volatile anaesthetics in CEA. The use of isoflurane has been associated with a lower critical blood flow at which EEG changes of ischaemia become apparent (Michenfelder et al., 1987), however there is no evidence that isoflurane use translates into improved outcome (McCleary et al., 2001).

Although intravenous anaesthesia has been used for carotid surgery, there is again no evidence that it confers any clinical benefit over inhalational anaesthesia. The usefulness of etomidate in terms of cardiovascular stability is tempered by the risks of adrenocortical insufficiency and the risk of myoclonic movements (Ostwald and Doenicke, 1998). Propofol has a more favourable cardiovascular profile than the barbiturates and similar theoretical considerations for its use as a neuroprotective agent, but has not been shown in clinical studies to confer any benefit in carotid
surgery. More recently however, a crossover study comparing propofol to sevoflurane during CEA showed that propofol might have a cerebral haemodynamic advantage by causing less intracerebral vasodilatation and reducing the incidence of intracerebral steal (McCulloch et al., 2007).

Manipulation of CO\textsubscript{2}

Wells and colleagues (1963) highlighted the possible importance of hypercapnia during GA, the desired effect being cerebral vasodilatation in the belief that this would increase blood flow to the ischaemic area of the brain during cross-clamping of the carotid arteries. However, it became apparent that this might have no effect or even the opposite effect, since areas of the brain which are chronically under-perfused due to ipsilateral carotid stenosis with poor collateral supply may be already maximally vasodilated; further hypercapnia would tend to cause global vasodilatation and thus cause blood flow to be diverted from the ischaemic to the normal hemisphere (intracerebral steal) (Brian, 1998).

Later approaches to the management of intraoperative CO\textsubscript{2} levels led to the adoption of modest hypocapnia as the technique of choice. The concept behind this would be that hypocapnia-mediated vasoconstriction of the non-ischaemic territory would divert flow to the ischaemic territory, an ‘inverse steal’ phenomenon (Boysen et al., 1971). Whilst widely practiced, this approach failed to show consistent benefit.

In current GA for CEA, manipulation of CO\textsubscript{2} during anaesthesia appears to have been largely abandoned, and most anaesthetists maintain patients at normocapnia.
Intraoperative manipulation of blood pressure

The rationale behind BP manipulation is that increasing systemic ABP during the period of cross-clamping is likely to increase blood flow to the territory supplied by the clamped carotid artery via collateral flow. This has some substantiation in the experimental literature (Hayashi et al., 1984) and for CEA (Boysen et al., 1972), and indeed was one of the factors reported by Wells et al. (1963) as potentially beneficial. The use of GA has been postulated as allowing tight control of systemic pressure at a desired level by bolus dosing or continuous infusion of vasoactive drugs. However, it must be noted that anaesthetic agents have a significant vasoactive action; the ABP can be more labile during surgery with GA compared to LA, and extremes of both hypertension and hypotension can be detrimental, leading to increased myocardial oxygen demand and cerebral and myocardial hypoperfusion respectively (Howell, 2007). Further, induction and emergence from anaesthesia have been associated with significant periods of systemic haemodynamic lability; sympathetic activation during these times may also contribute to myocardial ischaemia and infarction.

(II) DISADVANTAGES OF GENERAL ANAESTHESIA

The main disadvantage of GA lies in the lack of a reliable means of assessment of the adequacy of ipsilateral cerebral perfusion during carotid cross-clamping to guide the deployment of a temporary shunt. A variety of methods have been described (measurement of stump pressure, EEG assessment, somatosensory evoked potentials, TCD monitoring of middle cerebral artery velocity, near-infrared spectroscopy assessment of cerebral oxygenation). All have methodological limitations and none
have been shown to have adequate accuracy in identification of the patient with critically low cerebral perfusion during cross-clamping (Bond et al., 2002b). A significant problem with evaluation of these techniques is the lack of a suitable gold standard; although studies have compared their performance against the ‘gold standard’ of awake neurological assessment during CEA under LA, this approach fails to take into account the differing effects of GA and LA on cerebral blood flow and metabolism and thus any conclusions may not be directly applicable to GA. However, in these series some patients have developed neurological deficit despite normal monitoring. Further, excellent outcome results have also been reported without the use of a shunt for GA, and meta-analysis of the studies comparing shunting policies and assessment methods has failed to identify any particular policy associated with improved outcome (Bond et al., 2002b).

1.3.3 Locoregional anaesthesia for CEA

The advantages of local anaesthesia primarily lie in the ability to assess the neurological status of the patient during surgery and thus guide the deployment of a shunt. Awake neurological testing is simple to perform, involving simple questions and tasks, and accurately detects critical cerebral ischaemia. It should be performed throughout the period of cross-clamping as late neurological deterioration has been described. Studies comparing the use of GA and LA have consistently shown a reduction in the use of a shunt compared with other techniques of assessment of cerebral perfusion. This avoids the use of a shunt and its inherent complications (more extensive dissection to allow shunt placement, risk of intimal damage,
embolisation) unless it is absolutely required (Halsey, 1992), and thus is of importance for those surgeons who wish to employ a shunt selectively.

LA may also have a favourable effect on the cerebral circulation as compared to GA; in the study by McCarthy (2002) CEA under LA was associated with better preservation of the ipsilateral cerebral circulation compared to GA as assessed by TCD. Further, McCleary (1996) showed that LA was associated with the preservation of ‘normal’ cerebral and systemic reflexes aiming to preserve cerebral oxygenation, by demonstrating spontaneous improvement in oxygenated cerebral haemoglobin as assessed by near-infrared spectroscopy during cross-clamp in LA but not GA patients. Although a defined mechanism for control of the systemic circulation via changes in cerebral perfusion in addition to the baroreceptor reflexes is not recognised, the authors suggested that the increase in HbO$_2$ was mediated by a rise in ABP during cross-clamp, possibly via stimulation of cerebral perfusion receptors.

Locoregional anaesthesia has also been shown to be beneficial in terms of cardiac and other non-neurological morbidity. In a systematic review of non-CEA cases, spinal or epidural anaesthesia was associated with significant reductions in mortality and serious morbidity, offering a reduction in mortality by about 30% (Rodgers et al., 2000). It should not however be accepted without question that LA is safer in terms of cardiorespiratory morbidity. Patients undergoing CEA under LA tend to have a higher ABP throughout surgery, and whilst this may be beneficial in terms of cerebral perfusion, it may contribute to myocardial ischaemia by increasing myocardial oxygen demand. Further, cases of respiratory distress with cervical LA
have been reported, and patients with chronic respiratory disease may find lying awake and flat for extended periods distressing. Finally, some of the benefits of regional anaesthesia for non-carotid surgery in terms of postoperative analgesia and prevention of postoperative cardiorespiratory complications may not be relevant, as the operative field for CEA is relatively small compared to e.g. laparotomy or thoracotomy.

1.3.4 Comparison of GA and LA CEA

(I) CLINICAL OUTCOME

The publication of a systematic review (Tangkanakul et al., 1997) and a Cochrane meta-analysis (Tangkanakul et al., 2000) of studies suggesting that CEA under LA might be associated with 50% reduction in stroke and death rate compared with GA confirmed the need for a suitably large randomised study. This led to the inception of the GALA Trial, an international, multicentre randomised study comparing CEA under LA and GA (Gough et al., 2008). In an attempt to improve generalizability and to be pragmatic in terms of feasibility, patients underwent surgery according to the usual indications and practices of each unit taking part in the Trial. The only prescription was that a temporary shunt during cross-clamp of the carotid arteries should only be deployed under LA on the basis of awake neurological testing. The study recruited 3526 patients and achieved 99.9% follow-up data, the primary endpoints measured being stroke, myocardial infarction (MI) or death within 30 days of surgery. Whilst the study was short of the projected 5000 patients needed to show a 30% relative risk reduction, nevertheless the recruitment target had been a fairly
conservative estimate compared to the effect suggested by the meta-analysis (Gough, 2008).

The data from the GALA Trial (Lewis et al., 2008) showed a primary event rate of 4.8% for GA and 4.5% for LA, a difference which was not statistically significant (risk ratio 0.94 CI 0.7 – 1.27). For stroke the rate was 4.0% for GA and 3.7% for LA, for death 1.5% for GA and 1.1% for LA and for MI 0.2% for GA and 0.5% for LA; these differences were not statistically significant. No effect was seen when age below or above 75 years was considered. For patients with contralateral carotid occlusion a trend was seen favouring LA (risk of primary event 10% for GA vs. 5% for LA, p=0.098) with a higher incidence of contralateral postoperative stroke in the GA group (54% of postoperative strokes were contralateral vs. 29% in LA).

When considered as part of the updated Cochrane meta-analysis of GA vs. LA in CEA, there remained no difference for combined primary outcome (Rerkasem and Rothwell, 2008). However, a trend favouring LA for reduced risk of perioperative death was seen although this was not statistically significant nor was the GALA Trial powered to show such a difference.

It is worth mentioning that a significant number of patients in the GA group had BP manipulation to achieve a higher MAP compared to the LA group (43% vs. 17%). This may reflect that anaesthetists aimed to reproduce the autoregulatory reflex hypertension seen in LA for patients under GA (McCleary et al., 1996), thus confounding the outcome results. In addition fewer patients underwent patch closure of the arteriotomy in the LA group, which may have biased the outcome data against LA.
Nevertheless the GALA Trial provided valuable data, not least showing that the results of CEA had improved compared to the landmark studies of CEA (NASCET, ECST) of the 1990s. Further, GALA provided reassurance that patient, surgeon or anaesthetist preference for LA or GA could be respected without concern regarding outcome. For certain patients it might be preferable to operate under LA (for example those with contralateral carotid occlusion). When the requirement for early surgery is considered, it remains important to identify patients in whom one anaesthetic technique is preferable, and correlation with pre- and postoperative cerebral haemodynamic status is of relevance.

(II) PATIENT AND SURGEON PREFERENCE AND COST-EFFECTIVENESS

For the surgeon, performance of CEA under LA may be associated with greater psychological stress; it has been suggested that the operation may be technically more difficult, particularly if the patient cannot remain still or exhibits significant neurological deterioration (McCleary et al., 2001). Use of GA permits surgery on a fully co-operative patient and permits the teaching of this technique without concerns regarding duration of procedure – although it should be noted that adverse outcome has been associated with procedures lasting less than 30 minutes or more than 2 hours (Bond et al., 2002c). On the other hand, the knowledge that the patient has adequate cerebral perfusion by means of awake neurological testing may mean that the surgeon may proceed with endarterectomy in an unhurried manner.

For the patient, LA may be associated with some pain (although further local anaesthetic can be infiltrated and light sedation administered during the procedure) and requires the patient to lie fairly still, which may prove uncomfortable. GA
however is associated with emergence from anaesthesia, which is often associated with nausea and vomiting.

The majority of published studies advocating the use of LA report that it is well tolerated by the patient and most would have LA again for CEA; in the questionnaire study by McCarthy (2004) comparing acceptability of LA vs. GA no significant difference for the two techniques was found, although LA was associated with a better perception of recovery.

Finally, there is evidence that the use of LA for CEA may be associated with significant hospital savings, since some studies have shown reduced length of stay in intensive care/high dependency units and in overall hospital stay (McCarthy et al., 2001, Syrek et al., 1999). The cost-effectiveness analysis of the data from the GALA Trial (Gomes et al., 2010) showed a rather modest cost saving associated with the use of LA, mainly due to less frequent use of consumables such as shunts, as well as shorter stay in critical care beds. However, this study did not take into consideration the costs of intraoperative monitoring (TCD, near-infrared spectroscopy, EEG and the associated operators), which would have clearly further favoured LA surgery.
1.4 Cerebral blood flow and its control

1.4.1 Normal control of cerebral blood flow

The brain is characterised by a high metabolic rate, dependence on glucose for its metabolism and the inability to ‘store’ energy; it is an obligate aerobe, and accounts for approximately 20% of total oxygen consumption. A constant supply of glucose and oxygenated blood is thus required, and it receives about 15% of the cardiac output, approximately 800 ml/min (Kety and Schmidt, 1948). The factors contributing to the maintenance of adequate blood flow and the influence of extracranial carotid disease will be considered in this section.

(1) ANATOMY OF THE CEREBRAL BLOOD SUPPLY

The main blood supply to the brain consists of the paired carotid and vertebral arteries; at the base of the brain they form the major contributors to the circle of Willis. At this level the anterior communicating artery forms an anastomotic connection between the paired anterior cerebral arteries, which are supplied by the internal carotid arteries. The internal carotid arteries also supply the middle cerebral arteries. The posterior communicating arteries provide a connection between the anterior (carotid, anterior and middle cerebral arteries) and posterior (vertebral via basilar arteries, posterior cerebral arteries) cerebral circulation. The precise configuration of the circle of Willis and its functional significance in terms of collateral supply varies between individuals; common anatomic patterns are shown in figure 1.4.1. Apart from these major communicating vessels, further anastomotic
channels exist between the external carotid arteries and the intracranial circulation via the ophthalmic and occipital arteries, as well as leptomeningeal and dural anastomoses with cerebral cortical vessels.

The adequacy of the collateral circulation becomes significant when blood flow through the major vessels becomes impeded or interrupted as a consequence of arterial pathology (atherosclerosis, dissection, embolism) or when flow is temporarily arrested during surgery, as during carotid cross-clamping for CEA.
Hypoplasia of the ACoA (1-37%)

Hypoplasia of the A₁ (1-13%)

Hypoplasia of the PCoA (16-64%)

Hypoplasia of the P₁ (9-15%)

Figure 1.4.1
Common variations of the circle of Willis and their reported prevalence. ICA = internal carotid artery, VA = vertebral artery, M₁ = middle cerebral artery, A₁ = precommunicating segment of anterior cerebral artery, P₁ = precommunicating segment of posterior cerebral artery, ACoA = anterior communicating artery, PCoA = posterior communicating artery, BA = basilar artery. Modified from Hoksbergen et al (Hoksbergen et al., 2000).
(II) REGULATION OF THE CEREBRAL CIRCULATION

Under normal conditions the cerebral blood flow is determined by the cerebral perfusion pressure and the cerebrovascular resistance. Cerebral perfusion pressure is the difference between systemic mean arterial pressure and intracranial pressure, whilst cerebrovascular resistance is determined by the tone of the cerebral arterioles.

At a tissue level, blood flow must be altered in response to changes in metabolic requirements. Although the mechanisms underlying this are not fully elucidated, experimental evidence suggests that local alterations in the concentrations of metabolites (nitric oxide, ATP, K\textsuperscript{+}, adenosine) are important (Kulik et al., 2008). Apart from local coupling of blood flow and metabolism, global CBF is influenced by a variety of factors: a major determinant of the resting CBF appears to be the interaction between the effects of vasodilating agents such as NO and of constricting agents such as thromboxane and endothelin (Markus, 2004); other important factors are cerebral autoregulation and the response of CBF to changes in arterial gases, particularly CO\textsubscript{2}. These factors will be considered in turn.

1.4.2 Cerebral autoregulation

The term ‘cerebral autoregulation’ is used to describe the phenomenon of CBF remaining relatively constant despite changes in cerebral perfusion pressure. The physiological mechanisms responsible for this effect are incompletely understood; although neurogenic (sympathetic and parasympathetic effects) (Sandor, 1999), myogenic (direct response of arteriolar smooth muscle to alterations in pressure) (Wallis et al., 1996), endothelial (Faraci and Heistad, 1998) and metabolic (release of
vasoactive metabolites in response to changes in cerebral blood flow) (Kulik et al., 2008) mechanisms have been described, the relative significance of each has yet to be clearly defined in vivo.

In the normal subject, the lower and upper limits of cerebral autoregulation are approximately 60 and 150 mmHg respectively (figure 1.4.2); above and below these limits cerebral blood flow increases or decreases approximately linearly with changes in perfusion pressure. The significance of cerebral autoregulation lies in the prevention of cerebral ischaemia at low perfusion pressures and in the protection of the brain against oedema at high perfusion pressures. The limits of autoregulation are not rigid however, and can be altered by a variety of physiological factors, including sympathetic stimulation and changes in \( \text{PCO}_2 \), and pathological states, such as chronic hypertension (figure 1.4.2). Impairment of normal autoregulation may occur in pathological states such as ischaemic stroke (Markus, 2004), malignant hypertension (Immink et al., 2004), subarachnoid haemorrhage (Voldby, 1988), head trauma (Enevoldsen and Jensen, 1978), and ipsilateral to carotid stenosis. The latter will be considered in more detail below.
Figure 1.4.2

Relationship of cerebral blood flow (CBF) and mean arterial pressure (MAP) to illustrate normal cerebral autoregulation. CBF remains relatively constant through a MAP of 60 – 160 mmHg. The curve shifts to the right in chronic hypertension (dashed line), and upwards during hypercapnia (dotted line). It is worth noting that this is a rather simplistic representation – the alterations of the curve are more dynamic than this diagram would imply (Gelb and Werner, 2003).
1.4.3 Response of CBF to changes in arterial gases – cerebrovascular reactivity

Cerebral blood flow is significantly affected by changes in the partial pressures of arterial blood gases, the most pronounced effect seen with changes in the partial pressure of CO$_2$ (P$_{CO_2}$). Increase in arterial P$_{CO_2}$ is a potent vasodilatory stimulus leading to increased CBF, whilst decreases in P$_{CO_2}$ cause cerebral vasoconstriction and thus reduction in CBF. Again, the mechanisms for these effects are still under investigation, but it appears that vasodilatation in response to raised P$_{CO_2}$ is due to corresponding changes in extracellular pH (Kontos et al., 1977), leading to changes in intracellular Ca$^{2+}$ concentration of vascular smooth muscle (Austin and Wray, 1995); other mediators may include nitric oxide and cyclic GMP (Faraci and Brian, 1994). A role for prostaglandins has been suggested, but this appears to be of relevance only in the neonate (Brian, 1998). For vasoconstriction due to low P$_{CO_2}$, little is yet known beyond the effect of alteration in pH and changes in intracellular Ca$^{2+}$.

The normal response of CBF to alterations in CO$_2$ can be characterised by a sigmoid curve, with asymptotes at the lower and higher levels of CO$_2$ where further decreases and decreases in P$_{CO_2}$ have elicited maximal vasodilatation and vasoconstriction respectively (Ringelstein et al., 1988). In the physiological range, i.e. in the range where CO$_2$ alterations are tolerated without physical symptoms of obtundation, paraesthesiae etc. (approximately 30 to 60 mmHg), the relationship between P$_{CO_2}$ and CBF is usually considered to be linear with a change in CBF of approximately 3%-5% per mmHg rise in P$_{CO_2}$ (Kirkham et al., 1986).
The response of CBF to changes in \( \text{PCO}_2 \) is commonly used to assess cerebrovascular ‘reserve’ in patients with carotid disease. Reduction in cerebral perfusion due to a critical carotid stenosis or occlusion in the presence of poor collateral supply via circle of Willis will result in compensatory maximal vasodilation of the corresponding cerebral vascular territory (Ringelstein et al., 1988, Kleiser and Widder, 1992). Increases in \( \text{PCO}_2 \) cannot cause further vasodilatation and thus have little effect on CBF. The reverse response to decreases in \( \text{PCO}_2 \) may be similarly blunted if perfusion is compromised to such an extent that tissue hypoxia counteracts the vasoconstrictive effect of hypocapnia (Harper and Glass, 1965) and cerebrovascular reserve may thus be considered to be ‘exhausted’ (Kleiser and Widder, 1992).

If the reduction in CPP reaches a critical level then the oxygen demand in the brain is satisfied by increasing the oxygen extraction ratio (misery perfusion) (Markus, 2004); further reduction in CPP beyond this makes ischaemic damage inevitable. The significance of cerebrovascular reactivity testing in the context of carotid disease will be considered below.

1.4.4 Methods of measurement of cerebral blood flow, autoregulation and vasoreactivity

The first method for accurate quantification of cerebral blood flow in the human brain was described by Kety and Schmidt in the 1940s, using the method of equilibration of arteriovenous cerebral difference of nitrous oxide and the Fick
principle to calculate blood flow (Kety and Schmidt, 1948). Since then, numerous techniques have been developed to measure CBF. They differ in their ability to measure absolute flow, in their spatial and temporal resolution, and in degree of invasiveness. Commonly used methods can be categorised as follows:

i. Nuclear medicine techniques - single photon emission computerised tomography (SPECT) or positron emission tomography (PET)

ii. CT-based techniques - Xenon CT (XeCT) or perfusion CT

iii. Magnetic resonance imaging techniques

iv. Near-infrared spectroscopy

v. Doppler ultrasound techniques (for example transcranial Doppler ultrasound).

Although a detailed description of each of these techniques is beyond the scope of this thesis (with the exception of transcranial Doppler), a brief summary is provided below. Other methods which have been used to measure cerebral blood flow include laser Doppler flowmetry and thermal methods; these are invasive, requiring direct placement of probes on the brain surface, and shall not be discussed further.

(i) **Nuclear medicine techniques**

Both SPECT and PET utilise radionuclides as tracers, and involve significant exposure to radiation. SPECT permits semi-quantitative measurements of CBF and cerebral blood volume to be performed. In pathological states it is usual to compare side-to-side differences, interpretation of which may be difficult (for example in
bilateral carotid disease). PET is expensive and less widely available, but permits quantification of CBF and blood volume as well as parameters related to cerebral metabolism (pH, oxygen extraction fraction, glucose utilisation) (Guadagno et al., 2003).

(II) CT TECHNIQUES

Two techniques are in common use for blood flow measurements: XeCT, which involves inhalation of Xenon gas (which is detectable on CT) and the calculation of the decay in concentration from equilibrium (the ‘washout’ method) (Yonas et al., 1996). Alternatively, perfusion CT involves administration of intravenous iodine-based contrast agent and the serial acquisition of images, with cerebral blood flow parameters calculated from the contrast enhancement curves generated (Wintermark et al., 2008).

