Non-invasive Imaging of Carotid Artery Stenosis

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Non-invasive Imaging of Carotid Artery Stenosis

(with a summary in Dutch)

Non-invasieve Beeldvorming van Arteria Carotis Stenose

(met een samenvatting in het Nederlands)

Proefschrift

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‘The doctor ’s assumption that health is a relative absence of disease is not good enough’

D.W. Winnicott (1896-1971)

Aan mijn ouders

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Chapter 1

Introduction

Presence of carotid artery stenosis is generally known as one of the risk factors for ischemic stroke. Approximately 20% of all ischemic strokes are considered to be caused by atherosclerosis of the carotid bifurcation. Other possible causes are cardio-embolic events or local atherosclerosis in the smaller arteries nearby the site of an infarct. For almost 60 years, patients with atherosclerotic lesions in the carotid bifurcation have been treated surgically by carotid endarterectomy.[1] The selection of those patients that benefit the most from this procedure, however, has remained unclear for a long period of time. In the last decade two large randomised trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have proven that endarterectomy reduces the risk of recurrent ipsilateral stroke in symptomatic patients with a severe stenosis (70-99%) of the internal carotid artery (ICA).[2,3] Subgroups of patients with a 50-69% stenosis may also expect a benefit from carotid endarterectomy, however, this benefit is only marginally significant. Furthermore, it has been shown that an increasing degree of stenosis yielded increasing benefit from surgery. Therefore, a precise estimate of the degree of stenosis in the ICA is crucial in selecting the patients that benefit from carotid endarterectomy.

In the trials mentioned above the degree of stenosis was assessed with digital subtraction angiography (DSA), which consequently has become the standard of reference in the diagnosis of carotid artery stenosis. This invasive procedure, however, has a small but significant risk of morbidity and mortality, which decreases the potential overall benefit of endarterectomy.[4] Even patients without apparent neurological complications after DSA have been shown to develop minor asymptomatic infarctions due to micro-embolisms.[5] Medical technology, however, is rapidly developing and new diagnostic imaging techniques have become available. To date, non-invasive tests such as duplex ultrasound (DUS) and magnetic resonance angiography (MRA) are increasingly used in the diagnosis of carotid artery stenosis. These tests do not carry the potential risk of complications. However, with regard to the results of the carotid surgery trials, it remains very important that the correct group of patients is selected by new test strategies.

Over the last decade, many diagnostic studies have been published in which DUS, MRA, or combinations of these tests were compared with DSA.[6-8] In Chapter 2 of this thesis a systematic review of the literature on diagnostic studies from 1994 to 2001 is described. Recently, in line with our findings, a review of previous publications on this topic published between 1993 and 1998 criticised the design of the studies.[9] Often, the study populations were small, or the diagnostic test results were collected retrospectively. Furthermore, from the limited published evidence available to date, the cost-effectiveness of carotid endarterectomy and of the preoperative investigations remains unclear.[10] Apparently still insufficient evidence is available to take considered policy decisions on the replacement of DSA by non-invasive testing. The need for a prospective diagnostic study including a cost-effectiveness analysis has repeatedly been recognised in the literature.[11]

The objective of this thesis was to determine if DSA could be replaced by non-invasive testing. First, it was important to obtain a valid thorough evaluation of non-invasive imaging techniques and to provide reliable estimates of the diagnostic accuracy of DUS, MRA, and a combination of these tests compared to DSA as reference standard. From January 1997 to November 2000 nearly 400 consecutive patients suspected of having carotid artery stenosis, in whom carotid endarterectomy was considered, were included in a prospective diagnostic study. All patients underwent DUS, MRA, and DSA examination. The complete content of this study and the estimates of the accuracy of the non-invasive tests are presented in Chapter 3. The limitations of a diagnostic study are discussed and the best non-invasive strategy is presented based on the diagnostic performance. However, to be able to understand the consequences of implementation of non-invasive imaging strategies from a societal perspective, a valid estimate of the diagnostic accurasy is not sufficient. Additionally, a cost-effectiveness analysis was performed, which is presented in Chapter 4. The long-term implications, expected quality of life, and total lifetime costs could be studied by means of a diagnostic and prognostic decision model.

In the Chapters 5 and 6 further test specific characteristics of MRA are described. In Chapter 5 the overestimation of the degree of stenosis by MRA compared with DSA is analysed and a possible explanation is proposed. In Chapter 6, the occurrence of flow related artefacts, one of the drawbacks of MRA, is investigated and its meaning in clinical practice is discussed. A recent development in MRA imaging is contrast-enhanced MRA (CE-MRA). This technique utilises a small amount of intravenous contrast. CE-MRA was studied in a sub-population of 50 consecutive patients and the diagnostic value is described in Chapter 7. Finally, in Chapter 8, the patients' preferences for DUS, MRA, and DSA, and possible discomforts related to the particular tests are presented. In Chapter 9 the results of the different studies are recapitulated and discussed.

