Summary and discussion

The beneficial effect of CEA depends on several surgical and patient related factors. Ultimately, the risk for a new cerebrovascular event must be balanced against the risk of perioperative morbidity and mortality and to date there is increasing consensus for basing the decision to operate or not on a mathematical model. The number needed to treat and the number needed to harm are common concepts in medical practise.
For an optimal result the surgical risk of CEA must be as low as possible, as it will be clear that the benefit of CEA decreases as the operative risk increases. Outcome of CEA must therefore be monitored to justify the procedure and possible surgical risk-bearing aspects should be eliminated. Consequently, vascular trainees starting to perform carotid surgery and with hardly any experience in CEA, should have comparable and favourable outcome and results as in published prospective trials and these were described in the addendum of this thesis.
Risk analyses, however, have shown, that even in the most favourable situation of a 30 days operative risk of 0%, there are still patients, who will undergo surgery, but who would never develop a future stroke even without surgery. Further filtering of patients with no or increased risk of future strokes is desirable. New insights in the pathophysiology of carotid artery disease and cerebral perfusion can improve patient selection. One diagnostic tool with the potential to select patients with increased risk of stroke is PET, as it is possible to perform quantitative measurements of cerebral perfusion and metabolism.
However, PET availability is limited, and it is expensive and demands technical support. In the Netherlands, VUmc was the first to start cerebrovascular PET studies using oxygen-15 bolus technique. $H_2{}^{15}O$, $C^{15}O$ and $^{15}O_2$ were used to measure CBF, CBV, OEF and $CMRO_2$. Initial experience together with results of cerebrovascular PET measurements in carotid artery stenosis is described in this thesis.

Chapter 2 reviews the known facts about asymptomatic carotid artery stenosis and current thinking about the question whether to operate or not. In addition, suggestions are made how patient selection could be improved in the future. The main findings were:

- To prevent 1 future stroke, the number needed to operate is about 20 patients.
- The prevalence of asymptomatic CAS>80% is between 1 and 2%.
- The risk of stroke for asymptomatic CAS>80% is between 1 to 5% per year.
- Screeningsprograms for asymptomatic CAS are not worthwhile.
- There is no consensus about the importance of stenosis progression, silent infarcts and contralateral carotid artery disease with respect to risk of stroke and indication for CEA
- Risk of cardiac related death seems to be higher than risk of stroke
- Plaque morphology and/or instability and cerebral hemodynamics and/or metabolism may contribute to improved patient selection for CEA, but their role

has to be determined.

To date, the benefit of operating an asymptomatic carotid artery stenosis is small and surgery is mainly based on the degree of stenosis and personal view of the vascular surgeon. Refinement in patient selection for surgery is needed by identifying that subset of patients, who have carotid atherosclerosis and increased risk of future stroke, but presently no prognostic markers are available.

In **chapter 3** the correlation between TCD (BFV and CO_2 reactivity) and PET findings (CBF and CBV, MVTT) was investigated in 9 patients with symptomatic carotid artery stenosis before and after CEA. Although velocity (cm/sec) is not the same as flow (cm^3/sec or ml/sec), it is generally accepted that BFV is a reliable index of cerebral perfusion because the calibre of the MCA does not change significantly. Using PET it is possible to test this hypothesis. Instead of two-dimensional regions of interest, PET measurements were performed using three-dimensional volumes of interest corresponding with reconstructed MCA territories. All TCD and PET studies were performed one day preoperatively and the first day postoperatively.

Postoperatively, BFV and CBF were significantly increased on both ipsi- and contralateral sides and it was shown that BFV correlated well with CBF irrespective of side, pre- or postoperative state and the use of total, white or grey matter MCA territories, although preoperative correlations were stronger. No association between CO_2 reactivity and either CBV or MVTT was found.

The correlation between BFV and CBF was only studied in patients with a symptomatic carotid artery disease and after uncomplicated CEA. In patients with other neurological disease, such as subarachnoid hemorrrhage, cerebral vasospasm or increased intracranial pressure, this correlation is less evident according to the literature.

Several comments can be make about this study, as described in the original article. Nevertheless, it is one of the few studies investigating and confirming the assumption that BFV reflects CBF in symptomatic carotid artery disease.