(III) MR TECHNIQUES

Measurement of CBF with MR has increased in popularity due to the continued improvement in accuracy of this technique and the avoidance of ionizing radiation. It can be performed either with administration of intravenous gadolinium-based contrast agent or using blood water as an endogenous contrast agent (Harris et al., 2009). Although the latter technique is completely non-invasive and permits frequent repetition, it has poorer signal-to-noise ratio compared to gadolinium-enhanced methods. Despite initial hope to the contrary, contrast agents used for MR examinations do carry a risk of acute kidney injury (Ledneva et al., 2009).
(IV) NEAR-INFRARED SPECTROSCOPY (NIRS)

Although typically used to continuously measure changes in concentration of oxyhaemoglobin and deoxyhaemoglobin and cytochrome aa3 oxidation/reduction status, NIRS has been used to measure CBF changes and vasoreactivity by measuring the influx and decay of indocyanine green through the cerebral circulation (Terborg et al., 2009). The usefulness of this technique is limited by contamination of the signal from ‘noise’ generated by extracranial tissue.

(V) ULTRASOUND TECHNIQUES

Ultrasound assessment of the carotid and vertebral arteries can provide direct, non-invasive measurement of flow volume in these vessels, and give information regarding flow into a vascular territory, but do not provide information regarding perfusion of the intracranial vascular territories.
1.4.5 Transcranial Doppler ultrasound

Transcranial Doppler ultrasound assessment of the basal cerebral vessels has revolutionised the assessment of cerebral blood flow. Initially described in the early 1980s by Aaslid, it permits continuous, non-invasive measurement of blood flow velocity in the basal cerebral arteries (Aaslid et al., 1982). It should be noted that this technique gives data on blood flow velocity and not flow per se, but in most circumstances changes in blood flow and velocity can be assumed to be proportional provided the diameter of the insonated vessel and the angle of insonation remain constant (Panerai et al., 2005). It is thus most useful for determining relative changes in blood flow rather than absolute values; this variability is reflected by the variance in reported normal values for the flow velocities detected in the basal cerebral arteries.

The ability to monitor cerebral blood flow over long periods of time coupled with excellent temporal resolution has allowed this method to be used for assessment of static and dynamic autoregulation, measurement of cerebral vasoreactivity, clinical monitoring for blood flow velocity changes and presence of emboli during surgery, and to guide therapeutic interventions such as thrombolysis in acute stroke.

(1) Testing of Cerebral Autoregulation with TCD

Cerebral autoregulation has been traditionally assessed using static techniques, where values of CBF are obtained at steady state for a range of arterial pressures. Pressure changes are achieved by administration of vasoactive drugs or by inducing changes in relative blood volume during tilt-table testing (Panerai, 1998).
The temporal resolution of TCD permits assessment of rapid changes in cerebral blood flow velocity (CBFV), and thus dynamic autoregulatory responses can be evaluated. For dynamic autoregulation to be assessed, a rapid change in arterial pressure is induced (usually by rapid deflation of thigh-cuffs inflated above systolic arterial pressure), and the rate of recovery of CBFV towards baseline compared to the rate of change of arterial pressure towards baseline provides an index of dynamic autoregulation (Aaslid et al., 1989). Other workers have used the moving correlation coefficient between beat-to-beat values of arterial blood pressure and middle cerebral artery velocity (MCAV) to assess the autoregulatory response to spontaneous fluctuations in blood pressure (Reinhard et al., 2005), or assessed the impact of the blood pressure changes during the Valsalva manoeuvre on MCAV (Tiecks et al., 1995b). However, debate remains as to whether these techniques are measuring the same intracerebral mechanisms of maintenance of blood flow, or whether they are complementary (Tiecks et al., 1995a).

(II) MEASUREMENT OF CEREBROVASCULAR REACTIVITY (CVR)

Measurement of the CBF response to a vasodilatory or vasoconstricting stimulus has been performed with virtually all the techniques described above (PET, SPECT, MRI, XeCT, NIRS), but the use of TCD due to its non-invasiveness, temporal resolution and relative ease of use has led to its wide adoption; numerous protocols have been described for testing this response using TCD with considerable methodological differences.

In broad terms studies have assessed the response of the cerebral circulation to a maximal vasodilating stimulus (such as continuous inhalation of 7-8% CO₂ or the
intravenous administration of acetazolamide) and calculation of the percentage change in cerebral blood flow velocity from baseline; this however can lead to greater systemic haemodynamic changes which may confound measurement (Markus and Cullinane, 2001). More commonly used is sub-maximal stimulation (inhalation of 5-6% CO₂, rebreathing or increasing ventilatory dead-space, with or without induction of hypocapnia by hyperventilation) with continuous measurement of end-tidal CO₂, and calculation of percentage change in blood flow velocity per unit change in end-tidal CO₂. A further test, the breath-holding index (BHI), measures the % increase in MCAV over the duration of breath holding, has been used as a screening test (Silvestrini et al., 1996).

Apart from methodological differences, measurement of cerebrovascular reactivity may also be affected by changes in arterial pressure and haematocrit. Some debate also continues regarding the influence of possible alterations in the diameter of the insonated vessel during studies of cerebral autoregulation; most studies agree that the MCA diameter changes very little and that the relationship between CBF and CBFV is linear, and this is supported by angiographic (Huber and Handa, 1967) and MRI studies (Serrador et al., 2000), as well as direct observation of the calibre of the MCA during craniotomy (Giller et al., 1993).

Finally, changes in PO₂ may also affect the cerebral circulation: hypoxia and to a lesser extent hyperoxia have vasodilating and vasoconstricting properties respectively; hypoxia is a potent cerebral vasodilator at PO₂ below 7 kPa, whilst hyperoxia (inhalation of 100% or hyperbaric oxygen) is a much more modest vasoconstrictor compared to the effects of CO₂ (Markus, 2004).
The variation in measurement methods and the potential confounding physiological parameters have led to a lack of consensus as to the normal range for the cerebrovascular reactivity index (CVRI). CVRI is usually expressed as the per cent change in MCAV per unit change in end-tidal CO2 (a surrogate for Pco2). Several authors however have suggested a lower limit of between 11 and 12 %/kPa beyond which cerebrovascular reactivity may be considered impaired (Widder et al., 1994, Thiel et al., 1995, Dumville et al., 1998)
1.4.6 Cerebrovascular autoregulation and vasoreactivity in carotid disease

Although the primary mechanism of stroke due to extracranial carotid disease is thromboembolism, a subgroup of patients experience neurological events due to hypo-perfusion. These patients have a critically reduced perfusion pressure with maximal vasodilatation of the cortical arterioles and increased oxygen extraction ratio; as a consequence, cerebrovascular reactivity is diminished or exhausted, and thus such patients should be identifiable with TCD testing of cerebrovascular reactivity. Further, several studies have indicated that patients with impaired reactivity have a higher incidence of neurological symptoms during follow-up.

Ringelstein (1988) studied 40 patients with unilateral and 15 patients with bilateral ICA occlusions. CVR was significantly lower in both groups of patients compared to controls; significantly lower CVR was seen for patients with symptomatic unilateral occlusions compared to asymptomatic patients, and those with evidence of ‘low-flow’ cerebral infarcts on CT compared to those with no CT evidence of infarction. A further association between ‘low-flow’ infarctions, ischaemic ophthalmopathy and hypostatic TIAs was seen with patients with the most severely reduced reactivity. It is notable that significant reduction in vasoreactivity was also seen in the contralateral hemisphere in patients with unilateral occlusion. Reith and colleagues (1990) studied patients with carotid stenosis of $\geq 70\%$ and identified a significant reduction in CVR in these patients compared with controls; further, a trend towards lower vasoreactivity was seen for symptomatic vs. asymptomatic patients. Kleiser and colleagues (1991) found a significant association for presence
of neurological symptoms in the 3 months prior to CVR testing and reduced CVR in the presence of ICA occlusion. Chimowitz (1993) identified a significant association between impaired vasoreactivity to acetazolamide in patients with unilateral carotid stenosis or occlusion and history of TIAs; similar findings, using inhalation of CO₂, were observed by Widder (1994). Silvestrini and colleagues (1996) identified significant reduction in CVR for the symptomatic hemisphere for 24 patients with unilateral severe carotid stenosis, although no reduction in CVR was identified for the asymptomatic hemisphere was seen. Finally, a study by Fearn et al (2003) examining the relationship between changes in cognitive function following CEA for >70% symptomatic stenosis and CVR identified only 8/95 patients with normal vasoreactivity bilaterally.

Examining the relationship between cerebrovascular reactivity, carotid disease and risk of neurological symptoms, Gur and colleagues (1996) used acetazolamide to assess reactivity in 44 asymptomatic patients with >70% ICA stenosis followed up for 2 years; 7/21 patients with impaired vasoreactivity had an ipsilateral ischaemic event whilst patients with sufficient reactivity had no events. Vernieri and colleagues (1999) examined the incidence of ischaemic events over 24 months in 65 patients with ICA occlusion; the annual risk of ischaemic events and stroke in the cohort was 14.6% and 12.5% respectively, and the risk of ischaemic events was significantly associated with impaired CVR as determined by the BHI and with increasing age. Similar findings were reported by Silvestrini and colleagues (2000) in a study of 94 patients with asymptomatic carotid stenosis over 28.5 months. In a further prospective study of 107 patients with carotid occlusion or stenosis over a 2
year period (Markus and Cullinane, 2001), exhausted cerebrovascular reactivity was significantly associated with risk of ipsilateral stroke and TIA in both groups.

The importance of these findings lies in the possibility that surgery to improve cerebral perfusion distal to occlusive carotid disease (carotid endarterectomy or EC-IC bypass) may reduce the risk of stroke in this population of patients with impaired cerebral haemodynamics. Whilst the trials of symptomatic carotid stenosis have defined the role of surgery unequivocally, ACST demonstrated a more modest benefit in asymptomatic disease and the EC-IC bypass study failed to show benefit of surgery. It has been postulated therefore that in selected subgroups of patients with impaired reactivity and either asymptomatic stenosis the demonstrated benefit of surgery may be enhanced, and in patients with occlusion surgery may of benefit. As yet neither of these assumptions has been tested in clinical studies; evidence also suggests that the impairment of CVR associated with carotid occlusion tends to improve over time (Widder et al., 1994), further adding complexity to this issue. Nevertheless, several studies show improvement in cerebral autoregulatory parameters following carotid endarterectomy, and this shall be discussed in the following section.

1.4.7 Effect of CEA on cerebrovascular autoregulation and reactivity

If the impairment of CVR ipsilateral to a haemodynamically significant carotid stenosis is accounted for by reduction in perfusion pressure due to inadequate collateral supply then it would be expected that reactivity would be improved
following CEA. Indeed this appears to be the case in the majority of patients: studies conducted between 3 days and 6 months following CEA suggest that patients with the worst impairment pre-operatively tend to return to normal, whilst patients with intact vasoreactivity experience no change, improve or show some deterioration.

Using the i.v. Xe-133 technique, Bishop et al. (1987) demonstrated increased cerebrovascular reactivity to hypercapnia six months following CEA in 14 patients; the same group had previously demonstrated improved reactivity in a cohort of 8 patients 3 months following EC-IC bypass.

Schroeder et al. (1987a) studied 32 patients undergoing CEA using the i.v. Xe-133 technique and administration of acetazolamide to assess CVR. A significant increase in reactivity at five days was observed in the whole series, most marked in the ipsilateral hemisphere of patients with > 50% ICA stenosis; the latter group had reduced reactivity in the ipsilateral hemisphere preoperatively, and this improvement was sustained at 77 days.

Cikrit and colleagues (1992) performed a retrospective analysis of acetazolamide-enhanced SPECT data from 25 patients before and at a mean of 12 days after carotid endarterectomy. In 18 patients improved CVR compared to the preoperative scan was demonstrated in the ipsilateral hemisphere, whilst this was bilateral in four cases and contralateral in two cases. A further study by the same author (Cikrit et al., 1997) found poor vascular reactivity on SPECT in 50/64 patients before CEA, 39 of these had improved reactivity at about two weeks postoperatively.

A further study (Hosoda et al., 1998) using SPECT and acetazolamide identified impaired CVR in 18/36 patients with unilateral ICA stenosis of 70% and above, and
this improved significantly at 34 days post-cea in 15/31 patients (all those with preoperative impairment who also went postoperative assessment), whilst no significant difference was seen of those who had normal reactivity preoperatively.

Naylor and colleagues (1993a) studied 69 patients undergoing CEA using a technique to quantify mean cerebral transit time (MCTT). Twenty-one patients (all of whom had ICA stenosis > 60%) had evidence of impaired reactivity preoperatively in the symptomatic hemisphere, and repeat assessment four days postoperatively demonstrated a return to normal reactivity in 17 of 21 patients, and by six months reactivity had returned to normal in 20 of 21 patients.

Studying the cerebral metabolic effect of CEA, Uno et al. (2001) identified improved vasoreactivity to acetazolamide detected on SPECT 1-3 months postoperatively in 7 of 8 patients with impaired reactivity preoperatively; the single patient who showed no improvement had a distal tandem lesion which may have contributed to a degree of persisting haemodynamic impairment.

Using TCD and the BHI, Markus and colleagues (1993) studied 10 patients before and one month following CEA, and demonstrated significant increase in vasoreactivity both on the operated side and the contralateral side; in particular, contralateral improvement was also evident in 2/3 of patients with contralateral occlusion and the one patient with contralateral asymptomatic 90% stenosis.

Hartl and colleagues (1994) studied the CO₂ reactivity of the cerebral resistance index with TCD for 63 patients prior to and three months following CEA. Patients had unilateral high-grade carotid artery stenosis and approximately half were
symptomatic. The side-to-side asymmetry was used as the indication of abnormal reactivity; 10/63 had reduced reactivity in the ipsilateral hemisphere whilst the situation was reversed in 12/63, and the remainder had no asymmetry. Following CEA reactivity was not significantly affected in the cohort overall, however in all patients with preoperative side to side asymmetry this was corrected, with ipsilateral reactivity increasing significantly in the group with preoperative impairment of that hemisphere, and contralateral reactivity increasing significantly in patients with preoperative impairment of the contralateral hemisphere. The side to side asymmetry was not affected in patients without preoperative abnormality. An interesting finding from this study was the demonstration of intracerebral hypercapnic steal from the contralateral to the ipsilateral hemisphere.

Thiel and colleagues (1995) studied 94 patients undergoing CEA, the majority of which were symptomatic. CO₂ reactivity was assessed with TCD preoperatively and four days postoperatively. 12 patients had impaired reactivity preoperatively, and this improved significantly postoperatively; in the remaining cases no significant difference was found. This study found no relationship between impaired CVR and the incidence of critical somatosensory evoked potential changes or critical intraoperative TCD changes.

Barzo et al. (1996) studied 40 patients undergoing CEA for greater than 70% stenosis of the ICA. Cerebrovascular reactivity was measured using acetazolamide and TCD evaluation, before surgery and eight days after surgery. Preoperative cerebrovascular reactivity was lower on the side of surgery compared to the contralateral side in the entire cohort. All patients demonstrated improvement in reactivity on the side of surgery postoperatively; contralateral improvement was also
seen in patients with impaired reactivity in both hemispheres, whilst no significant change was seen in the groups with normal reactivity in at least one hemisphere.

Visser et al. (1997) studied 65 patients with >70% carotid stenosis before and 3 months after CEA, and found significant increase in reactivity compared to baseline in the 21 patients with impaired preoperative reactivity. A similar finding was seen for the contralateral side; patients with normal reactivity showed no change in either cerebral hemisphere. Further, significantly lower preoperative reactivity was seen in patients with contralateral carotid occlusion.

Micieli et al. (1999) studied 20 patients with symptoms due to unilateral significant carotid stenosis. Reactivity was assessed preoperatively and three months postoperatively with TCD in response to CO₂ and L-arginine (which also induces nitric oxide-mediated vasodilation of cerebral resistance vessels (Moncada et al., 1989)). No significant difference between preoperative and postoperative reactivity for either CO₂ or L-arginine was found, although asymmetry between cerebral hemispheres in response to L-arginine was eliminated by CEA. The authors indicated that the absence of significant increase may be explained either by lower sensitivity of method in detecting small reductions in reactivity but also by the absence of major impairment of intracranial circulation in their patient group.

D’Angelo and colleagues (1999) studied reactivity to rebreathing-induced changes in CO₂ with TCD in 25 symptomatic patients with predominantly unilateral carotid stenosis; a significant improvement was seen in the group as a whole. Preoperative reactivity was lowest in patients with >90% ipsilateral stenosis and/or contralateral carotid occlusion; again, the greatest improvement following CEA was seen in patients with the lowest preoperative reactivity.
Vriens et al. (2001) studied 148 patients with 70% stenosis before and 3 months following CEA. Reactivity to inhaled 5% CO₂ was assessed using TCD. A significant improvement was seen overall for the ipsilateral side, but not the contralateral side. When patients with contralateral stenosis were examined however, reactivity increased significantly in both hemispheres.

Soinne and colleagues (2003) studied 46 patients with unilateral high-grade stenosis, 23 of which were asymptomatic, using TCD and the BHI. Examinations were carried out preoperatively, at 3 days, and at 100 days postoperatively. The reactivity was similar in asymptomatic and symptomatic groups preoperatively, but significant improvement only occurred in symptomatic patients. Asymptomatic patients had a lower reactivity postoperatively although statistical significance was not reported for this group. The same patients underwent MRI assessment of CBF, and the improvement in reactivity was mirrored by normalisation of inter-hemispheric MRI parameter asymmetries.

A further TCD study by Reinhard (2004) identified a significant improvement in reactivity in the ipsilateral hemisphere for predominantly symptomatic patients 3 days following CEA (n=41) and carotid angioplasty and stenting (n=17). A similar improvement was documented for dynamic cerebral autoregulation parameters. However, no significant change was observed in the contralateral hemisphere.

Finally, a more recent study by Telman (2006) showed improvement in ipsilateral reactivity compared to baseline 3 months post-CEA in both symptomatic and asymptomatic patients.
In summary, cerebrovascular autoregulatory indices have been shown in numerous studies to improve following CEA on the ipsilateral side, and this change seems to occur by 3 days following surgery and is maintained 3-6 months subsequently. Some variation in the effect on the contralateral hemisphere is reported, but it appears that CEA for a stenosis accompanied by contralateral occlusion improves haemodynamics in both hemispheres, suggesting potential benefit for operating on an asymptomatic carotid stenosis associated with contralateral occlusion. The relationship of symptom status, impairment in reactivity and the effect of CEA seem as yet unresolved, although symptomatic patients seem to have greater improvement in CVR on the background of impaired preoperative vasoreactivity. The variation in reported findings as regards relationship of reactivity changes post-CEA may be explained by the variety of techniques used for assessment (CBF techniques, TCD with acetazolamide, rebreathing, administration of various concentrations of CO₂ and the BHI, different calculations of autoregulatory indices) and the heterogeneity (particularly regarding unilateral vs. bilateral disease and/or occlusion, or for symptom status) in patient groups between studies. Despite these variations, a consistent finding seems to be improvement in reactivity, particularly in patients with the most impaired preoperative reactivity. There is little information in the literature however on the time-course of reactivity and cerebral autoregulation in the first 24-48 hours following CEA. These changes may be of significance particularly in the presence of postoperative haemodynamic lability or the development of cerebral hyperperfusion. Furthermore, the development of the post-CEA hyperperfusion syndrome has been associated with impaired vasoreactivity and cerebral autoregulation. This shall be further discussed in a subsequent section.
1.4.8 Effect of CEA on cerebral blood flow during and following surgery, and effect of LA vs. GA on these parameters

Cerebral blood flow may be influenced by CEA at various stages: during induction of anaesthesia, during cross-clamping of the carotid arteries, during the period of insertion of a temporary shunt, during restoration of flow and in the postoperative period. LA and GA have differing effects on CBF and its autoregulation in non-CEA surgery. Few studies have compared the effect of LA vs. GA on cerebral autoregulation or vasoreactivity during CEA.

(1) THE EFFECT OF ANAESTHETICS ON CBF AND MCAV

Most rCBF studies suggest that inhalational anaesthetics (isoflurane, halothane, N₂O) tend to produce cerebral vasodilatation and decreased cerebral metabolic rate: CBF increases provided arterial blood pressure is maintained. Conversely, the intravenous agents (thiopental, etomidate, propofol) tend to reduce CBF in association with reduction in cerebral metabolic rate. Opioids are not thought to have significant effect on CBF (Kofke, 1999).

Thiopental administered in doses required to produce burst suppression on the EEG is associated with a 50% reduction in MCAV (Young et al., 1991). For indices derived from TCD assessment, a 20% decrease in MCAV has been observed on induction of anaesthesia with thiopental (Dong et al., 1996). Midazolam appears to have a dose-dependent effect, with decrease in MCAV of up to 25% after administration of 40 µg/kg (Cheng et al., 1993). Propofol has been reported to
decrease CBF and MCAV by approximately 35% in EEG burst-suppression doses in animal studies (Werner et al., 1992), whilst human studies have suggested a similar reduction with concomitant cerebral vasoconstriction (Eng et al., 1992).

The effects of the volatile agents are more variable depending on the setting studied: Sevoflurane has been shown to induce a reduction in MCAV (Cho et al., 1996), whilst a further study examining the effects of halothane, sevoflurane and isoflurane found a dose-dependent increase in MCAV with halothane and no effect of the latter two agents (Kuroda et al., 1997).

Although several studies document the effects of intravenous injection of local anaesthetics on cerebral blood flow, there appears to be little evidence regarding the effect of infiltration of local anaesthetics per se on MCAV.

(I) EFFECT OF ANAESTHETIC AGENTS ON CEREBRAL AUTOREGULATION

The inhalational anaesthetics are considered to impair cerebral autoregulation to varying degrees in a dose-dependent manner (Strebel et al., 1995). A possible exception may be sevoflurane which has been shown to have little appreciable effect when assessing static autoregulation (Gupta et al., 1997), but causing some impairment when dynamic autoregulatory indices are considered (Summors et al., 1999). Sevoflurane however causes cerebral vasodilatation and may therefore cause intracerebral steal during carotid cross-clamping (McCulloch et al., 2007).

Propofol, particularly when coupled with remifentanil, has been shown to preserve cerebral autoregulation and cerebrovascular resistance (Strebel et al., 1995, Cole et
al., 2007). This has made it a popular choice in neurosurgical anaesthesia, particularly in the presence of raised intracranial pressure (Dagal and Lam, 2009).

