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Torbjørn Dahl

Carotid artery stenosis

Diagnostic and therapeutic aspects

Doctoral Thesis

NTNU
Norwegian University of
Science and Technology
Thesis for the
degree philosophiae doctor
Faculty of Medicine
Department of Circulation and Medical Imaging

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Innovation and Creativity

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Trondheim, May 2007

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Content

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List of papers

This thesis consists of the following publications, which will be referred to by roman numerals:

I Bang J, Dahl T, Bruinsma A, Kaspersen, JH, Hernes TAN, Myhre HO. A new method for analysis of motion of carotid plaques from RF ultrasound images. Ultrasound in Med. & Biol., 2003;29:967-976

II Dahl T, Bang J, Ushakova A, Lydersen S, Myhre HO. Parameters describing motion in carotid artery plaques from ultrasound examination: A reproducibility study. Ultrasound in Med. & Biol., 2004;30:1133-1143

III Dahl T, Rudjord K, Altreuther M, Myhre HO. Data quality of surgery for carotid artery stenosis. Are the national vascular registries reliable? Eur J Vasc Endovasc Surg 2006;31:381-385

IV Dahl T, Aasland J, Romundstad P, Johnsen HJ, Myhre HO. Carotid endarterectomy. Time-trends and results during a 20-year period. Int Angiol 2006;25:241-248

V Dahl T, Cederin B, Myhre HO, Indredavik B. The prevalence of carotid artery stenosis in an unselected hospitalized stroke population. Submitted for publication

Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
AF	Amaurosis Fugax
BMT	Best Medical Treatment
CAS	Carotid Artery Stenting
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
CT	Computer assisted Tomography
DRG	Diagnosis Related Groups
DUS	Duplex Ultrasound Scanning
ECA	External Carotid Artery
ECST	European Carotid Surgery Trial
ICA	Internal Carotid Artery
MRI	Magnetic Resonance Imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NorKar	Norwegian Vascular Registry
NPR	Norwegian Patient Register
RCT	Randomised Controlled Trial
TIA	Transient Ischaemic Attack
TCD	Transcranial Doppler
RIND	Reversible Ischaemic Neurologic Deficit

Introduction

Stroke is a disease with a sudden neurological deficit attributable to a focal vascular cause. It is estimated that about 16000 people in Norway suffer a stroke each year, and in addition about 5000 people experience a transient ischaemic attack (TIA) (Indredavik 2001). Although the exact cause of stroke cannot always be established (Warlow et al 2001), we assume that about 80% of all strokes are thromboembolic of origin (Indredavik 2001). The origin of emboli can be the heart, aortic arch or precerebral vessels. The precerebral arteries may be responsible in up to 20% of the cases (Bamford et al 1991). For a long time, stroke was attributed to intracranial vascular disease alone. However, reports on ulcerating plaques in precerebral arteries, emboli formation and subsequent cerebrovascular insufficiency in addition to the technique of cerebral angiography initiated the surgical treatment of carotid artery stenosis for the prevention of stroke (Thompson 1993).

Carotid artery stenosis and cerebrovascular ischemic events

A carotid artery stenosis may be termed symptomatic if cerebrovascular events in the artery's territory have occurred, and asymptomatic if no such event has occurred during the last 6 months (ACAS 1995, ACST 2004). Emboli from the carotid arteries may cause transient monocular visual loss (amaurosis fugax, AF), speech disorders or hemimotor or hemisensory signs. Patients with focal cerebral ischemia have been divided into clinical subgroups, according to the duration of their symptoms. The terms transient ischaemic attack (TIA), crescendo TIA , reversible ischaemic deficit (RIND) and completed stroke have been used. A patient with a TIA should be fully recovered within 24 hours, while a RIND could last up to one week and a completed stroke would leave the patient with a permanent neurologic deficit. Attempts to develop a more precise terminology have been made by Baker (1988). In a recent paper from The American Heart Association/American Stroke Association Council on

Stroke, it was stated that the distinction between TIA and ischemic stroke has become less important, since many of the preventive measures are useful for both patient groups (Sacco et al 2006). Traditionally, patients with focal neurological deficits lasting less than 24 hours are diagnosed as having had a TIA, while deficits lasting longer than 24 hours will be referred to as a stroke. Due to new imaging techniques, brain infarcts can be discovered earlier and this may lead to yet another classification. An ischemic stroke may be classified according to the presumed mechanism of brain injury and the type and localization of the vascular lesion. (Bamford et al 1991, Adams et al 1993, Sacco et al 2006). The so-called TOAST-classification describe five subgroups of ischemic stroke according to etiology; large-artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other undetermined etiology and stroke of undetermined etiology (Adams et al 1993).

TIA may be regarded as a harbinger of a stroke. The severity of the initial symptom seems to be related to the subsequent risk of stroke. Thus, a patient suffering a TIA will have a greater chance of developing a stroke compared to one only having experienced temporary visual loss (Wilterdink et al 1992). A resulting stroke may be described as disabling or non-disabling (Bamford et al 1991). Several scales and definitions describe the functional impairment after stroke, but a modified Rankin scale has been widely accepted (Rankin 1957, Sulter et al 1999, Halliday et al 2004) (Table 1). A patient with a grade 0 to 2 according to the modified Rankin scale can be characterised as having had a non-disabling stroke, whereas a grade 3 to 5 is regarded as a disabling stroke.

Studies on the natural history of patients with an asymptomatic carotid artery stenosis, have indicated that their risk of having a stroke was small, in the range of 1 to 4 % annually (Chambers et al 1986). Correspondingly, there is no uniform agreement on the benefit of screening for carotid artery stenosis (Roederer et al 1984, Hankey 1995). During the Asymptomatic Carotid Surgery Trial (ACST), it was recognized that 211 (19%) out of a total

of 1142 patients had a silent cerebral infarction on computer assisted tomography (CT) ipsilateral to their asymptomatic carotid artery stenosis (Robless et al 1998). Some authors consider this to be a sign of previous or ongoing embolisation, leaving the patients with a higher risk of symptoms at a later stage.

Table 1

The modified Rankin scale (Rankin 1957, Sulter et al 1999)

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

Imaging

Traditionally, the carotid artery was investigated by angiography. Intra-arterial angiography was considered mandatory before carotid endarterectomy was performed (Cairols 1995). The angiography itself, however, may cause stroke in 0,45-1,2% of the patients (Dean et al 2001, ACAS 1995). In the early 1980's, the ultrasound doppler technique permitted non-invasive investigation of the carotid arteries. The simple Doppler technique was gradually replaced by duplex ultrasound scanning (DUS) where B-mode imaging, colour blood flow and Doppler velocity measurements were combined (Zwiebel 1992). Due to improvement in this

technique, some surgeons based the indication for surgery on clinical symptoms and ultrasound images alone (Loftus et al 1998). In a Norwegian survey from 2002, only 30% of the departments used intra-arterial angiography on a regular basis before carotid endarterectomy (CEA) (Dahl et al 2006). Many surgeons would prefer to use magnetic resonance imaging (MRI) if there is doubt about the grade of stenosis or the distal anatomy of the internal carotid artery (ICA). In the future, both MRI and CT-angiography could play a greater role in the evaluation of these patients (Norris et al 2004). The beneficial effects of carotid surgery have been related to the preoperative grade of stenosis as evaluated by angiography (ECST 1991, NASCET 1991). By comparing DUS and intra-arterial angiography, threshold values for stenosis could be established. (Cairols et al 1995). However, there are several types of velocity criteria to classify the carotid artery stenosis by DUS (Zwiebel 1992), and it has been recommended that each individual vascular laboratory establish its own criteria (Curley et al 1998, Byrd et al 1998). An irregular surface or ulceration of the carotid plaque as seen in angiography, may leave the patients at high risk of embolisation (Rothwell et al 2000). DUS has been used to characterize the lipid content of the carotid plaque as echolucent or echogenic areas (Langsfeld et al 1989). The echolucent or lipid-rich plaques seem to be more prone to embolisation. The relation between an echolucent plaque in asymptomatic patients, and subsequent risk of stroke is yet to be determined (Groenholdt et al 2001, Mathiesen et al 2001). Other authors have found a high risk of embolisation associated with heterogenic plaques on DUS (AbuRahma et al 2002).

Treatment of carotid artery stenosis

Carotid artery stenosis is considered a marker of generalised atherosclerotic disease (Ogren et al 1995). A majority of the patients with carotid atherosclerosis also have atherosclerotic manifestations in the coronary arteries and the arteries of the lower limbs. The general treatment of these patients must be directed towards the treatment of common risk factors for atherosclerosis, like hypertension, diabetes, hypercholesterolemia and smoking (Antiplatelet Trialists' Collaboration 1988, Heart Protection Study Collaborative Group 2002).

First of all, aspirin or another platelet aggregation inhibitor should be given. Usually, the addition of a statin to lower the patient's cholesterol would be indicated. Medical therapy to reduce the stroke risk in patients with carotid artery stenosis has been intensified over the years, and was not fully utilised during the large studies on CEA in the early 1990's (Sacco et al 2006). Medical treatment alone however seems to be inferior to surgical removal of the carotid plaque in certain patient groups (Naylor 2004).

As previously stated, there is a risk that TIA or AF is followed by a stroke. When TIA or AF event is recognised, surgical treatment for carotid artery stenosis may prevent a subsequent stroke. For symptomatic patients with carotid stenosis of more than 70% diameter as described by the NASCET-method, there is a significant benefit of CEA over medical treatment alone. Rothwell et al (2004) found that in male symptomatic patients, the benefit of CEA over best medical treatment alone is also present when the stenosis passes 50% diameter reduction. However, this beneficial effect of surgery is dependent on the interval between the cerebrovascular event and surgery, as the preventive effect gradually declines. Coexisting diseases may alter the beneficial effects of CEA in favour of medical therapy (Sacco et al 2006). CEA, either as a conventional endarterectomy or by the eversion technique, has been the "Gold Standard" in the invasive treatment of carotid artery stenosis (Zarins 1996).

Parallell to the development of endovascular techniques in other areas of vascular surgery, a new technique of balloon angioplasty and stenting has emerged (CAVATAS investigators 2001). This technique is considered to be less invasive and less traumatic to the patients, and the risk of peripheral nerve injury is minimized (Coward et al 2004). This might be advantageous for patients with a history of previous neck surgery, irradiation or those with a distal or recurrent stenosis (Veith et al 2001, Sacco et al 2006). Carotid artery stenting (CAS) and CEA have performed equally well in some randomised controlled trials, but the results after surgery in these studies have been inferior to other studies (Archie 2000, CAVATAS investigators 2001, LaMuruglia et al 2004,Yadav et al 2004). Also, it has been concern about the increasing number of various specialists who take on carotid artery stenting with inappropriate indications for treatment (Beebe et al 1996, Narins et al 2006).

Surgical treatment

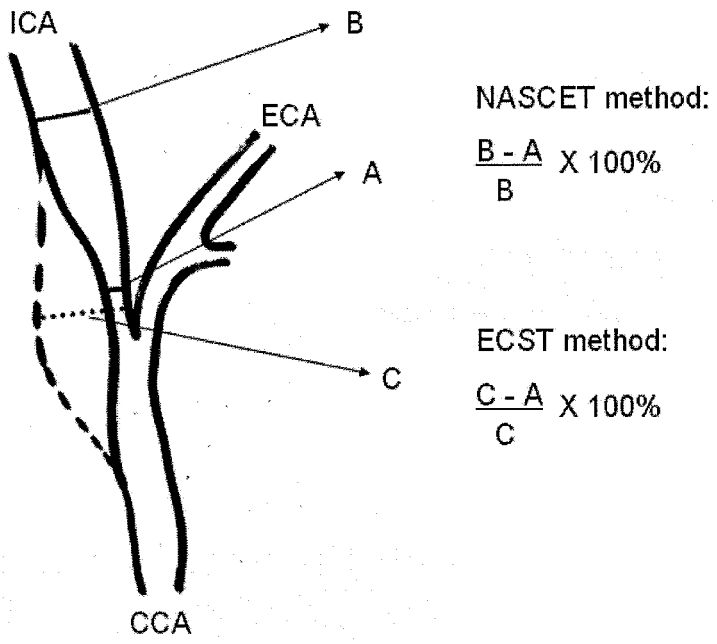
Symptomatic carotid artery stenosis

DeBakey performed the first endarterectomy of a carotid plaque in 1953, and this relieved the patient's symptoms, but was not reported until 22 years later (DeBakey 1975). In 1954, Eastcott and colleagues performed a resection of the carotid bifurcation and then direct arterial anastomosis in a woman with recurrent, transitory ischaemic attacks (Eastcott et al 1954). The TIA's disappeared, and this operation initiated an increasing number of procedures, especially in the US, where carotid endarterectomy eventually became the most common peripheral vascular operation (Thompson 1993). However, the number of procedures declined, as it was shown that some hospitals had an unacceptable high rate of perioperative strokes (Barnett et al 1984, Tu et al 1998). The procedure itself caused the disease that it was supposed to prevent. This lead to two large, randomized controlled trials where patients with carotid stenosis and cerebrovascular symptoms received the current best medical treatment (BMT) plus CEA or BMT alone, respectively. In 1991 the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) were published. These two studies defined the subgroups of symptomatic patients with carotid artery stenosis that would benefit most from surgical treatment. The selection of patients was based on the degree of stenosis as shown by intra-arterial angiography. Although the grading of stenosis was different in the two studies (Fig. 1), the benefit of surgery was confined to patients with a certain degree of stenosis, more than 70% diameter reduction in NASCET and more than 80% in ECST respectively. Patients with stenosis of less than 50%, however, were better off with medical treatment alone, whereas the effect of CEA in patients with a stenosis in the category 50-69% still is uncertain, although male patients operated upon close to the event seem to benefit (Cina CS et al 2000, Rothwell et al 2004) Subgroup analyses in the two

studies have defined other variables that contribute to the beneficial effects of surgery in terms of sex, initial symptom and timing of surgery (Rothwell et al 2004, Sacco et al 2006).

Figure 1

Different measurement of stenosis according to NASCET and ECST by angiography



Asymptomatic carotid artery stenosis

Over the years, several vascular surgeons have offered carotid endarterectomy to patients with asymptomatic carotid artery stenosis. This has been most apparent in the US, while European surgeons were reluctant to this indication for CEA (Naylor 2004). In 1995, the Asymptomatic Carotid Atherosclerosis Study (ACAS) was published. This study showed that the stroke rate in patients undergoing carotid endarterectomy was reduced by 50% compared to medical treatment alone (ACAS 1995). The absolute risk reduction was small, however – from 2% stroke annually with medical treatment alone compared to 1% stroke after medical treatment and surgery in combination. The stroke/mortality rate after surgery was 2,8%, and 1,2% of the strokes were caused by the preoperative carotid angiography. This study supported in some way the American strategy for the treatment of patients with asymptomatic carotid artery stenosis. However scepticism about the patient selection made the European vascular surgeons reluctant to do CEA in these patients on a regular basis (Naylor 2004). In 1993, a European randomised controlled trial (RCT) between BMT alone, or BMT in combination with CEA in patients with asymptomatic carotid artery stenosis was started. In 2004, the results of The Asymptomatic Carotid Surgery Trial (ACST) was published, confirming the ACAS-results from 1995 (Halliday et al 2004). The projected benefit of carotid endarterectomy and best medical treatment over best medical treatment alone during a 5-year period was 6,4% stroke/mortality rate in the surgical group and 12,3% stroke/mortality rate in the medical group. Presumably, ACST is more representative of the general vascular surgical practice in European Centers. In ACST, it is concluded that patients under 75 years, irrespective of gender, with a carotid stenosis of more than 60% diameter reduction, have a more effective stroke prevention after BMT plus CEA than after BMT alone. This benefit may be even greater over the years, and the 10-year results from the ACST study are awaited. In spite of the positive effect of surgery confirmed by the ACST study, the absolute risk

reduction of surgical treatment for asymptomatic carotid artery stenosis is still small. We need information on the patients who are at highest risk for embolization from their carotid plaques (Chambers et al 2005).

Monitoring of surgical results and the use of registers

CEA is a preventive operation, and a high complication rate would easily eliminate the benefit of the treatment. Despite of a stroke/mortality rate of 5,8 - 7,5% in the two large symptomatic carotid artery stenosis trials (ECST, NASCET), CEA has been proven to be of benefit. Recommendations for acceptable surgical results according to presenting symptoms have been given as guidelines from the American Heart Association (Moore et al 1995). Many have argued that CEA should be centralised to large hospitals where each surgeon could get a higher number of procedures. A Finnish study concluded that the surgeons performed better if they did more than 10 carotid endarterectomies a year (Kantonen et al 1998). Some of the large American studies have investigated the number of perioperative deaths after CEA in low-volume and high-volume hospitals. Although high volume hospitals have a significantly lower mortality, the difference is relatively small and postoperative death is a very rare event anyway (Birkmeyer et al 2003). The results from each hospital should be compared with other hospitals by reporting to a central vascular registry, like the Norwegian NorKar, the Swedish SWEDVASC, the Finnish Finnvasc or the Danish Karbase (Troeng et al 1992, Jensen et al 2000). In SWEDVASC, it has been recommended that the results of the last 50 operations should be considered as representative for the performance of the vascular surgery department (www.swedvasc.se). The Norwegian Vascular Registy (NorKar) was established in 1996, and after some years of practice, approximately 80% of the total number of vascular surgical procedures in Norway are reported to the register (III). However, the interest for the register has varied widely among the different hospitals, and there has been

doubt about the completeness of the data. Suggested standards for different vascular procedures have been discussed by the members of the Norwegian Society for Vascular Surgery.

Study objectives

Paper I

The aim was to develop a 2D ultrasound method to describe the motion pattern of a carotid artery plaque during the heart cycle.

Paper II

The purpose of this study was to investigate the reproducibility of the ultrasound method described in paper I, and to investigate which motion pattern would reproduce well between patients, number of ultrasound examinations and number of heart cycles.

Paper III

The aim of this study was to validate the Norwegian Vascular Registry (NorKar) in terms of completeness for number of carotid endarterectomies and in-hospital postoperative stroke/mortality rate compared to an official administrative register, the Norwegian Patient Register (NPR).

Paper IV

The aim of this study was to describe the stroke/mortality rate within 30 days of surgery in our own hospital over a 20 year period. Secondary aims were registration of other postoperative complications, technical details of CEA and pre- and postoperative treatment of patients with carotid artery stenosis.

Paper V

The aim of this study was to investigate the number and degree of carotid artery stenoses in patients admitted to a stroke unit, and the possible association between the stenoses and the relevant cerebrovascular lesions.

Material and methods

Paper I

On the day before scheduled carotid endarterectomy, consecutive DUS examinations of six patients were done. The examination was done with a standard ultrasound scanner (GE Vingmed System FiVe, Horten Norway) equipped with a linear 12 MHz probe and by the same scanner operator. In order to analyze the raw data from the examination, a software to extract the radio-frequency (RF) data was installed. First, we performed a standard duplex ultrasound examination to ensure that the carotid artery of interest was patent. The area with the greatest stenosis was identified. This was done on a longitudinal image section. Only the section at the point of maximal stenosis was investigated further. Upon maintaining the probe position, we changed to a radio-frequency (RF) - mode and a scanning sequence was recorded. At the same time, the heart rate was registered with Electrocardiogram (ECG), and displayed on the ultrasound screen. The ECG data were stored with the ultrasound data. Typically, a sequence of three heart beats were recorded, and the carotid plaque motion could be linked to each heart cycle. After transferring the data to a central computer, the recorded sequence was imported in a programme (Matlab version 5.2 on a Macintosh Computer) for analysis. The plaque border was manually outlined on one of the picture frames captured by the analysis tool, and this was done by the scanner operator who performed the initial examination. Subsequently, the different motion parameters were quantified by a frame to frame correlation technique. The motion was calculated relative to a reference area placed below the adventitia adjacent to the base of the plaque.

Paper II

Six patients who were admitted for elective carotid surgery because of a symptomatic, carotid artery stenosis were examined with DUS and motion analysis before the operation. They were compared with six patients with asymptomatic carotid artery stenoses. The subjects in the latter group had participated in the Asymptomatic Carotid Surgery Trial (ACST), receiving best medical treatment only. Up to five consecutive recordings of the carotid plaque region were done, and the probe was repositioned between each examination. We studied the reproducibility of the different motion patterns. A high number of parameters potentially describing plaque motion were investigated. By analysis of the standardized variance, we found that three consecutive recordings over two heart cycles gave a representative sample. A source of error during the ultrasound scanning, could be movement of the examiner's hand and the probe. This rather slow hand movement would probably be outweighed by the high frame rate of the acquisition, and the effect was further diminished by calculating relative to the reference area below the outlined plaque.

Paper III

After permission from the board of The Norwegian Vascular Registry (NorKar), data from member hospitals for the years 2000-2001-2002 were retrieved. We then performed a cross-match of the number of carotid endarterectomies in the Norwegian Vascular Registry (NorKar) with the corresponding number of CEA in the administrative and official, Norwegian Patient Register (NPR). A manual search through NorKar data from the central registry for the years 2000-2001-2002 was done. Then the number of procedures and complications after surgery were registered. These numbers were compared with a printed data selection from NPR, where procedures including codes for "carotid artery stenosis" and "carotid endarterectomy" were investigated. The annual report from NorKar has been based

on the number of patients with a mark for "indication carotid stenosis" on their registration form, and not the procedure code itself. These patients could therefore easily be identified and compared to the final, "official" diagnosis at discharge from hospital. We have previously shown that several different diagnosis codes for carotid endarterectomy are used, even within the same hospital. Although most of these diagnosis - procedure codes are consistent, a search for the right number of CEA´s based on this could be misleading (Altreuther et al 2004).

Paper IV

We did a retrospective, cohort study of all patients operated for carotid artery stenosis in our department during the years 1983-2002. The patients were identified in the hospital database according to diagnosis code or procedure code related to carotid artery stenosis. The disadvantage of a retrospective study like this, is that the quality of recorded medical data is not uniform. The reports on carotid angiography are a good example, as a great number of them failed to give the exact grade of stenosis. This was the case even after 1991, when the results of RCT´s had shown that the degree of stenosis had a great impact on the effects of surgery and thereby indication for operation (ECST 1991, NASCET 1991). All reports on the surgical procedure were thoroughly checked, and details on perioperative complications were searched for in the discharge reports, nursing reports or examinations by other medical specialists. In addition, we visited local hospitals and searched the medical records for data on patients that had died, to explore whether there were any indication of a stroke after CEA. The analysis of survival and the impact of risk factors were done with the Kaplan-Meier Method and Cox-multivariate regression analysis. Also, the relative survival was calculated, as women had a significantly better survival in the first, unadjusted analysis. The Norwegian Registrar´s Office of Births and Deaths was checked for survival by Dec 1 2004 for all

patients. Otherwise, status on the last reported information in the medical file was considered as an endpoint. The cause of death was obtained from the diagnosis on discharge, or information in the medical records.

Paper V

This was a cohort study of 144 patients admitted to the stroke unit at St. Olav's Hospital, suspected of having had a stroke. We consecutively examined the carotid arteries of patients admitted to this stroke unit over a 6 month period in 1996. Four different vascular surgeons performed the duplex ultrasound scanning of the patients. Specific veloctiy criteria for grading of stenosis were given (Langlois et al 1983, Taylor et al 1987), and the scanning operator was asked to grade the stenosis into one out of four groups, according to the different stenosis groups reported in the NASCET-study. We used the same velocity criteria as in the Asymptomatic Carotid Surgery Trial (ACST), and their method has a well-defined peak systolic velocity (PSV) for more than 50% stenosis, but stenoses of a lesser degree are poorly defined by DUS (Zwiebel 1992). The cut-off values for grading of stenosis when using duplex ultrasound are still controversial. The examinations were done with the same ultrasound scanner, and usually by one scanner operator. This may lead to inaccuracies that could have been minimized with a repeat examination by another operator.

Summary of results

Paper I

We have developed an ultrasound method to describe the motion of carotid plaques induced by the pulse wave from each heart beat. The method was based on 2-dimensional ultrasound scanning, and a frame to frame correlation technique. The analysis was done on radio-frequency data collected from a standard ultrasound scanner.

Paper II

We used the ultrasound technique described in paper I, and studied 27 motion parameters. It was observed that seven different parameters reproduced well after three consecutive image sequences and two heart cycles. The identified parameters represented patterns of motion amplitude, tension and torsion of the carotid plaque.

Paper III

A comparative study of the Norwegian Vascular Registry and The Norwegian Patient Register showed that 16% of carotid endarterectomies had not been reported to the vascular registry. Also, in-hospital stroke and death after carotid endarterectomy were incompletely recorded in NorKar during the years 2000-2002. The discrepancy in the stroke/mortality rate varied from 0,1 – 1,7%, and was most pronounced in the year 2001.

Paper IV

A retrospective study of all carotid endarterectomies performed at Trondheim University Hospital in the years 1983-2002 indicated a 5,4% in-hospital stroke/mortality rate. 556 CEA´s had been carried out among 496 patients with a median age of 67 years. 60% of the patients were men. 86% of the operations were done because of a symptomatic carotid artery stenosis,

and 17% of the patients had had a minor stroke prior to surgery. Twelve patients (2,2%) had an reoperation because of haemorrhage, but no vein patch rupture was seen. The median postoperative stay was 5 days, and this was virtually unchanged during the study period. Few restenoses were discovered on the routine follow-up, and no patient had an operation for recurrent carotid artery stenosis.

Paper V

In a consecutive study of 144 patients admitted to a stroke unit, the grade of carotid stenosis ipsilateral to the cerebral lesion was investigated with duplex ultrasound scanning. The study showed a stenosis of 30-69% in 14 cases, a stenosis of more than 70% in 4 cases and occlusion in 3 cases.