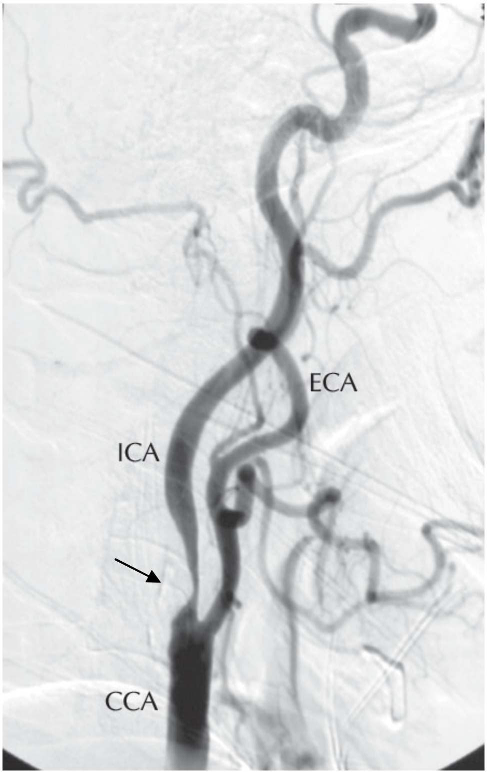

Figure 1. Example of a digital subtraction angiography (DSA) showing a severe stenosis (arrow) in the internal carotid artery (ICA). The common carotid artery (CCA) and the external carotid artery (ECA) in this image show a normal lumen.

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Chapter 2

Duplex ultrasound and MR angiography compared to digital subtraction angiography in carotid artery stenosis: a systematic review

Paul J Nederkoorn, Yolanda vd Graaf, MG Myriam Hunink.
Submitted

Abstract

Purpose:

To review and compare the published data on the diagnostic value of Duplex ultrasonography (DUS), Magnetic resonance angiography (MRA) and conventional Digital subtraction angiography (DSA) for the diagnosis of carotid artery stenosis.

Data sources:

Systematic review of published studies retrieved through PUBMED, bibliographies of review papers, and experts.

Study selection:

The English-language medical literature was searched for studies that met the following selection criteria: 1) publications published between 1994 and 2001; 2) time-of-flight MRA or contrast-enhanced MRA and/or DUS were performed to estimate the severity of carotid artery stenosis; 3) DSA was used as the standard of reference; 4) the absolute numbers of true-positives, false-negatives, true-negatives, and false-positives were available or derivable for at least one definition of disease (degree of stenosis).

Data extraction:

Two authors (Y.vd.G and P.J.N) independently extracted predefined clinical and diagnostic parameters from eligible studies.

Results:

Sixty-three publications on duplex, MRA, or both were included in the analysis, yielding the test results of 64 different patient series on DUS and 21 on MRA. For the diagnosis of a 70-99% vs <70% stenosis, MRA had a pooled sensitivity of 95%(CI, 92% to 97%) and a pooled specificity of 90% (CI, 86% to 93%). These numbers were 86% (CI, 84% to 89%) and 87% (CI, 84% to 90%) for DUS, respectively. For recognizing occlusion MRA yielded a sensitivity of 98% (CI, 94% to 100%) and a specificity of 100% (CI, 99% to 100%) and DUS had a sensitivity of 96% (CI, 94% to 98%) and a specificity of 100% (CI, 99% to 100%). A multivariable summary ROC analysis for diagnosing 70-99% stenosis demonstrated that the type of MR scanner predicted the performance of MRA, whereas the presence of verification bias predicted the performance of DUS. For diagnosing occlusion no significant

heterogeneity was found for MRA; for DUS the presence of verification bias and type of DUS scanner were explanatory variables. In the comparative multivariable summary ROC model with adjustment for the explanatory covariates, MRA had a significantly better discriminatory power than DUS in diagnosing 70-99% stenosis (regression coefficient 1.6 (CI, 0.37 to 2.77)). No significant difference was found in detecting occlusion (0.73 (CI, -2.06 to 3.51)).

Conclusions:

The results suggest that MRA has a better discriminatory power compared with DUS in diagnosing 70-99% stenosis and is a sensitive and specific test compared to DSA in the evaluation of carotid artery stenosis. For detecting occlusion both DUS and MRA are very accurate.