(III) Effect of CEA on Intraoperative CBF and MCAV

Regardless of the anaesthetic technique employed, the haemodynamic effect of CEA includes the effect of temporary interruption of flow through the common, internal and external carotid arteries. This leads to cessation of forward flow through the ipsilateral ICA and thus flow through the cerebral vessels depends on the state of the collateral circulation and the completeness of the circle of Willis. If the blood flow reduces beyond a critical level then cerebral ischaemia is threatened and a temporary shunt is placed. This generally restores a similar flow pattern to the brain (although some variation may occur depending on flow characteristics of the various types of shunts commonly employed (Wilkinson et al., 1997, Hayes et al., 2000)).

Completion of endarterectomy then allows restoration of flow. Often a temporary ‘overshoot’ of the MCAV is demonstrated immediately upon clamp release (Naylor et al., 1993b). Depending on the haemodynamic effect of the pre-existing carotid stenosis, flow will then increase to about 20% of preoperative values and remain elevated or return to preoperative values (Nielsen et al., 2002). However, the presence of a sustained increase of MCAV $>100\%$ from baseline raises the concern of development of the cerebral hyperperfusion syndrome, which will be discussed in the next section.
1.5 Cerebral autoregulation, the cerebral hyperperfusion syndrome and intracerebral haemorrhage

1.5.1 Background

Hyperperfusion is commonly defined as increase in CBF above 100% from preoperative values, but not all such increases are necessarily associated with clinical features. Asymptomatic modest increases in ipsilateral cerebral blood flow (20-40% from preoperative values) are common in most patients immediately after carotid endarterectomy, and these may last for several hours or days (Naylor et al., 1993b, Nielsen et al., 2002). In some patients, severe and long-lasting increases in CBF to levels of 100-200% over baseline may occur, which are often maximal 3-4 days after surgery, fall to a steady state by the sixth or seventh postoperative day, but can last up to 2 weeks (van Mook et al., 2005).

Spetzler first described the phenomenon of cerebral hyperperfusion after surgical treatment of cerebral arteriovenous malformations (Spetzler et al., 1978), highlighting the presence of impaired autoregulation in the region of the operated brain. Sundt and colleagues (1981) subsequently described the “cerebral hyperperfusion syndrome” after CEA as a triad of atypical migrainous phenomena, transient focal seizure activity, and intracerebral haemorrhage (ICH), attributing the clinical features to excessive CBF (demonstrated by the Xenon-133 washout technique) following reperfusion of the relevant carotid territory. Since then, increased awareness and increased availability of CBF-measuring techniques has expanded the recognised clinical features of the syndrome.
The cerebral hyperperfusion syndrome (CHS) now refers to a disorder characterised by some or all of headache, eye pain, seizures, nausea and vomiting, associated with increased CBF and often blood pressure, and carrying the risk of ICH.

1.5.2 Incidence and predisposing factors

The incidence of CHS has been reported from 0.2% to 18.9% (van Mook et al., 2005). This broad range of reported incidence rates can be explained by differences in sample size and patient inclusion criteria in the reported series, as well as variation in the definition for CHS used. Further, since most studies are retrospective some patients with mild symptoms, those presenting to another hospital or clinical team with the sequelae of unrecognised hyperperfusion and those lost to follow-up may not be accounted for. Nevertheless, most of the larger series suggest an incidence of 0.75%-3%, which may reflect the true incidence more accurately.

It is recognised that patients described as experiencing the CHS are a heterogeneous group, mainly due to the absence of universally recognised clinical or haemodynamic parameters defining CHS. The vast majority of published reports provide evidence of postoperative increases in CBF or MCAV of >100% over baseline (Sundt et al., 1981, Piepgras et al., 1988, Gossetti et al., 1997, Dalman et al., 1999, Keunen et al., 2001, Hosoda et al., 2001, Ogasawara et al., 2003a, Hosoda et al., 2003, Ogasawara et al., 2005, Fukuda et al., 2007), although the techniques used for CBF measurement vary. However exceptions to such CBF increases are reported: a study using Xenon-133 found that one third of patients presenting with postoperative symptoms of CHS had only modest CBF increases of up to 36%
(Reigel et al., 1987). A further study found less than 30% increase in CBF in half of the patients developing ICH (Schroeder et al., 1987b). A more recent study showed that patients with symptoms compatible with CHS had up to 44% increased CBF on the ipsilateral side on perfusion MRI, but only moderate increase of MCAV on TCD assessment (Karapanayiotides et al., 2005). It is therefore likely that the development of the syndrome depends on additional factors apart from the magnitude of CBF increase alone.

A summary of the reported risk factors for the development of CBF are summarised in table 1.5.1.
**Table 1.5.1. Risk factors for the cerebral hyperperfusion syndrome (adapted from van Mook et al. (2005) and Moulakakis et al. (2009))**

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<th>Preoperative</th>
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<td><strong>Comorbidity</strong></td>
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<td>Diabetes mellitus</td>
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<td>Longstanding hypertension ± hypertensive microangiopathy</td>
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<td>Minor stroke in presenting history</td>
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<td>Recent (&lt;3 months) contralateral CEA</td>
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<td><strong>Flow related</strong></td>
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<td>Preoperative hypoperfusion</td>
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<td>- High-grade carotid artery stenosis</td>
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<td>- Contralateral carotid occlusion</td>
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<td>- Incomplete circle of Willis &amp; poor collateral flow</td>
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<td>Diminished cerebrovascular reactivity ± intracerebral steal</td>
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<th>Intraoperative or postoperative</th>
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<td>Increased intraoperative CBF or MCAV after clamp release</td>
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<td>Intraoperative carotid stump pressure &lt;40 mmHg</td>
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<td>Persistence of hyperperfusion longer than several days postoperatively</td>
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<td>Severe systemic hypertension</td>
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<td>Use of (high doses of) volatile halogenated hydrocarbon anaesthetics</td>
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<td>Use of anticoagulants or antiplatelets</td>
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<tr>
<td>Periprocedural cerebral infarction</td>
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1.5.3 Clinical features of the cerebral hyperperfusion syndrome

The CHS commonly occurs a few hours to a few days after CEA, although it has been reported up to approximately 30 days post-surgery (Ogasawara et al., 2004b). The triad of symptoms as described by Sundt et al has been expanded to include ipsilateral frontotemporal, periorbital and sometimes diffuse headache, eye and face pain, vomiting, confusion, macular oedema, visual disturbances, focal motor seizures ± secondary seizure generalisation, focal neurological deficits, and ICH. Associated hypertension is often reported but appears not to be essential for the development of the syndrome. Most patients however have only mild symptoms and signs, and this adds to the difficulty in the diagnosis and definition of the syndrome. For instance, headache of varying degrees has been reported to occur in about 60% of patients following CEA (Tehindrazanarivelo et al., 1992), nausea and vomiting are not unusual in the postoperative period, and seizures or neurological deficit also occur as a consequence of thromboembolism. Nevertheless, hyperperfusion should always be considered as a possible explanation for atypical postoperative symptoms.

1.5.4 Cerebral hyperperfusion and cerebrovascular autoregulation

When a chronically hypoperfused region of the brain with reduced cerebrovascular reserve and impaired cerebral autoregulation is reperfused, arteriolar vasoconstriction does not occur due to transient impairment of normal cerebrovascular autoregulatory responses leading to regional hyperperfusion (Sundt et al., 1981). This is characterised by transudation of fluid into the pericapillary astrocytes and the cerebral interstitium resulting in cerebral oedema (Schwartz, 2002). Other pathological changes include fibrinoid necrosis (Mansoor et al., 1996),
swelling of endothelial cells and red cell extravasation (Bernstein et al., 1984); frank intracerebral haemorrhage may also occur.

The precise mechanisms contributing to the impairment of autoregulation and consequent hyperperfusion remain to be elucidated, but failure of myogenic autoregulation from endothelial dysfunction due to chronic ischaemia (Sundt et al., 1981), mediation by NO (Janigro et al., 1994), microvascular angiopathy or autonomic neuropathy due to diabetes (Skydell et al., 1987), and free radical damage (Soong et al., 1996) have all been described.

Support for the concept of impaired autoregulation as a predisposing factor for CHS was lent by a study by Sbarigia et al. (1993), who studied 36 patients for diminished cerebrovascular reactivity using TCD and administration of acetazolamide. All 3 patients with impaired reactivity developed severe ipsilateral headache and a significant rise in postoperative MCAV, whilst those with normal CVR were asymptomatic with no significant change in postoperative MCAV. Hosoda et al. (2001) studied 26 patients with SPECT following CEA, and found significant increase in CBF in patients with impaired CVR to acetazolamide of whom two developed symptomatic CBF increase of >100% on the first postoperative day, whilst those with normal CVR showed no significant change. Using the same technique, Ogasawara and colleagues (2003b) measured CBF increase of >100% in 8/12 patients with impaired CVR, two of whom developed features of CHS.

Other factors responsible for CHS may include ischaemic insults to an already hypoperfused region of the brain due to embolisation or cross-clamping (Soong et al., 1996) (Weigand et al., 1999). Baroreceptor dysfunction and lability of systemic arterial blood pressure (Bove et al., 1979), particularly in pre-existing hypertension,
have been implicated in the development of this syndrome. Finally neuroeffector mechanisms centred on the trigeminovascular reflex, with release of vasodilatory neuropeptides contributing to increased cerebral blood flow may also be relevant (Macfarlane et al., 1991).

### 1.5.5 Management of cerebral hyperperfusion

Identification of patients at risk for CHS is important although there is as yet no consensus on how best this should be done. Dalman and colleagues (1999) showed that TCD monitoring reliably predicted the incidence of symptomatic hyperperfusion after CEA. In their study of 789 CEAs in 688 patients, 62 patients (9%) fulfilled criteria for hyperperfusion (peak cerebral artery velocity and/or pulsatility index* increase >100%). Close observation and postoperative blood pressure control led to a decrease in ICH incidence from 2.1% in the early 90s to 0.3% in that study. Similar management may be beneficial for patients exhibiting impaired preoperative cerebrovascular autoregulation, although routine testing of autoregulation may not be achievable for many centres. Ogasawara and colleagues (Ogasawara et al., 2004a) suggested that pre-treatment with edaravone, a free radical scavenger, may prevent post-CEA hyperperfusion based on a series of 51 CEAs. However the study was limited by one patient only exhibiting hyperperfusion on SPECT, and comparing the edaravone-treated group with a historical control group.

Postoperatively the management of CHS depends on timely recognition; suspicion should be raised for patients experiencing severe headache, focal or generalised seizures or other neurological symptoms, particularly when associated with

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* Gosling’s Pulsatility Index = (MCAV\text{sys} - MCAV\text{dia})/MCAV_{mean}
hypertension. Again there appears to be little consensus regarding the best method for diagnosis and this will to an extent depend on local expertise, but CT of the brain may show cerebral oedema, perfusion MR or CT may show increased cerebral perfusion and TCD may show increased MCAV. Despite the absence of definite diagnostic criteria, most authors seem to concur that aggressive blood pressure management is appropriate if CHS is suspected (Piepgras et al., 1988, Reigel et al., 1987, Dalman et al., 1999, Mansoor et al., 1996). Jansen et al. (Jansen et al., 1994) reported that 8% of patients without aggressive postoperative blood pressure control after CEA experienced postoperative CHS. The same group when monitoring MCAV with TCD using aggressive BP control showed a drop in the incidence of CHS to 1% without any patients developing ICH. The agents recommended for treatment of blood pressure are labetalol and clonidine; treatment with vasodilating agents may contribute further to CHS (van Mook et al., 2005).

1.5.6 The cerebral hyperperfusion syndrome and intracerebral haemorrhage

The most serious consequence of hyperperfusion is the development of ICH. The relative importance of ICH as a cause of post-CEA stroke has steadily increased, since although the thromboembolic stroke rate has tended to fall with advances in perioperative management, the rate of haemorrhagic stroke has remained unchanged at approximately 0.5% (Russell and Gough, 2004). In addition, the prognosis of patients suffering ICH is usually dismal, carrying a reported 36-60% risk of death and up to 80% of serious disability (Naylor and Ruckley, 1995).
ICH usually occurs following the onset of other symptoms consistent with CHS, although cases of hyperperfusion progressing to ICH without other prodromal symptoms have also been reported. Piepgras et al. (1988) found a 3.3% incidence of ICH amongst patients with hyperperfusion (defined as a >100% increase in CBF), whilst only 0.24% of patients with <100% increase in CBF developed ICH. Sundt et al. (1981), studying 1145 CEAs, reported 5 postoperative intracerebral haemorrhages of which four were fatal; this was associated with an almost 3-fold increase in CBF. The timing of ICH was 5 to 7 days postop, was associated with transient seizure activity and was not associated with significant blood pressure changes; two patients were treated with continuous heparin infusion at the time of the ICH.

From the above it is evident that the course of cerebral autoregulatory reflexes in the early period after CEA is of particular importance in the context of the development of CHS and the predisposition to ICH. Although the preservation of normal autoregulatory reflexes during LA CEA and their impairment during GA CEA has been described above, there are no published studies comparing the effect of the type of anaesthesia on postoperative cerebral autoregulation.
1.6 Protein S100β and neurone-specific enolase in carotid surgery

1.6.1 Biomarkers of cerebral injury

Carotid endarterectomy is characterised by relatively low rates of adverse neurological events (for example 3.7-4.0% in the GALA trial (Lewis et al., 2008)), and high-volume experienced centres commonly report even lower rates of events. Further, the clinical manifestation of cerebral injury can be highly variable, ranging from the catastrophic to the subclinical. Considerable interest exists therefore to identify markers of cerebral injury which may permit detection of early, subtle or even subclinical changes. This would permit better-powered studies of smaller cohorts of patients and might allow earlier detection of cerebral injury or provide data of prognostic significance in the case of a clinically significant neurological event.

Biochemical markers of cerebral injury have been widely studied in the setting of acute stroke, traumatic brain injury, cardiac arrest, cardiac surgery and, of course, CEA. Increasing experimental evidence is available for two of these biomarkers in CEA, the protein S100β and the enzyme neurone-specific enolase (NSE), and these will be each discussed in turn.
1.6.2 Protein S100β

(1) BACKGROUND

S100 is an acidic calcium-binding protein of the S100-calmodulin-troponin superfamily with molecular weight 21 kDa, which is present in astroglial cell cytoplasm but is also found bound to membrane. The protein was first isolated in 1965 from bovine brain (Moore, 1965), and was thus termed due to its solubility in 100% saturated ammonium sulphate at neutral pH. Two subunits exist, α and β; high concentrations of the ββ dimer are present in glial and Schwann cells (Zimmer et al., 1995). The αβ isoform is mainly found in glial cells and the αα isoform is present in striated muscle, heart and renal tissue. Detection of the β subunit can therefore be considered largely specific to the brain and central nervous system. S100 appears to be important in various calcium-dependent activities, such as communication between neuronal and glial cells and intracellular signal transduction; in addition it is linked to various intracellular activities such as calcium homeostasis, prevention of oxidative damage, cell proliferation and cell differentiation (Fano et al., 1993) (Selinfreund et al., 1991), and may play a role in learning and memory (Donato, 1999). S100 is metabolised in the kidney and excreted in the urine, and its biological half-life is approximately 2 hours (Jonsson et al., 2000).

Astroglial cells release S100β in the CSF upon hypoxic injury (Buttner et al., 1997). If the integrity of the blood-brain barrier is compromised S100β can be detected in the serum. Besides the release upon damage, S100β is secreted under normal circumstances in low concentrations in the CSF and the cerebral interstitial fluid where it may exert some of the biological functions described above (Shashoua et al., 1984). Detection of S100β in peripheral serum may thus be a result of increased
permeability of the blood-brain barrier with or without astroglial cell injury (Kapural et al., 2002). Maximum serum levels of the protein can be detected 20 minutes following cerebral injury (Jonsson et al., 2000).

(II) S100β IN CEREBRAL INJURY

Experimental studies of traumatic and ischaemic brain injury have shown increases of S100β in CSF and in serum (Hardemark et al., 1989). In humans, increased levels of S100β have been detected in patients with Alzheimer’s disease (Peskind et al., 2001), Down’s syndrome (Fano et al., 1995) and HIV infection (Stanley et al., 1994). Unfavourable outcomes have been associated with increased S100β levels following severe head injury (Raabe et al., 1998); following minor head injury with no focal neurological signs and complete recovery increased levels of S100β have been associated with abnormal neuropsychological assessment at 6 months (Herrmann et al., 2001) and deficit in tests of attention after 12 months (Waterloo et al., 1997).

In the setting of acute stroke elevated levels of S100β have been identified in up to 80% of patients, and peak levels of S100β are reached between the second and third day following stroke (Buttner et al., 1997). In addition the level of increase of serum S100β correlates with infarct volume on computerised tomography and with stroke severity scores, and thus outcome (Missler et al., 1997); patients with poor functional or fatal outcome following stroke seem to have the highest elevations in S100β in serum (Martens et al., 1998). This has not however been a universal finding and the position of S100β in terms of prognostic significance following stroke remains unclear (Fassbender et al., 1997), although it may be more useful when considered as
part of a diagnostic panel of several biomarkers (Lynch et al., 2004). When minor stroke or TIA is considered however, there are conflicting reports with studies showing both increase and no significant change when measuring S100β in CSF or serum (Persson et al., 1987, Herrmann et al., 2000b). High levels of S100β compared to controls have been detected in patients with intracerebral haemorrhage (Wiesmann et al., 1997). In cardiac arrest the highest levels of S100β have been found on the first post-arrest day, and levels of S100β seem to correlate with survival; in a study of 41 patients all patients with a serum S100β level ≥0.2 µg/L died whilst 89% of those with levels below this survived (Rosen et al., 1998).

S100β has been extensively studied in cardiac surgery, a field where stroke is seen in up to 2% of patients following coronary bypass surgery (Dellagrammaticas and Gough, 2007). Elevation of S100β levels have been measured from 20 min of placement on cardio-pulmonary bypass (CPB) with maximum levels at the end of CPB (Johnsson et al., 1995) followed by a steady decline to baseline. Similar elevations have not been seen in patients undergoing cardiac surgery off-bypass (Westaby et al., 1996, Kumar et al., 1997). Increases in S100β are associated with increasing age, and neurological complications following cardiac surgery (delayed awakening from anaesthesia, stroke or post-operative confusion) are associated with higher levels of S100β (Johnsson et al., 1995, Shaaban Ali et al., 2000). In addition patients with cerebral infarction following cardiac surgery exhibit sustained elevation of S100β levels (Blomquist et al., 1997, Astudillo et al., 1996), which would indicate sustained release into the circulation from damaged astroglial cells via a disrupted blood-brain barrier. Up to 70% of patients may exhibit subtle cognitive impairment following CPB and elevated S100β has been linked to neurocognitive dysfunction following cardiac surgery (Jonsson et al., 1999,
Herrmann et al., 2000a. Elevated S100β levels have also been found in patients with increased frequency of microemboli detected by TCD particularly during cannulation of the aorta (Grocott et al., 1998). Concern however has been raised that it is impossible to distinguish S100β from intracerebral sources from those released elsewhere (Anderson et al., 2001), and that this may confound the observed differences in cardiac surgery.

In a pilot study of patients undergoing oncologic neck dissection, Leindecker and colleagues (2010) found that postoperative neurocognitive deficit was present in 7 of 26 patients and this was associated both with the detection of microemboli assessed by TCD and with increased S100β levels.

(III) S100β IN CAROTID SURGERY

Gao and colleagues (2000) studied serum (n=10) and CSF (n=6) S100β levels for patients during and after CEA under GA using a temporary intraluminal shunt. They found normal S100β levels in serum for all patients except one with severe postoperative hypertension who showed increased S100β at 1 hour following surgery. This was sustained at 6 weeks and was associated with worsening of neurological symptoms (although the baseline neurology was not described in this paper). For CSF, S100β levels increased for 3 of 6 patients at 15 minutes following shunt insertion and at the end of surgery, and at 6 months postoperatively two patients with the greatest rise in CSF S100β had worsening of their neurological symptoms when assessed at 6 months. No correlation between S100β levels and changes in MCA blood flow velocity was demonstrated, and imaging to demonstrate development of new ischaemic lesions was not undertaken.
Rasmussen and colleagues (2000) studied 22 patients undergoing CEA under GA and compared this cohort to patients undergoing open aortic aneurysm repair. Patients underwent a battery of neuropsychometric tests and serum was taken at 12, 24, 36 and 48 hours following surgery. A significant change in median S100β for the patients undergoing aneurysm repair but not for CEA patients was found. Two patients had a stroke in the CEA cohort, the one in the ipsilateral cerebral hemisphere and associated with perioperative ICA thrombosis and the other in the contralateral hemisphere 24 hours following surgery; only the former patient showed increased S100β levels in serum. Overall no association of S100β with changes in cognitive function was found.

In a study comparing patients undergoing CEA under LA vs. GA, Calvey and colleagues (2000) found lower levels of jugular venous S100β in the LA group; the same cohort showed greater improvement in cognitive function in the LA group compared to the GA group.

Godet and colleagues (2001) studied 100 patients undergoing carotid endarterectomy under GA. Blood samples were taken intraoperatively, in the recovery room and on the first postoperative day. Whilst all patients exhibited an increase in serum levels of S100β which reached its peak at the end of surgery and began to return to preoperative levels by the first postoperative day, for 5 patients exhibiting transient or permanent neurological deficit in the postoperative period no significant difference was found in S100β compared to those patients without neurological deficit.

Connolly and colleagues (2001) studied 53 patients undergoing CEA under GA, and measured S100β levels before surgery, before clamping the carotid arteries, and at
24, 48 and 72 hours after surgery. The patients underwent a battery of neuropsychometric tests pre- and postoperatively. The authors found that the 12 patients exhibiting a decline in performance on neuropsychometric testing showed significantly higher levels of S100β at all measured time points compared to the 41 patients without deficit. However, in a subsequent study by the same group (Sahlein et al., 2003), measurement of jugular bulb venous blood S100β levels failed to predict the cognitive decline observed in 13 of the 43 studied patients. The authors did find a trend towards elevated S100β levels in jugular compared to peripheral arterial blood, and there was significant elevation of S100β levels from the jugular bulb at 15 minutes following carotid clamping compared to baseline levels. This difference was not observed in the peripheral arterial samples at any time point of testing, but a non-significant trend was observed for association of cognitive injury with S100β levels from peripheral arterial blood at 15 minutes after carotid cross-clamping. The authors suggested that the observation of the difference in jugular versus arterial blood S100β levels lends weight to the theory that there are two mechanisms of S100β release, the one reflecting transient blood-brain barrier permeability increase (and thus detectable in jugular venous blood but not necessarily in peripheral arterial blood due to dilution and mixing of jugular with peripheral blood), and the other reflecting glial injury with concomitant blood-brain barrier dysfunction and higher or sustained S100β release into the peripheral circulation.