Discussion

Carotid plaque

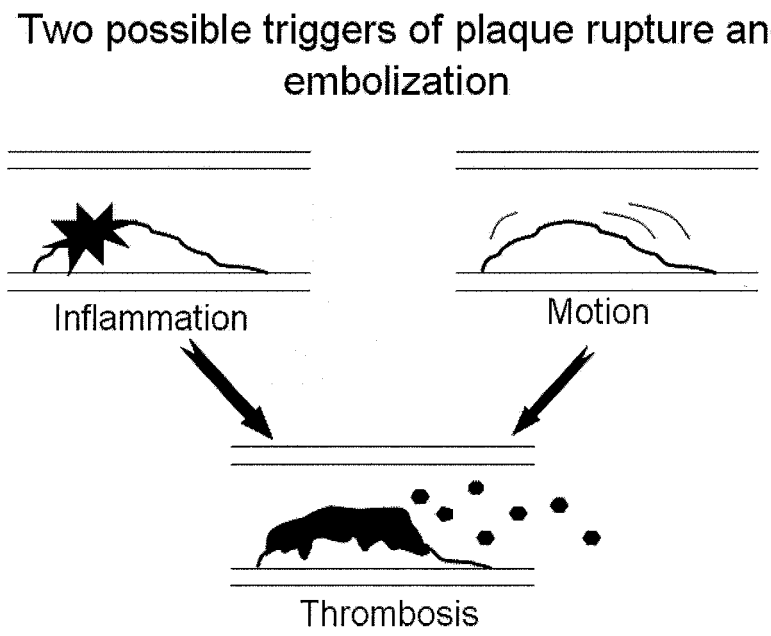
The unstable carotid plaque

Therapy for the prevention of stroke in a previously symptomatic patient with carotid artery stenosis has become well established. However, some patients with a carotid artery stenosis had a stroke as the first manifestation of their atherosclerotic disease (Roederer et al 1984). Observational studies of patients with asymptomatic carotid artery stenosis indicate a small stroke risk (Chambers et al 1986), and the stroke risk in the individual patient is difficult to assess (Nicolaides et al 2005).

The mechanisms for plaque rupture and subsequent thrombosis and emboli are not fully understood (Falk 1992, Golledge et al 2000, Loftus et al 2000). Vascular spasm, inflammatory cells in the fibrous cap, bleeding in the vasa vasorum of the carotid artery and plaque motion have been suggested as pathogenetic factors in plaque rupture (Falk 1992, Meairs et al 1999, Loftus et al 2000, Hennerici 2004). The plaque core is covered by a fibrotic cap. When this cap ruptures, the contents of the plaque is exposed to the platelets and coagulation system of the blood, and a thrombus could form (Fig 2). Clinical studies indicate that soft plaques are more prone to rupture, but this association has been difficult to establish for patients with asymptomatic carotid stenosis (Groenholdt et al 2001, Mathiesen et al 2001). After several years of research, no firm recommendations for surgery based on plaque appearance alone can be made. The ACST study failed to prove whether a plaque that was more than 25% echolucent (soft) predicted a greater risk of stroke (Halliday et al 2004). In the Asymptomatic Carotid Stenosis and Risk for Stroke Study (ASCRS), patients with high grade of stenosis measured by the ECST-method, a history of contralateral, symptomatic carotid artery stenosis and creatinine of more than 85 μmol/l, defined a patient group with an

annual stroke risk of about 4%, compared to 1-2% stroke risk that has previously been reported (Nicolaides et al 2005).

Figure 2



Carotid plaque motion as a pathogenetic factor in plaque rupture

Differences in plaque movement between patients with and without symptoms, were demonstrated by Meairs and Hennerici in 1999, but only a few reports on this topic followed (Golemati et al 2003, I, Lenzi et al 2007). We have described plaque motion with a 2D ultrasound method (I). Such motion could theoretically lead to a fatigue fracture of the fibrous cap. The idea was that ultrasound B-mode and duplex examination is a standard procedure in

carotid artery examinations, and that simultaneous processing of raw ultrasound data could provide a measure of plaque motion. We assumed that patients with a recent cerebrovascular episode caused by a relevant carotid artery stenosis might have a specific motion pattern. The theory was that the same motion pattern could be identified in some patients with a previously asymptomatic carotid artery stenosis, and represent a higher risk of embolization. Accordingly one might be able to identify three groups of patients; one group with a symptomatic carotid artery with a "symptomatic" motion pattern, a second group of patients with an asymptomatic stenosis and an "asymptomatic" motion pattern and a third group of patients with an asymptomatic stenosis and an "symptomatic" motion pattern (Table 2). The latter group would probably be at higher risk of an embolic event in the future compared with the second group, and these patients could then be offered CEA. In this way, CEA might be avoided in the low risk group. This corresponds well with the recent observations from Lenzi et al (2007).

Table 2

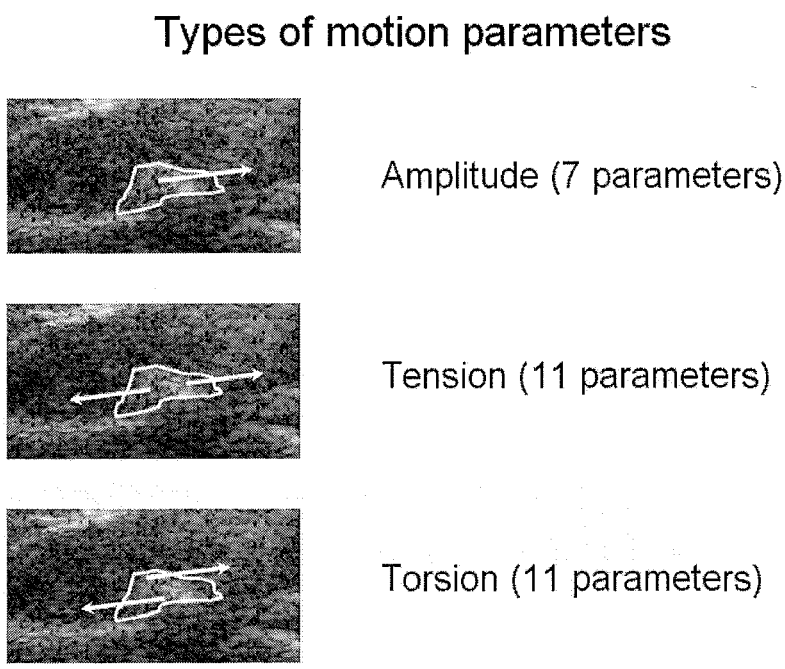
Hypothetical plaque motion patterns and stroke risk

Clinical situation	Symptomatic patient with carotid plaque	Asymptomatic patient with carotid plaque	Asymptomatic patient with carotid plaque
Plaque motion pattern	"Symptomatic"	"Asymptomatic"	"Symptomatic"
Stroke risk	High	Low	High

We investigated a number of motion parameters that could be calculated from the ultrasound data (II). These parameters represented stretch/compression and torsion of the plaque, as well

as mere displacement (motion amplitude)(Fig 3). The study showed that the ultrasound examination should be repeated three times and analyzed over two heart cycles to give reliable data (II). In clinical practice, this might be possible during a routine examination of the carotid arteries. However, the calculation of plaque motion had to be done on radio - frequency (RF) data. At present, this still necessitates data transfer to a separate computer with appropriate software, and the processing time for the prototype software was unacceptable for real-time analysis. To be of value for the clinical routine, the motion analysis should be incorporated in the software of the ultrasound scanner. By colour coding, different areas of plaque motion could be displayed and evaluated.

Figure 3



Limitations in the use of motion parameters

A disadvantage of our method is that this motion sequence only represents a snapshot view of the plaque. Plaque motion may vary over time, just as the plaque may undergo changes due to growth or regression. The use of a cholesterol lowering agent, like statins, could stabilize the plaque (Crisby et al 2001, MRC/BHF Heart Protection Study 2002, Amarenco et al 2004, Sacco et al 2006). By comparison of the motion results in relation to plaque appearance (GSM; gray scale median values), there were no obvious correlation between a low GSM-value and high plaque motion. Hence, it is possible that plaque motion analysis is an independent indicator for plaque instability. During the same time period, Golemati (2003) presented a similar method to ours, that showed differences in longitudinal plaque motion in symptomatic and asymptomatic patients. A previous study of 3-dimensional carotid plaque motion was rather complex, requiring specialized ultrasound equipment (Meairs et al 1999). To show the predictive value of carotid plaque motion pattern in an asymptomatic patient, the patients should be followed for a longer period. This necessitates a multicenter study, which probably would need to include a large number of patients. It took almost 10 years to complete the last randomized clinical trial in patients with an asymptomatic carotid artery stenosis (ACST) (Halliday et al 2004). Since knowledge of plaque appearance has not lead to an appearant change in the treatment policy for carotid artery stenosis after all these years, it is unlikely that plaque motion would be readily accepted as a method for evaluation of carotid artery plaques (Nighoghossian et al 2005). The identification of parameters that might separate between symptomatic and asymptomatic plaque motion still remains a challenge. The reproducibility study provided a number of potentially useful parameters (II). We performed a preliminary analysis of these parameters by comparing the symptomatic and asymptomatic values statistically. However, this analysis showed no significant difference between the two patient groups. The lack of difference may be due to the small number of

patients. In addition, the selection of the plaque region for analysis might have influenced on the results. Future work should therefore concentrate on additional analysis of plaque regions, and thereafter possibly the inclusion of a larger number of patients.

Carotid operations in vascular registers

How valid are the results from the national registers?

A study of abdominal aneurysms in Norway showed an underreporting of the number of procedures and deaths in NorKar (Haug et al 2005). We conducted a similar study to investigate the completeness of carotid endarterectomies, and the stroke/mortality rate within each hospital (III). Over a three-year period from the year 2000, we found that 16% of the CEA´s were missing in NorKar when compared to the Norwegian Patient Register (NPR). Some of the departments are small, leaving one or two vascular surgeons with a manual registration, sometimes excluding one or more years. Furthermore, there was an underreporting of postoperative stroke and death, although the corrected figures were comparable to the official NorKar-numbers for year 2000 and 2002. There was a discrepancy of 1,7% in 2001, and this was probably due to underreporting of strokes and deaths when patients were referred to other departments postoperatively within the same hospital (III). Since the complete registration of codes for diagnosis, surgical procedures and postoperative complications leads to the appropiate DRG-reimbursement for the hospital, we assume that complications are thoroughly registered in NPR (Aardal et al 2005). However, the number of postoperative strokes in NPR may not be completely true, as we have not performed any search in the medical records to investigate how the diagnosis of stroke was established. When it comes to postoperative death, this registration is more likely to be complete, because death within hospital is represented by a specific code in NPR.

It is possible that the later introduction of a separate registration for postoperative stroke or death after CEA on the NorKar paper form, has contributed to a more precise registration.

How could the register quality be improved?

A stronger effort to make NorKar more complete and accurate should be done, and reporting should be mandatory for every hospital where vascular surgery is performed. Registration could be encouraged by the use of NorKar in the vascular surgery training, and the need to document the necessary numbers of procedures required for authorization as a specialist. The present registration on paper forms used by several surgeons, with subsequent transfer into a computer, might be replaced by an on-line registration procedure. If the vascular register had been linked to the patient's electronic medical record, completion of the hospital stay and discharge report might be made impossible unless the register data also were updated. Until then, some sort of regular, manual surveillance system for register data should be established, preferably by office staff. Also, there are obvious limitations in the present version of The Norwegian Patient Register. An individual patient has a unique identification code within the same hospital within the same year, and admissions with related diagnosis can be found. However, admissions to another hospital for complications after surgery in the first hospital, will not be discovered through the register. A patient identifiable register, could overcome the difficulties of patient tracking over different years and hospitals. The restrictive policy of The Norwegian Data Inspectorate however, does not approve that different registers with personal information should be linked together. There are however, medical personell that advocate the establishment of a patient-identifiable register (Valen 2002), which also is a political issue.

CEA in Trondheim

Results after carotid endarterectomy at St. Olavs Hospital

There is an ongoing debate on the surgical details of CEA. Issues like type of anaesthesia, the use of shunting, closure of the endarterectomy, patch type and intraoperative quality control are frequently discussed. Some of the issues have been evaluated in The Cochrane Collaboration (Cao et al 2001, Bond et al 2002, Bond et al 2004, Rerkasem et al 2004). Constant monitoring of results and studies on perioperative care, have clearly improved the results in some departments (Naylor et al 2000). However, despite the search for technical perfection, the procedure itself has a certain cost in terms of complications (Troeng et al 1999). Every department should therefore keep record on their own results. This is of particular importance, because the traditional CEA is challenged by carotid artery stenting (CAS), that is likely to be requested by patients in the future. CEA is a well documented method, and performs well compared to CAS in randomized studies (CAVATAS 2001, Yadav et al 2004, Coward et al 2004). The results from large studies, however, are not always achieved in other departments. Carotid endarterectomy according to the principles mentioned below was introduced in our department in 1983. Our standard approach is a vertical neck incision, 10000 units of Heparine before carotid clamping, use of a shunt if stump pressure is below 50 mmHg, standard endarterectomy, patch closure in most cases and reversal of half the Heparine dose with Protamine. We believe that a standarized approach to carotid endarterectomy is important. Over the years, the technique has been passed on to several vascular surgeons in training, and the majority of CEA´s in the central part of Norway has been done at our institution. Surgical technique varied little over the years, and we found an acceptable stroke/mortality rate of 5,4% (IV). The incidence of reoperation for postoperative bleeding was in agreement with other reports (Archie 2000, LaMuruglia et al 2004), and we had no cases of vein patch rupture. There has been considerable scepticism on the use of a

saphenous vein patch, especially from the ankle (Gaunt et al 1993). Provided the vein is of good quality, this should not represent a problem. No operation for recurrent carotid artery stenosis was done, and our indication for such reoperation would have been restricted to patients with symptoms. Since we only have duplex ultrasound data at one year follow-up in most cases, the real incidence of carotid artery restenosis is unknown. With the use of saphenous vein patch in most cases, no patch infection has been seen. Other authors have reported an incidence of 0,9% Dacron patch infection after CEA in a group of 633 patients (Asciutto et al 2007). Even though this a small number, it represents a serious problem in terms of treatment and on morbidity (Asciutto et al 2007). The indications for CEA were established by the large studies during 1991 (ECST,NASCET), but in spite of this the classification of the carotid stenosis in our institution was often inaccurate on angiography. Angiography was gradually replaced by duplex ultrasound as a preoperative diagnostic method. The material included 16% operations for asymptomatic carotid artery stenosis, mostly patients operated within the ACST-study. The number of procedures varied little within 5 year periods, and the duration of the postoperative hospital stay remained almost unchanged. Except for a shorter hospital stay because preoperative carotid angiography has been omitted, little has been done to reduce the length of the postoperative stay (Calligaro et al 2004). Local anaesthesia was abandoned because of patient anxiety and discomfort. Perioperative duplex ultrasound as completion control of the endarterectomy, was tried for a period of time, but was impractical because of inappropriate ultrasound probes (Myhre et al 1993). At present, we mainly use flow measurement to ensure that the carotid artery is patent at the end of the operation. However, perioperative DUS is likely to be used more frequent in the future if the equipment will be improved.

Timing of carotid surgery in relation to the cerebrovascular event

The timing of surgery with symptomatic carotid artery stenosis is important (Rothwell et al 2004), since the preventive effect of surgical treatment is gradually lost as time passes after the initial cerebrovascular event. We have focused on the time interval between event and surgery, and showed in paper IV that 90% of the patients were operated within 100 days of the event. Recently we have tried to do the operation as soon as possible, and given that the patients are referred from our own hospital, we try to perform CEA within less than two weeks from a TIA or a minor stroke with good recovery (Gasecki et al 1994, Hoffmann et al 1999, Ballotta et al 2002, Rothwell et al 2004, Aleksic et al 2006). A recent report however, has questioned the policy of early CEA in patients who have had a stroke (Rockman et al 2006). We have cooperated with the stroke unit and the department of neurology to achieve a rapid evaluation of patients who are candidates for CEA. The organization of the care for patients with symptomatic carotid artery stenosis is however far from perfect (Mätzsch 1997), and some have discussed whether patients with a TIA and carotid artery stenosis should be treated as emergencies (Naylor 2006).

Carotid stenosis in the stroke unit

Carotid stenosis in patients admitted to a stroke unit

The exact number of strokes caused by emboli from the precerebral arteries is unknown (Warlow et al 2001). Stable patients with small or moderate neurologic sequelae who might be candidates for CEA should undergo DUS of the carotid arteries. The Norwegian Medical Society issued in 1996 a number of guidelines for investigation and treatment of patients with cerebrovascular disease. It was suggested that DUS of the precerebral arteries could be useful in the diagnostic work-up of the patients if CEA was considered, but also when a cardiac source of emboli was suspected (Dahl et al 1996). Some patients may experience stroke as a first manifestation of their carotid artery disease. Since the number of carotid endarterectomies in Norway has been low, compared to other countries, we figured that a fair number of patients within a stroke unit could possibly have an undiagnosed carotid artery stenosis. In an unselected population of patients admitted to a stroke unit with a mean age of 75 years, only four patients with a carotid artery stenosis of more than 70% were found (V). By adding carotid occlusions and arteries with stenosis of 30-69%, a carotid artery stenosis ipsilateral to the cerebral lesion was seen in 14,6% of the patients. This corresponds to another Norwegian study (Friis et al 2001). From a practical point of view, only patients within a stroke unit who are good candidates for CEA may be referred to DUS. However, the status of the carotid arteries may have implications for other treatment modalities, like antihypertensive and lipid-lowering medication, smoking cessation and other life style modifications. Whether the number of CEA´s in Norway is too small has been debated (Hanoa 2003, Mathiesen 2006). Hankey (1995) has estimated the effect of CEA in all Australian patients aged 50-74 years with an asymptomatic carotid artery stenosis of 60-99% luminal obstruction. He considers that the operation of 80000 people in this category, would

prevent about 800 strokes per year at a cost of 1,24 billion Australian Dollars (6,44 billion NOK). Still, only 3% of the annual 26000 first strokes in Australia would have been prevented.

Future treatment of carotid artery stenosis

Our retrospective 20-year study on CEA serves as a local standard if carotid artery stenting is to be introduced (LaMuruglia et al 2004). Although our department has been a national pioneer within the field of endovascular treatment of aortic aneurysms (Lundbom et al 2004), we have been reluctant to use CAS except in patients with previous neck irradiation. We consider a patient with a symptomatic carotid stenosis and previous radical neck dissection and irradiation as a good candidate for CAS, which could also be indicated in patients with distal lesions or recurrent stenosis (Veith et al 2001). Our scepticism has been based on the modest results after CEA and CAS in two randomised studies (CAVATAS investigators 2001, Yadav et al 2004). CAS performed just as well as CEA in these studies, but the overall surgical results were inferior to what have normally been regarded as acceptable. Also, the results of the recent EVA 3-S study concluded that CAS were inferior to CEA (Mas et al 2006). CAS and CEA will probably be complementary methods in the future, and we have chosen to wait for the results of ongoing studies before introducing CAS in routine clinical practice (Naylor 2007). It is likely that more patients will be offered CEA for an asymptomatic carotid artery stenosis (Gottsäter et al 2004). There is probably still a case for intensified risk modification by aggressive treatment of hypertension, new platelet inhibitors and cholesterol-lowering medication (Sacco et al 2006). Agents that modify the actual carotid plaque could be used to restore the vessel wall (Ogren et al 1995, Crisby et al 2001, Nighoghossian et al 2006) . New imaging modalites, may also predict the risk of plaque

rupture with higher accuracy (Nighoghossian et al 2005), and then more patients with an asymptomatic carotid artery lesion could be offered CEA.

Main conclusion

- We have developed an imaging technique to describe carotid plaque motion by 2-dimensional ultrasound scanning. Furthermore, we have shown that 3 consecutive recordings over 2 heart cycles are necessary to obtain reproducible results with this method.
- Only seven motion parameters reproduced well, but 3 different patterns of motion were represented. The analysis of data is time-consuming, and should be simplified to allow for regular clinical use. The role of carotid plaque motion as a pathogenetic factor in plaque rupture is still unclear.
- By a comparative register study, we have shown an underreporting of 16% regarding the number of carotid endarterectomies in NorKar. Also, the stroke/mortality rate was misleading, and register quality should be improved if surgical results are to be used for research purposes or other documentation.
- The stroke/mortality rate of 5,4% after CEA in our own department is in line with other vascular departments and with the results from large, international studies. We therefore choose to continue our current practice for carotid endarterectomy.
- In an unselected stroke population we found 4 carotid artery stenosis of more than 70% and 3 carotid artery occlusions ipsilateral to the cerebrovascular lesion.

REFERENCES

Aardal S, Berge K, Breivik K, Flaatten HK. Medical records, DRG and intensive care patients. Tidsskr Nor Laegeforen 2005; 125: 903–906 (in Norwegian).

AbuRahma AF, Thiele SP, Wulu JT. Prospective controlled study of the natural history of asymptomatic 60% to 69% carotid stenosis according to ultrasonic plaque morphology. J Vasc Surg 2002; 36: 437–442.

ACAS – See "Executive Committee for the Asymptomatic Carotid Atherosclerosis Study"

ACSRS – See "Nicolaides"

ACST – See "Halliday"

Adams HP jr, Bendixen BH, Kappelle LJ, Biller J, Love BB et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clincial trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24: 35-41

Aleksic M, Rueger MA, Lehnhardt FG, Sobesky J, Matoussevitch V et al. Primary Stroke Unit Treatment Followed by Very Early Carotid Endarterectomy for Carotid Artery Stenosis after Acute Stroke. Cerebrovasc Dis 2006; 22: 276-281

Altreuther M, Dahl T. Koding av pasienter med carotisstenose i NorKar. Abstract. (In Norwegian). Winter meeting, Norwegian Society for Vascular Surgery 2004

Amarenco P, Labreuche J, Lavallée P, Touboul P-J. Statins in Stroke Prevention and Carotid Atherosclerosis. Systematic Review and Up-to-Date Meta-Analysis. Stroke 2004; 35: 2902-2909

Antiplatelet Trialists´ Collaboration 1988. Secondary Prevention of vascular disease by prolonged antiplatelet treatment. Br Med J 1988; 296: 320-331.

Archie JP. A fifteen-year experience with carotid endarterectomy after a formal operative protocol requiring highly frequent patch angioplasty. J Vasc Surg 2000; 31: 724-35.

Asciutto G, Geier B, Marpe B, Hummel, Mumme A. Dacron Patch Infection After Carotid Angioplasty. A Report of 6 cases. Eur J Vasc Endovasc Surg 2007; 33: 55-57

Baker JD, Rutherford RB, Bernstein EF, Courbier R, Ernst C et al. Suggested standards for reports dealing with cerebrovascular disease. J Vasc Surg 1988; 8: 721-729

Ballotta E, Da Giau G, Baracchini C, Abbruzzese E, Saladini M, Meneghetti G. Early versus delayed carotid endarterectomy after nondisabling ischemic stroke: A prospective randomized study. Surgery 2002; 131: 287-293.

Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991; 337: 1521-1526

Bang J, Dahl T, Bruinsma A, et al. A new method for analysis of motion of carotid plaques from RF ultrasound images. Ultrasound Med Biol 2003; 29: 967–976.

Barnett HJM, Walton JN, Plum F. Carotid endarterectomy: an expression of concern. Stroke 1984; 15: 941-943

Beebe HG, Archie JP, Baker WH, Barnes RW, Becker GJ et al. Concern About Safety of Carotid Angioplasty. Stroke 1996; 27: 197-198

Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003; 349: 2117-27.

Bond R, Berkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev. 2004;(2):CD000160. Review

Bond R, Rerkasem K, Counsell C, Salinas R, Naylor R et al. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database Syst rev. 2002; (2).: CD000190.

Byrd S, Robless P, Baxter A, Emson M, Halliday A. Carotid duplex ultrasonography: importance of standardisation. Int Angiol 1998; 17: 248-254

Cairols MA, Cotillas J, Miralles M, Dolz JL, Capdevila A. Accuracy of Duplex Scanning, Arteriography and Magnetic Resonance Angiography for Carotid Imaging in Surgical Patients. In Greenhalgh RM (ed). Vascular Imaging for Surgeons. WB Saunders 1995; pp.107-119

Calligaro KD, Doerr KJ, McAfee-Bennett S, Mueller K, Dougherty MJ. Critical Pathways Can Improve Results with Carotid Endarterectomy. Semin Vasc Surg 2004; 17: 253-256.

Cao PE, de Rango P, Zannetti S, Giordano G, Ricci S et al. Eversion versus conventional carotid endarterectomy for preventing stroke. Cochrane Database Syst Rev. 2001; (1): CD001921.

CAVATAS investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357: 1729-1737

Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. N Engl J Med 1986; 315: 860-865

Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database Syst Rev. 2005 Oct 19; (4): CD001923.

Cina CS, Clase CM, Haynes RB. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2000; (2): CD001081 Review

Coward LJ, Featherstone RL, Brown MM. Percutaneous transluminal angioplasty and stenting for carotid artery stenosis. Cochrane Database Syst Rev. 2004; (2): CD000515 Review

Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J et al. Pravastatin Treatment Increases Collagen Content and Decreases Lipid Content, Inflammation, Metalloproteinases, and Cell Death in Human Carotid Plaques. Circulation 2001; 103: 926-933

Curley PJ, Norrie L, Nicholson A, Galloway JMD, Wilkinson ARW. Accuracy of Carotid Duplex is Laboratory Specific and Must be Determined by Internal Audit. Eur J Vasc Endovasc Surg 1998; 15: 511-514

Dahl T, Indredavik B, Mamen K, Russell D, Thomassen L, Waaler HM. Utredning og behandling av pasienter med cerebrovaskulær sykdom. Skriftserie for leger: utdanning og kvalitetssikring (in Norwegian). Den norske laegeforening, Lysaker 1996

Dahl T, Bang J, Ushakova A, Lydersen, Myhre HO. Parameters describing motion in carotid artery plaques from ultrasound examination: A reproducibility study.
Ultrasound Med Biol. 2004 Sep; 30: 1133-43.

Dahl T, Rudjord K, Altreuther M, Myhre HO. Data quality of surgery for carotid artery stenosis. Are the national vascular registries reliable? Eur J Vasc Endovasc Surg. 2006; 31: 381-5.

Dahl T, Myhre HO, Johnsen HJ. The practice of surgery for carotid artery stenosis in Norway. A questionnaire based investigation. Tidsskr Nor Laegeforen 2006; 126: 1466-1469 (Norwegian, Engl abstract).

Dahl T, Aasland J, Romundstad P, Johnsen HJ, Myhre HO. Carotid endarterectomy. Time-trends and results during a 20-year period. Int Angiol. 2006; 25: 241-8.

Dean CC, Johnston MD, Kristine M, Chapman MD, Goldstein LB. Low rate of complications of cerebral angiography in routine clinical practice. Neurology 2001; 57: 2012-2014

DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. JAMA 1975; 233: 1083-1085

Eastcott HH, Pickering GW, Rob CG Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. Lancet. 1954; 267: 994-6.