In **chapter 4** it was investigated whether peroperative neuromonitoring techniques were correlated with preoperative PET measurements.

In 10 patients absolute SP, mean SP<40 mmHg, TCD- and/or EEG- changes and selective shunting during CEA were compared with preoperative PET parameters in ipsilateral MCA, ipsilateral hemisphere and whole cerebrum. The following PET parameters were used: CBF, OEF, $CMRO_2$,CBV, MVTT and CPP.

Criteria for shunting: (1) a mean SP <40 mmHg, (2) for TCD a decrease of mean blood flow velocity in the MCA (mBFV-MCA) of >70% after carotid clamping compared to the preclamping mBFV-MCA values ór an absolute mBFV-MCA < 10 cm/sec, (3) and for EEG a diminution or loss of EEG frequency in the alpha and beta activity. Selective shunting was performed when, during clamping, one of these criteria were met, irrespective of the results of the other techniques.

The initial hypothetis was that SP could be correlated with CPP, TCD findings with CBF and EEG changes with $CMRO_2$.
Although some tendencies were noticed for correlations of TCD with CBF in ipsilateral MCA and hemisphere, of TCD with MVTT in ipsilateral MCA, of TCD with CPP in ipsilateral MCA, hemisphere and total brain and of selective shunting with $CMRO_2$ in ipsilateral MCA and hemisphere, none of the PET parameters showed a significant correlation with peroperative neuromonitored findings. It was concluded that, at present, cerebrovascular PET examinations are not useful for predicting the need for shunting during CEA.
It was a remarkable fact that the incidence of shunting (n=6) in this small series of overall 10 patients (60%) was unusually high, compared to literature values (10%). A possible explanation could be that the used threshold of a mean arterial pressure of 70 mmHg during CEA is too low in case of general anaesthesia. In addition, 8 out of 10 patients had a history of hypertension and 5 patients had severe contralateral carotid artery disease. Higher arterial pressures during CEA are recommended by some authors, indeed 10 mmHg higher than baseline systemic pressure [1-3].
Furthermore it can be argued that PET studies in awake patients cannot be compared with neuromonitoring techniques under general anaesthesia. It looks to be a more rational approach to compare preoperative PET results with patients undergoing CEA under local anaesthesia and need for shunting. However blood pressure in patients undergoing CEA under local anaesthesia seems to play a minor role in the decision whether to shunt or not [4].
Of course, it is questionable to know preoperatively whether patients need a shunt or not, but if there had been a strong correlation or cut-off value, preoperative planning becomes more obvious.
Perhaps the role of collaterals should also be included in PET-studies. A combination of MRI or TCCD evaluation of the circle of Willis and PET findings will provide more detailed information about cerebral hemodynamic and metabolic parameters and vulnerability.
Finally, it is likely that cerebrovascular PET studies should not only be performed in a larger number of patients with carotid artery disease, but also in more selected patients with carotid pathology. For example, in patients with symptoms of low-flow states (global cerebral ischemia) and/or in patients with an incomplete circle of Willis, it could be worthwhile to search for areas in the cerebrum that are more susceptible to hypoperfusion, which could actually be evaluated by pre and postoperative PET studies.

Chapter 5 describes hemodynamic changes in CBF, CBV and MVTT, measured with PET, before and after CEA in the three arterial territories on ipsi- and contralateral sides. In 10 patients absolute and relative (ipsi- versus contralateral ratio) values of CBF, CBV and MVTT were assessed one day before and one day after operation.
Although no differences between ipsi- and contralateral sides were found, the mean absolute CBF was significantly increased in all arterial territories postoperatively. For CBV no differences were found and for MVTT only a significant decrease was found in the ipsilateral MCA region after CEA. The ratios of CBF, CBV and MVTT after operation were unaffected,

except that the ratio of CBF increased more in the ipsilateral MCA region (1.06 ± 0.21 versus 0.97 ± 0.15; p=0.02).
This overall absolute increase suggests that all arterial territories, on both ipsi- and contralateral sides will benefit from an operation, although this benefit was highest in the ipsilateral MCA.
The PET findings confirmed results of other studies with TCD, SPECT and MRI, where an increase in CBF after CEA had been shown. In addition, PET showed improved CBF in all arterial territories. There is evidence, however, that hemodynamic changes rely on the time between CEA and perfusion measurement. The initially hemodynamic improvement, early after CEA, will adapt downwards over time but remain higher than the preoperative situation. In future studies, it would therefore be of interest to repeat these PET examinations 3 to 6 months after operation, but patients burden (arterial cannulation, radioactive-labelling, duration PET) should not be taken lightly. Initially these follow-up studies were therefore not included in our study design.