Mussack and colleagues (2002) studied 21 patients undergoing CEA under general anaesthesia, aiming to correlate changes in somatosensory evoked potentials (SSEP) and neurological outcome with changes in peripheral arterial S100β levels before intubation, at cross-clamping, unclamping, prior to extubation and 6 hours
postoperatively. For 14 patients no change in SSEP was found, but all showed a transient significant increase in serum S100β levels at unclamping, but a return to baseline levels after this; no neurological deficit was found in this group. For the patients with loss of SSEP, temporary shunting was employed: this resulted in reappearance of SSEP in 5 and no reappearance in two. Although not explicitly stated by the authors, the figure summarising the data for the group losing SSEP during cross-clamping suggests a significant increase in S100β levels compared to baseline at unclamping, with return towards baseline levels subsequently. However the authors state that no significant change in S100β was seen for the 5 patients with return of SSEP following shunt insertion, whilst for the two patients with sustained loss of SSEP there was sustained increase in S100β levels postoperatively as well as clinical neurological deterioration. Statistical significance could not be demonstrated in the association of S100β levels and neurological symptoms, a finding which is perhaps accounted for by the small number of patients and even smaller number of neurological events.

In a further study by the same group (Mussack et al., 2006), 45 patients undergoing either CEA (n=31) or carotid artery stenting [CAS] (n=14) had S100β levels measured in peripheral blood before, during and at the end of the procedure, and at 6 hours post-procedure. Patients undergoing coronary angiography and hemithyroidectomy were used as respective controls. Neither median control nor CAS patient S100β levels exhibited change from baseline, despite three post-procedural events (two TIAs and one cerebral infarct) occurring in the CAS group. By contrast, median S100β in the CEA group rose significantly from baseline by the end of surgery and by 6 hours postoperatively were not significantly different to baseline, CAS or controls. However three patients exhibited postoperative
neurological events (two TIAs and one stroke) and had persistently elevated S100β at 6 hours after surgery. It is worth noting that two of the patients with neurological complications seem to be the same as Mussack’s earlier study (Mussack et al., 2002), although this is not explicitly stated. The authors concluded that the elevation in S100β may be related to changes in blood-brain barrier permeability due to hypoperfusion during CEA, whilst in CAS the use of cerebral protection devices allowing flow through the carotid arteries with minimal periods of carotid occlusion would have prevented such a transient increase in blood-brain barrier permeability.

Di Legge and colleagues (2003) studied 28 patients undergoing CEA, of which 27 had LA CEA. A transient increase in S100β levels in serum from peripheral venous blood samples was detected in 11 patients, of whom 8 had had symptomatic carotid disease leading to CEA. Two of these had raised S100β levels throughout all the sampling points including the baseline samples, and these had lower MMSE scores compared to the remainder of the cohort as well as evidence of multiple cortical infarcts on CT. The remainder of the patients showed elevation of S100β levels during CEA, with return towards baseline by 48 hours postoperatively. However no correlation was found with S100β levels and new neurological events following surgery.

In a further assessment of 25 patients undergoing CEA, Jaranyi and colleagues (2003) found that transient elevation of S100β levels was found after cross-clamping the carotid arteries. Post-declamping values however were not significantly different compared to baseline. Further, this transient elevation of S100β levels was only found in jugular venous blood and not from peripheral venous samples. No neurological events were seen, and the changes in S100β were not associated with preoperative hypertension or duration of carotid cross-clamping.
Brightwell and colleagues (2007) studied 52 patients with carotid disease, of whom 24 had CAS and 28 CEA under LA. Levels of S100β were measured from peripheral blood at baseline and during the procedure (prior to declamping of the carotid arteries in CEA or at emboli prevention device retrieval during CAS) and at 6, 12, 24 and 48 hours postoperatively. Patients also underwent TCD monitoring throughout the procedures, and high intensity transient signals (HITS - indicating possible peri-procedural emboli) and MCA velocity changes were recorded. Using a general estimation equations modelling statistical analysis, the authors found that elevation in S100β levels were associated with post-procedural neurological deficit (3 in the CEA and 1 in the CAS group) and with increasing number of HITS (more frequent HITS in the CAS group). There was no significant difference between CEA and CAS, although a non-significant trend for higher levels during and immediately after CEA compared to CAS was apparent.

Aleksić and colleagues (2007) studied 45 patients undergoing CEA under LA. Blood was taken at five time points: at baseline (radial artery sample), just prior to carotid cross-clamping, just prior to declamping and at the end of surgery (jugular venous blood and radial artery samples), and 6 hours postoperatively (radial artery sample). No neurological complications were reported, and the authors found no statistically significant increase in S100β levels throughout although a modest rise of 18% was seen in the sample taken just prior to carotid declamping compared to the first intraoperative sample, followed by return to baseline levels by the end of surgery. Of interest was the finding that jugular venous samples showed significantly higher median S100β levels compared to the arterial samples taken at the same time point.

Palombo and colleagues (2007) randomised 96 patients with unilateral carotid disease undergoing CEA under GA to receive intraoperative temporary carotid shunt
placement or not. Blood was taken from the jugular vein before and after clamping of the carotid arteries. Two postoperative TIAs were documented but the authors did not specify in which group; no major stroke was observed. No significant differences in S100β levels were detected perioperatively in either group (either within or between groups). However, it is worth noting that no patient would have received a shunt if the authors’ normal criteria for selective shunting (ICA stump pressure <50 mmHg) had been observed.

In an attempt to characterise differences between LA and GA CEA, Wijeyaratne et al. (2009) studied 27 patients undergoing CEA for symptomatic carotid stenosis. Blood was taken from the jugular bulb just prior to carotid clamping and 5 min prior to declamping. Further samples were taken 5 min, 2, 4, 6, 8, 12 and 24 hours after declamping. No neurological events occurred in either group, and S100β levels did not change significantly from baseline.

In a study comparing CAS (n=23) with CEA under LA (n=20), Capoccia et al. (2010) measured S100β levels at baseline, 5 min after declamping (CEA) or emboli protection device retrieval (CAS) and at 2, 6, 12 and 24 hours post-procedure. No neurological morbidity was reported, other than a temporary cranial nerve lesion in the CEA group. Five patients undergoing CAS had evidence of new ischaemic cerebral lesions on diffusion-weighted (DW-) MRI as opposed to no such lesion in the CEA group, and this was associated with deterioration in performance in the mini-mental state examination. An increase in S100β levels above 25% of baseline was evident in significantly more CAS patients compared to CEA were significantly higher in CAS patients compared with CEA at 24 hours. No significant elevation in S100β levels was seen for CEA patients, although a trend for elevation of S100β levels compared to baseline was seen for patients undergoing CAS.
1.6.3 Neurone-Specific Enolase

(I) BACKGROUND

Neurone-specific enolase (NSE) is the neurone-specific form of the glycolytic enzyme enolase, which is also present in smaller concentrations in red blood cells and platelets (Gao et al., 1997). It is an intracytoplasmic dimer composed of αγ or γγ subunits and has molecular weight of 78 kDa (Cooper, 1994). In serum, the normal half-life of NSE is approximately 20 hours (Ingebrigtsen and Romner, 2003). NSE is considered to be specific for neuronal damage, reaching peak concentration 7-48 hours following cerebral injury (Missler et al., 1997).

(II) NEURONE-SPECIFIC ENOLASE IN CEREBRAL INJURY

In animal studies, serum NSE levels were elevated as early as 2 hours following experimental cerebral injury (Barone et al., 1993). In humans, NSE is increased in CSF after cardiopulmonary bypass and valve-replacement surgery (Herrmann et al., 1999), and higher levels are associated with postoperative neurological dysfunction. There is conflicting evidence regarding the usefulness of NSE in terms of prediction of functional outcome after stroke, but its concentration is correlated with the extent of cerebral infarct volume (Missler et al., 1997). NSE levels can rise before irreversible neuronal death occurs, reflecting cytoplasmic loss due to ischaemia (Barone et al., 1993, Hardemark et al., 1989). Further, the elevation in NSE levels may follow a biphasic pattern, with an early elevation reflecting initial neuronal
injury followed by a later peak due to neuronal damage from intracerebral oedema and raised intracranial pressure (Capoccia et al., 2010).

(III) Neurone-Specific Enolase in Carotid Surgery

All of the studies examining carotid intervention studied NSE together with S100β, and therefore this section refers to many of the studies already discussed in the section on S100β.

In the study of 10 patients undergoing CEA under GA, Gao et al. (2000) found mean levels of serum NSE levels increased significantly with cross-clamping, returning to normal 4 hours after surgery; however elevation of CSF NSE concentration was not seen in the six patients who had simultaneous CSF sampling. In addition the elevation of serum NSE failed to correlate with neurological sequelae or with S100β levels.

In the study comparing 22 patients undergoing GA CEA with a cohort of 16 patients undergoing open abdominal aortic aneurysm repair, Rasmussen et al. (2000) found no correlation of mean serum NSE levels with neurological deficit after CEA. Significant elevation of NSE was seen for the one patient experiencing ipsilateral intraoperative stroke, but for a second patient who developed a contralateral stroke 24 hours after surgery a similar rise was not seen. Interestingly the levels of NSE at baseline were significantly higher in patients undergoing CEA compared to patients undergoing aortic surgery; 48 hours after CEA NSE levels had dropped to those seen in the aortic surgery patients, in whom NSE levels did not change following surgery.
The authors suggested that this elevation at baseline might reflect the presence of symptomatic carotid disease.

Sahlein et al. (2003) found no differences in NSE levels in their study of 43 patients undergoing CEA under GA. NSE levels in particular did not vary between patients exhibiting neurological deficit on the basis of neuropsychometric testing, nor was there a gradient between jugular bulb and arterial samples for NSE.

In the comparison of 28 patients CEA under LA with 24 patients undergoing CAS by Brightwell et al. (2007), serum NSE levels did not correlate with neurological outcome, number of HITS or intraoperative MCA velocity changes. However, baseline NSE levels were higher than normal in all patients; a downward trend was evident for CAS patients but not for CEA, but this did not reach statistical significance.

In the randomised study of 96 patients with unilateral carotid disease undergoing CEA under GA comparing elective temporary shunting or not, Palombo et al. (2007) found no difference in NSE levels in blood taken from the jugular vein. As for S100β, NSE levels showed no correlation with neurological outcome.

In the study comparing LA with GA CEA by Wijeyaratne et al. (2009), mean levels of NSE in jugular venous 2 hours following surgery were significantly elevated from baseline for the 13 GA patients; levels were also significantly elevated compared to the 14 LA patients, in whom there was no significant change compared to baseline at any time point.

Capoccia and colleagues (2010), in line with their findings for S100β, found significant percentage elevation of mean NSE levels at 24 hours in 23 patients
following CAS as opposed to no significant change for 20 patients undergoing CEA under LA.

1.6.4 Summary

The evidence for S100β and NSE in CEA is limited by several factors. First, the study cohorts are small, particularly considering the relatively low incidence of significant neurological symptoms. Second, the populations examined are fairly heterogeneous, with no standardisation regarding the pattern of carotid disease with regards the contralateral carotid and the circle of Willis (with the exception of the study by Palombo et al. (2007)). Some studies have used surrogate markers of cerebral injury (such as DW-MRI or neuropsychometric testing) to correlate S100β and NSE with subclinical injury but the absence of a gold standard for detection of early or subclinical cerebral injury makes drawing firm conclusions difficult. The finding of differing jugular and peripheral S100β levels has been generally consistent and has thus encouraged sampling of jugular venous blood; there has been no reported jugular vs. peripheral concentration gradient for NSE.

It remains plausible that increases in serum S100β or NSE may occur as a consequence of hypoperfusion or microembolisation (or both) and may reflect blood-brain barrier dysfunction as well as more significant cerebral injury resulting in neuronal or glial cell loss, and that these differences may be affected by the type of anaesthesia. However, although some intraoperative haemodynamic data has been reported by Brightwell et al. (2007), there has been no attempt to correlate changes in S100β levels in patients undergoing CEA with the state of cerebral autoregulation.
or vasoreactivity. As discussed previously, the impact of hypoperfusion or microembolisation may be modulated by the preoperative state of cerebral haemodynamic control and the intraoperative preservation of normal autoregulatory reflexes. It would therefore follow that greater understanding of these changes during CEA might further clarify the observed differences in the levels of these biomarkers with particular regard to the type of anaesthesia employed.
1.7 Aims of study

The primary aims of this work were:

i. To determine if patients undergoing carotid endarterectomy under general or locoregional anaesthesia exhibit different patterns of cerebral blood flow, cerebral autoregulation and cerebral vasoreactivity during the intra- and postoperative periods.

ii. To examine the association between cerebral haemodynamic parameters following carotid endarterectomy and biochemical markers of subclinical cerebral injury, i.e. protein S100β and neurone-specific enolase.

The secondary aim of this study was to assess the impact of anaesthetic method, cerebral autoregulation and vasoreactivity and biochemical markers of cerebral injury on the development of cerebral hyperperfusion following carotid endarterectomy.
Methodology
2.1 Patient selection and exclusions

All patients undergoing CEA at the General Infirmary at Leeds (LGI) were eligible to be recruited to the trial. It was expected that a substantial proportion would be enrolled in the GALA Trial, thus providing similar numbers of patients receiving either GA or LA. However no randomisation was undertaken for the purposes of this trial.

Patients were excluded in the following situations:

i. Failure to obtain informed consent

ii. Responsible consultant adjudging patient too high-risk to undergo additional tests for non-clinical purposes

iii. Inability to obtain Doppler signal of the ipsilateral MCA

iv. Combination of CEA with another procedure e.g. cardiac surgery.

Other clinical characteristics did not form part of exclusion criteria but were systematically recorded.

2.1.1 Recruitment

Patients were recruited with the co-operation of the vascular surgeons at the LGI (initially three; subsequently joined by a further 4 Consultants as a result of the amalgamation of the LGI and St. James’ Hospital Vascular Units). Patients were identified prior to surgery either at the outpatient clinic or prior to admission by regular checks of the admission lists for each Consultant. The suitability of each
patient for involvement in a research project was confirmed with each responsible
Consultant prior to recruitment.

Once a suitable patient was identified, they were approached either in clinic or on the
day prior to surgery and offered a complete explanation of the study by one of the
two primary investigators and given written information. Patients were then given at
least 24 hours to consider the study prior to signing a written consent form.

Approval for the study was granted by the Leeds (West) Research and Ethics
Committee under the title ‘Pilot study to examine haemodynamic control and its
relationship to cerebral hypo- and hyperperfusion during carotid endarterectomy
under general or local anaesthesia’. Written informed consent was obtained from all
patients.

2.1.2 Collection of baseline characteristics

Data regarding demographics, indication for surgery, details of presenting relevant
symptoms, past medical history (in particular cardiovascular disorders), relevant
medication, current neurological status, smoking history, and details of pre-operative
imaging were recorded at recruitment. Brief neurological assessment (Glasgow
Coma Score, power in all 4 limbs, evidence of facial weakness, pupillary size and
mini-mental state) was recorded.
2.2 Operative details

The standard procedures used for CEA in this study are described below. Variations in the techniques will be described in the results section.

2.2.1 Anaesthetic technique

All patients underwent anaesthesia using the protocols for GA and LA recommended in the GALA Trial, summarised in table 2.2.1. All patients had continuous intraoperative invasive arterial pressure, ECG, and oxygen saturation (SaO\textsubscript{2}) monitoring, and GA patients had continuous end-tidal (EtCO\textsubscript{2}) and anaesthetic volatile agent monitoring.

(i) GENERAL ANAESTHESIA

Patients were pre-oxygenated with FiO\textsubscript{2} = 1.0. Anaesthesia was induced with propofol 1-2 mg/kg and either fentanyl 1-2 µg/kg or an initial slow bolus of remifentanil of 0.5 µg/kg followed by an infusion at a rate of 0.1-0.25 µg/kg/min. Neuromuscular blockade was achieved with atracurium or vecuronium, followed by standard endotracheal intubation. Anaesthesia was maintained with sevoflurane in an air/O\textsubscript{2} mixture at an end-tidal concentration of 1.5-2.0%.

Intraoperative blood pressure was adjusted to within 20% of baseline with judicious use of vasopressors (primarily phenylephrine, norepinephrine or metaraminol boluses ± infusion), or β-blockers (labetalol). Episodes of bradycardia (≤40 bpm) were corrected with glycopyrrolate.
(II) LOCAL ANAESTHESIA

Patients were anaesthetised using local infiltration and superficial cervical plexus block using a 0.25% bupivacaine with epinephrine 1:100,000. Additional anaesthesia was provided intraoperatively with local infiltration of 1% lidocaine. The carotid sinus nerve was routinely anaesthetised using 1% lidocaine. During surgery minimal intervention of haemodynamic parameters was performed; systolic blood pressure was allowed to rise to 200 mmHg during cross-clamping prior to intervention with hypotensive agents, whilst hypotension (>20% drop of systolic arterial pressure from baseline) was treated with bolus i.v. vasopressors supplemented with continuous infusion if required.
Table 2.2.1 - Anaesthesia protocols (adapted from (Gough et al., 2008))

<table>
<thead>
<tr>
<th>General anaesthesia</th>
<th>Local anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication: benzodiazepine or none</td>
<td>Premedication: benzodiazepine or none</td>
</tr>
<tr>
<td>Intravenous access</td>
<td>Intravenous access</td>
</tr>
<tr>
<td>Arterial line under local anaesthetic</td>
<td>Arterial line under local anaesthetic</td>
</tr>
<tr>
<td>Intravenous induction + opiate analgesia</td>
<td>Judicious sedation</td>
</tr>
<tr>
<td></td>
<td>(benzodiazepine or propofol ± opiate)</td>
</tr>
<tr>
<td>Muscle relaxant (atracurium or vecuronium)</td>
<td>Superficial cervical plexus block + local anaesthetic infiltration</td>
</tr>
<tr>
<td></td>
<td>(bupivacaine + epinephrine)</td>
</tr>
<tr>
<td>Tracheal intubation, ventilation to normocapnia</td>
<td>Intra-operative top-up of lidocaine if required</td>
</tr>
<tr>
<td>Maintain systematic blood pressure to within 20% of pre-operative levels (intravenous fluids/vasoactive drugs if required)</td>
<td>Maintain systematic blood pressure to within 20% of pre-operative levels (intravenous fluids/vasoactive drugs if required)</td>
</tr>
<tr>
<td>*except during cross-clamping</td>
<td>*except during cross-clamping</td>
</tr>
<tr>
<td>Reversal of anaesthetic and extubation</td>
<td>O₂ by nasal cannulae/mask during cross-clamping of carotid vessels</td>
</tr>
<tr>
<td>O₂ overnight by nasal cannulae/mask</td>
<td>O₂ overnight by nasal cannulae/mask</td>
</tr>
</tbody>
</table>

*Under GA systemic BP was manipulated up if stump pressure or TCD assessment of MCAV during cross-clamping was borderline for shunting, whilst under LA systolic BP was allowed to rise to 200 mmHg before treatment with hypotensive agents.
2.2.2 Surgical technique

Exposure of the carotid artery was performed using an oblique incision anterior to sternomastoid, approaching the carotid sheath anterior to the internal jugular vein. The common, internal and external carotid arteries were dissected and controlled with soft slings. Following administration of heparin, clamps were applied to the carotid arteries to interrupt blood flow.

Adequacy of ipsilateral perfusion and the consequent need for an intraluminal shunt was determined by awake neurological testing in the LA patients (recital of patient’s address, simple counting exercises and assessment of motor function of the contralateral upper and lower limb) and by stump pressure measurement and/or TCD monitoring.

A Javid shunt was used in cases requiring a shunt. The criteria for shunt insertion under GA were:

i. Mean stump pressure <50 mmHg with non-pulsatile wave form, and/or

ii. Drop in mean MCAV by 50% compared to baseline following induction of anaesthesia.

Longitudinal arteriotomy was performed and following shunt insertion (if necessary) endarterectomy performed, paying particular attention to the distal ICA limit of the endarterectomy. Distal tacking sutures were inserted if there was any concern regarding the adherence of the intima at this point. After thorough flushing of the ICA with heparinised saline and brief release of the CCA and ICA clamps, the
arteriotomy was closed with a Dacron patch. Haemostasis was ensured and the skin closed over a 10 French gauge suction drain.

2.2.3 Postoperative care

All patients were transferred to the post-anaesthesia care unit (PACU) where observation with continuous arterial pressure, SaO₂, ECG and TCD monitoring were continued for approximately 2 hours. Patients in satisfactory condition at the end of this period of observation were returned to the ward. Patients exhibiting haemodynamic lability (SBP >180 mmHg or <90 mmHg or bradycardia <50 bpm) were transferred to the high-dependency unit (HDU) for further monitoring, and correction where appropriate, of haemodynamic parameters. Patients were usually discharged on the second postoperative day, clinical condition permitting.
2.3 Transcranial Doppler studies

2.3.1 Pre- and postoperative TCD assessments & intraoperative monitoring

Patients had assessment of their middle cerebral artery (MCA) by TCD (Embo-Dop, DWL Elektronische Systeme GmbH, Singen, Germany) during the day prior to surgery. This was performed on the ward with the patient supine after a 10 minute period of rest. Both the left and right MCA were insonated in succession by placement of a 2 MHz hand-held probe placed on the trans-temporal window. The probe position was optimised to achieve insonation of the MCA at a depth of 50-55 mm, according to the protocol described by Aaslid et al. (1982), as follows:

The Doppler probe was positioned at a point anterior to the tragus of the ear and above the zygomatic arch, angled antero-superiorly. The angle and position of the probe were then adjusted until the characteristic velocity spectrum of the MCA was seen (see figure 2.3.1). The depth of insonation was then adjusted with correction of angle so that the vessel was traced from 40 to 65 mm. At the depth of approximately 60 mm the presence of the characteristic waveform of the bifurcation confirmed insonation of the correct vessel. Traceability of the MCA along its course and the visualisation of the bifurcation further confirmed correct placement of the probe. Adjustment of power and gain were performed to allow the best maximum velocity envelope. Maximum, mean and minimum velocities of the MCA were obtained from the TCD hardware automatically. Time-averaged mean was similarly determined.
A continuous recording of at least 1 minute was then obtained, and immediately following this non-invasive recording of blood pressure was performed using an automated sphygmomanometer. Identical measurements were obtained, with the patient lying supine and following a 10 minute rest, on the first and second postoperative days.