ECST – See "European Carotid Surgery Trialists' Collaborative Group"

European Carotid Surgery Trialists` Collaborative Group (ECST). MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991; 337: 1235-1243.

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995; 273: 1421-1428

Falk E. Why do plaques rupture? Circulation 1992; 86(Suppl. III): III-30–III-42.

Friis P, Gjestvang FT, Fausa D, Kaass B. Thrombotic or embolic stroke? (in Norwegian). Tidsskr Nor Laegeforen 2001; 121: 2143-2146.

Gasecki AP, Ferguson GG, Eliasziw M, Clagett GP, Fox AJ, Hachinski V, et al. Early endarterectomy for severe carotid artery stenosis after a nondisabling stroke: Results from the North American Symptomatic Carotid Endarterectomy Trial. J Vasc Surg 1994; 20: 288-295.

Gaunt ME, Thompson M, White S, Naylor AR, Bell PR. Vein-patch rupture after carotid endarterectomy: an avoidable catastrophe. Br J Surg 1993; 80: 1490-1491

Golemati S, Sassano A, Lever MJ, et al. Carotid artery wall motion estimated from B-mode ultrasound using region tracking and block matching. Ultrasound Med Biol 2003; 29: 387–399.

Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. Review. Stroke. 2000; 31: 774-81

Gottsäter A, Mätzsch T. Kirurgi snart även primärprevention vid slaganfall av höggradig karotisstenos (in Swedish). Läkartidningen 2004; 101: 1821-22, 1825-7

Groenholdt MLM, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. Circulation 2001; 104: 68-73.

Halliday A, Mansfield A, Marro J, Peto C, Peto R et al. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363: 1491-1502.

Hankey GJ. Asymptomatic carotid stenosis: how should it be managed? Med J Aust 1995; 163: 197-200

Hanoa R. Carotiskirurgi for forebygging av hjerneslag [in Norwegian]. Tidsskr Nor Lægeforen 2003; 123: 767

Haug ES, Romundstad P, Sæther OD, Jørgenvåg R, Myhre HO. Quality of data reported on abdominal aortic aneurysm repair. A comparison between a national vascular and a national administrative registry. Eur J Vasc Endovasc Surg 2005; 29: 571–578.

Heart Protection Study Collaborative Group. MRC/BHF heart protection Study of Cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.

Hennerici MG. The unstable plaque. Cerebrovasc Dis 2004; 17: 17-22

Hoffmann M, Robbs J. Carotid endarterectomy after recent cerebral infarction. Eur J Vasc Endovasc Surg 1999; 18: 6-10.

Indredavik B. Embolism as the cause of stroke (in Norwegian). Tidsskr Nor Laegeforen 2001; 121: 2142.

Jensen LP, Tröeng T. Vascular registries - are they worth the effort? Eur J Vasc Endovasc Surg 2000; 20: 225–226.

Kantonen I, Lepäntalo M, Salenius J-P, Mätzke S, Luther M, Ylönen K and the Finnvasc Study Group. Influence of Surgical Experience on the Results of Carotid Surgery. Eur J Vasc Endovasc Surg 1998; 15: 155-160.

LaMuruglia GM, Brewster DC, Moncure AC, Dorer DJ, Stoner MC, Trehan SK, et al. Carotid Endarterectomy at the Millenium. What Interventional Therapy Must Match. Ann Surg 2004; 240: 535-546.

Langlois Y, Roederer GO, Chan A, Phillips DJ, Beach KW, Martin D, Chikos PM, Strandness DE. Evaluating carotid artery disease. The concordance between pulsed Doppler/spectrum analysis and angiography. Ultrasound in Med & Biol 1983; 9: 51-63.

Langsfeld M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. J Vasc Surg 1989; 9: 548–557.

Lenzi GL, Vicenzini E. The Ruler Is Dead: An Analysis of Carotid Plaque Motion. Cerebrovasc Dis 2007; 23: 121-125

Loftus IM, Naylor AR, Goodall S, Crowther NM, Jones L, Bell PR, Thompson MM. Increased matrix metalloproteinase-9 activity in unstable carotid plaques. A potential role in acute plaque disruption. Stroke 2000; 31: 40-47.

Loftus IM, McCarthy MJ, Pau H, Hartshorne T, Bell PRF, London NJM, Naylor AR. Carotid endarterectomy without angiography does not compromise operative outcome. Eur J Vasc Endovasc Surg. 1998 Dec; 16: 489-93.

Lundbom J, Hatlinghus S, Lange C, Ødegård A, Aasland J, Romundstad P, Myhre HO. Nine years' experience with endovascular treatment of abdominal aortic aneurysms] Tidsskr Nor Laegeforen. 2004 Nov 4; 124: 2757-9. (In Norwegian).

Mas J-L, Cahtellier G, Beyssen B, Branchereau A, Moulin T, Becquemin J-P. Endarterectomy versus stenting in patients with severe symptomatic stenosis. N Engl J Med 2006; 355: 1660-1671

Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis (the Tromsø study). Circulation 2001; 103: 2171–2175

Mathiesen EB. Carotiskirurgi – hvor, når og for hvem? (in Norwegian). Tidsskr Nor Lægeforen 2006; 126: 1465

Matzsch T. Carotid endarterectomy – what are we doing? Eur J Vasc Endovasc Surg. 1997; 14: 327-328.

Meairs S, Hennerici M. Four-dimensional ultrasonographic characterization of plaque surface motion in patients with symptomatic and asymptomatic carotid artery stenosis. Stroke 1999; 30: 1807–1813.

Moore WS, Barnett HJM, Beebe HG, Bernstein EF, Brener BJ et al. Guidelines for Carotid Endarterectomy (A Multidisciplinary Consensus Statement From the Ad Hoc Committee), American Heart Association. Circulation 1995; 91: 566-579

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial.
Lancet. 2002; 360: 7-22.

Myhre HO, Saether OD, Mathiesen SR, Angelsen BAJ. Colour coded duplex scanning during carotid endarterectomy. In : Greenhalgh RM, Hollier LH (eds.) Surgery for stroke. London: WB Saunders, 1993, pp. 253-258

Narins CR, Illig KA. Patient selection for carotid stenting versus endarterectomy: a systematic review. J Vasc Surg. 2006; 44: 661-72. Review.

NASCET – See "North American Symptomatic Carotid Endarterectomy Trial Collaborators"

Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, et al. Reducing the risk of carotid surgery: A seven year audit of the role of monitoring and quality control assessment. J Vasc Surg 2000; 32: 750-759.

Naylor AR. Does the modern concept of "best medical therapy" render carotid surgery obsolete? Eur J Vasc Endovasc Surg 2004; 28: 457-61

Naylor AR. The Asymptomatic Carotid Surgery Trial: bigger study, better evidence. Br J Surg 2004; 91: 787-789

Naylor AR. Early Carotid Endarterectomy after Ischemic Stroke:The Results of a Prospective Multicenter Italian Study. Eur J Vasc Endovasc Surg 2006; 32: 236-237

Naylor AR. Where Next after SPACE and EVA-3S: "The Good, the Bad and the Ugly!" . Eur J Vasc Endovasc Surg 2007; 33: 44-47

Nicolaides N, Kakkos SK, Griffin M, Sabetai M, Dhanjil S et al. Severity of Asymptomatic Carotid Stenosis and Risk of Ipsilateral Hemispheric Ischaemic Events: Results from the ACSRS Study. Eur J Vasc Endovasc Surg 2005; 30: 275-284

Nighoghossian N, Derex L, Douek P. The Vulnerable Carotid Artery Plaque. Current Imaging Methods and New Perspectives. Stroke 2005; 36: 2764-2772

Norris JW, Halliday A. Is ultrasound Sufficient for Vascular Imaging prior to Carotid Endarterectomy? Stroke 2004; 35: 370-371

North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325: 445-453.

Ogren M, Hedblad B, Isacsson S-O, Janzon L, Jungquist G, Lindell S-E. Ten year cerebrovascular morbidity and mortality in 68 year old men with asymptomatic carotid stenosis. BMJ 1995; 310: 1294-1298.

Rankin J. Cerebral vascular accidents in patients over the age of 60: Prognosis. Scot.Med J 1957; 2: 200-215

Rerkasem K, Bond R, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev. 2004; (2): CD000126. Review.

Robless P, Baxter A, Byrd S, Emson M, Halliday A. Prevalence of asymptomatic CT infarcts in the ongoing Asymptomatic Carotid Surgery Trial (ACST). Int angiol 1998; 17: 194-200

Rockman CB, Maldonando TS, Jacobowitz GR, Cayne NS, Gagne PJ et al. Early carotid endarterectomy in symptomatic patients is associated with poorer perioperative outcomes. J Vasc Surg 2006; 44: 480-487

Roederer GO, Langlois YE , Jager KA, Primozich JF, Beach KW et al. The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. Stroke. 1984; 15: 605-13.

Rothwell PM, Gibson R, Warlow CP. Interrelation Between Plaque Surface Morphology and Degree of Stenosis on Carotid Angiograms and the Risk of Ischemic Stroke in Patients With Symptomatic Carotid Stenosis. Stroke 2000; 31: 615-621.

Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004; 363: 915-24.

Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline.
Circulation. 2006 Mar 14; 113: e409-49.

Sulter G, Steen C, De Keyser J. Use of the Barthel Index and Modified Rankin Scale in Acute Stroke Trials. Stroke 1999; 30: 1538-1541

Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987; 15: 635-644.

Thompson J. Carotid Artery Surgery – Historical Review. In: Greenhalgh RM, Hollier LH (eds.) Surgery for stroke. London: WB Saunders, 1993, pp. 3-10

Troeng T, Bergqvist D, Einarsson E, Elfström J, Norgren L. Experiences from Swedvasc/VRISS. Ann Chir Gynaecol 1992; 81: 248–252.

Troeng T, Bergqvist D, Norrving B, Ahari SA. Complications after carotid endarterectomy are related to surgical errors in less than one-fifth of cases. Swedvasc-The Swedish Vascular registry and The Quality Committee for Carotid Artery Surgery. Eur J Vasc Endovasc Surg 1999; 18: 59-64.

Tu JV, Hannan EL, Anderson GM, Iron K, Keyi Wu et al.The fall and rise of carotid endarterectomy in the United States and Canada. N Engl J Med 1998; 339:1441-1447

Valen B. The use of patient register in surgery (In Norwegian). Tidsskr Nor Laegeforen 2002; 122: 2555-2557

Veith F, Amor M, Ohki T, Beebe, Bell PR et al. Current status of carotid bifurcation angioplasty and stenting based on a consensus of opinion leaders. J Vasc Surg 2001; 33 (suppl): 111-116

Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG et al. Stroke. A practical guide to management. Second edition. Blackwell Science Publishing, Oxford 2001.

Wilterdink JL, Easton D. Vascular Event Rates in Patients With Atherosclerotic Cerebrovascular Disease. Arch Neurol 1992; 49: 857-863.

Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT et al. Protected Carotid-Artery Stenting versus Endarterectomy in High-Risk Patients. N Engl J Med 2004; 351: 1493-1501

Zarins CK. Carotid endarterectomy: the Gold Standard. J Endovasc Surg 1996; 3:10-15

Zwiebel WJ. Color-duplex features of normal and abnormal carotid arteries. Doppler evaluation of carotid stenosis. In Zwiebel WJ (ed.) Introduction to Vascular Ultrasonography. W.B. Saunders Company, Philadelphia 1992: 105-132.

Paper I

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● *Original Contribution*

A NEW METHOD FOR ANALYSIS OF MOTION OF CAROTID PLAQUES FROM RF ULTRASOUND IMAGES

JON BANG,* TORBJØRN DAHL,† ANNEMARIEKE BRUINSMA,‡ JON HARALD KASPERSEN,* TORIL A. NAGELHUS HERNES* and HANS OLAV MYHRE†

*Ultrasound Department, SINTEF Unimed, Trondheim, Norway; †Surgical Department, St. Olavs Hospital, Trondheim, Norway; and ‡Faculty of Medicine, Utrecht University, Utrecht, The Netherlands

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Abstract—Motion of carotid artery plaques during the cardiac cycle may contribute to plaque disruption and embolism. We have developed a computerized method that objectively analyzes such motion from a sequence of ultrasound (US) radiofrequency (RF) images. A displacement vector map is obtained by 2-D correlation of local areas in consecutive images. From this map, motion dynamics can be quantified and presented as function of time, spatial (image) coordinates or as single numbers. Correct functionality has been verified on laboratory data. Applied to patient data, the method gives temporal results that correlate well with ECG data and the calculated peak systolic velocities of typically 10 mm/s agree well with values reported in the literature. The spatial analysis demonstrates that different plaque regions may exhibit different motion patterns that may cause internal stress, leading to fissures and plaque disruption. Thus, the motion analysis method may provide new and important information about the plaque characteristics and the prospective risk of cerebrovascular events. (E-mail: jon.bang.@sintef.no) © **2003 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Carotid artery stenosis, Plaque characterization, Embolism, Ultrasonography, Motion dynamics.**

INTRODUCTION

Ultrasound (US) imaging of the carotid artery plaque in connection with cerebrovascular events has mainly focused on the degree of stenosis and on the static and textural appearance of the plaque. Studies have shown that patients with heterogeneous plaques have a higher incidence of stroke, compared to homogeneous plaques (AbuRahma et al. 2002; Langsfeld et al. 1989). Echolucent plaques also indicate patients with increased risk of stroke (El-Barghouty et al. 1995; European Carotid Plaque Study Group 1995; Grønholdt et al. 2001; Mathiesen et al. 2001).

The mechanisms causing plaque disruption and embolization are not fully understood (Golledge 2000; Hennerici and Meairs 2000). It has been suggested that mechanical stress due to movement of the arterial wall during the cardiac cycle may lead to minor cracks and fissures (Falk 1992; Woodcock 1989). Another factor causing plaque disruption could be rupture of the vasa vasorum due to the relative movement between the plaque and the vessel wall (Iannuzzi et al. 1995; Woodcock 1989).

Few attempts on motion analysis on US image sequences have been reported in the literature. Chan (1993) investigated both a pixel feature similarity method and a boundary-tracking method for 2-D plaque motion analysis. The preliminary testing on clinical data indicated some potential, even for the small number of tracked points and low frame rate (1 frame/s) applied in the study. To our knowledge, Chan's work has not been followed up by more recent publications. Iannuzzi et al. (1995) studied the presence of plaque movement in patients with transient ischemic attacks. They found that longitudinal motion occurred more often in the ipsilateral plaques than in the contralateral ones. However, the motion was not quantified. Meairs and Hennerici (1999) considered a sequence of ECG-gated 3-D volumes, and analyzed the surface motion of the plaque between consecutive volumes. In terms of the maximum discrepant surface velocity, they found significant differences between asymptomatic and symptomatic plaques. The asymptomatic plaques exhibited homogeneous surface motion, and symptomatic plaques showed evidence of inherent plaque movement.

Address correspondence to: Jon Bang, SINTEF Unimed Ultrasound, NO-7465 Trondheim, Norway. E-mail: jon.bang@sintef.no

Table 1. Characteristics of the patient group used for the development of the motion-analysis method

Patient	Gender	Age	Heart disease*	Hypertension†	Diabetes	Current smoker	Cholesterol (μmol/l); non-fasting	Symptom‡	# Days since last event	Percentage internal carotid stenosis§
A	F	64	none	none	none	Yes	5.5	AF	46	> 80 (US)
B	F	69	none	none	none	Yes	4.9	AF	10	> 80 (US)
C	M	64	none	none	none	Yes	5.6	AF	111	> 80 (US)
D	F	68	none	Yes	none	Yes	5.1	TIA	239	80 (angio)
E	M	75	Yes	Yes	none	No	5.1	TIA	63	70–80 (US)
F	F	50	none	none	none	Yes	7.6	AF	227	> 80 (US)
G	M	59	none	Yes	none	No	5.4	none	–	80 (US)
H	M	58	Yes	Yes	none	No	–	TIA	8	90 (angio)
I	M	61	none	Yes	none	No	4.8	AF	111	90 (angio)
J	F	64	none	Yes	none	No	3.8	AF	396	> 80 (US)
K	M	55	none	Yes	none	Yes	5.1	AF	49	> 80 (US)

*Previous heart infarction, angina pectoris, coronary bypass surgery, or angioplasty; †defined as treatment with antihypertensive drugs; ‡AF = amaurosis fugax; TIA = transient ischemic attack; §US = duplex ultrasound.

The 4-D analysis of Meairs and Hennerici (1999) applied rather complex data-acquisition equipment and processing algorithms. Our aim was to investigate how the motion can be analyzed from sequences of 2-D images. This paper focuses on the algorithm and its applicability to the problem.

MATERIALS AND METHODS

Acquisition of ultrasound data

The development of the method was based on data from 11 patients. These patients were selected consecutively among those scheduled for carotid endarterectomy at St. Olavs Hospital in Trondheim in the period January through June 2002. One asymptomatic patient was operated within the ACST study (asymptomatic carotid surgery trial), but the indication for operation was tight symptomatic stenosis for the other 10 patients. The characteristics of the patient group are given in Table 1.

After admission to the hospital, the patients were routinely subjected to US re-examination to verify the stenosis of the artery. During this examination, they were invited to participate in our study and all gave their informed consent. The supplementary data for our study were acquired using a System FiVe US scanner (GE Vingmed, Horten, Norway) and a 10-MHz flat linear-array probe. The probe was held in a stable position during acquisition of images either longitudinally or transversally to the carotid artery. In both cases, we imaged the most stenotic region. Both standard B-mode (2-D tissue) data and radiofrequency (RF) data were acquired, in time sequences of typical duration 3–5 s. Most examinations were made at a frame rate of 53.7 frames/s, and the others were made at 36.4 frames/s and, in two initial cases, at even lower frame rates. Each B-mode image typically measured 35 × 30 mm (ca. 450 × 120 pixels), and RF data were acquired in the central region of the B-mode image, typically sized 20 × 20 mm (ca. 300 × 150 pixels). The pixel resolution was, thus, about 0.08 × 0.25 mm/pixel for the B-mode data and 0.07 × 0.13 mm/pixel in the RF images. Furthermore, electrocardiogram (ECG) data were acquired from the last six patients.

Processing of preoperative ultrasound images

The US images were processed by programs developed in Matlab (v. 5.2) on a Macintosh computer. An overview of the processing software is shown in Fig. 1. The three main elements are: grey-scale analysis of B-mode images; motion analysis by correlation of RF im-

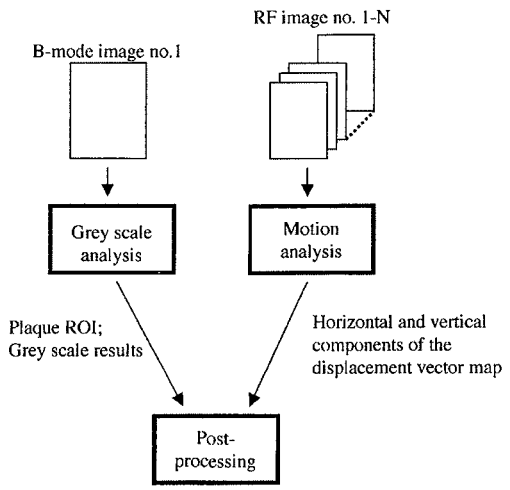

Fig. 1. Flow chart showing the three processing program units and the data flow between them.

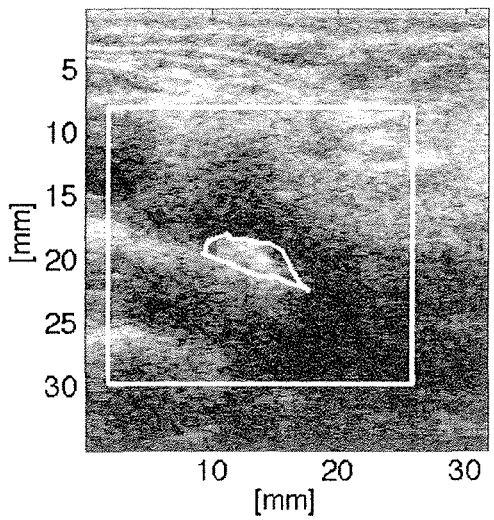

Fig. 2. Example of US B-mode image of the carotid artery, with plaque ROI outlined. The rectangular boundary encloses the region where RF data were acquired.

ages; and postprocessing of motion results. Each of these elements has been implemented as a separate program unit with a graphic user interface, where processing options and parameter settings can be specified interactively.

Grey-scale analysis

One of the first B-mode images of the sequence is selected for grey-scale analysis. First, the grey levels of the image are normalized so that the echo level of the blood corresponds to 1 and the echo level of the adventitia corresponds to 190, in accordance with previously reported procedures (Grønholdt et al. 2001; Lal et al. 2002; Sabetai et al. 2000). The plaque boundary is then outlined by an experienced vascular surgeon trained in US examinations. The boundary is a closed polygon that encloses the region-of-interest (ROI). Figure 2 shows a typical example. Within the plaque ROI, we calculate the grey-scale median (GSM) value and the percentage of pixels with echolucency less than 40 (PEP40), in accordance with other studies (Elatrozy et al. 1998; Lal et al. 2002).

Motion analysis

Input data. The motion analysis is done on RF images. We have also tested the algorithm using B-mode images as input; however, this gave movement velocities typically three to five times smaller than the correct

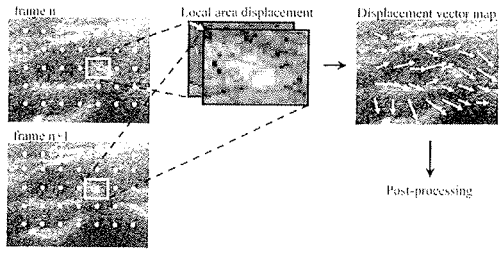

Fig. 3. Calculation of displacement vectors by 2-D correlation. Two consecutive RF images with overlaid grid points are shown to the left. Around each grid point, a small area is extracted for the correlation calculation, which yields the displacement vector (middle). This processing is done at all grid points and throughout the image sequence, resulting in the 3-D displacement vector map (right). The grid spacing, the correlation areas and the vector amplitudes are exaggerated in this illustration for clarity.

values (see the Velocity calibration section). After initial testing, we concentrated the efforts on longitudinal images of the artery.

Calculation of local displacement. The steps of the 2-D motion analysis are illustrated in Fig. 3. A regular point grid is superimposed onto every image frame. At each grid point, a local rectangular area is selected and a 2-D Hanning-shaped filter is applied to suppress the influence of the edge regions. A standard 2-D correlation is then calculated between the corresponding areas in two consecutive images. For fast execution, the correlation is performed by multiplying the Fourier transforms of the areas, followed by the inverse Fourier transformation of the product. We apply a standard 2-D fast Fourier transform (FFT) algorithm that requires zero-padding of the correlation areas to $2^n \times 2^m$ pixels before transformation. The result of the correlation shows a peak at a location corresponding to the relative displacement of the two areas. This displacement is the local tissue motion during the time lapse between the image frames. By interpolation in the correlation result matrix, we obtain the displacement with a resolution of 0.25 pixels.

For reliable results, the image structures and speckle patterns of the two local areas that are compared in the correlation should be fairly similar and exhibit only small displacements. Rotational movements between the images should be neglectable because the correlation algorithm only handles translation. These requirements are met by acquiring data at relatively high frame rates (see below and the Discussion section) and by using the edge-suppressing 2-D filter. In addition, extreme displacement results are discarded in a postprocessing step that is described below.

In the analysis, we use a grid point spacing of three

pixels (horizontally and vertically) and a local correlation area before zero-padding of 21 × 21 pixels. These parameter settings were determined from an investigation of the effect of processing parameters on the results (see below). The correlation of local areas is performed at all grid points and between consecutive image pairs throughout the captured sequence (Fig. 3). The horizontal and vertical components of all displacement vectors are stored in 3-D arrays, where the three dimensions are frame number and horizontal and vertical positions within the image. This 3-D data set will be referred to as the displacement vector map.

The analysis of one sequence (typically 700,000–1,000,000 grid points) took 4–6 h on a Power Mac G4 computer. The point grid then covered the whole RF data region. The number of grid points may be substantially reduced if the analysis is restricted to the plaque and its immediate vicinity.

Postprocessing of displacement vector map. The result files containing the grey-scale results and the displacement vector map are loaded into the postprocessing/analyzing program. This program is designed to accomplish several postprocessing tasks: 1. Scaling between B-mode and RF image coordinates and scaling of the displacement vector map to velocity; 2. discard invalid vectors from the displacement vector map; 3. optionally eliminate the effect of artificial motion; 4. optionally adjust the plaque ROI throughout the image sequence by using the displacement vectors; 5. estimate periodicity of ECG signal and motion results; 6. select subset of image frames to be analyzed or displayed; and 7. calculate and display characteristics of the displacement vector map.

The details of these tasks are as follows:

1. Due to the difference in image resolution, the plaque ROI must be scaled from B-mode coordinates to RF image coordinates. The displacement vectors (pixels/frame) are converted into movement velocities (mm/s) by using the RF image resolution and the time step between the images.
2. Extreme displacements found in the motion analysis will have poor accuracy, because they imply small overlap between the correlation areas. Therefore, we exclude all displacement vectors with amplitudes exceeding 1/4 of the correlation areas' dimensions from the postprocessing.
3. The displacement vector map comprises all displacements, including artefacts caused by, for example, unintentional probe movement during acquisition of the image sequence. To reduce such artefacts in the final results and, thus, facilitate comparison between different patients, we normalize the displacement vector map with respect to a particular image region. The region may be selected manually, or it may be automatically derived from the plaque ROI. The latter option is used for all examples in this article, yielding a reference region in the artery wall directly beneath the plaque (Fig. 4). We average the displacement components within this region and then subtract the average from all vectors in the entire image. This is done in every image, using the same reference region throughout the image sequence. The motion in the reference region is, thus, virtually eliminated, and the normalized vector map represents motion relative to this region.
4. The plaque ROI can optionally be updated throughout the image series, using the displacement vector map to perturb the ROI polygon's corners. The displacement vector at the actual corner position must then be estimated by interpolation in the vector map. However, initial testing indicated that this might lead to unacceptable distortion of the polygon (see the Discussion section). We have, therefore, used a fixed plaque ROI throughout the image sequence, for all examples in this article.
5. If the ECG signal exists, locations of the systolic peaks are estimated by thresholding and correlation along the time axis. This is further used to find the corresponding response in the motion data. If the ECG signal does not exist, the motion results are analyzed by correlation along the time axis to determine the periodicity.
6. The periodicity gives guidelines for selecting subsets of images from the whole sequence; however, the guidelines can be overridden after visual inspection of the ECG signal and the motion results. The subset may be a particular range of images; for example, one cardiac cycle, or all systolic or diastolic regions from the whole sequence.
7. The information contained in the displacement vector map can be evaluated and presented in several ways.