In **chapter 6** an overview is given of PET studies in patients with steno-occlusive carotid artery disease. Changes of hemodynamic and metabolic parameters to a decrease of cerebral perfusion are described.
A Pubmed search was done looking for publications reporting on the role of cerebrovascular PET in carotid artery disease, risk of stroke and PET measurement before and after cerebral revascularisation.
In general, in patients with steno-occlusive carotid artery disease, a decrease in CBF, $CMRO_2$, and CPP and an increase in CBV, MVTT and OEF has described. However there was substantial heterogeneity in reported results, changes were not always significant and effects were most pronounced in patients with carotid occlusion compared to stenotic lesions.
Data concerning risk of stroke and PET were mainly based on 2 studies including 121 patients (113 occlusions and 8 stenotic lesions). In summary the risk of recurrent ipsilateral stroke in patients with increased OEF seems 4 to 8 times higher compared to patients with normal OEF after 1 to 5 years.
After both extra-intracranial bypass (EIAB) surgery and CEA most studies showed an improvement of hemodynamic and metabolic parameters but none of the studies could prove that the risk for (new) cerebrovascular events was decreased after surgery. In addition, differences in PET procedures (absolute values versus ratios, time intervals, data acquisition and data analysis) made comparison of results and interpretation difficult.
A prospective trial (The Carotid Occlusion Surgery Study=COSS) was started in 2003 with the purpose to test the hypothesis that EIAB surgery reduces the risk of ipsilateral stroke and death with 40% [5]. Patients with increased OEF distal to a symptomatic occluded internal carotid artery were included and were randomized to EIAB surgery or medical treatment. It was estimated that 186 patients were needed in each group and about 930 patients had to be enrolled for PET scanning, because only 40% of patients will have increased OEF.

The huge number of patients required for this study and the lack of current evidence that PET examinations can improve patient selection for revascularization makes it clear that there is no place for routine PET examinations in patients with carotid artery disease.

Nevertheless, it can be postulated that, in the future, PET may still contribute to improved patient selection in carotid artery disease for CEA according to two strategies.

First cerebrovascular PET studies should be directed towards a subset of patients with carotid artery disease with a likelihood of cerebral hemodynamic or metabolic disturbances. This subset not only includes patients with symptoms of 'low-flow-states' but also patients with bilateral carotid artery disease. In these patients PET should be used to 'search' for areas of increased susceptibility to ischemia or 'low flow' or 'hypoperfusion'.

Although it is believed that carotid artery stenosis < 80% will have no hemodynamic effect, it is also assumed that absence of collateral circulation might play a role in ischemia [6]. Findings from other diagnostic cerebral investigations (MRI, TCD,TCCD) must be combined with PET studies. For example; white matter lesions (centrum semiovale) on MRI were correlated with PET abnormalities in the ipsilateral hemisphere suggesting hemodynamic compromised circulation [7]. Also more information is needed about normal values of the anatomical structures of the brain and regional differences in tissue fractions of grey and white matter [8].

A second application of PET could be identification of high risk plaques. High risk plaques for embolisation are characterized by inflammation and increased levels of matrix metallo proteinases (MMP). With FDG PET inflammatory carotid plaques can be visualized and this could be used as a possible marker for the risk of stroke although prospective studies are needed [9-11]. With the use of a radiolabelled MMP inhibitors, MMP activity in atherosclerotic disease can be imaged more specifically [12].

The prognostic value of all these PET applications in selecting high risk patients for intervention, thus preventing cerebrovascular events is promising, but still tentative.

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