**Intraoperative TCD monitoring**

TCD assessment of the MCA (Embo-Dop, DWL Elektronische Systeme GmbH, Singen, Germany) was performed continuously during surgery from the time of patient positioning on the operating table and prior to placement of surgical drapes, to the time when the patient was transferred off the operating table. The same probe was used, fixed securely to the head of the patient with an elastic headband. Insonation of the correct vessel was confirmed using the criteria mentioned above. Probe position was continuously monitored to achieve optimum signal from the MCA, and adjusted as necessary. Spectral waveforms and maximal velocity envelopes were continuously recorded. Although the intention was to record synchronous bilateral MCA data, this was not always possible due to technical and/or patient factors.

During surgery invasive arterial blood pressure was recorded onto a laptop (Toshiba SP6100) connected via RS232 cable to the anaesthetic monitors. These data were automatically transferred into a spreadsheet (Excel 2000, Microsoft Corporation) every 13 seconds, using software developed in-house by the cardiopulmonary physiology team of the cardiac theatres at the LGI.
Significant events during surgery (cross-clamping, shunting, de-clamping, administration of heparin or protamine, administration of vasoactive drugs) were manually recorded in the spreadsheet. Initially continuous recordings were obtained, subsequently modified to recordings of 20 minute successive periods to allow easier synchronisation of the BP and TCD recordings, the relationship of which were subsequently analysed (see data analysis section). Although the TCD equipment was capable of automatic micro-embolic signal (MES) detection and differentiation of solid from gaseous emboli, analysis was hampered by the use of a high gain setting to achieve an optimum velocity envelope tracing. This reduced the reliability of automated MES detection, serving only as a rough guide for clinical decision making (for example modification of dissection technique to permit early clamping of the distal internal carotid artery).

Following completion of surgery, the TCD machine was disconnected and the patient moved to the post-anaesthetic care unit (PACU). Following the safe transfer of the patient to PACU and re-establishment of the clinical monitoring devices, the TCD monitor was re-connected and the probe position re-established. Recordings of MCAV were then obtained every 5 minutes, and simultaneous invasive ABP recorded. Post-operative monitoring was continued for the duration of stay in PACU; the unit policy was for a two hour observation period.
Figure 2.3.1 Typical velocity spectral waveforms from insonation of the carotid siphon (top) and the MCA (bottom) in relation to the circle of Willis. The bottom waveform shows the ‘maximum velocity envelope’ as a white line following the maximum velocity for the waveform. (ICA = internal carotid artery, VA = vertebral artery, MCA = middle cerebral artery, A_1 = precommunicating segment of anterior cerebral artery, P_1 = precommunicating segment of posterior cerebral artery, ACoA = anterior communicating artery, PCoA = posterior communicating artery, BA = basilar artery)
2.3.2 Tilt-testing

The tilt test has been used with varying protocols (graded, to a specific angle for various durations, augmented with lower-body negative pressure, pharmacological augmentation) to test autoregulation (Panerai, 1998), orthostatic hypotension (Claydon and Hainsworth, 2004) and other cardiovascular reflexes. We conducted a modified graded tilt test with the aim to elicit changes in cerebral perfusion pressure (CPP) and correlate these with MCAV, considered a surrogate measure for CBF (Newell et al., 1994).

The tilting protocol used was derived from Bondar et al. (Bondar et al., 1997), but each phase (see below) was reduced from 5 to 2 minutes. This was chosen as our interest was to assess autoregulatory capacity but not the full range of autoregulation. Further, our aim was to avoid presyncope or substantial hypotension; in the preoperative phase this may have led to significant cerebral hypoperfusion and risk TIA, and in the postoperative phase risk cardiac hypoperfusion.

Patients underwent tilt-testing on the day prior to surgery and on the first or second postoperative day, depending on the clinical condition of the patient. Tilt-testing was undertaken at the temperature-controlled non-invasive physiology laboratory at the Leeds General Infirmary (LGI). Patients were rested supine for 15 minutes prior to commencement of the test. Mean arterial pressure (MAP) was assessed non-invasively using a monitor with automated sphygmomanometer (Hewlett Packard 78352C, Boebringen, Germany); ECG and SaO₂ were also continuously monitored. End-tidal CO₂ (EtCO₂) was monitored via nasal prongs connected to an infra-red CO₂ analyser (model Binos 1, Leybold-Haraeus Ltd, Koln, Germany). The patient was asked to refrain from talking and breathe exclusively through the nose.
The distance (d) in cm between the level of the TCD probe and the level of the middle of the blood pressure cuff was measured. This allowed calculation of the mean arterial pressure at the level of the brain \( (\text{MAP}_{\text{brain}}) \), corrected for the hydrostatic effect of a column of blood from the level of the cuff to the level of the brain, as follows:

\[
\text{MAP}_{\text{brain}} = \text{MAP} - \left( \frac{d \cdot \sin \theta}{1.36} \right)
\]

Where \( \theta \) = angle of tilt, and assuming blood exerts a similar hydrostatic pressure to water \( (1 \text{ cmH}_2\text{O} = 1.36 \text{ mmHg}) \).

Assuming that intracranial pressure was unlikely to change, \( \text{MAP}_{\text{brain}} \) was taken to reflect cerebral perfusion pressure (Dawson et al., 2004; Serrador et al., 2006).

The MCA was insonated with a 2 MHz probe (Multi-Dop X4, TCD-8.01, DWL Elektronische Systeme GmbH, Singen, Germany), fixed securely in place using an elastic headband. Probe position was continuously monitored and adjusted if necessary to achieve best signal quality. Gain settings were set high to achieve best fitting of the maximum velocity envelope.

Patients were laid supine in a custom-designed bed which permitted tilting at 15 degree increments. Patients’ feet were resting against a foot plate to avoid sliding down the bed when tilted head-up. Initial recording of MCAV and MAP was performed at baseline just prior to commencement of the tilt-test; MCAV was continuously recorded during the remainder of the test.
The bed was then angled in the following sequence, each position maintained for 2 minutes:

i. Supine

ii. 15 degrees head-down

iii. Supine

iv. 15 degrees head-up

v. 30 degrees head-up

vi. 45 degrees head-up

vii. 60 degrees head-up

At the end of each 2 minute period, a recording of MAP was performed and a corresponding electronic ‘bookmark’ saved onto the recording of the TCD output. Testing was discontinued if the patient became symptomatically hypotensive (systolic BP \( \leq 100 \) mmHg) or developed systolic blood pressure <80 mmHg regardless of symptoms.

Calculation of MCAV was then performed off-line by measuring the average of the MCAV from 6-10 continuous cardiac cycles (in practice the number of cardiac cycles per screen) preceding the mark placed during each tilt phase. This value was generated by the TCD equipment software.

The values for MCAV and the corresponding MAP\textsubscript{brain} were recorded into a spreadsheet (Excel 2000, Microsoft Corporation). For each individual test linear regression analysis and calculation of the correlation coefficient was performed.
(Panerai, 1998) using MAP_{brain} as the independent and MCAV as the dependent variables.

The integrity of cerebral autoregulation assessed by tilt-testing was examined by determining the correlation coefficient for the relationship between cerebral perfusion pressure (CPP) and MCAV, as well as the slope generated by linear regression analysis for these two variables. Universally accepted criteria for impaired static cerebral autoregulation remain elusive; Lam (Lam et al., 1997) suggested that significant impairment was present with a correlation coefficient of >0.5. However strong correlation can be present even with minute changes in the gradient of the MCAV vs. CPP; gradients of 0.5-3.0 %/mmHg have been proposed as thresholds for impaired autoregulation (Panerai, 1998). Therefore, autoregulation on the basis of tilt testing was considered impaired if the linear regression analysis of MCAV vs. CPP showed a gradient of >0.5 %/mmHg with a correlation coefficient >0.5.

Further calculations are described in the statistics methods (section 2.5).
2.3.3 CO₂ reactivity testing.

Rebreathing expired air and voluntary hyperventilation to achieve changes in PCO₂ was used in these experiments as it allowed the assessment of CVR in response to a patient-controlled, sub-maximal stimulus; the index of CVR (CVRI) calculated as an expression of change in end-tidal CO₂ (EtCO₂) (Markus and Cullinane, 2001). The method of rebreathing used was based upon the method described by Norcliffe-Kaufmann et al. (2008) and rebreathing has been previously used in the assessment of patients with carotid disease (D’Angelo et al., 1999, Russo et al., 2000).

Testing of CVR was performed following each tilt-test, on the day prior to surgery and the first or second postoperative day, depending on the clinical condition of the patient. Testing was undertaken at the temperature-controlled non-invasive physiology laboratory at the Leeds General Infirmary (LGI). After a minimum 5 minute rest in the supine position, the 2MHz TCD probe (Multi-Dop X4, TCD-8.01, DWL Elektronische Systeme GmbH, Singen, Germany) position was checked and adjusted, and the patient given a short disposable mouthpiece to breathe through, whilst a nose clip prevented nasal breathing. The mouthpiece was connected, via appropriate tubing, to an infra-red CO₂ analyser (model Binos 1, Leybold-Haraeus Ltd, Koln, Germany).

With the patient breathing room air at a normal rate, recording of the TCD signal commenced. Measurements of non-invasive mean arterial pressure (MAP) were taken at one minute intervals, and the point of each reading ‘bookmarked’ on the TCD recording. Values of EtCO₂ were recorded by hand. A minimum of 3 readings were obtained; 4 were obtained if the patient was able to comply.
The mouthpiece was then attached to a 2 metre length of anaesthetic circuit tubing at the open end of which a fine-bore tube supplying O₂ at the rate of 0.5 L/min was placed. Patients were then asked to breathe through the tube (effectively rebreathing expired air) until a corresponding elevation of at least 7 mmHg in EtCO₂ was seen, whilst observing that EtO₂ did not drop below 15%. Non-invasive MAP recordings were again taken repeatedly, marking again the points of MAP recording against the continuous TCD trace and manually recording values for EtCO₂. Again, 3 to 4 measurements were taken as described above.

Following this the tubing was removed from the mouthpiece, and the patient asked to breathe rapidly and deeply to achieve hyperventilation. With a drop in EtCO₂ of the order of 7 mmHg, 3 to 4 repeated measurements of MAP were performed. EtCO₂ was manually recorded for each MAP measurement and corresponding ‘bookmarks’ on the TCD recording were placed. Testing was discontinued at any point if the patient experienced any significant discomfort.

Offline analysis of the TCD recording was then undertaken. The average MCAV for each MAP measurement was obtained from the TCD software for the 10 cardiac cycles preceding each ‘bookmark’. The values for MCAV, MAP and EtCO₂ were entered into a spreadsheet (Excel 2000, Microsoft Corporation). Baseline MCAV (MCAV\textsubscript{normocapnia}) was defined as the average of the measurements taken at normocapnia. The per cent change in each measured MCAV value from baseline (%ΔMCAV) was calculated as follows:

\[
%\Delta MCAV = \left(\frac{MCAV - MCAV_{normocapnia}}{MCAV_{normocapnia}}\right) \times 100
\]
Linear regression analysis was performed with EtCO$_2$ as the independent and the per cent change in MCAV from baseline (%$\Delta$MCAV) as the dependent variables. The CVRI (%/kPa) was obtained from the slope of the linear regression function.

In an attempt to correct for changes in MAP during testing (Hetzel et al., 1999), the cerebrovascular resistance (CVRes) for each MCAV value was calculated as follows (Serrador et al., 2006):

$$CVRes = MAP / MCAV$$

And the per cent change in CVRes from baseline (%$\Delta$CVRes) was calculated as follows:

$$%\Delta CVRes = \left( \frac{CVRes - CVRes_{normocapnia}}{CVRes_{normocapnia}} \right) \cdot 100$$

The CVRes index (CVResI in %/kPa) was obtained from the slope of the linear regression analysis using EtCO$_2$ as the independent and %$\Delta$CVRes as the dependent variables.

For CO$_2$ reactivity testing, cerebrovascular autoregulation was considered impaired if < 11.5 %/kPa [see section 1.4.5(ii)]. Similar criteria have not been described for changes in cerebrovascular resistance to CO$_2$ and therefore categorisation into ‘intact’ or ‘impaired’ CVResI was not undertaken; rather, comparisons were made only for the values of CVResI.

Further analyses are described in the statistics methods (section 2.5).
2.4 Blood sampling

2.4.1 Collection and processing of samples

Blood samples were obtained for assessment of levels of protein s100β and neurone-specific enolase (NSE) during various phases of surgery and the postoperative period. Samples from the jugular vein as described by Wijeyaratne et al. (2009) as well as peripheral blood were obtained in order to identify small changes in cerebral venous effluent prior to dilution in the systemic circulation (Sahlein et al., 2003).

Six mL blood samples were taken from each patient at specified time-points in the perioperative period as described below. Each sample was collected into a 10 mL syringe and transferred immediately to a standard serum clot-separator tube.

Sample time-points:

i. Baseline (sample V₀) – taken before induction of GA or before administration of LA. In the initial part of the study this was collected on the preoperative day on venepuncture for routine blood testing, later in the study collected from a suitable forearm vein or freshly inserted arterial or venous cannula in the anaesthetic room prior to surgery.

ii. Pre-clamp (samples A₁ and J₁) – taken simultaneously from an indwelling arterial cannula used for continuous invasive arterial pressure monitoring and from a fine (6G) catheter (Vygon Leadercath: Vygon, Cirencester, UK) inserted under sterile conditions in the ipsilateral jugular vein and advanced into the jugular bulb.
iii. Post-clamp (samples A₂ and J₂) – taken simultaneously from the arterial and jugular catheters 5 minutes after clamping of the internal carotid artery.

iv. Post-declamp (samples A₃ and J₃) – taken simultaneously from the arterial and jugular catheters 10 minutes after declamping of all carotid arteries at the end of endarterectomy.

v. 1 hour post-op (samples A₄ and J₄) – taken from the arterial and jugular catheters.

vi. 6 hours post-op (samples V₆ and J₆) – taken from the jugular catheter and a suitable forearm vein.

vii. Day 1 post-op (samples V₂₄ and J₂₄) – taken from the jugular catheter and a suitable forearm vein between 22 and 26 hours post-operatively.

viii. Day 2 post-op (samples V₄₈ and J₄₈) – taken from the jugular catheter and a suitable forearm vein between 46 and 50 hours post-operatively.

After blood collection all samples were allowed to stand at room temperature for minimum 30 minutes and maximum 60 minutes followed by centrifugation at 3000 rpm for 10 minutes. Samples were then aliquoted into 2 mL cryotubes and frozen at -70°C pending further analysis. Samples V₀ to A₃/J₃ were refrigerated at 4°C until after samples A₄/J₄ were centrifuged, whilst samples A₄/J₄ to V₄₈/J₄₈ as well as those V₀ samples taken on the preoperative day were aliquoted and frozen immediately post-centrifugation. No sample was refrigerated more than 4 hours following venesection.
2.4.2 Assays

Serum NSE and S100β levels were analysed at the biochemistry laboratory of the LGI by staff blind to anaesthetic method and outcome of cerebrovascular autoregulation testing. Samples were analysed using a fully automated system (LIAISON®, Diasorin S.p.A, Saluggia, Italy).

S100β was measured using the LIAISON® S100 assay (Diasorin S.p.A, Saluggia, Italy), a 2-step chemiluminescence sandwich immunoassay which detects the β subunit of S100β as determined by three monoclonal antibodies. The detection limit of the assay is <0.02 µg/L and the measuring range 0.02 – 30 µg/L. The intra-assay coefficient of variation (CV) is 2.8 – 6.4% and the inter-assay CV 2.2 – 10.7%.

NSE was measured using the LIAISON® NSE assay (Diasorin S.p.A, Saluggia, Italy), a 1-step chemiluminescence sandwich immunoassay which detects the γ subunit of NSE as determined by two monoclonal antibodies. The detection limit of the assay is <0.04 µg/L and the measuring range 0.04 – 200 µg/L. The intra-assay CV is 0.9 – 2.3% and the inter-assay CV 4.0 – 5.3%.

Statistical analysis of these data is described in the statistics methods (section 2.5).
2.5 Statistical analyses

2.5.1 Power calculations

Although the impact of CEA on cerebrovascular autoregulation and vasoreactivity had been widely studied, most previous studies examined changes several days to weeks after surgery. In addition, previous studies did not examine the impact of the type of anaesthesia on the postoperative control of the cerebral circulation. Consequently no studies mirrored the present experiments sufficiently closely to allow a formal power calculation; in this respect the study was regarded as a pilot study and indeed received ethical approval as such. However, the extant studies allowed a sensible estimate of the number of patients to be studied, using the impact of type of anaesthesia on the change in cerebrovascular reactivity to CO$_2$ as the primary outcome measure.

Rutgers and colleagues (2001) examined the long-term effect of CEA in 19 patients undergoing GA CEA and were able to demonstrate a significant improvement in postoperative cerebrovascular reactivity to CO$_2$. Their published graph suggested this to be of the order of 15% with a standard deviation (SD) for the pre- and postoperative values of 20%.

A sample size calculation was performed (Stata 8, Timberlake Corporation, Texas, USA) with the following factors: Mean change in CO$_2$ reactivity of 15% with a SD for the absolute values of 20%, an $\alpha$ error of 0.05, a $\beta$ error of 0.9, the use of analysis of co-variance to adjust for baseline variation, and a correlation between the pre- and postoperative values of 0.7. With these assumptions, twenty-six patients would have
to be studied in each group (GA vs. LA). Given the pilot nature of the study, ethical approval was granted for 20 patients in each group.

For the analyses of data, statistical significance was assumed if $p<0.05$.

### 2.5.2 Analyses of TCD studies

Analyses were conducted according to the conformity of data to the normal distribution, assessed by visual inspection of the histograms for scale data and the Kolmogorov-Smirnov test for normality.

Comparisons of data within groups were conducted with paired t-tests (parametric data) or Wilcoxon signed rank tests (non-parametric data). Comparisons between groups were conducted using unpaired t-tests (parametric data) or Mann-Whitney U tests (non-parametric data). Analyses for repeated measures were conducted by repeated-measures analysis of variance (ANOVA) provided data conformed to the normal distribution. Logistic regression analyses were conducted to assess the impact of preoperative risk factors on the changes observed in the studies of cerebral autoregulation and vasoreactivity.

### 2.5.4 Analysis of biochemical marker data

Analyses were conducted according to the conformity of data to the normal distribution, assessed by visual inspection of the histograms for scale data and the Kolmogorov-Smirnov test for normality.
As these data were non-parametric, repeated measures analyses using Friedman’s test were conducted for within-group changes with post-hoc analyses with repeated Wilcoxon signed rank tests to assess difference at different time points, applying the Bonferroni correction to assess statistical significance.

In order to compare changes between groups, the difference from baseline for each time point was calculated. The resultant values were then compared using the Mann-Whitney U test for non-parametric data.

2.5.6 Statistical software

The following programs were used for analyses of data and creation of figures:

i. Excel 2003 Professional (Microsoft Corporation, USA)

ii. PASW Statistics (IBM Corporation, USA)

iii. Stata 8 (Timberlake Corporation, USA)
Experiments & results
3.1 General characteristics

3.1.1 Baseline characteristics

Twenty-two consecutive patients undergoing CEA under LA were studied. Despite enthusiastic recruitment into the GALA Trial at the LGI, many patients chose LA for CEA and thus fewer GA patients were available to study. During the available recruitment period therefore 18 consecutive GA patients were studied. Two patients in the LA group experienced a post-operative acute coronary event and withdrew from the study. One patient in the GA group had a postoperative acute coronary event and a further patient experienced persistent hypotension requiring a four-day stay in the high-dependency unit. Both these patients withdrew from the study. This left 16 patients in the GA group and 20 patients in the LA group.

The baseline characteristics of the two groups did not differ significantly, and these are summarised in table 3.1.1
Table 3.1.1 Baseline characteristics. Numbers are count (%) unless indicated otherwise.
* Unpaired t-test, † Fisher’s exact test, ‡ χ² test

<table>
<thead>
<tr>
<th></th>
<th>GA (n=16)</th>
<th>LA (n=20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years] (median – IQR)</td>
<td>67.0 (65.3-73.5)</td>
<td>71.5 (64.3-77.8)</td>
<td>0.582*</td>
</tr>
<tr>
<td>Male</td>
<td>11 (68.8%)</td>
<td>18 (90.0%)</td>
<td>0.204†</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1 (6.3%)</td>
<td>2 (10.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>16 (100.0%)</td>
<td>19 (95.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>12 (75.0%)</td>
<td>17 (85.0%)</td>
<td>0.675†</td>
</tr>
<tr>
<td>Diuretic</td>
<td>4 (25.0%)</td>
<td>4 (20.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Insulin</td>
<td>1 (6.3%)</td>
<td>2 (10.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Oral hypoglycaemic</td>
<td>2 (12.5%)</td>
<td>3 (15.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>PVD</td>
<td>4 (25.0%)</td>
<td>6 (30.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>DM</td>
<td>4 (25.0%)</td>
<td>6 (30.0%)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Current IHD</td>
<td>6 (37.5%)</td>
<td>10 (50.0%)</td>
<td>0.515†</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1 (6.3%)</td>
<td>2 (10.0%)</td>
<td>0.495‡</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>14 (87.5%)</td>
<td>18 (90.0%)</td>
<td></td>
</tr>
<tr>
<td>Contralateral stenosis &gt;70%</td>
<td>7 (43.8%)</td>
<td>7 (35.0%)</td>
<td>0.593‡</td>
</tr>
<tr>
<td>Contralateral ICA occlusion</td>
<td>4 (25.0%)</td>
<td>4 (20.0%)</td>
<td>1.000†</td>
</tr>
</tbody>
</table>
3.1.2 Intraoperative characteristics

All patients underwent conventional (rather than eversion) carotid endarterectomy (CEA). All except one underwent patch closure of the arteriotomy. All patients received intravenous heparin prior to application of carotid clamps and most received protamine reversal of anticoagulation.