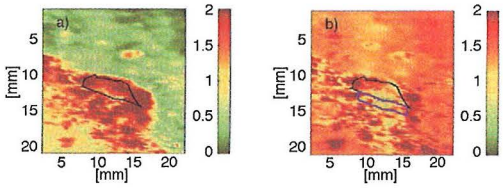

Fig. 4. Two representations of the motion analysis results. The pictures show the velocity amplitude, averaged over one cardiac cycle and color-coded according to the color bars (mm/s). The plaque ROI is shown by the black line in both images. (a) Velocity relative to the probe (upper image edge); (b) velocity relative to a reference region directly beneath the plaque ROI, shown by the blue line. The reference region is derived from the plaque ROI by the postprocessing program.

We have restricted the analysis to the following statistical parameters. Average over the plaque ROI of velocity amplitude and vertical and horizontal velocity components. These parameters are displayed as function of time. Also the average over time of velocity amplitude, and vertical and horizontal velocity components. These parameters are displayed in the image plane by color coding of the magnitudes. The parameters can further be expressed by single numbers (scalars) by averaging over both time and image coordinates. Examples are presented in the Results section.

Frame rate requirements

For the algorithm to yield reliable results, it is essential that the frame rate be sufficiently high. The choice of frame rate should be based on two criteria: 1. the in-plane motion; and 2. the out-of-plane motion. By in- and out-of-plane motion, we mean the tissue motion parallel to and perpendicular to the US image plane, respectively.

In-plane motion. Correct calculation of the in-plane motion requires that essential structures within the correlation area not be displaced too much. As an empirical criterion, we consider resulting displacements greater than ± 1/4 of the correlation area width or height to be invalid; hence, such displacements are excluded from the postprocessing analysis. For an area of extension L pixels (width or height), the frame rate F can then be given by:

$$F \geq \frac{v_{ip}}{r \cdot (L/4)}, \tag{1}$$

where v_{ip} is the in-plane velocity and r is the resolution (mm/pixel), both measured in the same direction as L. This gives $F \geq 27$ frames/s when $L = 21$ pixels, $r = 0.07$ mm/pixel and $v_{ip} = 10$ mm/s. The values for L and r are typical for our acquisition and processing procedures, and 10 mm/s is approximately the maximum velocity observed at the plaque surface (Meairs and Hennerici 1999).

Out-of-plane motion. Tissue structures moving in and out of the US image plane will degrade the image-to-image similarity and, thus, the correlation result. From similar argumentation as for in-plane motion, we restrict the displacement to ± 1/4 of the image thickness B. The frame rate is, thus, given by:

$$F \geq \frac{v_{\perp}}{B/4}, \tag{2}$$

where $v_{\perp}$ is the motion velocity perpendicular to the image plane. This gives $F \geq 40$ frames/s, when $v_{\perp} = 10$ mm/s and B is assumed to be 1 mm.

Most of our data sets were acquired at frame rates fulfilling these requirements. Consequences of using insufficient frame rates are discussed in the Discussion section.

Velocity calibration

The velocity calculated in the analysis was verified by a two-step calibration procedure. First, we manually modified a result file so that all displacement vectors were equal. This file was run through the postprocessing program and the calculated velocity was found to be constant over time and over the image, and equal to the input value. This step verified that the postprocessing, including scaling to mm/s, worked as intended.

Second, the whole analysis, including data acquisition and the correlation processing, had to be verified. This could be done in a laboratory experiment by imaging an object that moves in a controlled manner relative to the probe. However, because we did not have access to equipment for producing a realistic and well-defined movement at the scanning site, we chose another approach. We made freehand scans of a rubber-foam phantom in rest, by sideways translation of the probe (i.e., the motion direction lay in the US plane). In the image sequence, the phantom, thus, appears to move smoothly in the opposite direction, with the same intersection plane throughout the sequence (no change in phantom features or speckle pattern). A unidirectional and fairly smooth movement could be obtained over a period of a few s. The average velocity was estimated from the whole sequence of RF images, using our motion analysis program. The correct average velocity was found by the following independent analysis. We selected two RF images, typically 80–100 frames apart, at the beginning and the end of a smooth period. A well-defined phantom structure was identified in both images, and the coordinates of the intensity centroids (centers of gravity) were calculated in both images. The differences between the centroid coordinates gives the total displacement, which is scaled to mm by using the image resolution. Division by the time lapse between the images then gives the average velocity. Table 2 shows that the two results are in good agreement with each other.

A similar analysis on the B-mode images resulted in velocities found by our motion analysis program that were typically 3–5 times smaller than the velocities found from the RF images. The reason is probably that the B-mode images have been smoothed by rectification and filtering and, hence, are more likely to show similarity for many displacements. RF data, on the other

Table 2. Comparison of velocity calculated by averaging motion-analysis results ($\bar{V}_{mot\text{-}an}$) and average velocity found between first and last image frame $\bar{V}_{1\text{-}N}$, for two RF image sequences acquired during smooth movement of the US probe

	$\bar{V}_{mot\text{-}an}$ (mm/s)	$\bar{V}_{1\text{-}N}$ (mm/s)
Sequence A (n = 80 frames; 1.7 s)	0.32	0.31
Sequence B (n = 100 frames; 2.2 s)	1.32	1.40

hand, contain more distinct features that are utilized by the correlation algorithm. In particular, the phase information along the beam strengthens the ability to find the correct displacement in this direction.

Processing parameter settings

The displacement vectors and, thus, the postprocessing results, might depend not only on the actual tissue motion, but also on the parameter settings in the analysis. The parameters of possible influence are: 1. the spacing of the point grid; 2. the size of the local correlation area; 3. superimposing an edge-suppressing 2-D filter (Hanning shape in both directions) to the areas before correlation, vs. using no filter; and 4. obtaining the overall displacement through a separate correlation over a larger area ("gross window" GW), vs. performing only the local area correlation. The intention of the last option is to track large and abrupt motions by the GW and, then, use the small-area correlation merely for fine-tuning of local motion.

The size of the local correlation area is of particular concern, because it must be large enough to contain distinct structures in the images, but still small enough to give well-localized and representative displacement vectors. The use of an edge-suppressing filter can be expected to interact with the area size.

We have investigated the effects of the parameters listed above. The test settings are given in Table 3. The point grid spacing is varied by the following postprocessing step. All cases are run with spacing 3 × 3 pixels (the same spacing was applied in the horizontal and the vertical direction); however, by modifying the result file, every second row and column can be excluded, yielding an effective spacing of 6 × 6 pixels.

The parameter combinations were tested on two data sets: a recording of a foam-rubber phantom in rest, with smooth sideways motion of the probe, and a patient data set, where the plaque was easily visible and showed distinct motion. The results were evaluated by visually comparing the time plots of motion features similar to those shown in Fig. 5; however, the number of features was enlarged by including average motion-direction angle and SDs of total displacement and direction angle. All features were averaged over a rectangular ROI (enclosing 130 grid points) in the phantom data, and over the plaque ROI (81 grid points) in the patient data.

We observed only negligible effects of parameter settings. The details, given by the following list, are common to both the phantom and the patient data.

- The correlation area size has no influence, except from negligible changes in the direction angle;
- With filter on, the SDs increase slightly compared with filter off, whereas mean values remain unchanged;
- Using inactive GW instead of active GW yields slightly larger SDs, slightly less amplitude means and slightly more variation in direction angle;
- Changing the grid spacing from three to six pixels has no effect.

These effects are hardly visible and they are all considered insignificant compared with the deterministic variation in the time plots. Therefore, we chose the following setting for all further processing: point-grid spacing 3 × 3 pixels; correlation area 21 × 21 pixels; filter on; GW inactive. The high point-grid resolution is retained for the purpose of future postprocessing of new features.

Table 3. Processing parameters investigated for effects upon the motion results

	Correlation area size (pixels)				
	11 × 11	17 × 17	21 × 21	25 × 25	31 × 31
Filter on / GW active (10 pixels)	–	X	X	X	X
Filter off / GW active (10 pixels)	X	X	X	X	X
Filter on / GW inactive –	–	X	X	X	–

The 12 combinations marked by X were chosen as a reasonable experimental design, with respect to size and relevance of this investigation. Only quadratic correlation areas were considered. The filter is a 2-D Hanning filter with size equaling the correlation area dimensions. GW active means that the GW correlation was run before the local correlation, with maximum allowed GW displacement in parentheses. All parameter combinations were applied for grid resolutions of 3 or 6 pixels and on two data sets, giving a total of 48 test cases.

Table 4. Results from grey-scale analysis of the plaque ROI in B-mode images for three patients

	Patient D	Patient G	Patient K
Pixels in plaque ROI	1533	844	743
Grey-scale median	43.5	94.6	38.3
% pixels with echolucency < 40	46.1	10.3	52.9

The images were normalized that the echolucency of blood was 1 and the echolucency of the adventitia was 190.

RESULTS

To illustrate the potentials of the motion analysis, we include results from three of the patients listed in Table 1, viz. patients D, G and K. These three patients were chosen because they show interesting differences in both grey-scale and motion results. They are representative for the whole group with respect to age, cholesterol, degree of stenosis and concomitant diseases. Note, however, that patient G was the only asymptomatic patient in the group; patients D and K had experienced TIA and AF, respectively. The US frame rate was 36.4 frames/s for patient D and 53.7 frames/s for the other two. ECG data were not acquired for patient D.

Results from the grey-scale analysis are listed in Table 4. Patient G has higher grey-scale median and lower percent of pixels with echolucency below 40 than the other two patients. This agrees with the typical appearance of asymptomatic and symptomatic plaques (Grønholdt et al. 2001; Lal et al. 2002; Sabetai et al. 2000).

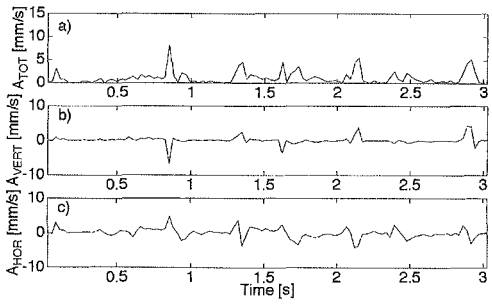

Fig. 5. Motion analysis results for patient D. Velocities averaged over the plaque ROI. The velocities are relative to a reference region directly beneath the plaque. (a) Average velocity amplitude; (b) and (c) average of vertical and horizontal velocities, respectively. ECG data were not acquired for this patient.

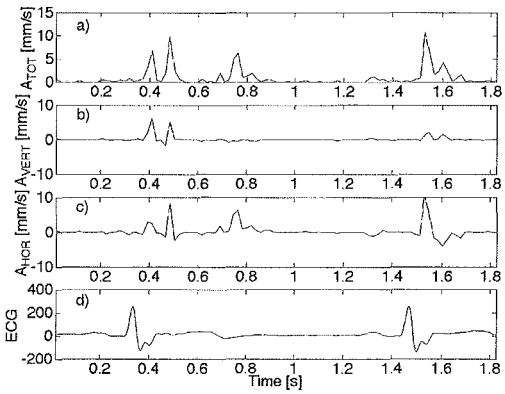

Fig. 6. Motion analysis results for patient G. Velocities averaged over the plaque ROI. The velocities are relative to a reference region directly beneath the plaque. (a) Average velocity amplitude; (b) and (c) average of vertical and horizontal velocities, respectively; (d) ECG signal.

Figures 5, 6 and 7 show the time development of the movement velocity (amplitude, vertical and horizontal components) averaged over the plaque ROI, for the three patients, respectively. We observe peak velocities in the order of 5–12 mm/s, which agree well with the maximum plaque surface velocity of 10 mm/s reported by Meairs and Hennerici (1999). These peaks typically occur 0.1 s after the QRS complex of the ECG signal. The movement is also seen when the original image sequences are run as movies. Thus, it is evident that the movement is

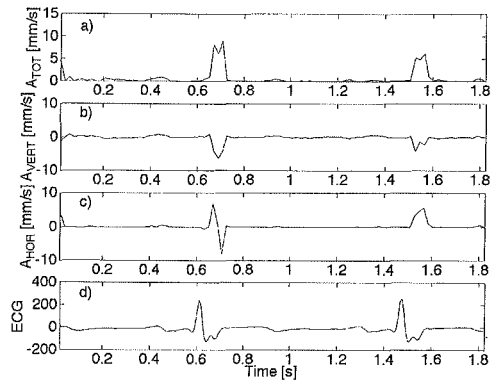

Fig. 7. Motion analysis results for patient K. Velocities averaged over the plaque ROI. The velocities are relative to a reference region directly beneath the plaque. (a) Average velocity amplitude; (b) and (c) average of vertical and horizontal velocities, respectively; (d) ECG signal.

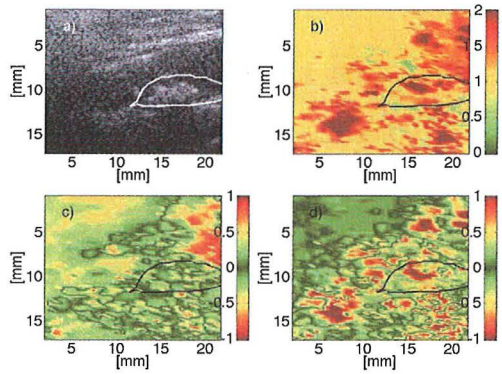

Fig. 8. Motion analysis results for patient D. Velocities averaged over one estimated cardiac cycle (2–2.8 s in Fig. 5). The velocities are relative to a reference region directly beneath the plaque. The color bars indicate the velocity in mm/s. (a) The first RF image of the sequence; (b) average of velocity amplitude; (c) and (d) average of vertical and horizontal velocities, respectively. The plaque ROI is superimposed on all displays.

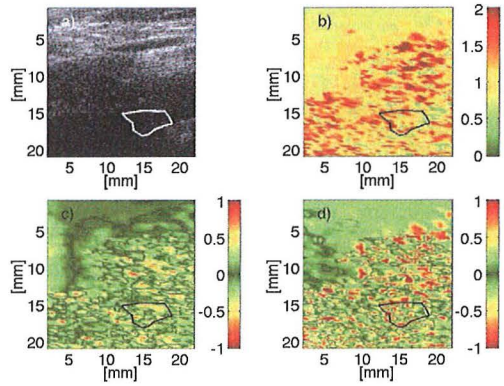

Fig. 10. Motion analysis results for patient K. Velocities averaged over one cardiac cycle (0.6–1.5 s in Fig. 7). The velocities are relative to a reference region directly beneath the plaque. The color bars indicate the velocity in mm/s. (a) The first RF image of the sequence; (b) average of velocity amplitude; (c) and (d) average of vertical and horizontal velocities, respectively. The plaque ROI is superimposed on all displays.

due to the pulse pressure wave passing the insonated region of the carotid artery. The velocity peaks are seen most clearly in Figs. 6 and 7. The movement at 0.7–0.8 s in Fig. 6 can also be observed in the original image sequence and is, thus, not a processing artefact; however, the physical reason for this movement is not clear. The less distinct results in Fig. 5 probably reflect the decrease in processing accuracy as the frame rate is reduced.

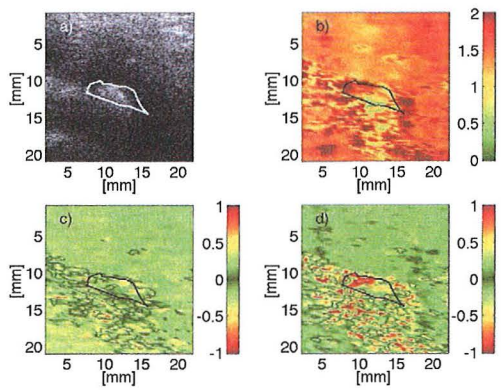

Fig. 9. Motion analysis results for patient G. Velocities averaged over one cardiac cycle (0.35–1.5 s in Fig. 6). The velocities are relative to a reference region directly beneath the plaque. The color bars indicate the velocity in mm/s. (a) The first RF image of the sequence; (b) average of velocity amplitude; (c) and (d) average of vertical and horizontal velocities, respectively. The plaque ROI is superimposed on all displays.

Figures 8, 9 and 10 show an RF image with the plaque ROI outlined, together with the movement velocity (amplitude, vertical and horizontal components) averaged over one cardiac cycle, for the three patients, respectively. Ideally, the tissue should return to the same position after one cardiac cycle and hence, each of the vertical and horizontal velocity components should average to zero. This is fairly well achieved, especially for the vertical movement, which is generally small (c), and for the sequences acquired at high frame rates (Figs. 9 and 10). The velocity amplitudes (b), however, may average to considerably higher values.

In Figs. 8, 9 and 10, it is particularly interesting to notice that some plaque regions exhibit large movements, and other regions are relatively immobile. This inhomogeneous motion pattern indicates that the plaque may be subject to internal forces that may eventually cause fissures and disruption. The quantification of such patterns may represent important information to the clinician. However, more work is needed to understand and interpret these patterns correctly.

We have further averaged each of the three velocity parameters over both the plaque ROI and over one cardiac cycle. These results, for all 11 patients, are listed in Table 5. Most of the mean amplitudes lie in the range of 1–2 mm/s, and the mean vertical and horizontal components are about an order of magnitude lower. More work is needed to determine the significance of these numbers as plaque risk indicators.

Table 5. Motion-analysis results averaged over the plaque ROI and over one cardiac cycle

Patient	Mean velocity amplitude (mm/s)	Mean vertical velocity (mm/s)	Mean horizontal velocity (mm/s)	Comments
A	2.19	0.00	0.01	No ECG; low frame rate
B	1.82	−0.12	−0.02	No ECG; low frame rate
C	0.85	−0.02	−0.02	No ECG; difficult to find cardiac cycle
D	1.25	0.07	−0.06	No ECG; low frame rate
E	1.64	−0.45	−0.10	No ECG
F	2.01	−0.05	0.10	Low frame rate
G	1.48	−0.17	0.17	–
H	1.66	0.03	0.00	–
I	1.41	0.06	0.16	–
J	–	–	–	Plaque ROI almost outside RF region
K	0.99	0.00	0.18	–

DISCUSSION

Method accuracy and error sources

Image quality. The RF data were obtained directly from the scanner, and no preprocessing was done before the correlation analysis. No scan conversion was needed because the examinations were done by a linear-array probe. The velocity calibration test and the parameter variation test confirm that the method works as intended and thus, factors such as image resolution and contrast appear to be appropriately set. However, for some of the patients (*e.g.,* plaque K, Figs. 7 and 10), visualizing and outlining of the plaque was difficult due to various reasons, such as tortuous vessels, low echogenicity and disturbing calcifications.

Accuracy. The quality of the results can be characterized by the accuracy of the components or magnitudes of the displacement vectors and by the resolution of the color plots. The color-plot resolution (Figs. 8, 9 and 10) is basically a consequence of using correlation areas with finite height and width. Because these correlation areas overlap, the corresponding displacement vectors will be partially correlated. The overlap and, thus, the correlation decreases to zero for points more than 21 pixels (size of correlation area; typically 1.5 mm) apart.

The accuracy of the method was confirmed by the velocity calibration on phantom data. The fairly good repetition of systolic and diastolic motion (Figs. 5, 6 and 7) indicates that the essential movement information is captured also from patient data. However, the accuracy of the clinical (patient) results is difficult to quantify and may differ from the method's inherent accuracy. This is because the tissue is imaged by 2-D slicing through the volume, whereas the actual movements take place in 3-D. The acquisition frame rate, thus, has important influence on the clinical accuracy.

Equations (1) and (2) indicate that frame rates above ~ 40 frames/s are necessary for proper analysis of the motion, for the given tissue velocities and processing parameter setting. This is supported by Figs. 5 through 10, which confirm that 54 frames/s seems adequate (patients G and K), whereas 36 frames/s may give a loss in accuracy (patient D). However, it must be taken into account that in-plane movements merely mean a translation of the tissue structure and speckle pattern, whereas out-of-plane movement implies a nonuniform distortion of the structures and speckle pattern. Thus, the out-of-plane motion, in particular, should not be neglected as error source.

Due to the cyclic nature of the movements, the displacement vectors at one location should form a closed loop during one cardiac cycle. A consequence of using a finite frame rate, which may imply less accurate results for the largest (most rapid) tissue movements, is that this may not always be the case. When checking this on our results, we typically find some drift that cannot be neglected. This implies that an update of the plaque ROI boundary using the displacement vector map becomes less accurate. We have, therefore, chosen to use a fixed plaque ROI throughout the analysis, although this undoubtedly introduces other uncertainties in the results. There are several ways to overcome these problems. Apart from increasing the frame rate, which is unrealistic for our present equipment and acquisition protocol, shorter periods of the cardiac cycle or appropriate averaging over several cycles might be considered. It is still a matter of research to determine the kind of information that can be gained from such results.

Future use of motion analysis

Only a few examples of information gained from the displacement vector map are shown in this paper. Of the three patients displayed in Figs. 5 through 10, the asymptomatic patient G shows the largest motion; however, both larger and smaller velocities can be found in the total patient group (Table 5). This indicates that the development of a symptomatic plaque might not be characterized by total motion alone, and that other properties

should also be evaluated. Our future work will address what kinds of parameters should be calculated from the displacement vector map and how to present these results in the most suitable form to the clinician. Reproducibility is also an issue that should be further investigated.

It is our intention to compare the motion results with results from the grey-scale analysis and with histopathologic description of the removed plaque specimens, when the data material is large enough to allow for statistical analysis. The ability of motion analysis to identify plaques with a high risk for disruption and complications should be evaluated through a prospective study on asymptomatic patients with carotid artery stenosis. However, due to the relatively low rate of cerebrovascular events in an unselected group of these patients, this approach would imply an extensive study. Therefore, we look for alternative strategies for verification of the method.

CONCLUSIONS

We have developed a method for analysis of 2-D motion in carotid artery plaques from sequences of RF US images. The method is based on standard 2-D correlation between small image areas from consecutive images. The basic outcome is a displacement vector map from which a variety of parameters may be calculated in the postprocessing steps. Two complementary ways of visualizing the motion velocity have been demonstrated in this paper: averaging over an image region, presented as a function of time and averaging over a time period, presented as an image. The latter option offers the opportunity to study motion heterogeneities within the plaque, which may be related to plaque composition and the risk of embolization.

Testing on laboratory data showed that the method works as intended. Applied to patient data, the motion analysis method yields velocity results corresponding with the movements observed by direct inspection of the image sequences and with the ECG signal. The systolic response shows peak velocities of typically 10mm/s, which agrees well with previously reported values. The main error source is assumed to be the motion component perpendicular to the image plane. This can be compensated for by using a sufficiently high frame rate during data acquisition, or by appropriately averaging the results.

The future work will address the significance and interpretation of parameters calculated from the displacement vector map, and how to present this information to the clinician. For this purpose, we will apply the motion-analysis method to a larger patient group.

To our knowledge, there are few quantitative studies of dynamic plaque behavior. Future clinical application of our analysis method is necessary to evaluate its potential for identifying patients with a high risk of plaque disruption and embolization.

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REFERENCES

AbuRahma AF, Thiele SP, Wulu JT. Prospective controlled study of the natural history of asymptomatic 60% to 69% carotid stenosis according to ultrasonic plaque morphology. J Vasc Surg 2002;36: 437–442.

Chan KL. Two approaches to motion analysis of the ultrasound image sequence of carotid atheromatous plaque. Ultrasonics 1993;31: 117–123.

Elatrozy T, Nicolaides A, Tegos T, Griffin M. The objective characterization of ultrasonic carotid plaque features. Eur J Vasc Endovasc Surg 1998;16:223–230.

El-Barghouty N, Geroulakos G, Nicolaides A, Androulakis A, Bahal V. Computer-assisted carotid plaque characterization. Eur J Vasc Endovasc Surg 1995;9:389–393.

European Carotid Plaque Study Group. Carotid artery plaque composition—Relationship to clinical presentation and ultrasound B-mode imaging. Eur J Vasc Endovasc Surg 1995;10:23–30.

Falk E. Why do plaques rupture? Circulation 1992;86(Suppl. III):III-30–III-42.

Golledge J, Greenhalgh RM, Davies AH. The symptomatic carotid plaque. Stroke 2000;31:774–781.

Grønholdt MLM, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. Circulation 2001;104:68–73.

Hennerici M, Meairs S. Imaging arterial wall disease. Cerebrovasc Dis 2000;10(Suppl. 5):9–20.

Iannuzzi A, Wilcosky T, Mercuri M, et al. Ultrasonographic correlates of carotid atherosclerosis in transient ischemic attack and stroke. Stroke 1995;26:614–619.

Lal BK, Hobson RW, Pappas PJ, et al. Pixel distribution analysis of B-mode ultrasound scan images predicts histologic features of atherosclerotic plaques. J Vasc Surg 2002;35:1210–1217.

Langsfeld M, Gray-Weale AC, Lusby RJ. The role of plaque morphology and diameter reduction in the development of new symptoms in asymptomatic carotid arteries. J Vasc Surg 1989;9:548–557.

Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis (the Tromsø study). Circulation 2001;103:2171–2175.

Meairs S, Hennerici M. Four-dimensional ultrasonographic characterization of plaque surface motion in patients with symptomatic and asymptomatic carotid artery stenosis. Stroke 1999;30:1807–1813.

Sabetai MM, Tegos TJ, Nicolaides AN, et al. Hemispheric symptoms and carotid plaque echomorphology. J Vasc Surg 2000;31:39–49.

Woodcock JP. Characterization of the atheromatous plaque in the carotid arteries. Clin Phys Physiol Meas 1989;10(Suppl. A):45–49.