Introduction

Two large randomized clinical trials, The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), have proven the benefit of carotid endarterectomy in patients with severe symptomatic carotid artery stenosis, 70-99%.[1,2] Recent publications have shown that subgroups of patients with a 50-69% stenosis may also expect a small benefit from carotid endarterectomy.[3] The diagnosis of severe stenosis (70-99%), however, remains crucial for the majority of patients. The degree of stenosis in the endarterectomy trials was established by DSA, which has become the standard of reference for selecting patients for carotid surgery. DSA, however, has a relatively high risk of morbidity and mortality ranging from 1% to 4% in patients with atherosclerosis.[4] Even patients without apparent neurological complications after DSA have been shown to develop minor asymptomatic infarctions due to micro-embolisms.[5]
Magnetic resonance angiography (MRA) and contrast-enhanced magnetic resonance angiography (CE-MRA) are increasingly used supplementary to duplex ultrasonography (DUS) and conventional digital subtraction angiography (DSA) in the diagnosis of carotid artery stenosis.[6] Many institutions have published diagnostic studies in which MRA and/or DUS were compared with DSA. The results suggest that the decision to perform carotid endarterectomy could be based one or a combination of these non-invasive tests. Two meta-analytic reviews have been published summarizing literature on the diagnostic performance of DUS and MRA from before 1996, one reporting an increasing role for non-invasive testing in carotid artery disease (DUS and MRA),[7] the other concluding moderate test results for MRA.[8] Recently a review of previous publications on this topic published between 1993 and 1998 criticized the design of the studies and proposed guidelines for diagnostic studies.[9]
The purpose of this study was to systematically review the contemporary literature and to compare the diagnostic performance of DUS, MRA, and CE-MRA. Our aim was to increase precision by combining published studies and to determine variables that might explain part of the difference in outcome across the studies. Recently published guidelines for meta-analyses of randomized controlled trials were followed where they were applicable to a meta-analysis on diagnostic tests.[10]

Methods

Study selection

We performed a literature search for publications on the diagnostic performance of either DUS, MRA, or a combination of these two modalities in patients with carotid artery stenosis in which DSA was used as the standard of reference. We chose to limit our search to the period from January 1994 to December 2001. Since 1994 there has been a rise in publications on MRA. We decided not to go further back in time because technical possibilities and imaging protocols of these non-invasive tests have developed considerably over time, making comparison between new and old studies less meaningful.
To find the studies we performed a PUBMED search using the following keywords and all possible related terms: *carotid artery, angiography*, combined with *magnetic resonance* and/or *duplex* or *ultrasound.* We limited the search to publications published in the English language. Reference lists of original and review publications on this subject were checked and experts on the subject were consulted to find additional studies.
Studies were included that met the following criteria: 1) published between 1994 and 2001; 2) MRA or CE-MRA and/or DUS were performed to estimate the severity of carotid artery stenosis; 3) DSA was used as the reference standard; 4) the absolute numbers of true-positive, false-negatives, true-negatives, and false-positives were available or derivable from the presented data for at least one cutoff criterion for the degree of stenosis based on DSA. We reconstructed these numbers if sensitivity, specificity, and the prevalence of the disease were presented.
Our intention was to collect the absolute numbers for each study as completely as possible for the following categories of carotid artery stenosis: 0-29%, 30-49%, 50-69%, 70-99%, 100%. Authors were contacted for two reasons: 1) to give them the opportunity to send us additional data so that we could work with a complete dataset for all described categories; 2) if neither absolute numbers or sensitivity/specificity were derivable but the study suggested availability of this data. Studies with occlusion as their main outcome (often describing diagnostic tests only to determine if occlusion was present or not) were excluded if the author did not respond to our request for more precise specification of the non-occlusion group. We excluded these studies because the main subject of our meta-analysis was treatment decisions based on the category of 70-99% stenosis and because the cutoff criterions used in these publications were too diverse to include in the meta-analysis. We also excluded studies with a population of less than 15 patients. If publications used the same or an overlapping population we chose the publication from which we could derive the required data in the most straightforward manner. We contacted the authors if it was not clear whether separate published populations were overlapping.