One patient was initially allocated to LA but did not tolerate the procedure during the dissection phase of the operation and was converted to GA, and was thus analysed as part of the GA group. One patient underwent GA CEA on both the left and right sides approximately six months apart and was regarded as two separate GA cases for this study.

The proportions of patients in each group requiring temporary shunt deployment during cross-clamping were similar to the published literature and higher in the GA group as expected, but this did not reach statistical significance.

All patients in the GA group required vasopressors to maintain MAP within 20% of baseline, whilst for the LA group only 7/20 required vasopressor support. This difference was highly significant.

Four patients in the LA group required intravenous glycopyrrolate or atropine to counter bradycardia <40 bpm, but this was not necessary for any GA patient. This difference was not however statistically significant.

The intraoperative characteristics of the patients are summarised in table 3.1.2.
**Table 3.1.2** Intraoperative characteristics. Numbers are count (%) unless indicated otherwise. * Mann-Whitney U test, † Fisher’s exact test.

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>LA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin dose [IU]</td>
<td>5000 (5000-5000)</td>
<td>5000 (5000-6875)</td>
<td>0.321*</td>
</tr>
<tr>
<td>(median – IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stump pressure [mmHg]</td>
<td>30.0 (20.0-51.0)</td>
<td>40.0 (34.5-64.0)</td>
<td>0.347*</td>
</tr>
<tr>
<td>(median – IQR)</td>
<td>(n = 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protamine</td>
<td>11 (68.8%)</td>
<td>15 (75.0%)</td>
<td>0.722†</td>
</tr>
<tr>
<td>Patch</td>
<td>15 (93.8%)</td>
<td>20 (100.0%)</td>
<td>0.444†</td>
</tr>
<tr>
<td>Shunt</td>
<td>7 (43.8%)</td>
<td>3 (15.0%)</td>
<td>0.073†</td>
</tr>
<tr>
<td>BP manipulated up</td>
<td>16 (100.0%)</td>
<td>7 (35.0%)</td>
<td>&lt;0.005†</td>
</tr>
<tr>
<td>HR manipulated up</td>
<td>0</td>
<td>4 (20.0%)</td>
<td>0.113†</td>
</tr>
</tbody>
</table>
3.1.3 Neurological assessments and outcome data

All patients underwent surgery without any development of new neurological events or deterioration in neurological symptoms or signs where such were already present. There were no changes in mini-mental test scores.

No patient experienced TIA or stroke prior to discharge from hospital. There was no mortality. Other than the patients who withdrew from the study as described in section 3.1.1, there were no further coronary events.

One patient developed a significant increase in MCAVm to >200% of baseline and remained on the high dependency unit for blood pressure control with intravenous labetalol, but did not develop symptoms of the cerebral hyperperfusion syndrome (CHS) and was discharged home without complication on the third postoperative day. No other patient exhibited signs or symptoms of CHS.
3.2 Basic systemic and cerebral haemodynamic data

All patients underwent assessment of MAP and ipsilateral mean MCAV (MCAVm) on the day prior to CEA and on the first postoperative day. For six patients (4 LA and 2 GA) contralateral MCAVm measurement was not possible due to an inadequate temporal window for insonation of the contralateral MCA.

Day 2 data was collected for 29 patients (16 LA and 13 GA), as the remainder were discharged home prior to assessment.

The two groups were not significantly different for baseline MAP and MCAVm (table 3.2.1).

For the combined cohort, mean MAP was significantly lower on the first and second postoperative days compared to baseline. When analysed according to anaesthetic allocation, only the LA group showed a significant drop in MAP on day 1 compared to baseline (105.5 to 94.5 mmHg) but not for day 2 (table 3.2.2a). However, % change in MAP from baseline to day 1 or day 2 was not significantly different between the GA and LA groups (table 3.2.2b).
### Table 3.2.1 Baseline systemic and cerebral haemodynamic data.
* Mann-Whitney U test, † unpaired t-test

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>LA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop MAP (mmHg)</td>
<td>97.0 (86.0-106.8)</td>
<td>105.5 (94.0-113.5)</td>
<td>0.171*</td>
</tr>
<tr>
<td>Preop Ipsilateral MCAVm (cm/s)</td>
<td>58.0 (45.9-65.0)</td>
<td>53.8 (41.2-68.3)</td>
<td>0.895†</td>
</tr>
<tr>
<td>Preop Contralateral MCAVm (cm/s)</td>
<td>53.0 (44.3-67.2)</td>
<td>52.1 (38.8-55.6)</td>
<td>0.478†</td>
</tr>
</tbody>
</table>

### Table 3.2.2 (a) Comparison of preoperative vs. postoperative MAP. (b) Comparison of mean per cent change in MAP for day 1 (% ΔMAP1) and day 2 (% ΔMAP2) in GA vs. LA. Units are mmHg except for (b). * Paired t-test, † Wilcoxon signed ranks test, ‡ unpaired t-test.

<table>
<thead>
<tr>
<th>(a)</th>
<th>Preop</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day1 vs Preop</th>
<th>Day2 vs Preop</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (all)</td>
<td>100.0</td>
<td>91.0 (91.5-111.3)</td>
<td>95.0 (84.5-106.0)</td>
<td>0.001*</td>
<td>0.045*</td>
</tr>
<tr>
<td>(median-IQR)</td>
<td>97.0 (86.0-106.8)</td>
<td>90.0 (79.0-98.8)</td>
<td>91.0 (79.0-105.0)</td>
<td>0.205†</td>
<td>0.504†</td>
</tr>
<tr>
<td>MAP (LA)</td>
<td>105.5</td>
<td>94.5 (94.0-113.5)</td>
<td>96.0 (86.0-107.0)</td>
<td>0.022*</td>
<td>0.273*</td>
</tr>
<tr>
<td>(median-IQR)</td>
<td>94.5 (78.0-104.5)</td>
<td>94.5 (78.0-104.5)</td>
<td>96.0 (86.0-107.0)</td>
<td>0.022*</td>
<td>0.273*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b)</th>
<th>GA</th>
<th>LA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ΔMAP1</td>
<td>-7.1 (-16.5 to 10.7)</td>
<td>-12.4 (-24.9 to -0.2)</td>
<td>0.240†</td>
</tr>
<tr>
<td>% ΔMAP2</td>
<td>-2.0 (-19.0 to 7.2)</td>
<td>-3.7 (-16.5 to 5.9)</td>
<td>0.767†</td>
</tr>
</tbody>
</table>
For the combined cohort, ipsilateral MCAVm was significantly higher compared to baseline on both day 1 and day 2. When analysed according to anaesthetic allocation the change from baseline to day 1 was significant for both GA and LA, but did not reach significance for day 2 (table 3.2.2a).

Contralateral MCAVm was significantly higher on day 1 for the combined cohort but not for day 2. The same pattern was seen when analysed according to anaesthetic allocation for the GA patients but not for the LA group (table 3.2.2b).

Analysis of per cent change of MCAVm for day 1 and day 2 for GA vs. LA did not show a significant difference (table 3.2.2c).
Table 3.2.3 (a) Comparison of preoperative vs. postoperative ipsilateral MCAVm. (b) comparison of preoperative vs. postoperative contralateral MCAVm. (c) Comparison of mean per cent change in MCAVm for day 1 (% ΔMCAVm1) and day 2 (% ΔMCAVm2) in GA vs. LA. Units are cm/s except for (c). * Paired t-test, † Wilcoxon signed ranks test, ‡ Mann-Whitney U test, § unpaired t-test.

<table>
<thead>
<tr>
<th>(a)</th>
<th>Preop</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAVm (all) (ipsilateral) (median-IQR)</td>
<td>56.6 (42.9-66.0)</td>
<td>64.1 (52.1-78.8)</td>
<td>64.2 (52.3-73.3)</td>
</tr>
<tr>
<td>Day1 vs Preop – p=0.001* Day2 vs Preop – p=0.034*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCAVm (GA) (ipsilateral) (median-IQR)</td>
<td>58.0 (45.9-65.0)</td>
<td>63.6 (53.5-78.0)</td>
<td>69.0 (56.3-73.2)</td>
</tr>
<tr>
<td>Day1 vs Preop – p=0.013* Day2 vs Preop – p=0.105*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCAVm (LA) (ipsilateral) (median-IQR)</td>
<td>53.8 (41.2-68.3)</td>
<td>64.1 (45.9-80.4)</td>
<td>63.4 (36.6-52.4)</td>
</tr>
<tr>
<td>Day1 vs Preop – p=0.039* Day2 vs Preop – p=0.158*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b)</th>
<th>Preop</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAVm (all) (contralateral) (median-IQR)</td>
<td>52.1 (41.9-56.7)</td>
<td>54.2 (43.7-71.7)</td>
<td>50.7 (42.1-59.9)</td>
</tr>
<tr>
<td>Day1 vs Preop – p=0.011† Day2 vs Preop – p=0.830‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCAVm (GA) (contralateral) (median-IQR)</td>
<td>53.0 (44.3-67.2)</td>
<td>62.5 (50.7-74.9)</td>
<td>56.3 (49.6-63.3)</td>
</tr>
<tr>
<td>Day1 vs Preop – p=0.021* Day2 vs Preop – p=0.320*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCAVm (LA) (contralateral) (median-IQR)</td>
<td>52.1 (38.7-55.6)</td>
<td>50.0 (39.4-61.9)</td>
<td>43.6 (36.6-52.4)</td>
</tr>
<tr>
<td>Day1 vs Preop – p=0.204* Day2 vs Preop – p=0.317*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(c)</th>
<th>GA</th>
<th>LA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ΔMCAVm1 (ipsilateral) (median-IQR)</td>
<td>21.7 (5.4-50.6)</td>
<td>11.4 (0.0-31.5)</td>
</tr>
<tr>
<td>p=0.324‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ΔMCAVm1 (contralateral) (median-IQR)</td>
<td>11.0 (-1.4-19.8)</td>
<td>8.5 (-8.1-15.8)</td>
</tr>
<tr>
<td>p=0.380§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ΔMCAVm2 (ipsilateral) (median-IQR)</td>
<td>14.0 (2.4-32.0)</td>
<td>10.2 (-5.3-32.9)</td>
</tr>
<tr>
<td>p=0.742§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% ΔMCAVm2 (contralateral) (median-IQR)</td>
<td>6.3 (-13.5-18.2)</td>
<td>1.4 (-13.8-9.7)</td>
</tr>
<tr>
<td>p=0.301‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3 Cerebrovascular autoregulation tests

Thirty-five patients (16 GA and 19 LA) underwent preoperative tilt-test assessment of ipsilateral cerebrovascular autoregulation (CA). Preoperative tilt-testing data was unavailable for one patient (LA) due to equipment failure, and three patients (2 LA and 1 GA) did not undergo postoperative tilt-testing due to unavailability of the tilt-table.

For the contralateral side, apart from the patients not tested as described above, tilt-test data was unavailable for a further 8 patients (5 LA and 3 GA) either due to unavailability of a second probe to permit simultaneous assessment of the ipsilateral and contralateral MCAV or due to inadequate temporal window for insonation of the contralateral MCA.

No significant difference was seen in preoperative vs. postoperative tilt gradients, regardless of anaesthetic allocation or laterality (table 3.3.1).

There was no difference in pre- or postoperative tilt gradients for GA vs. LA, both for the ipsilateral and for the contralateral sides (table 3.3.2a). Similarly, there was no significant difference in the % change from baseline of tilt gradient for GA vs. LA, both for the ipsilateral and for the contralateral sides (table 3.3.2b).
Table 3.3.1 Comparison of preoperative vs. postoperative values of tilt gradients for all patients, GA group and LA group. The ipsilateral and contralateral sides are shown separately. Units are %/mmHg. * Paired t-test.

<table>
<thead>
<tr>
<th>Ipsilateral</th>
<th>Preop</th>
<th>Postop</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tilt gradient (all) (median-IQR)</td>
<td>0.35 (0.15 to 0.52)</td>
<td>0.42 (0.08 to 0.63)</td>
<td>p=0.655*</td>
</tr>
<tr>
<td>tilt gradient (GA) (median-IQR)</td>
<td>0.43 (0.21 to 0.63)</td>
<td>0.38 (-0.02 to 0.71)</td>
<td>p=0.293*</td>
</tr>
<tr>
<td>tilt gradient (LA) (median-IQR)</td>
<td>0.31 (0.13 to 0.52)</td>
<td>0.42 (0.18 to 0.54)</td>
<td>p=0.591*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contralateral</th>
<th>Preop</th>
<th>Postop</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>tilt gradient (all) (median-IQR)</td>
<td>0.27 (0.60 to 0.50)</td>
<td>0.42 (0.10 to 0.74)</td>
<td>p=0.160*</td>
</tr>
<tr>
<td>tilt gradient (GA) (median-IQR)</td>
<td>0.32 (0.13 to 0.52)</td>
<td>0.42 (0.10 to 0.78)</td>
<td>p=0.430*</td>
</tr>
<tr>
<td>tilt gradient (LA) (median-IQR)</td>
<td>0.15 (-0.08 to 0.47)</td>
<td>0.37 (0.11 to 0.52)</td>
<td>p=0.267*</td>
</tr>
</tbody>
</table>
Table 3.3.2 (a) Comparison of preoperative and postoperative tilt gradients for GA vs. LA both for the ipsilateral and for the contralateral sides. (b) Comparison of per cent change in tilt gradient (% Δ[tilt gradient]) for GA vs. LA, both for the ipsilateral and contralateral sides. Units are %/mmHg except for (b). * Unpaired t-test, † Mann-Whitney U test.

(a) Comparison of preoperative and postoperative tilt gradients for GA vs. LA both for the ipsilateral and for the contralateral sides.

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>LA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preop [tilt gradient]</strong></td>
<td><strong>GA</strong></td>
<td><strong>LA</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td><em>(ipsilateral)</em></td>
<td>0.43 (0.21 to 0.63)</td>
<td>0.31 (0.13 to 0.52)</td>
<td>0.423*</td>
</tr>
<tr>
<td><em>(contralateral)</em></td>
<td>0.32 (0.13 to 0.52)</td>
<td>0.15 (-0.08 to 0.47)</td>
<td>0.202*</td>
</tr>
<tr>
<td><strong>Postop [tilt gradient]</strong></td>
<td><strong>GA</strong></td>
<td><strong>LA</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td><em>(ipsilateral)</em></td>
<td>0.38 (-0.02 to 0.71)</td>
<td>0.42 (0.18 to 0.54)</td>
<td>0.733*</td>
</tr>
<tr>
<td><em>(contralateral)</em></td>
<td>0.42 (0.10 to 0.78)</td>
<td>0.37 (0.11 to 0.52)</td>
<td>0.486*</td>
</tr>
</tbody>
</table>

(b) Comparison of per cent change in tilt gradient (% Δ[tilt gradient]) for GA vs. LA, both for the ipsilateral and contralateral sides.

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>LA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Δ[tilt gradient]</strong></td>
<td><strong>GA</strong></td>
<td><strong>LA</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td><em>(ipsilateral)</em></td>
<td>-35.5 (-109.2 to 55.7)</td>
<td>-16.8 (-72.2 to 192.4)</td>
<td>0.558†</td>
</tr>
<tr>
<td><em>(contralateral)</em></td>
<td>-0.1 (-71.5 to 156.8)</td>
<td>-56.5 (-222.9 to 156.6)</td>
<td>0.453†</td>
</tr>
</tbody>
</table>
Repeated measures ANOVA for tilt gradient at the preoperative and postoperative timepoints was also conducted, with anaesthetic modality (GA vs. LA) as the between-subjects factor. This did not show a significant difference between the two time points, both for the ipsilateral (F[1,30]=1.471, p=0.235) and contralateral (F[1,22]=0.169, p=0.685) sides.

When examining the state of CA (impaired vs. preserved, according to the criteria described in section 2.5), there was no significant difference in the proportion of patients with impaired preoperative CA for GA vs. LA on the ipsilateral (table 3.3.3a) or contralateral (table 3.3.3b) sides. Similarly postoperative values for CA were not significantly different (table 3.3.4).

For the whole cohort the proportion of patients with impaired CA preoperatively was not significantly different to the proportion of patients with postoperative CA impairment, regardless of assessed side (table 3.3.5).
Table 3.3.3 Comparison of GA vs. LA for preoperative cerebral autoregulation impairment. (a) Ipsilateral, (b) contralateral.

(a) Preoperative impairment of autoregulation (ipsilateral)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>no</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>13 (68.4%)</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>GA</td>
<td>11 (68.8%)</td>
<td>5 (31.3%)</td>
</tr>
</tbody>
</table>

(b) Preoperative impairment of autoregulation (contralateral)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>no</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>11 (84.6%)</td>
<td>2 (15.4%)</td>
</tr>
<tr>
<td>GA</td>
<td>9 (69.2%)</td>
<td>4 (30.8%)</td>
</tr>
</tbody>
</table>

Table 3.3.4 Comparison of GA vs. LA for postoperative cerebral autoregulation impairment. (a) Ipsilateral, (b) contralateral.

(a) Postoperative impairment of autoregulation (ipsilateral)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>no</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>13 (76.5%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>GA</td>
<td>8 (53.3%)</td>
<td>7 (46.7%)</td>
</tr>
</tbody>
</table>

(b) Postoperative impairment of autoregulation (contralateral)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>no</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>9 (75.0%)</td>
<td>3 (25.0%)</td>
</tr>
<tr>
<td>GA</td>
<td>7 (58.3%)</td>
<td>5 (41.7%)</td>
</tr>
</tbody>
</table>
**Table 3.3.5** Preoperative vs. postoperative impairment of cerebral autoregulation. (a) Ipsilateral, (b) contralateral.

<table>
<thead>
<tr>
<th>(a)</th>
<th>Postoperative impairment of autoregulation (ipsilateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Preoperative impairment of autoregulation (ipsilateral)</td>
<td>no</td>
<td>15 (71.4%)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>6 (54.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b)</th>
<th>Postoperative impairment of autoregulation (contralateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Preoperative impairment of autoregulation (contralateral)</td>
<td>no</td>
<td>14 (70.0%)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>2 (50.0%)</td>
</tr>
</tbody>
</table>
For patients with impaired CA at baseline, 5/6 LA patients’ CA returned to ‘intact’
levels, whilst this occurred in only 1/5 GA patients; this difference however was
short of statistical significance (p=0.080, table 3.3.6). Overall the majority of
patients exhibited improvement of CA to ‘intact’ levels or maintained intact CA
regardless of anaesthetic or laterality. However, 6 patients (3 GA, 3 LA) showed
deterioration of previously intact ipsilateral CA to impaired levels (table 3.3.7).
Table 3.3.6 Postoperative impairment of autoregulation according to baseline autoregulation status and anaesthetic.

<table>
<thead>
<tr>
<th>Preoperative impairment of autoregulation (ipsilateral)</th>
<th>Postoperative impairment of autoregulation (ipsilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Anaesthetic</td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>8 (72.7%)</td>
</tr>
<tr>
<td>yes</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>GA</td>
<td>7 (70.0%)</td>
</tr>
<tr>
<td></td>
<td>3 (40.0%)</td>
</tr>
<tr>
<td>p=1.000 (Fisher’s exact test)</td>
<td></td>
</tr>
<tr>
<td>Anaesthetic</td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>5 (83.3%)</td>
</tr>
<tr>
<td>yes</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>GA</td>
<td>1 (20.0%)</td>
</tr>
<tr>
<td></td>
<td>4 (80.0%)</td>
</tr>
<tr>
<td>p=0.080 (Fisher’s exact test)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.3.7 Change in postoperative autoregulation status compared to baseline. (a) ipsilateral, (b) contralateral. Deterioration=intact at baseline, impaired postoperatively; improvement=impaired at baseline, intact postoperatively.

(a) Postoperative change in autoregulation (ipsilateral)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>deterioration</th>
<th>no change [impaired]</th>
<th>improvement</th>
<th>no change [intact]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>3 (17.6%)</td>
<td>1 (5.9%)</td>
<td>8 (47.1%)</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td>GA</td>
<td>3 (20.0%)</td>
<td>4 (26.7%)</td>
<td>7 (46.7%)</td>
<td>1 (6.7%)</td>
</tr>
</tbody>
</table>

(b) Postoperative change in autoregulation (contralateral)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>deterioration</th>
<th>no change [impaired]</th>
<th>improvement</th>
<th>no change [intact]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA</td>
<td>3 (25.0%)</td>
<td>0</td>
<td>8 (66.7%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>GA</td>
<td>3 (25.0%)</td>
<td>2 (16.7%)</td>
<td>6 (50.0%)</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>
Logistic regression analysis of postoperative impairment of cerebral autoregulation as determined by tilt testing with a model containing preoperative impairment of autoregulation and type of anaesthesia and their interaction did not reveal a significant effect of baseline impairment of autoregulation or of anaesthetic modality ($\chi^2=5.664$, df=3, p=0.129). A further model incorporating bilateral carotid disease status, symptom status and the interaction of each with baseline impairment of autoregulation was also non-significant ($\chi^2=6.898$, df=6, p=0.330).

The above logistic regression analyses were repeated for the contralateral side, again yielding non-significant results for the first ($\chi^2=2.385$, df=3, p=0.496) and second ($\chi^2=9.040$, df=6, p=0.171) models respectively.

When examining the studied cohort as a whole, patients with impaired CA at baseline had a significant decrease in the tilt gradient (i.e. improvement in CA) compared to baseline (mean gradients: baseline 0.69 %/mmHg [SD 0.19] vs. postoperative 0.49 %/mmHg [SD 0.24], p=0.050, paired t-test), whilst no overall change was seen for the patients with intact CA at baseline (mean gradients: baseline 0.20 %/mmHg [SD 0.22] vs. postoperative 0.26 %/mmHg [SD 0.42], p=0.525, paired t-test) [figure 3.3.1].
Figure 3.3.1 Preoperative vs. postoperative ipsilateral tilt gradients depending on baseline cerebral autoregulation (CA). Y-axis units are %/mmHg.
3.4 Cerebrovascular reactivity tests

For the ipsilateral side, all 36 patients underwent preoperative assessment of cerebrovascular reactivity (CVR) to CO$_2$. However, one patient (LA) was not able to hyperventilate to generate data for the hyperventilation phase of the preoperative CVR test and was thus excluded from further CVR testing, and for one further patient (GA) preoperative CVR test data was lost due to software error and thus postoperative testing was abandoned. Postoperatively, one further patient (LA) was unable to complete the hyperventilation phase of the CVR test and was excluded from further analysis of CO$_2$ reactivity, and data for another patient (GA) was not recorded due to software malfunction.