Paper II

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• *Original Contribution*

PARAMETERS DESCRIBING MOTION IN CAROTID ARTERY PLAQUES FROM ULTRASOUND EXAMINATION: A REPRODUCIBILITY STUDY

TORBJØRN DAHL,* JON BANG,† ALEXANDRA USHAKOVA,‡
STIAN LYDERSEN‡ and HANS OLAV MYHRE*
*Department of Surgery, St. Olavs Hospital, Trondheim, Norway; †Department of Medical Technology, SINTEF Health Research, Trondheim, Norway; and ‡Faculty of Medicine, Unit for Applied Clinical Research, NTNU, Trondheim, Norway

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Abstract—We have previously developed a method for quantifying motion in carotid artery plaques from sequences of ultrasound (US) radiofrequency images. Here, we examine the intraoperator reproducibility of the results. Five independent recordings were made on each of six symptomatic and six asymptomatic patients, and processed off-line into 29 motion parameters, representing motion amplitude, stretch/compression and shear motion. For the statistical analysis, we used a linear mixed model and investigated the parameters for contributions from individual patients, contributions from recordings on each patient and contributions from heart cycles within each recording. The model was valid for seven parameters calculated over the entire heart cycle (four calculated over the systole only), which all showed good reproducibility (intraclass coefficient for variance over all patients $\rho_\alpha \geq 0.4$). Averaging three recordings of two heart cycles each gives acceptable accuracy (normalised variance of patient means $\lambda < 0.3$). This acquisition scheme is reasonable in a clinical situation. (E-mail: jon.bang@sintef.no) © **2004 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Carotid artery stenosis, Plaque characterisation, Embolism, Ultrasonography, Motion analysis, Parameter reproducibility, Intraoperator study.**

INTRODUCTION

Ultrasound (US) is commonly applied for noninvasive investigation of atherosclerotic plaques in the carotid arteries. It can select patients for carotid endarterectomy based on the degree of stenosis, provide preoperative anatomical information and may indicate the risk for embolisation (AbuRahma et al. 2002; Landwehr et al. 2001).

The analysis of grey-scale values and other texture parameters in single US images is a well-established technique, and echolucent plaques have been shown to represent an increased risk for cerebrovascular events (Grønholdt et al. 2001; Mathiesen et al. 2001). However, such analyses do not incorporate the dynamic behaviour of the plaque, which may play an important role in the process of plaque rupture and embolisation. The plaque and the surrounding tissue exhibit a periodic motion driven by the pulsating blood pressure in the artery. It has been suggested that such movement of the arterial wall might cause mechanical stress leading to minor cracks and fissures (Falk 1992; Woodcock 1989). Another effect might be rupture of the vasa vasorum due to relative movement between the plaque and the vessel wall (Iannuzzi et al. 1995; Woodcock 1989).

Golemati et al. (2003) give a concise overview of various methods for calculation of motion in US images. However, the literature shows few examples of analysis of the plaque motion. Iannuzzi et al. (1995) investigated patients with transient ischemic attacks and found that longitudinal motion occurred more often in the ipsilateral plaques than in the contralateral ones. However, they did not quantify the motion. Chan (1993) demonstrated 2-D motion analysis in US images, at low frame rates and for a small number of tracked points. Meairs and Hennerici (1999) analysed plaque surface movement by an optical flow method and found significant differences in some velocity parameters between symptomatic and asymptomatic patients. They used a 4-D acquisition and analysis procedure (several 3-D data sets gated by ECG signal). Using a 2-D cross-correlation (block matching)

Address correspondence to: Dr. Jon Bang, SINTEF Health Research, Medical Technology, NO-7465 Trondheim Norway. E-mail: jon.bang@sintef.no

technique on US images captured at 25 frames/s, Golemati et al. (2003) have recently demonstrated region tracking and quantification of relative motion between a limited number of points within the plaque and in the vessel wall and surrounding tissue.

We have developed a method for motion analysis of carotid plaque from sequences of US images (Bang et al. 2003). The cross-correlation technique is similar to that applied by Golemati et al. (2003); however, by using higher frame rates and a finer mesh of analysis points, we obtain high resolution in both time and space. We have demonstrated that heterogeneous motion internal to the plaque can be quantified and visualised.

For the method to have clinical relevance, it is crucial that the motion results contain genuine information that eventually can be related to the plaque condition. This implies that the results must reproduce satisfactorily when the measurements are repeated under unchanged conditions. In this article, we investigate the intraoperator reproducibility of the motion results by performing repeated data acquisition on a number of patients. All recordings were done by the same examiner. Statistical analysis on these data then shows the relative magnitude of variations between patients, between recordings and between heart cycles within each recording. We also address the question of how many repetitions are needed for reliable results.

MATERIALS AND METHODS

The patient group

This prospective study comprised six patients with a symptomatic carotid stenosis and six asymptomatic patients. The asymptomatic patients had participated in the Asymptomatic Carotid Surgery Trial (ACST) (Halliday et al. 1994) for 3 to 8 years (average 5.7 years), receiving only medical treatment. They came from the local area, and were invited for an examination in addition to the ACST follow-up. The symptomatic patients were selected consecutively among those scheduled for carotid endarterectomy at St. Olavs Hospital, Trondheim, in the period March through September 2003. Three of these patients had experienced their cerebrovascular events more than 6 months earlier and would thus be termed asymptomatic according to the ACST criteria (Halliday et al. 1994). The symptomatic patients were examined 1 to 3 days before carotid endarterectomy in connection with the routine preoperative scanning. Characteristics of the patient group are given in Table 1.

Data acquisition

The patients were subject to US examination using a System Five scanner (GE Vingmed, Horten, Norway) and a 10-MHz flat linear-array transducer. All examinations were done by the same operator, who is an experienced vascular surgeon trained in US examinations. All patients were examined in the supine position with the head turned to the opposite side of the artery being examined. The transducer was held in a fixed position for longitudinal imaging of the most stenotic region of the artery (i.e., the position yielding the highest peak systolic blood velocity). We identified the plaque using a default carotid study scanner application (B-mode imaging with Doppler colour flow), with the gain setting adjusted for optimal image quality. With the transducer in the same position, we switched to a scanner application for acquisition of both tissue and radiofrequency (RF) data, and recorded image sequences over typically 3 s at a frame rate of 53.7 frames/s. This corresponds to two to three heart cycles, as shown by the simultaneously recorded ECG. For reproducibility analysis, we made five recordings on each patient. These recordings were made within 30 to 45 min, separated by approximately 5 min. The transducer was repositioned according to the above procedure between each of the recordings. Figure 1 illustrates the hierarchical structure of the recorded data.

Table 1. Characteristics of the patient group.

	Symptomatic	Asymptomatic	All
Number	6	6	12
Mean age (range) [years]	63.0 (56–76)	70.8 (66–78)	66.9 (56–78)
Male/female	3/3	5/1	8/4
Coronary heart disease	4	2	6
Hypertension	2	4	6
Diabetes	1	0	1
Mean cholesterol (range) [mmol/L], nonfasting	4.7 (3.2–7.1)	not measured	–
Cholesterol-lowering medication	5	4	9
Degree of stenosis (US)	>70%	>70%	>70%
Presenting symptom	1 stroke; 1 transient ischemic attack; 4 amaurosis fugax	–	–
Time from last event to examination	1 week or less: 3; more than 6 months: 3	–	–

Data processing

The tissue and RF data were transferred to a computer for off-line analysis by programs developed in Matlab® (The MathWorks Inc., Natick, MA). The RF data were subject to motion analysis by the method described in Bang et al. (2003). The basic steps of the analysis are illustrated in Fig. 2. In short, the method tracks motion by 2-D correlation of local regions (21 × 21 pixels with Hanning-shaped edge suppression) in consecutive RF images. This is done throughout the image area at analysis points with indexes (u,v) separated by $dy \approx 0.2$ mm vertically and $dx \approx 0.4$ mm horizontally, and for all images $w = 1, 2, \ldots N$. The resulting displacement vectors are converted to velocity vectors $\vec{V}(u,v;w)$ and stored to file. The vascular surgeon who conducted the US examinations then outlined the plaque region-of-interest (ROI) in one of the B-mode images. Note that the grey-scale values resulting from this processing are not used further in this article; however, they are calculated and stored for future comparison with the motion parameters. In a subsequent postprocessing step, various motion characteristics can be derived from the velocity vectors. Invalid vectors are identified by several criteria and are discarded from the postprocessing. To reduce the influence of artificial movements due to patient or probe disturbances, vector component means are calculated over a reference region in each image, and subtracted over the entire image. The reference region is located in the vessel wall adjacent to the plaque, and is automatically derived from the plaque ROI by shifting a section of the wall-adjacent ROI boundary down by a constant amount. For more details on the processing of RF images, see Bang et al. (2003).

We investigate three classes of motion characteristics: velocity vector components and magnitude, tension (stretch/compression), and torsion (shear motion). Mathematically, these quantities are calculated, respectively, as the amplitude A, divergence D and curl C of the vector

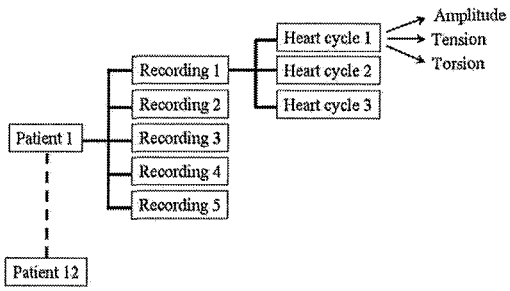

Fig. 1. The hierarchical structure of the ultrasound examination of the carotid artery and data processed from these recordings.

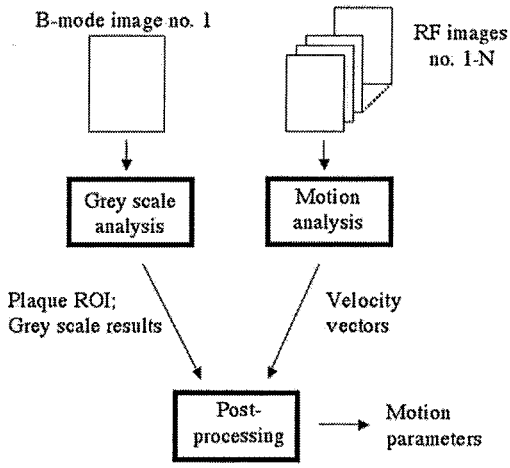

Fig. 2. Flow chart for the processing of motion parameters (adapted from Bang et al. 2003).

field $\vec{V}(u,v;w) = [V_x(u,v;w), V_y(u,v;w)]$ (Lewis and Ward 1989):

$$A(u,v;w) = \left|\vec{V}(u,v;w)\right| = \sqrt{V_x(u,v;w)^2 + V_y(u,v;w)^2} \tag{1}$$

$$\begin{aligned} D(u,v;w) &= div(\vec{V}(u,v;w)) \\ &= \frac{V_x(u+1,v;w) - V_x(u,v;w)}{dx} \\ &\quad + \frac{V_y(u,v+1;w) - V_y(u,v;w)}{dy} \end{aligned} \tag{2}$$

$$\begin{aligned} C(u,v;w) &= \pm \left|curl(\vec{V}(u,v;w))\right| \\ &= \frac{V_y(u+1,v;w) - V_y(u,v;w)}{dx} \\ &\quad - \frac{V_x(u,v+1;w) - V_x(u,v;w)}{dy}. \end{aligned} \tag{3}$$

Note that these formulas describe the discrete approximation to divergence and curl in two dimensions (the image plane uv), and that C is the signed magnitude of the curl vector. w is merely an image counter and, as such, does not take part in the divergence and curl operations.

All results can be presented in several ways. Three options are suggested in Bang et al. (2003): 1. colour-coded images, by averaging over the time dimension; 2. time-depending parameters, by averaging over predefined image regions such as the plaque ROI; and 3. single numbers, by either averaging or extracting mini-

mum/maximum values, over each of the time and image dimensions. In this study, we used the last option to create single-valued parameters as input to the statistical analysis. All the investigated parameters are listed in Table 2. Note, in particular, that the definition of A_6 is similar to the maximal discrepant surface velocity (MDSV) parameter studied by Meairs and Hennerici (1999), although MDSV is derived from the plaque surface in 3-D, whereas A_6 is derived from the 2-D cross-section area. Furthermore, A_7 is the 95th percentile value of the same quantity, defined in this way to exclude amplitude outliers.

We did the statistical analysis for two time ranges: parameters calculated over the entire heart cycle and parameters calculated over the systolic range of the cycle only. Both ranges were defined using the ECG signal. The duration of the entire heart cycle was found by autocorrelation of the ECG signal; however, the start of this period relative to the QRS complex was arbitrarily defined to utilise the complete recording. For the systolic range, we identified the Q wave and the end of the T wave. This range was expanded by 20% beyond the latter point to give the systolic part. The empirical expansion is intended to account for the time delay between the ECG signal and the arterial pressure pulse.

Statistical analysis

We used a linear mixed model (McCulloch and Searle 2001, pages 13–14) for the measured value (parameter) Y_{ijk} for the kth heart cycle in recording j on patient i:

$$Y_{ijk} = \mu + \alpha_i + \beta_{j(i)} + \varepsilon_{k(ji)}, \quad (4)$$

where μ is the overall mean; α_i is the (unobserved) effect of patient number i; $\beta_{j(i)}$ is the (unobserved) effect of recording j on patient i; and $\varepsilon_{k(ji)}$ is the deviation from the (unobserved) mean at recording j on patient i.

The quantities α_i and $\beta_{j(i)}$ are random effects, and $\varepsilon_{k(ji)}$ is an error term. These were assumed to be independent, normally distributed variables with homogeneous variances σ^2_α, σ^2_β and σ^2_ε, respectively. The variance components σ^2_α, σ^2_β, and σ^2_ε were estimated using restricted maximum likelihood (REML) which provided unbiased estimators (McCulloch and Searle 2001, page 21). The analysis was carried out in SPSS version 11 (SPSS Inc., Chicago, IL).

Table 2. Motion parameters investigated in this study.

Parameter	Definition	Comments
Amplitude parameters (A = velocity amplitude)		
A_1	mean_{time} of $\{\text{mean}_{ROI}(A)$ in each frame$\}$	
A_2	mean_{time} of $\{\text{min}_{ROI}(A)$ in each frame$\}$	
A_3	mean_{time} of $\{\text{max}_{ROI}(A)$ in each frame$\}$	
A_4	mean_{time} of $\{\text{mean}_{ROI}(V_y)$ in each frame$\}$	V_y = vertical velocity comp.
A_5	mean_{time} of $\{\text{mean}_{ROI}(V_x)$ in each frame$\}$	V_x = horizontal velocity comp.
A_6	max_{time} of $\{\text{range}_{ROI}(A)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$
A_7	95-percentile in time of $\{\text{range}_{ROI}(A)$ in each frame$\}$	95-percentile of A_6
Tension parameters (D = divergence)		
D_1	mean_{time} of $\{\text{mean}_{ROI}(D)$ in each frame$\}$	
D_2	min_{time} of $\{\text{mean}_{ROI}(D)$ in each frame$\}$	for ln transform: $-D_2$
D_3	max_{time} of $\{\text{mean}_{ROI}(D)$ in each frame$\}$	
D_4	range_{time} of $\{\text{mean}_{ROI}(D)$ in each frame$\}$	$= D_3 - D_2$
D_5	mean_{time} of $\{\text{min}_{ROI}(D)$ in each frame$\}$	for ln transform: $-D_5$
D_6	range_{time} of $\{\text{min}_{ROI}(D)$ in each frame$\}$	
D_7	mean_{time} of $\{\text{max}_{ROI}(D)$ in each frame$\}$	
D_8	range_{time} of $\{\text{max}_{ROI}(D)$ in each frame$\}$	
D_9	mean_{time} of $\{\text{range}_{ROI}(D)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$
D_{10}	min_{time} of $\{\text{range}_{ROI}(D)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$
D_{11}	max_{time} of $\{\text{range}_{ROI}(D)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$
Torsion parameters (C = curl)		
C_1	mean_{time} of $\{\text{mean}_{ROI}(C)$ in each frame$\}$	
C_2	min_{time} of $\{\text{mean}_{ROI}(C)$ in each frame$\}$	for ln transform: $-C_2$
C_3	max_{time} of $\{\text{mean}_{ROI}(C)$ in each frame$\}$	
C_4	range_{time} of $\{\text{mean}_{ROI}(C)$ in each frame$\}$	$= C_3 - C_2$
C_5	mean_{time} of $\{\text{min}_{ROI}(C)$ in each frame$\}$	for ln transform: $-C_5$
C_6	range_{time} of $\{\text{min}_{ROI}(C)$ in each frame$\}$	
C_7	mean_{time} of $\{\text{max}_{ROI}(C)$ in each frame$\}$	
C_8	range_{time} of $\{\text{max}_{ROI}(C)$ in each frame$\}$	
C_9	mean_{time} of $\{\text{range}_{ROI}(C)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$
C_{10}	min_{time} of $\{\text{range}_{ROI}(C)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$
C_{11}	max_{time} of $\{\text{range}_{ROI}(C)$ in each frame$\}$	$\text{range}_{ROI} = \text{max}_{ROI} - \text{min}_{ROI}$

Transforming an input parameter by a nonlinear function may yield better agreement with the model assumptions. Visual analysis of our data, as well as application of a stabilising variance (Box–Cox) method (Box et al. 1978, pages 232–234) showed that, for some of our parameters, the measured values should be used directly whereas, for others, the natural logarithm of the parameters agreed better with the model. In one case the square root should be used. The transforms were only applied to parameters that were either always positive or always negative throughout the patient group (in the latter case, the sign was changed first). Logarithmic and square root transformations are denoted by ln and sqrt in the following, respectively.

The assumptions of normality for the within-group error (ε in our model) and for the random effects (α and β) were assessed with normal probability plots (*QQ*-plots) of the residuals for each level (Walpole et al. 1998, pages 213–215). From these graphs, we also identified outliers.

Checks on the model assumptions of homogeneity of variances for the residuals were performed by visual inspection of the input, and by Bartlett's test for homogeneity (Walpole et al. 1998, pages 470–473). Homogeneity of the variance $\sigma_\beta^2 + \sigma_\varepsilon^2$ was checked by Bartlett's test on the "patient residuals"

$$y_{ijk} - \overline{y_{i..}}, \tag{5}$$

where

$$\overline{y_{i..}} = \frac{1}{\sum_{j=1}^{m_i} n_{j(i)}} \sum_{j=1}^{m_i} \sum_{k=1}^{n_{j(i)}} y_{ijk} \tag{6}$$

is the mean over all recordings and heart cycles of patient i, $n_{j(i)}$ is the number of heart cycles in recording j and m_i is the number of recordings. Under the assumptions of our model, for patient i, the measurements y_{ijk} are correlated within each recording j. It can be shown that the correlation coefficient between two measurements within the same recording is:

$$\rho = \frac{\sigma_\beta^2}{\sigma_\beta^2 + \sigma_\varepsilon^2}. \tag{7}$$

Therefore, Bartlett's test, which is valid for independent variables, can be used for small values of ρ only. Monte Carlo simulations justified that Bartlett's test confirmed homogeneity of the variances only for $\rho < 0.75$ (empirical value), or $\sigma_\varepsilon^2 > \sigma_\beta^2/3$.

Further, homogeneity of the variances σ_β^2 was checked by Bartlett's test on the "recording residuals"

$$\overline{y_{ij.}} - \overline{y_{i..}}, \tag{8}$$

where

$$\overline{y_{ij.}} = \frac{1}{n_{j(i)}} \sum_{k=1}^{n_{j(i)}} y_{ijk} \tag{9}$$

is the mean over all heart cycles within recording j on patient i.

The outcome of Bartlett's test is a p value that is close to 0 when the variances are heterogeneous.

The intraclass coefficient (McGraw and Wong 1996) is a measure of the proportion of the variance that is attributable to objects of measurement. In our model,

$$\rho_\alpha = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\beta^2 + \sigma_\varepsilon^2} \tag{10}$$

is the proportion of the total variance that is attributable to between-patient variation. Roughly speaking, large values of this coefficient (close to 1) correspond to situations where the parameter gives good discrimination between patients.

The overall goal was to provide an estimate of the "true value" for each patient that was sufficiently precise to discriminate between patients. The mean $\overline{y_{i..}}$ is an estimator for this value. Its variance is given by

$$Var(\overline{y_{i..}}) = \frac{1}{m}\left(\sigma_\beta^2 + \frac{1}{n}\sigma_\varepsilon^2\right). \tag{11}$$

This expression is valid for an equal number n of heart cycles in all recordings, and an equal number m of recordings on all patients (balanced data set). A good estimate of the "true value" $\mu + \alpha_i$ is obtained when:

$$\lambda = \frac{Var(\overline{y_{i..}})}{\sigma_\alpha^2} = \frac{1}{m \cdot \sigma_\alpha^2}\left(\sigma_\beta^2 + \frac{1}{n}\sigma_\varepsilon^2\right) \tag{12}$$

is small.

RESULTS

Of the 60 recordings (5 on each of 12 patients), 3 were discarded due to poor image quality (1) or patient discomfort causing movement disturbances (2). In 7 of the other cases (5 patients), the image quality was somewhat reduced, and the plaque ROIs were difficult to outline. However, these cases are included in the study. Amplitude parameters (A_1–A_7) for one patient were excluded from the analysis, because the automatic reference region could not be established in the vessel wall.

The ECG signal showed three complete heart cycles in 41 of the 57 examinations, and two heart cycles in the other 16 examinations, because of variations in heart rate. Considering the systolic part only, one, two, three and four

systoles were found in 4, 29, 22 and 2 examinations, respectively. The number of systoles is generally lower than the number of complete heart cycles because the "systolic part" is directly related to the ECG signal, leading to possible discarding of much of the acquired time lapse, whereas the "heart cycle," as defined here, has an arbitrary starting point.

Figure 3 shows examples of input data, calculated over the entire heart cycle. The choice of parameters was based on the outcome of Bartlett's test. Thus, the parameters

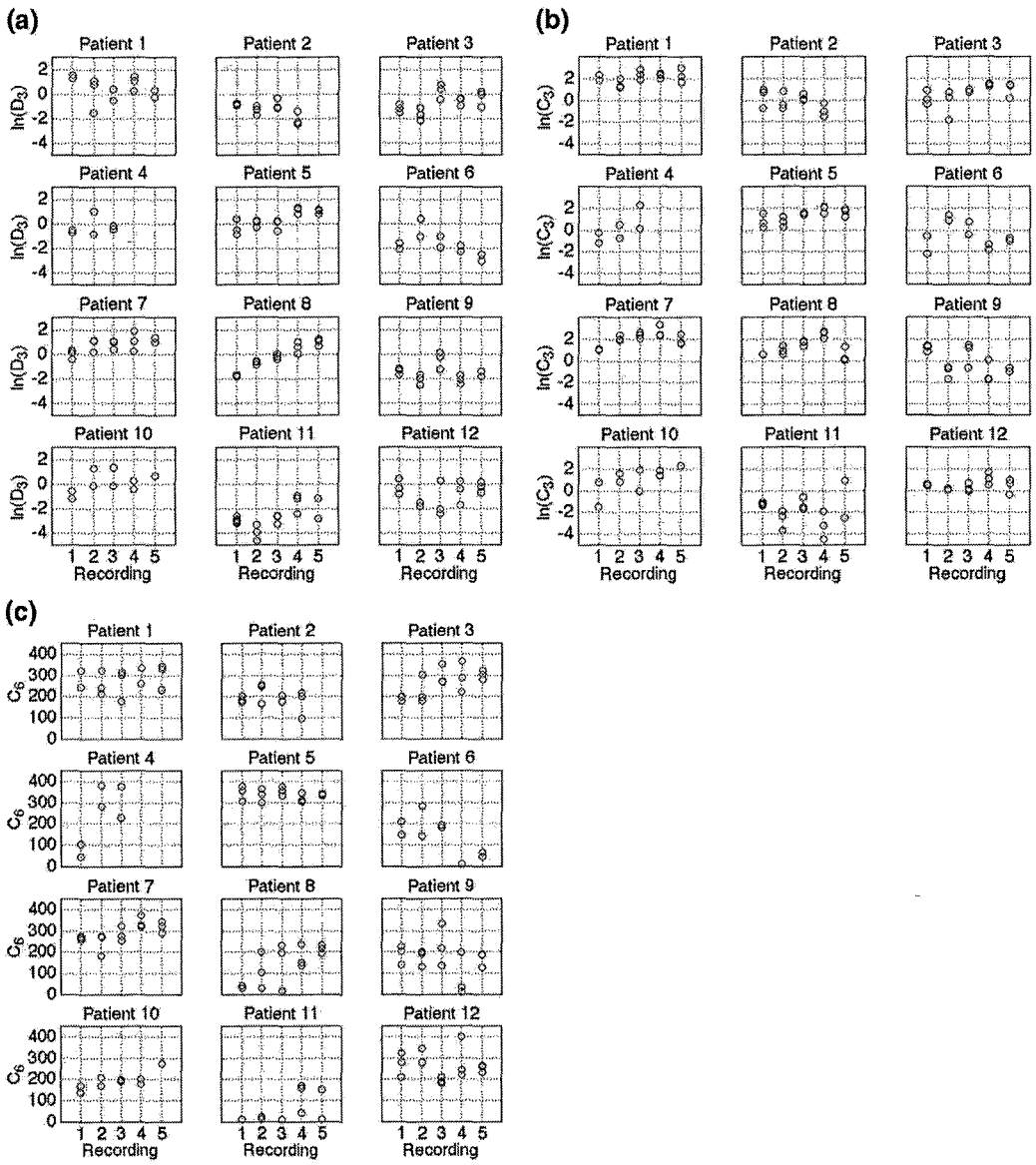

Fig. 3. Examples of input data for the statistical analysis, calculated over the entire heart cycle and sorted according to patient and recording. Each circle represents the parameter value from one heart cycle. The parameters exhibit varying degrees of variance homogeneity, as revealed by Bartlett's test: (a) $\ln(D_3)$; (b) $\ln(C_3)$; (c) C_6.

demonstrate cases of fairly homogeneous variances, both over heart cycle and recording ($\ln(D_3)$), homogeneity in variances between recordings but not over heart cycles ($\ln(C_3)$), and overall heterogeneity of variances (C_6). Visual inspection of the figure can only confirm this qualitatively.

Tables 3 and 4 show the results of the statistical analysis, for data calculated over the entire heart cycle and over the systolic part, respectively. The variances are estimated using the REML method. The model assumptions are checked by *QQ*-plots, Bartlett's test, and visual inspection of plots of input data such as Fig. 3; all these criteria must be fulfilled before the reproducibility results should be trusted. The criteria are met by seven parameters in Table 3 and four parameters in Table 4. For these parameters, λ from eqn(12) at $m = 3$, $n = 2$ and ρ_α from eqn(10) are included in the tables. The ρ_α values indicate that all parameters fulfilling the model assumptions reproduce fairly well ($\rho_\alpha \geq 0.4$).

Table 5 summarises the parameters showing good reproducibility. Figure 4 shows a crossplot of ρ_α vs. λ for these parameters. The approximately inverse relation between λ and ρ_α is not surprising, considering their respective dependence upon the variances σ_α^2, σ_β^2 and σ_ε^2. The best reproducibility is obtained for high values of ρ_α, corresponding to small values of λ.

Figure 5 shows the dependence of the normalised variance λ on the number of recordings m and the number of heart cycles n, for two motion parameters. These parameters exhibit the typical range of values and ratios for σ_α^2, σ_β^2 and σ_ε^2, among those parameters showing good reproducibility. From this figure, we can determine the necessary number of repeated measurements (see the Discussion section).

DISCUSSION

Input data

The analysis was carried out on velocity parameters. However, these were directly proportional to the tissue displacement and, therefore, representative for the motion.

The motion parameters investigated in this study were chosen because they might carry important and characteristic information about the plaque's dynamic behaviour. The motion amplitude was an obvious feature for investigation, and this parameter was also easy

Table 3. Statistical results for data from entire heart cycle.

Parameter	Estimated variance components σ_α^2	σ_β^2	σ_ε^2	Test for normal distribution (*QQ*-plots)	Homogeneity of variances, p value σ_β^2	$\sigma_\beta^2 + \sigma_\varepsilon^2$, if $\sigma_\varepsilon^2 > \sigma_\beta^2 3$	Visual check of input data	All criteria	λ for $m = 3$, $n = 2$	ρ_α
$\ln(A_1)$	0.299	0.213	0.0409	Ok	0.436	NR*	Ok	Ok	0.260	0.541
$\ln(A_2)$	0.125	0.166	0.0267	Ok	0.614	NR	Ok	Ok	0.478	0.394
A_3	53.8	5.11	6.46	No	NR	NR	No	–	–	–
A_4	0.00530	0.00775	0.0269	No	NR	NR	No	–	–	–
A_5	0.0	0.0118	0.0454	No	NR	NR	No	–	–	–
A_6	26.0	41.1	27.3	No	NR	NR	No	–	–	–
$\ln(A_7)$	0.286	0.407	0.0682	No	NR	NR	No	–	–	–
D_1	0.0	0.000681	0.00814	No	NR	NR	No	–	–	–
$\ln(-D_2)$	0.709	0.376	0.312	Ok	0.859	0.394	Ok	Ok	0.250	0.508
$\ln(D_3)$	0.971	0.392	0.350	Ok	0.911	0.728	Ok	Ok	0.195	0.567
$\ln(D_4)$	0.788	0.272	0.145	Ok	0.311	0.237	Ok	Ok	0.146	0.654
$\ln(-D_5)$	0.871	0.175	0.0569	Doubtful	0.003	<0.001	No	–	–	–
D_6	1104.9	260.9	579.1	No	NR	NR	No	–	–	–
$\ln(D_7)$	0.821	0.179	0.0420	Doubtful	<0.001	<0.001	No	–	–	–
D_8	1082.8	303.9	446.5	Doubtful	<0.001	<0.001	No	–	–	–
sqrt(D_9)	5.67	0.710	0.347	No	NR	NR	No	–	–	–
D_{10}	Almost all values = 0									
D_{11}	3766.4	1203.4	1281.0	Doubtful	<0.001	<0.001	No	–	–	–
C_1	0.00468	0.0	0.0408	No	NR	NR	No	–	–	–
$\ln(-C_2)$	1.28	0.289	0.519	Ok	0.583	0.557	Ok	Ok	0.143	0.613
$\ln(C_3)$	1.15	0.431	0.481	Ok	0.422	0.002	Ok?	Ok?	–	–
$\ln(C_4)$	1.07	0.329	0.254	Ok	0.687	0.186	Ok	Ok	0.143	0.647
$\ln(-C_5)$	0.966	0.172	0.0579	Ok	<0.001	<0.001	No	–	–	–
C_6	6216.0	1909.4	2783.9	Ok	0.013	<0.001	No	–	–	–
$\ln(C_7)$	0.929	0.151	0.0705	Doubtful	0.002	<0.001	No	–	–	–
C_8	5553.7	1600.2	3036.5	Ok	0.005	<0.001	No	–	–	–
$\ln(C_9)$	0.939	0.161	0.0559	Doubtful	<0.001	<0.001	No	–	–	–
C_{10}	Almost all values = 0									
C_{11}	18716.2	7922.6	6632.7	Doubtful	0.011	<0.001	No	–	–	–

* NR = Not relevant.

Table 4. Statistical results for data from systolic part of heart cycle.

Parameter	Estimated variance components			Test for normal distribution (QQ-plots)	Homogeneity of variances, p value		Visual check of input data	All criteria	λ for $m = 3$, $n = 2$	ρ_α
	σ_α^2	σ_β^2	σ_e^2		σ_β^2	$\sigma_\beta^2 + \sigma_{\varepsilon_j}^2$ if $\sigma_e^2 > \sigma_\beta^2/3$				
$\ln(A_1)$	0.282	0.225	0.0394	Ok	0.072	NR*	No	–	–	–
$\ln(A_2)$	0.145	0.134	0.0507	Ok	0.535	NR	No	–	–	–
A_3	69.7	9.46	10.6	Ok	0.057	<0.001	No	–	–	–
A_4	0.0233	0.0120	0.0531	Ok	<0.001	<0.001	No	–	–	–
A_5	0.0	0.0218	0.117	No	0.005	<0.001	No	–	–	–
A_6	28.5	35.7	29.8	No	<0.001	<0.001	No	–	–	–
A_7	64.6	45.4	34.8	No	<0.001	<0.001	No	–	–	–
D_1	0.0	0.0	0.0220	No	<0.001	<0.001	No	–	–	–
$\ln(-D_2)$	0.723	0.339	0.352	Ok	0.423	0.088	Ok	Ok	0.237	0.511
$\ln(D_3)$	0.963	0.468	0.329	Ok	0.749	0.618	Ok	Ok	0.219	0.547
$\ln(D_4)$	0.772	0.342	0.100	Ok	0.083	NR	Ok?	Ok?	–	–
$\ln(-D_5)$	0.821	0.179	0.0682	Ok	0.010	<0.001	No	–	–	–
D_6	1133.2	257.8	583.8	Ok	<0.001	<0.001	No	–	–	–
$\ln(D_7)$	0.827	0.187	0.0971	Doubtful	<0.001	<0.001	No	–	–	–
D_8	1085.4	274.9	465.3	Doubtful	<0.001	<0.001	No	–	–	–
$\ln(D_9)$	0.793	0.188	0.0532	Ok	0.003	NR	No	–	–	–
D_{10}	Almost all values = 0									
D_{11}	3807.5	1173.9	1259.2	Ok	<0.001	<0.001	No	–	–	–
C_1	0.0198	0.0	0.0925	No	<0.001	<0.001	No	–	–	–
$\ln(-C_2)$	1.30	0.304	0.621	Ok	0.372	0.570	Ok	Ok	0.157	0.585
$\ln(C_3)$	1.23	0.425	0.476	Ok	0.159	<0.001	Ok?	Ok?	–	–
$\ln(C_4)$	1.09	0.327	0.290	Ok	0.229	0.058	Ok	Ok	0.144	0.639
$\ln(-C_5)$	0.910	0.193	0.0684	Ok	0.006	<0.001	Ok	Ok?	–	–
C_6	5535.1	2329.1	2897.2	Ok	0.015	0.005	No	–	–	–
$\ln(C_7)$	0.858	0.147	0.0915	Doubtful	0.020	<0.001	Ok?	–	–	–
C_8	5062.7	1402.2	3522.4	Ok	0.006	<0.001	Ok	Ok?	–	–
$\ln(C_9)$	0.872	0.166	0.0720	No	0.007	<0.001	No	–	–	–
C_{10}	Almost all values = 0									
C_{11}	17757.3	8577.8	7185.7	Ok	0.011	<0.001	Ok	Ok?	–	–

* NR = not relevant.

to extract from the velocity vectors. Divergence and curl parameters describe the tensional (stretch, compression) and torsional (rotation, shear) movements, respectively. It is reasonable to believe that such movements may lead to rupture and embolisation. Similar effects are discussed in the review article by Falk (1992).

Error sources and accuracy associated with the acquisition and processing of data were discussed in Bang et al. (2003). The parameters listed in Table 2 are more or less robust as input, for various reasons. The purpose of the automatic reference region is to eliminate the overall translational movement of this region from the entire image, thereby making the region a reference (with zero translational motion) for the adjacent plaque. Without this elimination, the comparison of results between

Table 5. Motion parameters showing good reproducibility.

	Parameter	Reproducibility: Entire heart cycle	Reproducibility: Systolic part
$\ln(A_1)$	Time average of mean velocity amplitude over plaque ROI	Ok	–
$\ln(A_2)$	Time average of minimum velocity amplitude in each plaque ROI	Ok	–
$\ln(-D_2)$	Minimum in time of mean velocity divergence over plaque ROI	Ok	Ok
$\ln(D_3)$	Maximum in time of mean velocity divergence over plaque ROI	Ok	Ok
$\ln(D_4)$	Range over time of mean velocity divergence over plaque ROI	Ok	–
$\ln(-C_2)$	Minimum in time of mean velocity curl over plaque ROI	Ok	Ok
$\ln(C_4)$	Range over time of mean velocity curl over plaque ROI	Ok	Ok

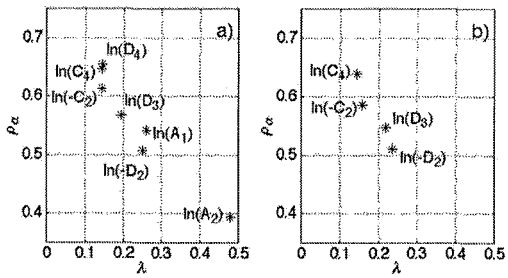

Fig. 4. Crossplots of normalised variance λ (at $m = 3$ and $n = 2$) and intraclass coefficient ρ_α, for parameters showing good reproducibility (Table 5). Input data calculated (a) over entire heart cycle and (b) over systolic part of heart cycle.

different patients or recordings will be less valid. The cancelling of overall translation therefore affects the amplitude parameters by a value that depends on the actual size and position of the reference region. Cf. eqn(1), where adding a constant to V will change A. However, this is not the case for the divergence or curl parameters. Cf. eqns. (2) and (3), where adding a constant to V will not change D or C. Furthermore, the reference region cannot compensate for all kinds of unintended movements (e.g., rotational) of the probe during acquisition and this may have influence upon one or more of the parameter classes. In general, we expect the average of a parameter to be a more robust value than the minimum, maximum or range. It is, therefore, interesting to notice that all the parameters showing good reproducibility involve the average over either image region or time, or both.

Statistical analysis

The literature does not give clear advice as to whether maximum likelihood (ML) or restricted maximum likelihood (REML) ought to be used in a case like ours (McCulloch and Searle 2001, pages 177 to 178). We estimated the variances with both methods and found approximately the same results. The REML method was preferred because, for balanced data sets, its solutions are minimal variance unbiased, and even minimal variance quadratic unbiased. For our model, it was also important that REML estimators are not so sensitive to data outliers, as ML estimators are.

There exists a method for constructing the confidence interval of the intraclass coefficient ρ_α, and for corresponding tests. However, we have not used it on our data because this method assumes balanced data sets.

We have studied one parameter at a time. However, it is possible that several parameters simultaneously, such as a linear combination, could produce measures with good reproducibility. This could, for example, be investigated using a multivariate linear mixed model. This has not been addressed here, but might be the subject for future work.

Which parameters can describe plaque motion?

The motion parameters displayed in Table 5 and Fig. 4 show good reproducibility and they are, therefore, candidates for further investigation with respect to discrimination between plaque features in different clinical cases. These parameters cover all the postulated motion patterns; amplitude, tension and torsion. The other parameters do not comply with the model and we can, therefore, not conclude on their reproducibility.

Meairs and Hennerici (1999) found that the MDSV discriminated well between symptomatic and asymptomatic plaques. Our parameters that are based on a similar difference between maximum and minimum velocities (A_6 and A_7), however, did not fulfill the model assumptions.

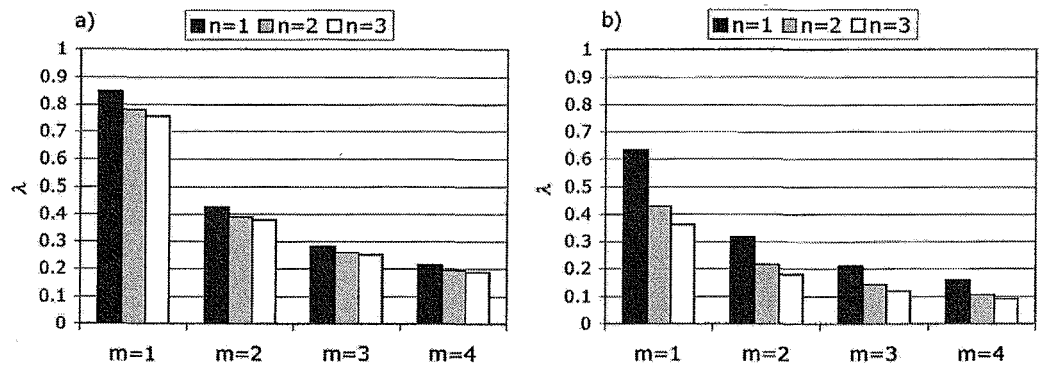

Fig. 5. Effect of increasing the number of recordings (m) and heart cycles (n) on normalised variance λ, eqn (12). (a) ln(A_1); (b) ln(C_2). The input data were calculated over the entire heart cycle (variances listed in Î).

It is interesting to notice that roughly the same parameters were found to reproduce well, whether they were calculated over the entire heart cycle or over the systolic range only. This indicates that the selection of the time range was not critical, at least as long as the largest movements were covered. This observation may be useful for the practical implementation of the method.

The parameter's average, minimum, maximum and range were calculated over the entire plaque ROI. It can be expected that calculation over smaller image regions (e.g., the plaque edge or the shoulder region near the vessel wall) might give more accurate results. This may also reduce the processing time, but requires improved tracking of the specific plaque region.

Clinical application

The number of repeated recordings will be a compromise between required accuracy and factors such as patient comfort, available examination time and processing time. The accuracy can be assessed from Fig. 5. Considering first the number of recordings (m), $\lambda \leq 0.3$ is obtained for $m \geq 3$, and the improvement from 3 to 4 recordings is roughly 25% or lower. We therefore consider that averaging three repeated recordings should give a good estimate of the motion parameter. In addition to being a practicable number in most examination situations, it offers the possibility of detecting erroneous conditions of a single recording. The number of heart cycles within each recording (n) is limited by the required acquisition frame rate in combination with the scanner memory capacity. Figure 5 shows that $n = 2$ is a reasonable choice, allowing for detection of outliers, whereas $n = 3$ yields only marginal improvements to λ.

The present procedure for data acquisition and processing is somewhat cumbersome and time-consuming; however, this is basically due to nonoptimised scanner applications and prototype algorithm implementation, which both may be considerably improved. Another important question is how the information is best conveyed to the clinician, for example by colour-coding overlaid on the B-mode images. Requiring only 2-D image acquisition and essentially automated processing, we consider that our method has the potential to become a practical examination method.

The possible benefit of this method is that it may provide the clinician with essentially new information. Supplementing the knowledge on the degree of stenosis and the plaque echogenicity, information on the dynamic behaviour may help in describing plaque stability. This may ultimately predict which plaques are prone to rupture, if previously asymptomatic plaques show motion patterns similar to those of the symptomatic ones. This may have significant consequences to the decisions on treatment of the individual patients.

Further work

We intend to investigate whether or not the parameters with good reproducibility show significant differences between various patient groups, by, for example, comparing motion results with patient history and plaque echogenicity. This will include both patients with and without cerebrovascular events. Furthermore, a validation study involving a greater number of patients is necessary to demonstrate the full potential of the method.

CONCLUSIONS

We have investigated 29 plaque motion parameters for intraoperator reproducibility, by statistical analysis of data from 12 patients. The results show that seven parameters reproduce well and should, therefore, be subject to further investigation. These parameters describe tensional and torsional motion, in addition to mere velocity amplitude. The other parameters do not fit with the assumptions of the statistical model.

The analysis was carried out on parameters calculated over the entire heart cycle and over the systolic region only, with fairly coinciding results. This indicates that the time range may not be critical to the measurements. Furthermore, we addressed the number of repetitions necessary for reliable results and found that averaging over three repeated recordings, each covering at least two heart cycles, yields acceptable accuracy. These numbers also allow for detection of outliers, in addition to representing a practical examination protocol.

The future work will address whether or not the identified parameters can discriminate between patient groups and how the motion characteristics agree with other plaque features such as echogenicity and degree of stenosis.

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REFERENCES

AbuRahma AF, Thiele SP, Wulu JT. Prospective controlled study of the natural history of asymptomatic 60% to 69% carotid stenosis according to ultrasonic plaque morphology. J Vasc Surg 2002;36: 437–442.

Bang J, Dahl T, Bruinsma A, et al. A new method for analysis of motion of carotid plaques from RF ultrasound images. Ultrasound Med Biol 2003;29:967–976.

Box GEP, Hunter WG, Hunter JS. Statistics for experimenters. New York: John Wiley & Sons, 1978.

Chan KL. Two approaches to motion analysis of the ultrasound image sequence of carotid atheromatous plaque. Ultrasonics 1993;31: 117–123.

Falk E. Why do plaques rupture? Circulation 1992;86(Suppl. III):III-30–III-42.

Golemati S, Sassano A, Lever MJ, et al. Carotid artery wall motion estimated from B-mode ultrasound using region tracking and block matching. Ultrasound Med Biol 2003;29:387–399.

Grønholdt MLM, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. Circulation 2001;104:68–73.

Halliday AW, Thomas D, Mansfield A. The asymptomatic carotid surgery trial (ACST). Rationale and design. Steering committee. Eur J Vasc Surg 1994;8(6):703–710.

Iannuzzi A, Wilcosky T, Mercuri M, et al. Ultrasonographic correlates of carotid atherosclerosis in transient ischemic attack and stroke. Stroke 1995;26:614–619.

Landwehr P, Schulte O, Voshage G. Ultrasound examination of carotid and vertebral arteries. Eur Radiol 2001;11:1521–1534.

Lewis PE, Ward JP. Vector analysis for engineers and scientists. Wokingham, England: Addison-Wesley, 1989.

Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis (The Tromsø study). Circulation 2001;103:2171–2175.

McCulloch CE, Searle SR. Generalized, linear and mixed models. New York: John Wiley & Sons, 2001.

McGraw KO, Wong SP. Forming interferences about some intraclass correlation coefficient. Psychol Methods 1996;1(1):30–46.

Meairs S, Hennerici M. Four-dimensional ultrasonographic characterization of plaque surface motion in patients with symptomatic and asymptomatic carotid artery stenosis. Stroke 1999;30:1807–1813.

Walpole RE, Myers RH, Myers SL. Probability and statistics for engineers and scientists. 6th ed. New Jersey: Prentice Hall, 1998.

Woodcock JP. Characterization of the atheromatous plaque in the carotid arteries. Clin Phys Physiol Meas 1989;10(Suppl. A):45–49.

Paper III

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Data Quality of Surgery for Carotid Artery Stenosis. Are the National Vascular Registries Reliable?

T. Dahl,[1,2] K. Rudjord,[3] M. Altreuther[1] and H.O. Myhre[1,2]*

Departments of [1]Surgery, St Olavs Hospital, University Hospital of Trondheim, [2]Circulation and Medical Imaging, The Norwegian University of Science and Technology, and [3]SINTEF Health Research, Trondheim, Norway

Objectives. *To study completeness of reporting carotid endarterectomies, including peri-operative stroke and mortality rate, in a national vascular registry, NorKar, and a national administrative registry, The Norwegian Patient Register (NPR).*
Design. *Comparative registry-based national study.*
Materials. *Member hospitals of NorKar, including 89% of carotid endarterectomies in Norway, were compared with relevant data in NPR for the years 2000–2002.*
Methods. *We compared procedure-codes, diagnosis-codes, in-hospital death and the occurrence of peri-operative stroke after treatment for carotid artery stenosis in the two registries to evaluate completeness.*
Results. *Compared with the NPR numbers, 16% of carotid endarterectomies were missing in the reports from member hospitals of NorKar. Further, during this three-year period, there was an under-reporting of seven strokes and two deaths. The discrepancy was most pronounced in 2001.*
Conclusions. *There is an under-reporting of patients operated on for carotid artery stenosis in NorKar according to NPR numbers as well as an under-reporting of early deaths and strokes. There is a need for better quality data in the NorKar Registry. Registry quality would be likely to improve if patient identifiable data were available in both registries.*

Keywords: Carotid surgery; Registries; Coding; Completeness.

Introduction

There is an increasing demand for documentation of results following surgical intervention. This is of special importance for prophylactic surgery like carotid endarterectomy. In Norway there are more than 60 official patient registries; one of them is the Norwegian Registry for vascular diseases (NorKar).[1] We have previously demonstrated an under-reporting of early death following abdominal aortic aneurysm surgery to this registry.[2] Increasingly patient registries are used for scientific studies. Therefore, quality control of the registries becomes more important.[3–5]

The objective was to study quality of data on carotid endarterectomy in a national vascular registry compared to a national administrative registry. We focused on completeness of reporting procedures, in-hospital death and in the occurrence of perioperative stroke. Finally, we evaluated how missing post-operative events could influence the results regarding stroke and mortality after carotid surgery.

Material and Methods

The Norwegian vascular registry (NorKar)

The national registry for vascular surgery was established in 1995 and includes various arterial procedures. It belongs to the Norwegian Society for Vascular Surgery. Seventeen out of 23 departments performing vascular surgery are reporting to the registry. NorKar is based on local databases with patient-identifiable data in member hospitals. Data are collected on paper forms and entered into the database. Cases are then reported anonymously to the central registry. The registry contains diagnosis-codes (limited to a maximum of three) and procedure-codes (limited to a maximum of six) for each treatment. Complications following surgery are also

*Corresponding author. Prof H.O. Myhre, MD, Department of Surgery, St Olavs Hospital, University Hospital of Trondheim, N-7006 Trondheim, Norway.
E-mail address: hans.myhre@ntnu.no

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recorded in addition to other variables. Data from Norkar were retrieved on Microsoft Excel® files.

Norwegian patient register (NPR)

The Norwegian Patient Register was established in 1997 and is an independent registry of all patient treatments in public health care in Norway. The registry is owned by the Norwegian Ministry of Health and Social Affairs. Reporting to the administrative registry is compulsory to formally discharge a patient from hospital. Both hospital stays as well as out-patient consultations are recorded in the registry. The hospitals receive compensation from the authorities on the basis of the volume of reported diagnoses[6] and procedure codes[7] according to a DRG (diagnosis related groups)-based system and NPR consists of the reported data. Therefore, there is a strong incentive for the hospitals to report their activity completely.[8] SPSS® was used to extract data from NPR.

Coding practice

We wanted to examine patients undergoing carotid endarterectomy for carotid artery stenosis during the years 2000–2002. The annual reports from NorKar regarding perioperative stroke and death following carotid endarterectomy are based on the number of patients with indication 'carotid stenosis, symptomatic or asymptomatic'. The use of operation codes PAF20, PAF21 or PAF22[7] for carotid endarterectomy are recommended, but not compulsory. Based on the indication, endovascular procedures also will be represented in the annual report. The number of strokes occurring during the hospital stay is based on a remark in the NorKar form for post-operative complications, and post-operative deaths are noted with the date and cause of death. Postoperative complications are divided into 'surgical' and 'general', and should be marked in the appropriate box on the register form. Seventeen out of 23 departments of vascular surgery are members reporting to the registry.

In NPR we searched for the operation codes, PAF20-22, or the code I65.2 (ICD 10 1998) for carotid artery stenosis. Operation codes describing thrombectomy, exploration and ligation of the internal carotid artery also were included, as they probably represent procedures performed for carotid artery stenosis. First, we controlled the number of reported carotid endarterectomies from each individual department in both registries. The reported strokes among these patients in the NorKar registry were identified in NPR.

Table 1. Relevant ICD-10 diagnosis codes for patients who were operated for carotid artery stenosis

ICD-10 Chapter IX	Text*
Section I65	
I65.2	Occlusion and stenosis of the carotid artery
Section I61	
I61.0-8	Specific forms of cerebral haemorrhage
I61.9	Unspecific cerebral haemorrhage
Section I63	
I63.0-8	Specific brain infarction
I63.9	Unspecific brain infarction
Section I64	
I64	Stroke, not specified as haemorrhage or infarction
Section I69	
I69.0-8	Sequelae following brain vessel diseases

* Translation of the Norwegian version.

We further recorded patients who had strokes reported to NPR, but had not been reported in NorKar at discharge. Whenever a patient had been discharged after more than 5 days in hospital with a secondary and new diagnosis, I61–I61.9, I63–I63.9 or I64,[6] we presumed that the patient had suffered a peri-operative stroke. Patients with a secondary diagnoses I69.0–I69.8 indicating sequelae following cerebrovascular disease, were excluded because we anticipated that they had suffered from their stroke prior to surgery. Table 1 indicates the different peri-operative diagnosis codes for stroke according to ICD-10. The numbers of hospital deaths also were compared for both registries.