A further 7 patients (4 LA and 3 GA) did not have contralateral testing of CVR, either due to unavailability of a second probe to permit simultaneous testing, or due to inadequate temporal window for insonation of the contralateral MCA.

3.4.1 Cerebrovascular reactivity

No significant difference was seen in preoperative vs. postoperative CVRI, regardless of anaesthetic allocation or laterality (table 3.4.1).

There was no difference in pre- or postoperative CVRI for GA vs. LA, both for the ipsilateral and for the contralateral sides (table 3.4.2a). Similarly, there was no significant difference in the per cent change from baseline of CVRI for GA vs. LA, both for the ipsilateral and for the contralateral sides (table 3.4.2b).
Table 3.4.1 Comparison of preoperative vs. postoperative values of CVRI for all patients, GA group and LA group. The ipsilateral and contralateral sides are shown separately. Units are %/kPa. * Paired t-test.

<table>
<thead>
<tr>
<th>Ipsilateral</th>
<th>Preop</th>
<th>Postop</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVRI (all)</td>
<td>15.9 (11.9 to 21.3)</td>
<td>16.7 (13.7 to 20.5)</td>
<td>0.460*</td>
</tr>
<tr>
<td>CVRI (GA)</td>
<td>19.1 (11.9 to 22.6)</td>
<td>17.9 (13.2 to 20.6)</td>
<td>0.740*</td>
</tr>
<tr>
<td>CVRI (LA)</td>
<td>15.9 (11.9 to 19.1)</td>
<td>16.0 (14.5 to 20.6)</td>
<td>0.168*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contralateral</th>
<th>Preop</th>
<th>Postop</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVRI (all)</td>
<td>18.4 (13.0 to 22.8)</td>
<td>14.3 (11.5 to 20.4)</td>
<td>0.088*</td>
</tr>
<tr>
<td>CVRI (GA)</td>
<td>17.2 (12.0 to 26.5)</td>
<td>14.3 (10.6 to 20.3)</td>
<td>0.276*</td>
</tr>
<tr>
<td>CVRI (LA)</td>
<td>18.4 (14.1 to 20.7)</td>
<td>14.9 (11.5 to 21.0)</td>
<td>0.120*</td>
</tr>
</tbody>
</table>
Table 3.4.2 (a) Comparison of preoperative and postoperative CVRI for GA vs. LA both for the ipsilateral and for the contralateral sides. (b) Comparison of per cent change in CVRI (% ΔCVRI) for GA vs. LA, both for the ipsilateral and contralateral sides. Units are %/kPa except for (b). * Unpaired t-test, † Mann-Whitney U test.

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>LA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop CVRI (ipsilateral) (median-IQR)</td>
<td>19.1 (11.9 to 22.6)</td>
<td>15.9 (11.9 to 19.1)</td>
<td>p=0.237*</td>
</tr>
<tr>
<td>Preop CVRI (contralateral) (median-IQR)</td>
<td>17.2 (12.0 to 26.5)</td>
<td>18.4 (14.1 to 20.7)</td>
<td>p=0.545*</td>
</tr>
<tr>
<td>Postop CVRI (ipsilateral) (median-IQR)</td>
<td>17.9 (13.2 to 20.6)</td>
<td>16.0 (14.5 to 20.6)</td>
<td>p=0.868*</td>
</tr>
<tr>
<td>Postop CVRI (contralateral) (median-IQR)</td>
<td>14.3 (10.6 to 20.3)</td>
<td>14.9 (11.5 to 21.0)</td>
<td>p=0.634*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b)</th>
<th>GA</th>
<th>LA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>%ΔCVRI [ipsilateral]</td>
<td>-5.1 (-31.4 to 27.0)</td>
<td>7.7 (-4.9 to 25.2)</td>
<td>p=0.119†</td>
</tr>
<tr>
<td>%ΔCVRI [contralateral]</td>
<td>-22.9 (-39.6 to 16.6)</td>
<td>-12.9 (-33.5 to 6.3)</td>
<td>p=0.885†</td>
</tr>
</tbody>
</table>
Repeated measures ANOVA for CVRI at the preoperative and postoperative timepoints was also conducted, with anaesthetic modality (GA vs. LA) as the between-subjects factor. This did not show a significant difference between the two time points, both for the ipsilateral ($F[1,30]=1.342, p=0.256$) and contralateral ($F[1,22]=0.249, p=0.623$) sides.

When examining the state of CVR (impaired vs. preserved, according to the criteria described in section 2.5), there was no significant difference in the proportion of patients with impaired preoperative CVR for GA vs. LA on the ipsilateral (table 3.4.3a) or contralateral (table 3.4.3b) sides. Similarly postoperative values for CVR were not significantly different (table 3.4.4).

For the whole cohort the proportion of patients with impaired CVR preoperatively was not significantly different to the proportion of patients with postoperative CVR impairment, regardless of assessed side (table 3.4.5).

Of the 6 patients with impaired preoperative ipsilateral CVR, 5 showed improvement to ‘intact’ levels and one remained impaired. However, there were 3 patients with intact preoperative CVR whose postoperative CVR deteriorated to ‘impaired’ levels (table 3.4.6a). Three patients also exhibited deterioration in CVRI on the contralateral side (table 3.4.6b).
Table 3.4.3 Comparison of GA vs. LA for preoperative CVR impairment.
(a) Ipsilateral, (b) contralateral.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative impairment of CVRI (ipsilateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Anaesthetic</td>
<td>LA 15 (78.9%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td></td>
<td>GA 13 (86.7%)</td>
<td>2 (13.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Preoperative impairment of CVRI (contralateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Anaesthetic</td>
<td>LA 12 (92.3%)</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td></td>
<td>GA 10 (83.3%)</td>
<td>2 (16.7%)</td>
</tr>
</tbody>
</table>

Table 3.4.4 Comparison of GA vs. LA for postoperative CVR impairment.
(a) Ipsilateral, (b) contralateral.

<table>
<thead>
<tr>
<th></th>
<th>Postoperative impairment of CVRI (ipsilateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Anaesthetic</td>
<td>LA 16 (88.9%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td></td>
<td>GA 12 (85.7%)</td>
<td>2 (14.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Postoperative impairment of CVRI (contralateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Anaesthetic</td>
<td>LA 12 (85.7%)</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>GA 8 (72.7%)</td>
<td>3 (27.3%)</td>
</tr>
</tbody>
</table>
### Table 3.4.5
Preoperative vs. postoperative impairment of cerebral autoregulation. (a) Ipsilateral, (b) contralateral.

<table>
<thead>
<tr>
<th>Preoperative impairment of CVRI (ipsilateral)</th>
<th>Postoperative impairment of CVRI (ipsilateral)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Preoperative impairment of CVRI (ipsilateral)</td>
<td>23 (88.5%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>yes</td>
<td>5 (83.3%)</td>
<td>1 (16.7%)</td>
</tr>
</tbody>
</table>

p=0.099 (Fisher’s exact test)

<table>
<thead>
<tr>
<th>Preoperative impairment of CVRI (contralateral)</th>
<th>Postoperative impairment of CVRI (contralateral)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Preoperative impairment of CVRI (ipsilateral)</td>
<td>18 (85.7%)</td>
<td>3 (14.3%)</td>
</tr>
<tr>
<td>yes</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
</tr>
</tbody>
</table>

p=0.099 (Fisher’s exact test)

### Table 3.4.6
Change in postoperative CVR status compared to baseline. (a) Ipsilateral, (b) contralateral. Deterioration=intact at baseline, impaired postoperatively; improvement=impaired at baseline, intact postoperatively.

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Postoperative change in CVRI (ipsilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>deterioration</td>
</tr>
<tr>
<td>LA</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>GA</td>
<td>2 (14.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Postoperative change in CVRI (contralateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>deterioration</td>
</tr>
<tr>
<td>LA</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>GA</td>
<td>2 (18.2%)</td>
</tr>
</tbody>
</table>
Logistic regression analysis of postoperative impairment of ipsilateral CVRI with a model containing preoperative impairment of ipsilateral CVRI and type of anaesthesia and their interaction did not reveal a significant effect of baseline impairment of ipsilateral CVRI or of anaesthetic modality ($\chi^2=1.596$, df=3, $p=0.660$). A further model incorporating bilateral carotid disease status, symptom status and the interaction of each with baseline impairment of ipsilateral CVRI was also non-significant ($\chi^2=4.070$, df=6, $p=0.667$).

The above logistic regression analyses were repeated for the contralateral side, again yielding non-significant results for the first ($\chi^2=5.372$, df=3, $p=0.146$) and second ($\chi^2=7.623$, df=5, $p=0.178$) models respectively.

When examining the studied cohort as a whole, patients with impaired CVR at baseline had a significant increase in CVRI (i.e. improvement in CVR) compared to baseline (median CVRI 8.64 %/kPa [IQR 3.04 – 10.66] vs. 13.19 %/kPa [IQR 10.88 – 20.99], $p=0.028$, Wilcoxon signed ranks test), whilst no overall change was seen for the patients with intact CA at baseline (median CVRI 17.32 %/kPa [IQR 14.95 – 22.66] vs. 16.83 %/kPa [IQR 15.13 – 20.38], $p=0.454$, Wilcoxon signed ranks test) [figure 3.4.1].
Figure 3.4.1 Preoperative vs. postoperative ipsilateral CVRI depending on baseline CVR. Bold line is median CVRI, boxes indicate IQR and whiskers show range. Y-axis units are %/kPa.
3.4.2 Cerebrovascular resistance

Analyses were then repeated for assessment of CVResI in order to take into account any effect of changes in MAP during CO\textsubscript{2} reactivity testing.

CVRI and CVResI values were all strongly correlated ($r>0.5$), suggesting little impact in changes of MAP on CVR in this cohort (table 3.4.7).

Similar to the analyses of CVRI, there was no significant difference in postoperative CVResI compared to baseline regardless of anaesthetic allocation or laterality (table 3.4.8), and values for CVResI at each assessment point and for each side were not significantly different for GA vs. LA (table 3.4.9). The per cent change in CVResI compared to baseline was not significantly different for GA vs. LA (table 3.4.10).

Repeated measures ANOVA for preoperative and postoperative CVResI with anaesthetic modality (GA vs. LA) as the between-subjects factor failed to show a significant difference for the ipsilateral ($F[1,30]=1.221$, p=0.278) or contralateral ($F[1,22]=0.809$, p=0.378) sides.
**Table 3.4.7** Correlation between CVRI and CVResI.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipsilateral CVRI vs. ipsilateral CVResI</td>
<td>$r=0.743$</td>
<td>$p&lt;0.005$</td>
<td></td>
</tr>
<tr>
<td>contralateral CVRI vs. contralateral CVResI</td>
<td>$r=0.824$</td>
<td>$p&lt;0.005$</td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipsilateral CVRI vs. ipsilateral CVResI</td>
<td>$r=0.608$</td>
<td>$p&lt;0.005$</td>
<td></td>
</tr>
<tr>
<td>contralateral CVRI vs. contralateral CVResI</td>
<td>$r=0.654$</td>
<td>$p&lt;0.005$</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.4.8** Comparison of preoperative vs. postoperative values of CVResI for all patients, GA group and LA group. The ipsilateral and contralateral sides are shown separately. Units are %/kPa. * Paired t-test.

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>Postop</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipsilateral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVResI (all) (median-IQR)</td>
<td>15.2 (10.4 to 17.8)</td>
<td>15.1 (10.9 to 19.1)</td>
<td>$p=0.154^*$</td>
</tr>
<tr>
<td>CVResI (GA) (median-IQR)</td>
<td>15.4 (10.1 to 16.6)</td>
<td>14.5 (9.8 to 18.9)</td>
<td>$p=0.874^*$</td>
</tr>
<tr>
<td>CVResI (LA) (median-IQR)</td>
<td>15.0 (10.5 to 17.8)</td>
<td>15.5 (11.2 to 19.3)</td>
<td>$p=0.111^*$</td>
</tr>
<tr>
<td><strong>Contralateral</strong></td>
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<tr>
<td>CVResI (all) (median-IQR)</td>
<td>15.3 (11.9 to 22.0)</td>
<td>14.5 (10.2 to 25.5)</td>
<td>$p=0.378^*$</td>
</tr>
<tr>
<td>CVResI (GA) (median-IQR)</td>
<td>13.4 (6.5 to 23.4)</td>
<td>12.2 (9.8 to 20.8)</td>
<td>$p=0.967^*$</td>
</tr>
<tr>
<td>CVResI (LA) (median-IQR)</td>
<td>15.4 (12.2 to 22.0)</td>
<td>14.5 (10.5 to 17.5)</td>
<td>$p=0.076^*$</td>
</tr>
</tbody>
</table>
Table 3.4.9 (a) Comparison of preoperative and postoperative CVResl for GA vs. LA both for the ipsilateral and for the contralateral sides. (b) Comparison of per cent change in CVResl (%ΔCVResl) for GA vs. LA, both for the ipsilateral and contralateral sides. Units are %/kPa except for (b). * Unpaired t-test, † Mann-Whitney U test.

<table>
<thead>
<tr>
<th></th>
<th>GA</th>
<th>LA</th>
<th>p-value</th>
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<tr>
<td>(a)</td>
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<tr>
<td>Preop CVResl</td>
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<tr>
<td>(ipsilateral)</td>
<td>15.4 (10.1 to 16.6)</td>
<td>15.0 (10.5 to 17.8)</td>
<td>0.791*</td>
</tr>
<tr>
<td>(contralateral)</td>
<td>13.4 (6.5 to 23.4)</td>
<td>15.4 (12.2 to 22.0)</td>
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</tr>
<tr>
<td>Postop CVResl</td>
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</tr>
<tr>
<td>(ipsilateral)</td>
<td>14.5 (9.8 to 18.9)</td>
<td>15.5 (11.2 to 19.3)</td>
<td>0.498*</td>
</tr>
<tr>
<td>(contralateral)</td>
<td>12.2 (9.8 to 20.8)</td>
<td>14.5 (10.5 to 17.5)</td>
<td>0.742*</td>
</tr>
<tr>
<td>(b)</td>
<td></td>
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<tr>
<td>%ΔCVResl</td>
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<tr>
<td>[ipsilateral]</td>
<td>6.1 (-25.1 to 26.9)</td>
<td>5.8 (-22.6 to 45.4)</td>
<td>0.939†</td>
</tr>
<tr>
<td>[contralateral]</td>
<td>1.4 (-24.9 to 64.6)</td>
<td>-22.3 (-43.7 to 19.1)</td>
<td>0.087†</td>
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</tbody>
</table>
3.4.3 Correlation of indices of cerebrovascular autoregulation and reactivity

No correlation between CVRI and the values of the gradients obtained by linear regression analysis of the relationship between estimated cerebral perfusion pressure and MCAV during tilt-testing (‘tilt gradient’) was found. In particular, no patient in this cohort demonstrated both impaired CA and impaired CVR, either pre- or postoperatively. Note that all the patients with tilt-gradient >0.5 %/mmHg also had correlation coefficient >0.5 thus satisfying both conditions for impaired CA as defined in section 2.3.2.

These relationships are illustrated in figure 3.4.2.
Figure 3.4.2 Correlation of the tilt-gradient and CVRI. Dotted lines indicate the threshold between impaired and intact CA or CVR (impaired CA: >0.5%, impaired CVR: <11.5%). Note that there are no subjects in the top-left quadrant (impaired CA and impaired CVR). Y-axis units are %/mmHg, X-axis units %/kPa.
3.5 Intraoperative haemodynamic data

Intraoperative haemodynamic data was available for 34/36 patients; for two patients intraoperative data were lost due to software error leading to failure to save the intraoperative recordings. The intraoperative recordings of mean MCAV (MCAVm) and mean arterial pressure (MAP) were evaluated and differences for specific intraoperative time points were analysed using non-parametric tests (neither MAP nor MCAVm data conformed to the normal distribution).

MAP was consistently higher for patients undergoing LA CEA compared to GA CEA, reaching maximum just after clamping; the values then converge towards the end of surgery. By 1 hour post-operatively MAP was not significantly different between GA and LA. (figure 3.5.1).

When impairment of cerebral autoregulation (CA) as measured by tilt-testing was considered, the median MAP for the group with impaired baseline CA was higher at the pre- and post-clamp timepoints but this did not reach statistical significance (figure 3.5.2).

Patients with impairment of cerebrovascular reactivity (CVR) at baseline did show significantly different patterns of intraoperative MAP (figure 3.5.3).
Figure 3.5.1: Comparison of median MAP at key intraoperative time points for GA vs. LA. LA MAP is significantly higher throughout, the values converging at 1 hour postoperatively. Significant differences are shown (Mann-Whitney U tests). Y-axis values are mmHg.
Figure 3.5.2 Comparison of median MAP at key intraoperative time points for impaired vs. intact CA. The trend for higher pre- and post-clamp MAP for patients with impaired CA is evident, but is not statistically significant (Mann-Whitney U tests). Y-axis values are mmHg.

Figure 3.5.3 Comparison of median MAP at key intraoperative time points for impaired vs. intact CVR. Again no statistically significant differences are seen (Mann-Whitney U tests). Y-axis values are mmHg.
The trends in % change in MCAVm from the first value of MCAV after induction of anaesthesia (GA) or after administration of LA were then examined.

For the comparison of the GA and LA groups there were no significant differences at any time point. As expected, cross-clamping the carotid vessels resulted in significant drop in MCAVm, and this was followed by increase in MCAVm from baseline upon de-clamping (figure 3.5.4). Similarly, there was no difference in MCAVm at any time point when baseline impairment of CA was considered (figure 3.5.5).

However, patients with impaired preoperative CVR showed significantly higher post-declamp MCAVm increases compared to patients with intact CVR at baseline (figure 3.5.6). This difference continued to be significant at 1 hour post-surgery. On the first postoperative day, % change in MCAV was not different between those with impaired baseline CVR vs. those with intact baseline CVR (39.9% [IQR -5.7 – 93.4] vs. 11.4% [IQR 3.7 – 28.8], p=0.331, Mann-Whitney U test). Only one patient exhibited ipsilateral MCAV increase >100% 24 hours after surgery, compared to 5 patients on restoration of ICA blood flow during CEA.
Figure 3.5.4 Comparison of median % change in MCAVm at key intraoperative time points for GA vs. LA. No statistically significant differences are observed between GA and LA. (Mann-Whitney U tests).

Figure 3.5.5 Comparison of median % change in MCAVm at key intraoperative time points for impaired vs. intact CA. No statistically significant differences are observed (Mann-Whitney U tests).
Figure 3.5.6 Comparison of median % change in MCAVm at key intraoperative time points for impaired vs. preserved CVR. MCAVm increase is significantly greater post-declamp and at 1 hour post-op, and the trend is similar (although not statistically significant) at the end of surgery (Mann-Whitney U tests). Note scale change from previous two figures.
3.6 Biochemical markers of cerebral injury

Data for markers of cerebral injury were available for 24/36 patients (12 LA, 12 GA). This was a consequence of a freezer failure early in the study period leading to the loss of the first 11 stored samples, and sampling difficulties due to inability to aspirate from the jugular and arterial lines for the majority of samples in one patient.

For these 24 patients, less than 3% of values were unavailable due to sampling failure. This was either due to inability to draw blood from a displaced or occluded jugular catheter or due to occlusion of the arterial line during intraoperative sampling. To permit repeated-measures analyses, these missing data points were replaced by multiple imputation analysis (fully conditional specification method [10 iterations], 5 imputations by linear regression) using PASW statistics version 18 (IBM corporation, USA).

Neither the data for S100β nor those for NSE conformed to the normal distribution, and attempts at simple transformation (logarithmic, square root) failed to achieve normality. Analyses were thus constrained to tests for non-parametric data.

3.6.1 Comparison of jugular vs. peripheral blood sampling

Non-parametric repeated measures analysis of results from the jugular bulb for S100β levels showed a significant increase in levels [p<0.005, Friedman’s test]. The same trend from peripheral blood sampling was not significant [p=0.074, Friedman’s test] (figure 3.6.1a). Post-hoc analysis with Bonferroni correction showed that jugular S100β levels were significantly higher at the post-clamp and post-declamp
timepoints (both p<0.0005, Wilcoxon signed ranks test), whilst the remainder of values were not significantly different from baseline.

Comparison of jugular vs. peripheral sampling showed that jugular S100β levels were significantly higher than peripheral levels at the post-clamp (0.086 [IQR 0.053 – 0.161] µg/L vs 0.061 [IQR 0.045 – 0.094] µg/L, p=0.016, Wilcoxon signed ranks test) and post-declamp (0.087 [IQR 0.059 – 0.111] µg/L vs 0.075 [IQR 0.040 – 0.115] µg/L, p=0.033, Wilcoxon signed ranks test) timepoints.

For NSE, the trends over time for jugular and peripheral sampling were both significant [p<0.005, Friedman’s test] (figure 3.6.1b). Post-hoc analysis with Bonferroni correction showed that both jugular and peripheral NSE levels were significantly lower at the pre-clamp, post-declamp and 1-hour postop timepoints (both p<0.0005, Wilcoxon signed ranks test), whilst the remainder of values were not significantly different from baseline.

Comparison of jugular vs. peripheral sampling showed jugular NSE levels were statistically significantly higher on the first postoperative day although the magnitude of this difference was very small (10.84 [IQR 8.71 – 14.27] µg/L vs. 10.67 [IQR 9.23 – 12.50] µg/L, p=0.026, Wilcoxon signed ranks test). No other difference for jugular vs. peripheral NSE levels was encountered.
Figure 3.6.1 Comparison of jugular and peripheral blood sampling for each time point. (a) S100β, (b) NSE. Bars show median values, whiskers are 95% CI. Y-axis units are µg/L.
3.6.2 Comparison of GA vs. LA for S100β

Median baseline S100β levels were significantly different for GA vs. LA (0.07 [IQR 0.05 – 0.12] µg/L vs. 0.04 [IQR 0.03 – 0.06] µg/L respectively, p=0.006, Mann-Whitney U test).

The absolute values for jugular and peripheral levels of S100β stratified according to anaesthetic are shown in figure 3.6.2.