Results

NorKar reported 651 procedures for carotid artery stenosis[9] and 612 of these fell into the category PAF20-22. After correction of seven double entries and a few inconsistent diagnosis-procedure combinations, 616 patients remained for comparison with NPR data from the same hospitals. One case of double registration and one inconsistent diagnosis-procedure combination were found in NPR, leaving a total of 735 patients for investigation. NorKar reported 22 post-operative strokes, including one fatal stroke and one stroke after balloon angioplasty. Two other deaths reported to NorKar had a diagnosis of acute myocardial infarction and ruptured abdominal aortic aneurysm, respectively. In addition, NPR included four strokes, diagnosed with codes I63.1, I63.3, I63.9 and I63.9, respectively, and three possibly fatal intracerebral haemorrhages with the codes I61.0, I61.0 and I61.9, respectively. Subsequently, there were two peri-operative deaths in NPR that had not been reported to NorKar. One patient had a diagnosis of stroke (I63.9)

Table 2. Reported number of carotid endarterectomies (CEA) and postoperative stroke and death in the Norwegian Registry for vascular diseases (NorKar) compared to the Norwegian Patient Register (NPR) for hospitals reporting to NorKar

Year	CEA in Norkar	CEA in NPR	Strokes in NorKar	Strokes in NPR	Deaths in NorKar	Deaths in NPR	Stroke/mortality rate in NorKar (%)	Stroke/mortality rate in NPR (%)
2000	164	226	3	4	1	1	2.4	2.2
2001	206	242	10	14	1	6*	5.3	7.0
2002	246	267	8	10	1†	1†	3.3	3.7
Total	616	735						

* Including three fatal strokes.
† Fatal stroke.

and unspecified angina pectoris (I20.9), indicating the possibility of a cerebral or cardial cause of death, and the other died of unknown cause. Combining the figures from NorKar and NPR, there were altogether eight peri-operative deaths in connection with carotid endarterectomy during the years 2000–2002. Under-reporting of patients in NorKar compared to NPR usually happened when the patient was transferred to other departments or readmitted with stroke within 30 days. The under-reporting varied over time and was most pronounced in 2001, when altogether four strokes and two deaths were missing in NorKar compared to NPR data (Table 2). In 2002 the official statistics of NorKar seemed to be more in accordance with NPR. Nevertheless, two strokes after carotid endarterectomy were missing and one stroke after balloon angioplasty and stenting had been included falsely. Finally, there was double recording of one fatal stroke in the official NorKar statistics. For the entire study period, NorKar reported a combined stroke and mortality rate of 3.8%.[9] According to NPR-data, there were 28 postoperative strokes, four of which were lethal, in addition to the two other deaths not reported to NorKar and two deaths within NorKar. This would have given a combined stroke and mortality rate of 4.4%.

Discussion

A significant proportion of patients (16%) undergoing surgery for carotid artery stenosis were missing from the National Vascular Registry, NorKar when compared with NPR data for NorKar member hospitals. This is similar to data from the Finnvasc and SWEDVASC registries, where the mean percentage of missing cases compared to hospital records were 19 and 16%, respectively.[10,11] The present investigation indicates an under-reporting of operative procedures as well as stroke and mortality following carotid endarterectomy in the National Vascular Registry compared to the National Administrative Registry. This is a serious problem since stroke and mortality are well-defined end-points of major importance for the definition of quality of carotid artery surgery. Usually less severe complications, like wound problems, are more likely to be omitted from registration.[12] Under-reporting is also more frequent for emergency procedures,[10] but carotid endarterectomy in most cases is performed on an elective basis. The reporting to NPR is likely to be almost complete because reporting is compulsory for formal discharge of a patient from hospital, and subsequent reimbursement from the health authorities. In the National Vascular Registry there is no economic motivation or administrative demand for reporting to the registry. These facts may explain some of the discrepancy in numbers reported to the two registries for some of the member hospitals. Some of the departments did not report to the central NorKar registry every year. This impairs the quality of the registry and contributed heavily to the discrepancy between the two registers.

There is a theoretical possibility that the administrative registry could over-estimate the number of cases.[4] One double entry was found in the NPR, probably because the hospital had reported the same procedure twice, but otherwise only admissions with both diagnosis-code and procedure-code relevant to carotid endarterectomy were counted. Furthermore, patients have a unique i.d. number and readmissions within the same calendar year are readily identified. Therefore, we think that over-reporting is unlikely to represent a problem.

In the NorKar registry the patient is supposed to be followed at the out-patient clinic 1 month and 1 year after surgery. Complications occurring during the interval from discharge until 30 days should be reported in the NorKar form. Under-reporting of three patients or more was seen in six different departments, indicating that there were no departments systematically under-reporting to NorKar. We suppose that the under-reporting to NorKar is due to lax reporting standards for this registry. For example, when patients are transferred to other units because of a complication, they may be treated by groups of personnel other than surgeons, who may be unaware

of the vascular registry.[11,12] We also think that reporting of 1 month follow-up at the out-patient clinic was unsatisfactory. No matter the reason, early mortality and stroke rate following carotid surgery are crucial data and it is important to improve these results in our local vascular registry. Also in NPR, readmissions to the same institution are recorded, whereas admissions to other hospitals for a complication or an operation will not be identified. This could result in under-reporting of complications. Making the two registries patient identifiable can solve most of these problems.

During the study period the combined annual stroke-mortality rate varied. According to NPR the highest complication rate was seen in 2001 when the stroke-mortality rate was 7% compared to 2.2% in 2000 and 3.7% in 2002. We have no indications that there were changes in operative technique or indications for surgery during these 3 years and the discrepancy is probably due to chance. It is pertinent that four deaths after carotid endarterectomy, probably were caused by intracerebral haemorrhage. This is consistent with the high mortality rate observed for post-operative cerebral haemorrhage after carotid endarterectomy.[13]

The total number of carotid endarterectomies in Norway for the 3 year period was 822 according to NPR. Thus, our study of 735 patients includes 89% of these. This selection should be fairly representative of routine practice and results. However, we have not studied the reporting in NPR of the remaining 11% of the patients operated with carotid endarterectomy, since these represent procedures that were not reported to NorKar.

How can we improve the register?

We believe that clearer guidelines for coding and proper instructions for participating surgeons could make the registration easier to use, safer and more complete.[3] Since, 2002 it has become compulsory to record specifically that there had been no post-operative cerebral complications after carotid endarterectomy in NorKar. Previously, a secondary diagnosis would not have given a clear indication of such complications since only 12 out of 22 patients with stroke after carotid endarterectomy had an adequate secondary diagnosis recorded. However, in 2002 there was still a certain amount of incorrect coding.

Medical registries are used increasingly for scientific work. However, we need a better strategy to get correct data from the NorKar registry. Matching of the two registries is one way of effecting quality control of NorKar, but improved quality can also be obtained by an algorithm to ensure complete recording of primary and secondary diagnoses. The responsibility for correct reporting should be given to one particular surgeon, and data transfer should be done by trained staff. Direct data entry into the computer, with warning systems for logical errors or improbable values, could make this easier and safer.[10] A validation of the registry should probably be done on a regular basis and random validation of a limited time span may be as effective as a more extensive comparison.[14] A short period of validation, monitoring and feedback to participating centres also may improve the quality of a register.[15]

In conclusion we have shown an under-reporting of carotid endarterectomies when comparing the National Vascular Registry (NorKar) with the National Administrative Regisity (NPR). Also early deaths and strokes were under-reported in NorKar. If NorKar data are to be used to establish a national standard and allow comparison between centres, there is a need for a better quality of the data in the NorKar registry.[16] We suggest that both NorKar and NPR are made patient identifiable.

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References

1 Health Technology Assessment. *An introduction. (In Norwegian) Norwegian center for health technology assessment. Report no 8* 2003 p. 58.
2 Haug ES, Romundstad P, Sæther OD, Jørgenvåg R, Myhre HO. Quality of data reported on abdominal aortic aneurysm repair. A comparison between a national vascular and a national administrative registry. *Eur J Vasc Endovasc Surg* 2005;**29**:571–578.
3 Laustsen J, Jensen LP, Hansen AK, The Danish National Vascular Registry. Accuracy of clinical data in a population based vascular registry. *Eur J Vasc Endovasc Surg* 2004;**27**:216–219.
4 Lofthus CM, Cappelen I, Osnes EK, Falch JA, Kristiansen IS, Medhus AW *et al.* Local and national electronic databases in Norway demonstrate a varying degree of validity. *J Clin Epidemiol* 2005;**58**:280–285.
5 Tröeng T, Bergqvist D, Einarsson E, Elfström J, Norgren L. Experiences from Swedvasc/VRISS. *Ann Chir Gynaecol* 1992; **81**:248–252.
6 *The international statistical classification of diseases and related health problems (ICD-10).* ISBN 82-07-01992-1, Norwegian; 1998.
7 Classification of surgical procedures, (NSCP). *Norwegian translation of the NOMESCO classification of surgical procedures.* ISBN 82-7846-052-3; 1999.
8 Aardal S, Berge K, Breivik K, Flaatten HK. Medical records, DRG and intensive care patients. *Tidsskr Nor Lægeforen* 2005; **125**:903–906 [in Norwegian].

9 Annual Report from the Norwegian Registry for vascular diseases (NorKar). Trondheim, Norwegian; 2003.
10 KANTONEN I, LEPÄNTALO M, SALENIUS JP, FORSSTRÖM E, HAKKARAINEN T, HUUSARI H *et al.* Auditing a nationwide vascular registry—the 4-year Finnvasc experience. *Eur J Vasc Endovasc Surg* 1997;**14**:468–474.
11 ELFSTRÖM J, STUBBERÖD A, TROENG T. Patients not included in medical audit have a worse outcome than those included. *Int J Qual Health Care* 1996;**8**:153–157.
12 GUNNARSSON U, SELIGSOHN E, JESTIN P, PÅHLMAN L. Registration and validity of surgical complications in colorectal cancer surgery. *Br J Surg* 2003;**90**:454–459.
13 NAYLOR AR, RUCKLEY CV. The post-carotid endarterectomy hyperperfusion syndrome. *Eur J Vasc Endovasc Surg* 1995;**9**:365–367.
14 LEPÄNTALO M, SALENIUS JP, LUTHER M, YLÖNEN K. Introduction of a population-based vascular registry: validity of data and limitations of registration. *Br J Surg* 1994;**81**:979–981.
15 FINE LG, KEOGH BE, CRETIN S, ORLANDO M, GOULD MM, for the Nuffield-Rand Cardiac Surgery Demonstration Project Group. How to evaluate and improve the quality and credibility of an outcome database: validation and feedback study on the UK cardiac surgery experience. *BMJ* 2003; **326**:25–28.
16 JENSEN LP, TROËNG T. Vascular registries—are they worth the effort? *Eur J Vasc Endovasc Surg* 2000;**20**:225–226.

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Paper IV

ORIGINAL ARTICLES

Carotid endarterectomy: time-trends and results during a 20-year period

T. DAHL [1], J. AASLAND [1], P. ROMUNDSTAD [2], H. J. JOHNSEN [3], H. O. MYHRE [1]

[1]*Department of Surgery, St. Olavs Hospital*
Institute of Circulation and Medical Imaging
University Hospital of Trondheim, Trondheim, Norway
[2]*Department of Public Health and General Practice*
Medical Faculty, Norwegian University of Science and Technology
Trondheim, Norway
[3]*Department of Neurology, St. Olavs Hospital*
Institute of Neuroscience, University Hospital of Trondheim, Trondheim, Norway

Aim. **The aim of this study was to evaluate the results following surgery for carotid artery stenosis in a single institution during a 20-year period.**
Methods. **In a retrospective study, 556 operations were performed in 496 patients during the period 1983-2002. Comorbidities, mortality, stroke and other surgical and general complications were recorded. Follow-up was performed and data retrieved from medical records, questionnaires, and visits to local hospitals. Data on late mortality were retrieved from the Norwegian Registrar's Office of birth and deaths.**
Results. **The mean age was 66.9 years (range 43-84 years), and 60% were men; 84% had symptomatic carotid artery stenosis. General anesthesia was applied in 95.5%. A shunt was used in 61.3%, and patch angioplasty in 95.1%. Autologous vein patch was used in almost all cases and there were no cases of patch rupture. Postoperative myocardial infarction occurred in 16 (2.9%) of the patients, and 5 were fatal. All types of stroke within 30 days of surgery occurred in 23 (4.1%) including 1 fatal stroke, and 7 patients died of other causes. The total stroke/mortality rate was 5.4%. Patients with previous coronary artery bypass had a favorable outcome regarding long-time survival. In contrast, increasing age, diabetes, renal failure and intermittent claudication predicted reduced long-term survival. No operations were performed for recurrent stenosis.**
Conclusion. **We have used fairly the same policy regarding operative technique during the 20-year period and the results are in agreement with those presented in large international trials. The long-term results were favorable, and improved over time, probably due to better preoperative evaluation of the patients, better timing of surgery and treatment of comorbidities.**
[Int Ang 2006;25:241-8]

Key words: **Endarterectomy, carotid - Long term results - Complications - Survival.**

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An increasing number of patients treated by stenting for carotid artery stenosis is being reported. On the other hand, there is still reluctance to adopt this technique, since the results following carotid endarterectomy (CEA) in general are favorable. From the US successful series of CEAs from single center, single surgeon experiences have been reported. However, the indications for CEA are different in Scandinavia compared to the US. In the former countries, mostly patients with symptomatic carotid artery stenosis are operated on. Before new treatment modalities are introduced into the clinical routine, they should be matched against established methods and both early and late results should be compared. Our purpose was therefore to investigate early and long-term results following CEA during a 20-year period. This could form a basis for comparison with new techniques.

Materials and methods

All patients operated for carotid artery stenosis at our institution during the period 1983-2002 were identified from local medical records including registers on diagnosis and procedure codes. During the first part of the period carotid artery stenosis was always confirmed by angiography and the degree of stenosis was measured. Since 1996, duplex ultrasound scanning has been used as the only preoperative imaging of the carotid

TABLE I.—*Patient characteristics and comorbidities in 496 patients operated for carotid artery stenosis.*

	No. of patients	%
Patients	496	
Male	297	59.9
Hypertension	212	42.7
Angina pectoris	137	27.6
Intermittent claudication	105	21.2
Previous myocardial infarction	100	20.2
Aortocoronary bypass	60	12.1
Diabetes	37	7.5
COPD	24	4.8
Cardiac arrhythmia	22	4.4
Renal failure (serum creatinine >140 μmol/L)	15	3

COPD: chronic obstructive pulmonary disease

TABLE II.—*Preoperative medication in 496 patients undergoing CEA.*

Drug	No. of patients	%
Aspirin	356	71.8
β-blocking agent	141	28.4
Calcium antagonist	105	21.2
Nitroglycerine	82	16.5
Warfarin sodium	79	15.9
Dipyridamole	63	12.7
Lipid lowering therapy	63	12.7
ACE-inhibitor	63	12.7
Digitalis	15	3

CEA: carotid endarterectomy.

TABLE III.—*Operative details of 556 CEAs.*

	No. of patients	%
Operation on the left side	292	52.5
General anesthesia	531	95.5
Use of shunt	341	61.3
Total no of vein patches	490	88.1
Vein patch from the ankle	419	75.4
Vein patch from the groin	26	4.7
Prosthetic patch	38	6.8
Primary closure of arteriotomy	25	4.5
Interposition vein graft	2	0.4

CEA: carotid endarterectomy.

TABLE IV.—*Postoperative complications following 556 CEAs.*

	No. of patients	%
Stroke (all)*	23	4.1
Stroke ipsilateral to CEA	17	3.1
Death within 30 days **	8	1.4
Postoperative hemorrhage (all reoperations)	12	2.2
Total number of nerve injuries	205	36.9
Cranial nerve injuries	44	7.9
Postoperative MI	16	2.9
Pneumonia	12	2.2
Superficial wound infection	8	1.4
Vein harvest site infection	15	2.7
Foot gangrene	1	0.2

*One patient was reoperated for stroke and one stroke was fatal. **Five deaths were caused by MI (myocardial infarction) while the cause of death was unknown in 2 cases. CEA: carotid endarterectomy; MI: myocardial infarction.

arteries, provided the images were satisfactory and confirmed by 2 scanning operators. In case of doubt about the diagnosis or the patency of the distal part of the internal carotid artery, angiography was performed. A CT-scan of the brain was included in the preoperative routine.

A longitudinal incision along the anterior border of the sternocleidomastoid muscle was used. A shunt was applied if the stump pressure was below 40-50 mmHg, whenever the contralateral carotid artery was occluded or the patient had suffered a stroke preoperatively. An amount of 10 000 IU of Heparin was given prior to clamping of the carotid artery. Endarterectomy was performed through a longitudinal arteriotomy and the incision usually closed with a patch. The patch was preferably taken from the long saphenous vein at the ipsilateral ankle, or from the groin if more suitable. Heparin was usually reversed with 50 mg of protamine before closure of the wound. Intraoperative control of the reconstruction using duplex ultrasound was used at the surgeon's discretion. A suction drain was applied. Dextran 500 mL was given in the afternoon after surgery, and repeated on the 1st and 3rd postoperative day. The patient was kept in the recovery room overnight and transferred to ordinary ward on the following day.

The patients were followed at the outpatient clinic one and 12 months postoperatively, and a duplex ultrasound examination was done simultaneously. Patients referred from other hospitals were appointed for a follow-up at their local institution. Postoperative history, the occurrence of stroke, early and long-term complications were recorded. The data were collected from medical files, medical records, questionnaires and visits to the local hospital to gather information on patients who had died before December 1st, 2004.

TABLE V.—*Stroke within 30-days of CEA according to presenting symptom.*

Symptom	No. of patients	No. of strokes	%	Ipsilateral to CEA	%
TIA	219	10	4.6	9	90
Amaurosis fugax	118	3	2.5	1	33.3
Stroke	92	4	4.3	4	100
RIND	24	0	0	0	0
Crescendo TIA	7	1	14.3	0	0
Retinal infarction	7	0	0	0	0
Unspecific symptoms	26	0	0	0	0
Asymptomatic	63	5	7.9	2	40

CEA: carotid endarterectomy; TIA: transient ischemic attack; RIND: reversible ischemic neurological deficit.

Statistical analysis

Data were collected on paper forms, and later transferred to SPSS for Windows, version 13.0 for analyses. Descriptive data were given as mean or median as appropriate. To investigate survival, the patients were followed from date of operation to date of death or the censor date December 1st, 2004. Overall survival was evaluated by the Kaplan Meier method, and Cox multivariate regression analysis was performed to study factors that could influence the long-term survival. Relative survival was estimated as the observed survival of the patients divided by the expected survival using the method of Ederer.[1] Expected survival was calculated from national mortality rates corrected for calendar period, age and sex.

TABLE VI.—*Stroke classification for 21 patients according to the modified Rankin Scale.*

No. of patients	Grade	Description
4	0	— No symptoms at all
3	1	— No significant disability despite symptoms: able to carry out all usual duties and activities
8	2	— Slight disability: unable to carry out all previous activites but able to look after own affairs without assistance
4	3	— Moderate disability, requiring some help, but able to walk without assistance
2	4	— Moderate severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
0	5	— Severe disability: bedridden, incontinent and requiring constant nursing care and attention

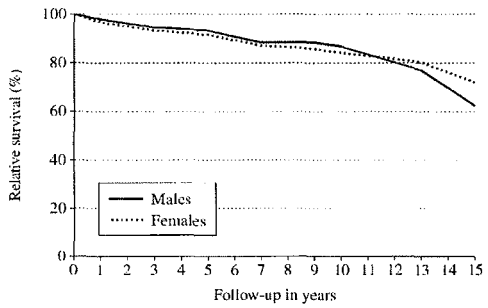
Two patients died within 8 days of surgery, and could not be classified.

Results

Median age was 67 years (range 43-84 years), and 60% were men. Patient characteristics and risk factors are given in Table I. A significant proportion of the patients had evidence of coronary heart disease, while 60 (12.1%) had undergone aortocoronary bypass surgery. Preoperative medication is indicated in Table II. Eighty-four percent of the operations were performed for symptomatic carotid artery stenosis. Transitory ischemic attack was the indication for operation in 219 (39.4%) while 118 (21.2%) had amaurosis fugax and 92 (16.5%) stroke as indication for surgery. Finally, 23 patients had unspecific symptoms like dizziness or suspected global ischemia. A total of 63 patients (11.3%) were classified as asymptomatic, and 19 of them were operated within the Asymptomatic Carotid Surgery Trial (ACST).[2] Sixty-seven percent of the patients had an audible bruit over the relevant carotid artery, and even if duplex ultrasound was used more frequently during the last part of the 20-year period, 87.6% of the patients had an angiogram prior to surgery. Only 69.4% of the patients had a CT-scan of the brain performed preoperatively. Altogether 61.3% of the patients required a shunt during the operation. Operative details are given in Table III.

The median time from presenting symptoms until CEA was 72 days and only 100 patients had an operation within 30 days of their cerebrovascular event. A postoperative stroke within 30 days of surgery occurred in altogether 23 (4.1%) cases, and there was 1 fatal stroke 8 days after surgery.

Eight patients (1.4%) died within 30 days. The causes of death were acute myocardial infarction in 5 cases, stroke in 1 and unknown in 2, for a stroke/mortality rate of 5.4% (Table IV). The presenting symptom of the patients who suffered a postoperative stroke is indicated in Table V. Most of the patients with a stroke had an excellent recovery, and their functional status according to the



Patients at risk (yrs)	1	5	10	15
Females	190	144	66	17
Males	280	198	84	22

Figure 1.—Fifteen-year relative survival after carotid endarterectomy in 199 females and 297 males performed during a 20-year period.

Modified Rankin Scale is given in Table VI. These data were estimated during follow-up and gave information on functional status 1-72 months after the operation.

A postoperative hematoma required reoperation in 12 (2.2%) patients. The hemorrhage was located at the patch suture in 7 cases and in the subcutaneous tissue in 5. Only 1 patient was reoperated because of a perioperative stroke. Vein patch from the ankle was used in 419 cases (75.4%), and patch rupture did not occur in any patients. However, delayed healing was seen following vein harvest in 15 patients, and 1 diabetic patient developed ulceration that later came to attention, and led to a below-knee amputation 3 months after surgery.

Perioperative myocardial infarction occurred in 16 (2.9%) patients (Table IV). There was virtually no difference in the frequency of myocardial infarction during the 4 5-year periods. Postoperative nerve injuries were rather frequent, but most often confined to the superficial, transversal fibers of the cervical plexus, leading to decreased sensibility of the skin of the neck and border of the mandible (Table IV).

The operations were done by altogether 27 different first surgeons, among them 13 surgeons in vascular surgery training who were assisted by a

TABLE VII.—*Multivariate Cox regression analysis of long-term mortality by age, sex, operation period and preoperative conditions among 496 patients operated with CEA.*

Covariate	N.	Hazard ratio	P-value	95% CI
Age at operation per 7.7 years (SD)	496	1.71	<0.001	(1.44 to 2.03)
Sex				
Females	199			
Males	297	1.37	0.032	(1.03 to 1.83)
Operation period				
Before 1988	99			
1988-1992	128	0.7	0.045	(0.49 to 0.99)
1993-1997	160	0.55	0.006	(0.36 to 0.84)
1998-2002	109	0.36	0.006	(0.17 to 0.75)
Preoperative conditions				
Hypertension	212	0.95	0.739	(0.7 to 1.29)
Angina pectoris	137	0.92	0.676	(0.61 to 1.38)
Myocardial infarction	100	1.43	0.057	(0.99 to 2.07)
Diabetes	37	2.26	<0.001	(1.44 to 3.54)
Intermittent claudication	105	1.42	0.03	(1.03 to 1.95)
Renal failure	15	3.17	0.001	(1.63 to 6.16)
COPD	24	1.08	0.827	(0.54 to 2.18)
Tuberculosis	26	1.22	0.511	(0.68 to 2.2)
Arrhythmia	22	0.66	0.176	(0.36 to 1.21)
Previous aortocoronary bypass	60	0.54	0.039	(0.30 to 0.97)
Preoperative medication				
Aspirin	356	1.03	0.893	(0.71 to 1.48)
Warfarin sodium	79	0.9	0.64	(0.59 to 1.38)
β-blocker	141	1.67	0.006	(1.16 to 2.42)
ACE-inhibitor	63	1.46	0.165	(0.86 to 2.5)
Lipid lowering medication	63	0.48	0.1	(0.2 to 1.15)

CEA: carotid endarterectomy; CI: confidence interval; COPD: chronic obstructive pulmonary disease; ACE: angiotensin converting enzyme.

consultant vascular surgeon. The mean duration of postoperative hospital stay was 5.5 days, which was largely unchanged during the whole period.

Follow-up data with duplex ultrasound were available for 400 patients, and occlusion of the operated artery was observed in 9 (1.6%) patients. Restenosis was indicated in the medical record in 19 (3.4%), but the grade of stenosis was not given in detail to form the basis of a meaningful analysis. Nevertheless, because no patients developed symptoms, reoperation for secondary stenosis was not performed in this series.

Approximately 75% of the patients were alive 5 years after surgery (Figure 1). In the initial analysis, women had significantly better long-term survival than men. After adjusting for the longevity of the general population, this difference was not confirmed. Furthermore, the long-term survival seemed to improve over time. Factors that significantly contributed to reduce longevity were age at operation, male sex, operation before 1988, diabetes, intermittent claudication, renal failure and the use of β-blockers. Previous coronary artery bypass surgery was associated with increased long-term survival. The results of the multivariate regression analysis on long-term mortality are indicated in Table VII. Dividing the material into 5-year periods, the largest numbers of CEAs was seen in the years 1993-1997.

Discussion

A stroke/mortality rate of 5.4% is comparable to the 7.5% stroke/mortality rate in the European Carotid Surgery Trial (ECST)-study,[3] 5.8% stroke/mortality rate in the North American Symptomatic Carotid Surgery Trial (NASCET) study [4] and 5.1% in a previously published Norwegian series.[5] However, comparison between various centers should be made with caution, since there may be differences in case-mix between the different series. In the present study, the stroke/mortality rate after surgery for asymptomatic carotid artery stenosis was similar to that after surgery for symptomatic stenosis. A relatively large number of patients need to be operated on to prevent one stroke in patients with asymptomatic carotid artery stenosis. In the beginning of the study period, we offered this treatment to patients with an asymptomatic stenosis of more than 70% diameter reduction, if they had had CEA for symptomatic disease on the contralateral side. This approach has also been supported by others.[6] The number of CEA for asymptomatic carotid artery stenosis was 25 (11%) during the first 10 years in our institution and 38 (13%) in the following 10-year period. It seems therefore that recent prospective randomized studies, in particular the Asymptomatic Carotid Surgery Trial,[2] has not led to any marked increase in the number of procedures for asymptomatic stenosis in our institution.

The probability of long-term survival improved over time, and we have seen this trend also in patients operated on for abdominal aortic aneurysm.7 This phenomenon could be due to better case selection, and by treating concomitant cardiac disease before CEA. In addition, the life expectancy is steadily increasing in the population. Overall long-term survival after CEA has been shown to be similar to that of the general population, provided the patients do not have symptomatic coronary heart disease.[5, 8] There was a trend towards worse outcome for patients with a history of coronary artery disease in our investigation, but this did not reach statistical significance.