The absolute change of jugular S100β from baseline for each time point was calculated and values for GA and LA compared (Mann-Whitney U test). There was no difference at any time point between GA and LA. Similar analysis of peripheral S100β again showed no difference between the two anaesthetic groups (figure 3.6.3).
Figure 3.6.2 Comparison of GA and LA S100β levels for each time point. (a) Jugular samples, (b) peripheral samples. Bars show median values, whiskers are 95% CI. Y-axis units are µg/L.

(a)

(b)
**Figure 3.6.3** Comparison of the change in S100β levels for GA and LA at each time point. (a) Jugular samples, (b) peripheral samples. Bars show median values, whiskers are 95% CI. Y-axis units are µg/L.
3.6.3 Comparison of GA vs. LA for NSE

There was no difference in baseline NSE levels for GA vs. LA (median 10.82 [IQR 9.65 – 15.81] µg/L vs. 10.32 [IQR 9.02 – 15.34] µg/L respectively, p=0.410, Mann-Whitney U test).

The absolute values for jugular and peripheral levels of NSE stratified according to anaesthetic are shown in figure 3.6.4. As for S100β, the absolute difference in jugular and peripheral NSE from baseline were calculated for each time point. No difference between GA and LA at any time point was found [Mann-Whitney U test] (figure 3.6.5).
Figure 3.6.4 Comparison of GA and LA NSE levels for each time point. (a) Jugular samples, (b) peripheral samples. Bars show median values, whiskers are 95% CI. Y-axis units are µg/L.
Figure 3.6.5 Comparison of the change in NSE levels for GA and LA at each time point. (a) Jugular samples, (b) peripheral samples. Bars show median values, whiskers are 95% CI. Y-axis units are µg/L.
3.6.4 Cerebral autoregulation and vasoreactivity and biochemical markers of cerebral injury

Further analyses of S100β and NSE were conducted according to baseline impairment of cerebral autoregulation by tilt-testing (CA) and cerebrovascular reactivity (CVR).

The absolute values at each time point according to intact vs. impaired CA and CVR respectively are shown in figures 3.6.6 and 3.6.7. There was no difference for the change of S100β or NSE from baseline at any time point regardless of CA or CVR status (Mann-Whitney U test).
Figure 3.6.6 Comparison of jugular and peripheral S100β levels according to (a) baseline CA impairment (b) baseline CVR impairment. Y-axis values are µg/L.
Figure 3.6.7 Comparison of jugular and peripheral NSE levels according to (a) baseline CA impairment (b) baseline CVR impairment. Y-axis values are µg/L.
Discussion
4.1 Discussion of main findings

The main aim of this work was to assess the effect of anaesthetic method on the control of the cerebral circulation after CEA. No difference was found between GA and LA both for assessment of cerebral autoregulation (CA) measured by tilt-testing and for assessment of cerebrovascular reactivity (CVR) to CO₂ measured by the rebreathing technique.

In addition, the pattern of intraoperative changes in middle cerebral artery blood flow velocity (MCAV) were not significantly different between GA and LA, despite GA associated with lower mean arterial pressure (MAP) for the period leading up to and including restoration of carotid blood flow. Further, no difference for MCAV was seen on postoperative days 1 and 2.

Intraoperative MAP was significantly higher for LA compared to GA for all stages except those after carotid declamping, and this is consistent with previous work comparing GA and LA (McCleary et al., 1996, McCarthy et al., 2002). This difference in MAP was despite all GA patients receiving vasopressors to manipulate blood pressure upwards, compared to only a third of LA patients, and this was similar to the pattern for intraoperative management of blood pressure seen in the GALA Trial (Gough, 2008). At 24 and 48 hours this difference had however resolved.

The pattern of intraoperative cerebral haemodynamics overall was of course consistent with the published literature (Naylor et al., 1993b, Nielsen et al., 2002); all patients exhibited drop in MCAV during cross clamping and a significant number exhibited overshoot on declamping.
What was evident from the behaviour of the group as a whole was that cerebral autoregulatory parameters improved within 48 hours of surgery for those patients with impairment preoperatively, but that for those with intact preoperative CA and CVR there was no significant overall change. In addition, although patients with preoperative impairment of CVR had significantly higher post-declamp and subsequent MCAV increases, by 24 hours this had resolved and only one patient continued to have >100% MCAV increase on the first and second postoperative days, which nevertheless remained asymptomatic. These changes were not reflected by similar changes in postoperative MAP.

The time course of improvement in these haemodynamic parameters measured by tilt-testing and CVR to CO$_2$ represents a finding not previously described. Previous studies (Schroeder et al., 1987a, Thiel et al., 1995, Barzo et al., 1996, Soinne et al., 2003, Reinhard et al., 2004), although showing results consistent with the present study, have examined these cerebral haemodynamic parameters 3 days after surgery or later. The speed of improvement in cerebral haemodynamic parameters would suggest that the main factor determining postoperative CA and CVR is the correction of carotid stenosis rather than the choice of anaesthetic. Therefore, even if anaesthesia has an effect on intraoperative autoregulation as suggested by McCleary et al. (1996), this effect is largely masked by the more profound effect of restoration of flow through an endarterectomised internal carotid artery. In addition, the anaesthetics used at the doses administered are thought to have relatively limited effect on cerebral pressure autoregulation (Dagal and Lam, 2009) in general, and
imply that the autoregulatory reflex seen during carotid cross-clamping described by McCleary et al. is not dependent on the usual response of the brain to changes in cerebral perfusion pressure.

Impaired CA seemed to have little influence on the intraoperative pattern of MAP or MCAV. In addition, there was no correlation between impaired CA as measured by the tilt-testing with CVR as measured by rebreathing, and no patient with impaired CVR also had impaired CA. This may be related to the measurement of a different autoregulatory pathway by each technique or due to a limitation of the method for assessment of CA. There is no suggestion from these data which it is, although the changes seen for the combined group (i.e. overall improvement after surgery) would suggest that a physiological parameter is indeed measured. Perhaps the threshold for determining impaired CA is too generous, classifying too many patients as ‘impaired’. Further, it is increasingly understood that a finite gradient for the relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) is not pathological (Lucas et al., 2010). The traditional concept of the CA with a plateau in CBF for the physiological range in CPP (see figure 1.4.2) as described by Lassen (1959) has been criticised, since his data were derived from pooling of data points from individual patients rather than assessing the trend from each patient and it is argued that a plateau in the relationship between CBF and CPP as classically described would require feedback mechanisms which are not physiologically possible (Panerai et al., 1996).
While the average response of patients with impaired baseline CA and CVR was in the direction stated above, some patients with intact autoregulation and CVR showed deterioration in these parameters postoperatively (6 for CA and 3 for CVR). None of these patients had TCD or clinical evidence of hyperperfusion or any other clinical adverse event, and this finding was unrelated to anaesthetic method. The reasons for this variability are not clear from these data, but possible explanations may be the influence of the pattern of the collateral circulation, autonomic dysregulation or disordered baroreceptor function. It would seem unlikely that acute postoperative occlusion due to thrombosis would have occurred in the absence of any clinical symptoms, but this was not explicitly sought, especially given the fact that calculations of CVR and CA were conducted off-line and did not impact on the clinical management of patients. A further examination of the patients at a later time point might have been helpful to evaluate the time course of this deterioration and assess whether there was subsequent return to normal patterns.

In contrast with previous work from this unit (Wijeyaratne et al., 2009), no differences between GA and LA for S100β and NSE were identified. In addition, changes in S100β and NSE were not influenced by baseline impairment in CA or CVR. However, the S100β data does correlate well with studies showing transient elevation during clamping (Godet et al., 2001, Di Legge et al., 2003) and implying transient increased in permeability of the blood-brain barrier without development of overt neurological symptoms (Sahlein et al., 2003, Jaranyi et al., 2003, Aleksic et al., 2007). This suggests that the transient increase in blood-brain barrier permeability is not affected by the state of baseline autoregulation impairment, nor is restoration of
flow injurious in most patients with impaired baseline CVR despite the
haemodynamic differences compared to those with intact CVR.

The present study is also consistent with the finding of others (Sahlein et al., 2003,
Jaranyi et al., 2003, Aleksic et al., 2007) that jugular and peripheral s100b levels
differ and that subtle changes are best measured from the jugular bulb. What it does
not do is explain the clinical significance of these elevations, as there were no
adverse events in the present group, and previous studies have been conflicting
regarding the clinical implications of these elevations.

Changes in NSE were more difficult to interpret, particularly the raised values at
baseline with a subsequent intraoperative drop. This finding is not dissimilar to that
reported by Brightwell et al. (2007), although predominantly for patients undergoing
carotid artery stenting with a less marked trend in the same direction for patients
undergoing CEA. Rasmussen and colleagues (2000) found a similar pattern for
patients undergoing uncomplicated CEA. It is possible that baseline cerebral injury
related to carotid stenosis exists which is ameliorated by restoration of normal blood
flow, and that this is reflected in the drop in NSE levels, but the data do not offer a
reasonable physiological explanation for this finding. It must be considered that
there may have been an unrecognised fault in sample processing; it is known that
NSE levels are particularly sensitive to haemolysis, and although this was not
grossly evident in our samples, it may be that spectroscopy of serum samples to
detect haemolysis prior to processing (Gao et al., 2000) would be appropriate for
future NSE studies in order to avoid concern regarding falsely elevated NSE levels.
4.2 Limitations of the present study

The main factor limiting this study was the small size of the patient groups, which was constrained in part by the recruitment target set by the Research and Ethics Committee; based on the initial power calculation, the original proposal had been to study 60 patients in total. Recruitment was also hampered by patient preference for LA leading to fewer GA patients available for study – this seemed to be impact on GALA Trial recruitment as well (personal observation). Further, there were few adverse cerebral events in the studied group: only one patient exhibited hyperperfusion on TCD criteria after the end of surgery, but was asymptomatic. Given the reported incidence of cerebral hyperperfusion of near 10% (Dalman et al., 1999), one might have expected more patients with >100% MCAV increase postoperatively.

In general, patients undergoing CEA are heterogeneous with differing presenting symptoms and degree of contralateral carotid disease. As far as the present GA vs. LA comparison is concerned the groups were well matched for baseline characteristics so it is less likely that a significant difference would be confounded by these factors.

A factor concerning heterogeneity in the study population is the timing of surgery from the last presenting neurological event. This information was not routinely collected in this study as the importance of timing of CEA in relation to outcome (Naylor, 2007) was not widely understood when this study was conceived. However, a separate audit of patients undergoing CEA at the LGI towards the end of
the study period (Dellagrammaticas and Gough, 2006) indicated that patients underwent surgery at a median time of 63 days and this is thus likely to represent the timeframe for surgery for the patients for the present study.

A further source for heterogeneity of the studied population may have been the state of the collateral supply from the circle of Willis for which considerable anatomic variation exists (Hoksbergen et al., 2000). In addition, it is possible that intracranial basal cerebral artery stenoses could have co-existed with extracranial carotid disease. The variation in these characteristics may explain in part the observation that despite the observed overall trend in favour of improvement of autoregulatory reflexes, some patients showed deterioration in both CA and CVR postoperatively.

Two methods could have been used to inform this further, of which one had been intended when this study was conceived:

First, complete mapping of the circle of Willis could have been conducted using TCD at the first preoperative assessment. Given the number of routine preoperative assessments and additional research examinations required, and that patients were all admitted the previous afternoon for surgery the following morning, such a detailed examination was not practically possible.

Second, the anatomy of the circle of Willis could have been demonstrated with magnetic resonance (MR) angiography and perfusion-MR could have provided information regarding regional cerebral blood flow after surgery, which would have been complementary to the TCD examinations. A further factor which could have been addressed by MR would have been the presence of subclinical cerebral injury using diffusion-weighted MR imaging.
MR examinations were part of the original study protocol but were abandoned after several patients refused to undergo MR examinations in addition to the TCD examinations and blood sampling. Further, MR protocols *circa* 2005 when this research was conducted were significantly more time consuming and this added to patient reluctance. It should also be borne in mind that many of these subjects were already participating in the GALA Trial as well as other studies of carotid plaque characterisation, so the reluctance to undergo more unpleasant examinations can be understood.

Given previous studies suggesting changes in S100β and NSE associated with CEA and anaesthetic method, it was anticipated that the chosen serum markers of cerebral injury might have been effective as surrogate markers; in fact they showed no significant changes in relation to changes in cerebral haemodynamics other than the documented transient rise in S100β during cross-clamping of the carotid arteries. This may of course imply that no cerebral injury occurred, and the clinical outcomes of our study group would support this. Practical problems such as the loss of samples due to freezer failure could not have been predicted and may also have played a significant part in not detecting significant differences in these biomarkers.

For studies of the impact of cerebral haemodynamic parameters a different marker may be necessary. This could be serum malondialdehyde or malondialdehyde-modified low-density lipoproteins, which are products of lipid peroxidation due to damage caused by free radicals generated due to ischaemia-reperfusion injury (Soong et al., 1996). Some work has shown association of malondialdehyde with hyperperfusion (Suga et al., 2007), as well as the mitigation of hyperperfusion.
syndrome with pretreatment with edaravone (Ogasawara et al., 2004a, Kobayashi et al., 2007), a free-radical scavenger.

A point of protocol that deserves consideration is the assessment of the impact of MAP on testing of CVR. Several authors have proposed that CVR measurement can be confounded by changes in MAP during testing (Dumville et al., 1998, Hetzel et al., 1999). This concept can be explained as maximal cerebral vasodilatation may occur in response to hypercapnia and thus cerebral blood flow becomes pressure-passive (Battisti-Charbonney et al., 2011). Elevation of MAP during this time therefore could result in CBF increases beyond the level accounted for by hypercapnia, thus underestimating the degree of impairment of CVR. The method for adjusting for MAP is a matter of debate; proposals range from assessment of cerebrovascular resistance [CPP/CBF ratio] (Serrador et al., 2006) to more complex statistical calculations involving multiple linear regression analyses (Dumville et al., 1998). In this study analyses were performed both with and without taking into account changes in MAP during CO2 reactivity, in order to examine the impact of changes in MAP but also to assess changes in a more comparable format to previous description of CVR changes (i.e. % change of MCAV per kPa) for which criteria for normal and impaired responses are better described.

Calculation of cerebrovascular resistance was chosen as a means to account for MAP changes. This was partly due to the obvious simplicity in calculations, but mainly as more complex statistical modelling with the relatively few available data points correlating MAP and MCAV would have lacked statistical power, as it was not technically possible to collect a larger number of data points from continuous MAP.
data during CVR testing (vide infra). As far as comparison between GA and LA was concerned, neither analysis methods showed a difference between the anaesthetic methods. Further, the indices for CVR and CVRes were strongly correlated. It would seem therefore that whilst an effect of MAP cannot be confidently excluded, its impact was limited in this study population.

The use of linear analysis for calculation of the CVR index could be criticised. The relationship between CBF and arterial PCO$_2$ has been described as a sigmoid curve rather than as a linear relationship (Battisti-Charbonney et al., 2011). This would indeed make physiological sense: if CVR is dependent on the change of calibre of cerebral arterioles then there will be a limit beyond which further vasodilatation or vasoconstriction is not possible. However CVR testing in the present study was conducted within the ‘physiological’ range with a sub-maximal stimulus (end-tidal CO$_2$ of ±7 mmHg from baseline) and not the extremes of reactivity to CO$_2$. This should lie within the linear part of the relationship between CBF and CO$_2$ (Brian, 1998), and thus linear regression seems reasonable.

Further, there was no control group in this study to derive normal values for CA and CVR indices from a healthy population using the same protocols used to study patients undergoing CEA, and therefore the criteria used to classify impaired vs. intact CA and CVR were derived from the literature [see sections 2.3.2 and 1.4.5(ii) respectively]. This clearly limits the strength of observations relating to the dichotomous classification of ‘intact’ vs. ‘impaired’ autoregulatory reflexes. Since this study was primarily aiming to compare GA vs. LA, a control group was not considered a priority; the speed of improvement of autoregulatory reflexes was not an anticipated finding and would warrant further evaluation. An additional factor which must be acknowledged is that assessment of reproducibility of the tests of CA
and CVR was not undertaken for the present study; this was because these tests were derived from protocols in routine use in the cardiovascular physiology laboratory at the Leeds General Infirmary, and were supported by the published literature (see methodology). Nevertheless the differences in detail of the protocols used for the study population described here may be sufficient to introduce some concern regarding reproducibility and thus confound the interpretation of the present findings.

The intraoperative systemic and cerebral haemodynamic data are consistent with previously reported findings. However they are limited in that they represent fairly short periods of the whole operation and thus lack sensitivity to detect transient or more subtle changes, and can give no accurate data regarding the state of cerebral autoregulation during surgery. Continuous intraoperative data obtained for some patients were of sufficient quality for the full duration of surgery, and thus are suitable for more detailed scrutiny (see directions for further research).

Finally, data regarding embolic events was not routinely collected although monitoring for obvious intraoperative embolic events was undertaken. This was intentional. In order to maximise the collection of haemodynamic data, maximum gain settings were used and this interfered significantly with the emboli detection algorithms of the TCD equipment. Given that there were no adverse neurological events it could be argued that significant embolisation did not occur, but clearly the possible impact of clinically silent microemboli cannot be evaluated.
4.3 Implications for clinical practice

The main implication for clinical practice is that postoperative cerebral autoregulatory reflexes are unlikely to be influenced by the mode of anaesthetic used. Since both CA and CVR improve rapidly following surgery in the presence of preoperative impairment of these parameters, and that for the remainder there is no overall change, it would seem that management of systemic haemodynamics (hyper- or hypotension, bradycardia) can be undertaken without undue concern for the cerebral circulation in the absence of symptoms of cerebral hyperperfusion. However, it should be borne in mind that a few patients may show deterioration in cerebral autoregulatory reflexes and thus caution is still required.

In terms of identifying patients at risk of postoperative hyperperfusion, assessing static CA by means of tilt-testing does not seem to be particularly useful. Although the improvement seen post-CEA suggests that a true physiological change was measured, it was not associated with any other significant systemic or cerebral haemodynamic changes either intra- or postoperatively.

On the other hand, the testing of CO₂ reactivity may be useful in stratifying patients at risk of cerebral hyperperfusion against those not. Whilst no clinical manifestation of hyperperfusion was seen, patients with impaired CVR had significantly higher MCAV following carotid declamping; thus the present study does not contradict the findings of previous work correlating impaired CVR with the risk of hyperperfusion (Hosoda et al., 2001, Ogasawara et al., 2003b). Patients with impaired CO₂ reactivity may be then subjected to more intensive monitoring or aggressive management of systemic blood pressure, whilst those with intact baseline CVR
might be safe to return to a general ward. However, there clearly are other factors which contribute to CHS about which this study cannot offer further insight. Given that the specificity of our protocol would seem rather low for detecting patients who might develop persistent hyperperfusion, it may be that a more simple screening protocol such as assessing CVR using the breath-holding index (Soinne et al., 2003) may be more useful. Although specificity would not necessarily be better, it would have the advantage of being easier to administer with the requirement of no equipment other than the TCD monitor, and would permit instant calculation of a measure of CVR.
4.4 Implications for further research

As discussed above, patients with carotid disease are a heterogeneous group and therefore it would be useful to assess haemodynamic changes in groups which are better matched or in whom the pattern of contralateral carotid disease and the anatomy of the basal cerebral arteries are well characterised. Current recommendations for carotid imaging recommend ultrasound as a screening assessment followed by confirmatory imaging with MR or CT angiography (Gough, 2011) and therefore such data would be more readily available. Both these modalities would demonstrate the anatomy of the collateral cerebral blood supply. This may permit the translation of cerebral haemodynamic research into ‘real world’ settings, but it is recognised that the anatomical pattern of collateral blood flow does not always correlate with the functional collateral blood supply in the presence of carotid stenosis. Functional brain imaging to assess regional cerebral perfusion [perfusion MRI (van Laar et al., 2008) or SPECT (McArthur et al., 2011)] would provide better information on these parameters.

Although no difference in postoperative CA or CVR between GA and LA was found, this does not mean that the modes of anaesthesia have the same effect on the cerebral circulation during CEA; as mentioned, the differing effects of the two anaesthetic methods favouring LA in preserving cerebral oxygenation have been shown by McCleary et al. (1996). Multilevel regression modelling or transfer function analysis has been used to assess dynamic cerebral autoregulation parameters, and some of the data for the patients from the present study together
with data from patients undergoing routine intraoperative monitoring from this institution is currently the subject of such statistical analysis. Preliminary unpublished data suggest that autoregulation is better preserved with LA.

In the preoperative and postoperative periods, assessment of the state of cerebral autoregulation can be achieved by means of analysis of beat-to-beat variation of MCAV and MAP. The latter can be assessed continuously non-invasively using the Peňáz method [volume-clamp assessment of finger pressure – for review see Bogert and van Lieshout (2005)], which is currently used in the Finometer® system (Finapres Medical Systems B.V., Amsterdam). This was also intended in the present study, however our obsolete Ohmeda Finapres monitor (the predecessor to Finometer®) failed early in the study and was not replaced due to considerations of cost.

These methods are well described (Hu et al., 1999, Haubrich et al., 2004, Simpson et al., 2001), seem to provide good correlation with other tests of cerebral autoregulation and may be better tolerated by patients particularly in the postoperative period. In addition they do not require the induction of haemodynamic challenges (infusion of vasopressors, rapid thigh-cuff release or carotid compression) which would be undesirable in the setting of CEA. The main disadvantage is the requirement for sophisticated mathematical analyses which limit the usefulness of such techniques for the clinical setting (Bellapart and Fraser, 2009).

Baroreceptor dysfunction associated with carotid stenosis has been associated with haemodynamic lability following carotid surgery (Bove et al., 1979, Nouraei et al., 2005). Testing of cerebral autoregulation using spontaneous MCAV and MAP
fluctuations could be combined with testing of baroreceptor function as described by Mense et al. (2010) and may provide further insight to the pathophysiology of the development of cerebral hyperperfusion.

In conclusion, the study of cerebral haemodynamic changes remains problematic, regardless of the clinical setting: there is little consensus regarding a gold standard for measuring cerebral autoregulatory mechanisms or the criteria for assessing their function as intact or impaired. When the effect of intra- or extracranial disease is considered together with the effects of cerebral ischaemia or infarction, this complexity can only increase. Until a better understanding of the complexity of the cerebral circulation is achieved, interpretation of cerebral haemodynamic tests will remain challenging.
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198


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