The occurrence of postoperative hemorrhage complications is similar to other investigations.[9-11] It is of note that there were no hemorrhages caused by rupture of the patch. In contrast, other workers have claimed that the use of vein patch from the ankle could be associated with an increased risk of patch rupture and bleeding.[10, 12] We used a vein patch from the ankle in 419 cases, stressing that the vein should be of good quality. It should be taken from the main stem and not from a tributary. However, we experienced delayed wound healing at the ankle in 15 cases. In one patient with diabetes, gangrene eventually developed and did not come to our attention before the foot was beyond salvage. Below-knee amputation became necessary 3 months after the CEA. This led to an increased awareness of alternative vein harvest site in diabetics, and in patients with history or signs of peripheral arterial disease. Nevertheless, we think that autologous vein is an ideal patch material, which is readily available and resistant to infection. The application of a patch is a safe way to close an arteriotomy without inducing stenosis, but care should be taken not to make the artery wider than normal. There is evidence

that support our routine use of patch angioplasty [13-15] to reduce the risk of restenosis, and we have not had operations for recurrent stenosis in any of our patients.

Nerve injuries were rather frequent, but cranial nerve injuries were only seen in 7.9% of the cases. Most were affecting the hypoglossal or facial nerve and all were of temporary character. Cranial nerve injuries have been reported in up to 50% of cases,[16] and were present in 8.6% of patients in the NASCET-study.[17] The number of these injuries varies widely, probably due to different routines for neurologic examination in the postoperative course. The high number of recorded sensory nerve disturbances in our study, makes it reasonable to believe that most nerve injuries have been discovered.

Patients with symptomatic heart disease will now be evaluated by a cardiologist before surgery. Preferably, coronary revascularization with aortocoronary bypass or percutaneous coronary intervention (PCI) should be done prior to CEA. We find that simultaneous coronary artery bypass surgery and CEA is rarely indicated, and only 10 such procedures were identified during the study period. However, they were not included in the investigation. We do not have any routine preoperative cardiac evaluation, or risk score assessment before operation. Pharmacologic stress echocardiography, coronary angiography whenever indicated and PCI has been performed more frequently during recent years with the intention to reduce cardiac events following CEA.

A total of 141 patients used β-blocking agents before operation, but this did not improve long-term survival. Perhaps this medication indicated hypertension or serious cardiac disease, which could then have a negative effect on long-term survival. Of note is that a rather small proportion of the patients used cholesterol lowering medication on admission and all of them were identified after 2001. Due to the prescription rules, this sort of medication had to be instituted by the general practitioners in the earlier years. Today, every patient with a carotid artery stenosis should be offered lipid lowering medication.[18] Nevertheless, CEA is still indicated, despite the fact that conservative treatment has improved during recent years.[2, 19]

Dextran has been given after CEA during the whole period, and transcranial Doppler examination has shown that this can prevent microembolism after surgery.[20] The indication for shunt has been based on measurement of stump pressure, the presence of contralateral occlusion or previous stroke. Different cut-off levels for use of a shunt have been described in the literature, but we have chosen a threshold of 50 mmHg, or 40 mmHg if a pulsatile pressure curve was present.[21, 22] A shunt was used in 61.3% of the cases, which is rather high compared to other series.[23] On the other hand it has the advantage of making the surgeon familiar with the application of the shunt. We found that the shunt was omitted in 35 cases, even if the stump pressure was below 50 mmHg. This may be due to the appearance of the pressure curve, or technical difficulties with insertion of the shunt as in patients with narrow internal carotid arteries.

Completion control of the endarterectomy site by means of duplex ultrasound seems to be an appropriate way to explore whether the artery is patent and free from residual flaps and thrombosis.[24] Although this method was used already in the 1980's at our institution, the method has been difficult to implement in daily practice because of the lack of convenient probes and sufficient experience to decide which residual changes should be corrected or left alone. More research to evaluate which method is optimal for intraoperative control following CEA is necessary.

It has been emphasised that surgery should be performed soon after the cerebrovascular event.[25] The median time from symptoms until surgery in our study was 72 days. Some of the extreme delays were due to late referral caused by insufficient knowledge about the presenting symptoms as well as further recommendations. In the first part of the study, it was customary to wait 4-6 weeks after a completed stroke in fear of producing hemorrhagic infarction in a hemodynamically unstable situation. Recent data indicate that CEA in a neurologically stable patient with a minor stroke can safely be done close to the incident.[26-28] However, the problems with early referral to surgery and expedient preoperative work-up, still represents a logistic problem for some institutions.[29] Our study indicates that a closer collaboration between neurologists, stroke units and general practitioners should be encouraged, to reduce the interval between the occurrence of symptoms and surgery. This represents a potential for improving the benefit of CEA, especially in low-grade stenosis.[25]

The mean postoperative stay was 5.5 days and there was practically no reduction over the last 10 years. Since carotid arteriography now usually can be omitted, this factor alone has saved several days of hospital stay in our setting. However, several of our patients live in rural areas. This makes the policy of admission and operation on the same day and then discharge on the following day hard to organize.[30, 31] However, a so-called critical pathway for CEA towards a 3-days postoperative course,[30, 31] should be within reach in our hospital.

Our hospital offers a complete vascular surgical training, including the carotid operations needed to become a certified vascular surgeon in Norway. Nevertheless, the total number of CEAs is low, and a national survey showed that in the year 2002 only 6 departments performed more than 20 endarterectomies.[32] This makes the number of CEAs per surgeon rather low. Even if these operations had been centralized to university hospitals, this would have a modest impact on the total number of CEAs in each teaching hospital. The relation between quality and volume in carotid surgery is not uniform, although there is some evidence that better results are achieved if each surgeon perform more than 10 operations per year.[11, 33] In our material, complicating strokes seemed to be evenly distributed among several surgeons, including those in training as well as consultant surgeons. We have not introduced carotid artery stenting (CAS), although our department has a relatively high activity of endovascular treatment for other arteriosclerotic manifestations. We feel that the results of randomized studies comparing stenting and endarterectomy,[34, 35] do not show any obvious advantage with endovascular treatment.[34, 35] One can also anticipate that if both CEA and CAS were to be done, the relative small number of carotid stenosis being treated would lead to 2 small treatment groups, thereby diluting the experience in each separate group.

Conclusions

Our policy regarding indications and surgical technique for CEA over a 20-year period has given acceptable results in terms of stroke and mortality. CEA has been performed by a high number of surgeons including trainees, who have been assisted by a consultant vascular surgeon. This does not seem to have influenced the results negatively. In our series there were no cases of patch rupture, although vein patch was routinely used. Furthermore, there were no operations for restenosis. The long-term survival improved over time. Nevertheless, there are potentials for improving the results, by decreasing the interval from presenting symptoms until operation, by better preoperative work-up and better treatment of comorbidities. Provided CAS is brought into routine use, the results of this study provide a local standard that this new treatment modality should be matched against.

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References

1. Esteve J, Benhamou E, Croasdale M, Raymond L. Relative survival and the estimation of net survival: elements for further discussion. Stat Med 1990;9:529-38.
2. MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363:1491-502.
3. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-43.
4. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:486-91.
5. Aune S, Amundsen SR, Trippestad A. Early morbidity and patterns of survival after carotid endarterectomy. Eur J Surg 1997;163:101-5.
6. Bunch CT, Kresowik TF. Can randomised trial outcomes for carotid endarterectomy be achieved in community-wide practice? Semin Vasc Surg 2004;17:209-13.
7. Haug E. Infrarenal abdominal aortic aneurysm. Comorbidity and results following open surgery. Doctoral thesis at the Norwegian University of Science and Technology, Trondheim, Norway; 2005.p.257.
8. Forssell C, Takolander R, Bergqvist D, Bergentz SE, Olivecrona H. Long-term results after carotid artery surgery. Eur J Vasc Surg 1988;2:93-8.
9. LaMuruglia GM, Brewster DC, Moncure AC, Dorer DJ, Stoner MC, Trehan SK *et al.* Carotid endarterectomy at the millenium. What interventional therapy must match. Ann Surg 2004;240:535-46.
10. Archie JP. A fifteen-year experience with carotid endarterectomy after a formal operative protocol requiring highly frequent patch angioplasty. J Vasc Surg 2000;31:724-35.
11. Kragsterman B, Logason K, Ahari A, Troëng T, Pärsson H, Bergqvist D. Risk factors for complications after carotid endarterectomy: a population-based study. Eur J Vasc Endovasc Surg 2004;28:98-103.
12. Beard JD, Mountney J, Wilkinson JM, Payne A, Dicks J,

Mitton D. Prevention of postoperative wound haematomas and hyperperfusion following carotid endaterectomy. Eur J Vasc Endovasc Surg 2001;21:490-3.
13. Eikelboom BC, Ackerstaff RG, Hoeneveld H, Ludwig JW, Teeuwen C, Vermeulen FE *et al.* Benefits of carotid patching: a randomized study. J Vasc Surg 1988;7:240-7.
14. Bond R, Rerkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2004;(2):CD000160.
15. AbuRahma AF, Khan JH, Robinson PA, Saiedy S, Short YS, Boland JP *et al.* Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: perioperative (30-day) results. J Vasc Surg 1996;24:998-1007.
16. Forssell C, Bergqvist D, Bergentz SE. Peripheral nerve injuries in carotid artery surgery. In: Greenhalgh RM, Hollier LH, editors. Surgery for stroke. London: W. B. Saunders; 1993.p.217-34.
17. Ferguson GG, Eliasziw M, Barr HWK, Clagett GP, Barnes RW, Wallace MC *et al.* The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. Stroke 1999;30:1751-8.
18. Hankey GJ. Preventable stroke and stroke prevention. J Thromb Haemost 2005;3:1638-45.
19. Naylor AR. Does the modern concept of "best medical therapy" render carotid surgery obsolete? Eur J Vasc Endovasc Surg 2004;28:457-61.
20. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM *et al.* Reducing the risk of carotid surgery: a seven year audit of the role of monitoring and quality control assessment. J Vasc Surg 2000;32:750-9.
21. Haimovici H, Callow AD, DePalma RG, Ernst CB, Hollier LH. Haimovici's vascular surgery: principles and techniques. Norwalk: Appleton & Lange; 1989.p.719-49.
22. Hunter GC, Sieffert G, Malone JM, Moore WS. The accuracy of carotid back pressure as an index for shunt requirement: a reappraisal. Stroke 1982;13:319-26.
23. Bond R, Rerkasem K, Counsell C, Salinas R, Naylor R, Warlow CP, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database Syst Rev. 2002;(2):CD000190.
24. Myhre HO, Saether OD, Mathiesen SR, Angelsen BAJ. Colour coded duplex scanning during carotid endarterectomy. In: Greenhalgh RM, Hollier LH, editors. Surgery for stroke. London: W. B. Saunders; 1993.p.253-8.
25. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004;363:915-24.
26. Gasecki AP, Ferguson GG, Eliasziw M, Clagett GP, Fox AJ, Hachinski V *et al.* Early endarterectomy for severe carotid artery stenosis after a nondisabling stroke: results from the North American Symptomatic Carotid Endarterectomy Trial. J Vasc Surg 1994;20:288-95.
27. Hoffmann M, Robbs J. Carotid endarterectomy after recent cerebral infarction. Eur J Vasc Endovasc Surg 1999;18:6-10.
28. Ballotta EB, Da Giau G, Baracchini C, Abbruzzese E, Saladini M, Meneghetti G. Early versus delayed carotid endarterectomy after nondisabling ischemic stroke: A prospective randomized study. Surgery 2002;131:287-93.
29. Mätsch T. Carotid endarterectomy: what are we doing? Eur J Vasc Endovasc Surg 1997;14:327-8.
30. Calligaro KD, Doerr KJ, McAfee-Bennett S, Mueller K, Dougherty MJ. Critical pathways can improve results with carotid endarterectomy. Semin Vasc Surg 2004;17:253-6.
31. Dardik A, Williams GM, Minken SL, Perler B. Impact of a critical pathway on the results of carotid endarterectomy in a tertiary university hospital: effect of methods on outcome. J Vasc Surg 1997;26:186-92.
32. Dahl T, Myhre HO. The practice of surgery for carotid artery stenosis in Norway. A questionnaire based investigation. Tidsskr Nor Laegeforen 2006;11:1466-9.
33. Kantonen I, Lepäntalo M, Salenius JP, Mätzke S, Luther M, Ylönen K and the Finnvasc Study Group. Influence of surgical experience on the results of carotid surgery. Eur J Vasc Endovasc Surg 1998;15:155-60.
34. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001;357:1729-37.
35. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ *et al.* Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.

Address reprint requests to: H. O. Myhre, MD, Prof. of Surgery, University Hospital of Trondheim, Department of Surgery, N-7006 Trondheim, Norway. E-mail: hans.myhre@ntnu.no

Paper V

The prevalence of carotid artery stenosis in an unselected hospitalized stroke population

Torbjoern Dahl, MD
Consultant surgeon
Department of Surgery, St. Olavs Hospital, Institute of Circulation and Medical Imaging
Norwegian University of Science and Technology

Bjoern Cederin, MD
Consultant in internal medicine
Stroke Unit
Department of Medicine, St. Olavs Hospital

Hans Olav Myhre, MD, PhD
Professor of Surgery
Department of Surgery, St. Olavs Hospital, Institute of Circulation and Medical Imaging
Norwegian University of Science and Technology

Bent Indredavik, MD, PhD
Consultant in internal medicine, Chief of the Stroke Unit
Department of Medicine, St. Olavs Hospital
Department of Neuroscience, Faculty of Medicine
Trondheim
Norway

Corresponding Author:
Hans O. Myhre
Department of Surgery
St. Olavs Hospital
NO-7006 Trondheim
Norway
Tel: + 47 73 86 83 63
Fax: + 47 73 86 74 28
E-mail: hans.myhre@ntnu.no

Running title: Carotid stenosis in stroke patients

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Key words: Stroke, carotid artery stenosis, prevalence, unselected stroke population, duplex ultrasound scanning

Abstract

Background: The aim was to describe the number and severity of carotid artery stenosis in an unselected stroke population in hospital.

Methods: The carotid arteries were investigated consecutively with colour-coded duplex scanning in patients suspected of having stroke and admitted to a stroke unit during a 6-month period. Percent internal carotid artery stenosis by diameter reduction was described.

Results: 144 patients were included in the investigation and the mean age was 75 years. The final diagnosis was stroke in 126 patients, while 18 had transitory ischemic attacks. On the side, relevant to the neurologic deficit, a stenosis of more than 70% diameter reduction was observed in 4 patients and occlusion in 3. Severe stenosis and occlusion was found to have almost the same incidence on the contralateral side. Altogether 46 stenosis above 30% (16.3%) was observed in 282 arteries investigated. The distribution was equal between the two sides.

Conclusion: These findings indicate that few patients are eligible for surgery. However, routine duplex ultrasound examination in stroke patients gives information whether there are carotid arterial lesions, which could be a source of emboli. Such information can also be a guide for further medical treatment and lifestyle modification.

Introduction

More than 60% of all strokes are thought to be of thromboembolic origin [1,2] . The source of emboli may be the heart, the aortic arch or the precerebral vessels. The diagnostic work-up is aimed at revealing conditions that could be treated and corrected. Furthermore, information about the status of the carotid arteries may be of importance for further medical therapy. The aim was to explore the incidence of carotid artery stenosis in patients admitted to a stroke unit.

Material and methods

The investigation was performed as a cohort study including stroke patients admitted consecutively to the stroke unit at our hospital during a 6-month period in 1996. Routine clinical examination, electrocardiogram and computed cerebral tomography scan (CT) were done on all patients. Ultrasound examination of the carotid arteries was performed with an Acuson 128 XP/10 (Mountain View, CA, USA) ultrasound scanner. A 7 MHz linear array transducer was used. The ultrasound examination was performed with the patient in the supine position, and the head turned away from the side of the neck being examined. Both B-mode imaging and colour Doppler technique were used to outline the atherosclerotic plaque, and the area of the tightest stenosis of the internal carotid artery (ICA) was sought. Peak systolic and end-diastolic velocities were recorded [3]. A default setting for carotid artery examination was used, and the gain setting was continuously adjusted to give the best possible image of the vessel wall. The grade of stenosis was given as percent diameter reduction, and was estimated according to the peak systolic and end-diastolic velocity values issued by the Asymptomatic Carotid Surgery Trial Group [4,5,6]. A stenosis of more than 50% diameter reduction, was diagnosed by a definite plaque in the internal carotid artery and a peak systolic

velocity of more than 1,25 m/s. Measurements of peak systolic velocity (PSV) were done in the distal part of the common carotid artery (CCA), then at the point of maximum stenosis in the internal carotid artery (ICA) and distally in the same artery. The velocity was consistently measured with angle correction and at a Doppler angle of less than 60° by adjusting the position of the probe, ultrasound beam and sample volume calipers. The patients were then divided into three groups, according to whether they had stenosis of less than 30%, 30-69% and more than 70% diameter reduction, using the classification of major clinical trials [7,8]. A diagnosis of carotid occlusion was based on absent colour doppler flow signal in the internal carotid artery (ICA), high-resistance pattern of the Doppler flow in the CCA and possibly reversal of blood flow at the origin of the ICA. Four vascular surgeons with experience in ultrasonographic scanning performed the examinations. Duplex ultrasound scanning of the carotid arteries were regarded a part of the routine diagnostic evaluation. Establishment of a local stroke registry had been approved by the Regional Ethics Committee for Medical Research. Hence, a written consent to perform the examination was not specifically asked for in each individual patient.

Statistics

The results of the ultrasound study were registered on paper forms, and thereafter transferred into SPSS®, version 12.0 (SPSS Inc., Chicago, IL). Mean and median values were calculated as appropriate.

Results

146 patients were included in the study, but two were excluded due to incomplete data collection, leaving 144 for the final analysis. There were 72 women and 72 men, with a mean age of 75 years (range 52-90 years). Data on concomitant diseases are given in table 1. Based

Table 1

on clinical and radiological data, 126 had a final diagnosis of stroke, while 18 had transitory ischemic attacks. The cause of stroke was possibly thromboembolism without cardiac origin in 85 cases, while a possible cardiac source was found in 28 patients. Finally, 13 strokes were caused by intracerebral haemorrhage. In the latter group, no carotid stenosis of more than 70% was found, but 2 stenosis of 30-69% were discovered on the same side as the cerebral lesion. None of the patients with a transitory ischemic attack had an ipsilateral carotid artery stenosis of 70% or more, but two relevant stenosis of 30-69% in the right carotid artery were found. The anatomical distribution of stroke and TIA is given in table 2. 236 carotid arteries were normal or had a stenosis of less than 30% diameter reduction, 29 stenosis between 30 and 69% were observed, while 11 stenosis were estimated to 70% or more. Finally, 6 carotid arteries were occluded. Six arteries could not be evaluated. The grading of stenosis and anatomical relation to the cerebral lesions are shown in table 3. Bilateral carotid stenosis in the area 30-69% were seen in 7 cases, 30-69% on one side and more than 70% on the other side were present in 5 cases, and in two cases a one-sided occlusion and a contralateral stenosis of 30-69% were observed.

Table 2

Table 3

Discussion

The study is probably representative for the general stroke population, because the majority of acute stroke patients in Central Norway are admitted to hospital [9]. There is probably a minority of elderly and frail patients with stroke, living in nursing homes, who are not brought to hospital though. The benefit of treatment in a stroke unit has been strongly documented in our catchment area [10]. The age distribution and frequency of concomitant diseases are also similar for the general stroke population in our geographical area [9]. Our patients mainly consisted of patients more than 60 years of age, while some of the youngest individuals with stroke are treated in other departments. However, previous studies have shown that patients

above 60 years of age, represent more than 90% of all stroke patients [10]. Our study shows that a minority of the patients had severe carotid artery stenosis. Thus, three had carotid artery occlusion and only 4 patients (2,8%) had a stenosis of more than 70% of the side, which was ipsilateral to the cerebral lesion. Taking into consideration that carotid artery surgery only may be indicated in patients with a minor stroke, the overall potential benefit of surgery is probably small in this group of patients.

Excluding carotid artery stenosis observed in patients with cerebral haemorrhage and adding stenoses on the relevant side in the range of 30-69% (n = 14), and more than 70% (n = 4) or occlusion (n = 3) indicates that carotid artery stenosis might have been responsible for 21/144 or 14.4% of the cerebral symptoms. In another Norwegian study, Friis and co-workers found an ipsilateral, severe carotid artery stenosis or occlusion in 10% of their stroke patients [11]. The small contribution of severe carotid artery disease to stroke in our study is also in accordance with a Swedish population study by Ogren (12). In a prospective cohort study of 470 men aged 68 years, carotid artery stenosis of more than 30% was not associated with an increased stroke risk (12). The risk for a cerebrovascular event however, was more often associated with occlusive disease of the lower limb arteries (12).

Data on plaque surface was not included in the present investigation. Although the diagnosis of plaque ulceration is difficult to confirm with duplex ultrasound [3], plaque surface irregularities as shown by angiography is associated with an increased risk of ipsilateral ischemic stroke [13]. It has previously been demonstrated that an echolucent or soft plaque in the ICA, is linked to an overall increased risk of stroke irrespective of side [14], and to an increased ipsilateral risk of stroke in patients with a previously symptomatic carotid artery stenosis [15]. Information about plaque appearance could therefore have contributed to the information about relevance of the carotid arterial lesions observed. Although some of the patients with TIA or stroke with minor sequelae might have been candidates for surgery at a

later stage, routine duplex ultrasound investigation of all patients in our stroke unit during the study period did not reveal a high number of carotid artery lesions eligible for surgery. However, it is useful to know whether atherosclerotic arterial lesions are present or not, since this may be of importance for further treatment. For example bilateral high-grade stenosis of the ICA may represent a risk if an attempt to reduce the blood pressure is performed in a hypertensive patient. Furthermore, medical treatment like lipid-lowering therapy and platelet inhibitors as well as lifestyle modification is indicated in patients with atherosclerotic carotid arterial disease. Surgical treatment for an asymptomatic carotid artery stenosis is still debated (16).

There are several limitations of the present investigation. Lesions in the proximal part of the common carotid arteries and the innominate artery could have been responsible for cerebral emboli. Some strokes may be caused by intracranial arterial obstructions (12). However, these arterial segments could not be investigated by our technique. Furthermore, an attempt of characterisation of the carotid lesion was made, but the data were insufficient for a meaningful analysis.

In conclusion, in an unselected stroke population with a mean age of 75 years, altogether 46 (%) carotid artery stenosis with diameter reduction more than 30% were observed in 282 arteries investigated. In the carotid artery relevant to the cerebral lesion, a stenosis of more than 70% was found in 2,8 % of the patients, and a moderate stenosis of 30-69% in 11,1 %. Although, only a few patients may be candidates for carotid surgery, routine duplex ultrasound examination in stroke patients gives information whether there are carotid arterial lesions, which could be a source of emboli. Such information could also be a guide for further medical treatment.

References

1 Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM, Wardlow JM. Stroke. A practical guide to management. Second edition. Blackwell Science Publishing, Oxford 2001.

2 Indredavik B. [Embolism as the cause of stroke] (in Norwegian). Tidsskr Nor Laegeforen 2001;121:2142.

3 Zwiebel WJ. Color-duplex features of normal and abnormal carotid arteries. Doppler evaluation of carotid stenosis. In Zwiebel WJ (ed.) Introduction to Vascular Ultrasonography. W.B. Saunders Company, Philadelphia 1992: 105-132.

4 MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363: 1491-1502.

5 Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-644.

6 Langlois Y, Roederer GO, Chan A, Phillips DJ, Beach KW, Martin D, Chikos PM, Strandness DE. The concordance between pulsed Doppler/spectrum analysis and angiography. Ultrasound in Med & Biol 1983;9:51-63.

7 European Carotid Surgery Trialists` Collaborative Group (ECST). MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 1991;337:1235-1243.

8 North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. NEJM 1991;325:445-453.

9 Ellekjaer H, Holmen J, Indredavik B, Terént A. Epidemiology of stroke in Innherred, Norway, 1994-96. Incidence and 30-day case-fatality rate. Stroke 1997;28:2180-2184.

10 Indredavik B, Bakke F, Solberg R, Rokseth R, Håheim LL, Holmen I. Benefit of a stroke unit: a randomized controlled trial. Stroke. 1991;22 :1026-31.

11 Friis P, Gjestvang FT, Fausa D, Kaass B. [Thrombotic or embolic stroke?] (in Norwegian). Tidsskr Nor Laegeforen 2001;121:2143-2146.

12 Ogren M, Hedblad B, Isacsson S-O, Janzon L, Jungquist G, Lindell S-E. Ten year cerebrovascular morbidity and mortality in 68 year old men with asymptomatic carotid stenosis. BMJ 1995;310:1294-1298.

13 Rothwell PM, Gibson R, Warlow CP. Interrelation Between Plaque Surface Morphology and Degree of Stenosis on Carotid Angiograms and the Risk of Ischemic Stroke in Patients With Symptomatic Carotid Stenosis. Stroke 2000;31:615-621.

14 Mathiesen EB, Boenaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis (The Tromsoe study). Circulation 2001;103:2171–2175.

15 Groenholdt MLM, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. Circulation 2001;104:68 –73.

16 Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD001923.

Table 1

Concomitant conditions and diseases in 144 patients admitted to a stroke unit.

Condition	**Number**	**Percentage**
Hypertension	51	35,4
Coronary heart disease	37	25,7
Current smoker	36	25,0
Atrial fibrillation	30	20,8
Diabetes	21	14,6
Intermittent claudication	6	4,2

Table 2

Anatomical distribution of the cerebral lesion causing stoke or TIA in 144 patients.

Clinical picture according to area	**Frequency**	**Percent**
Anterior circulation left side	66	45,8
Anterior circulation right side	59	41,0
Posterior circulation	12	8,3
Undetermined/unclassified	5	3,5
Missing	2	1,4
Total	144	100

Table 3

Carotid arterial stenosis and relevance to side of symptoms.

		Anterior circulation		**Posterior circulation**	
Side	**Percent stenosis (diameter reduction)**	**Ipsilateral to cerebral lesion side**	**Contralateral to cerebral lesion**		**Total**
Left	< 30	38	70	12	120
	30-69	8*	5	0	13
	> 70	4	2	0	6
	Occluded	2	1	0	3
	Undetermined	0	0	0	2
	Total	**52**	**78**	**12**	**144**
Right	< 30	38	67	11	116
	30-69	8**	8	0	16
	> 70	0	4	1	5
	Occluded	1	2	0	3
	Undetermined	0	0	0	4
	Total	**47**	**81**	**12**	**144**

* One stenosis was seen in connection with ipsilateral cerebral haemorrhage

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