Data extraction

Two authors (YvdG) and (PN) independently extracted data from all publications. All abstracts collected from PUBMED on the basis of the described search criteria were evaluated. The full text was studied to check the inclusion criteria from all studies that could not definitely be excluded on the basis of the abstract. From the included publications the absolute numbers of true-positives, false-negatives, true-negatives, and false-positives of the described test modalities were extracted as completely as possible for all the different categories of stenosis: 0-29%, 30-49%, 50-69%, 70-99%, 100%. Sensitivity and specificity were extracted or calculated from the data and absolute numbers were derived if the prevalence was reported. Additionally the following variables were extracted for each study population: mean age and range, percentage of men and women, percentage of symptomatic patients, type of symptoms (amourosis fugax, transient ischemic attack, or stroke), and if the tests were studied in a consecutive patient population. The following test characteristics were determined: used method of stenosis measurement on DSA (according to NASCET or ECST criteria or a different method), type of MR and/or DUS machine, time interval between DUS and/or MRA and DSA, the number of visualized carotid arteries and whether a different cutoff was used to define severe stenosis (eg. 60% or 80% instead of 70% stensosis). We converted cutoff values determined according to ECST criteria to their corresponding NASCET criteria. In studies presenting DUS results, often more than one velocity parameter (peak systolic velocity, end diastolic velocity, mean velocity) or a ratio was used to determine the degree of stenosis. We chose the parameter that the authors considered as optimal. Single PSV-values referring to a degree of stenosis of 70% were extracted if available. We determined whether the DUS thresholds were defined before the study was performed or if the optimal thresholds had been analyzed afterwards on the basis of the results (yielding a higher diagnostic performance). We also noted if verification bias was present, which may exist if the decision to perform the reference standard procedure depends on the results of the test under investigation.[11] (In practice DUS is often used as the screening test to select patients for DSA). In the MRA studies use of a protocol with an intaveneous contrast agent was noted. Finally, we determined whether tests were read with the observer blinded for the results of the other test(s). Discrepancies between the two observers in the extracted data were discussed and in all cases resolved through consensus.

Analyses

The analyses presented are limited to two groups: 70-99% (severe stenosis) vs <70% and 100% (occlusion) vs < 100%. The data collected from the other subgroups under the 70% threshold (0-29%, 30-49%, 50-69%) were not included in the presented

Table 1: Variables extracted from publications and analysed in the described models for each study population.

1. Test specific positivity criterion (S)
2. Publication year
3. Proportion symptomatic (assuming all symptomatic if not mentioned)
4. Consecutive patients included in the cohort
5. Verification bias
6. Blinded interpretation of test results
7. Measuring of stenosis by NASCET-method
8. Choice of a different cutoff to define severe stenosis
9. Type of DUS machine used
10. Gadolinium (contrast agent) used for MRA
11. Type of MR machine used
12. Time between non-invasive test and angiography
13. Peak systolic velocity (PSV) cutoff value for 70% stenosis on DUS
14. PSV positivity criterion determined after the study
15. Age

analyses. The data in these groups contained too many missing values for a meaningful analysis, even though some publications presented a very complete description of the data and some of the authors gave enthusiastic replies to our request for additional data. Furthermore, we thought that the data of the 30-49% and 50-69% stenosis categories might suffer from selection and/or verification bias because many institutions use a threshold nearby 50% stenosis on DUS as their inclusion criterion to perform DSA. For both reasons the analyses in these stenosis groups gave very inconsistent preliminary results.
All variables that were analyzed are listed in Table 1. Gender and distribution of disease (i.e. localization of the event) were often missing which precluded meaningful analysis.

Pooled weighted analysis

We calculated the pooled weighted results of sensitivity, specificity, and the diagnostic performance. The diagnostic performance was defined as the natural logarithm of the diagnostic odds ratio $D=\ln[(TP \times TN)/(FP \times FN)]$. Weighting was done with the inverse of the variance. We used a random effects model to account for the heterogeneity across studies.

Summary ROC Analysis

To adjust for the heterogeneity in positivity criteria a summary ROC analysis was performed for each test.[12] Summary ROC analysis is a meta-analytic method to summarize true- and false positive rates from different diagnostic studies.[13] In this method the postivity criterion of each study is approximated by calculating $S=\ln[(TPxFP)/(TNxFN)]$.
Initially we applied both a fixed and a random effects model in all analyses. The fixed effects model assumes that the operating points from the individual studies lie on one underlying true ROC-curve, and that the differences in test results can be explained by differences in positivity criteria and other definable covariates. The random effects summary ROC model assumes there is always some residual cross-study heterogeneity even after adjustment for differences in positivity criteria and characteristics such as population-size, age, gender, definition of disease, scanner-type, blinded-scoring, and verification bias.[14] In the remaining sections of this paper we will only present the methods and results of the random effects summary ROC model. In the discussion we will elaborate on the differences in outcome between the random and the fixed effects model.

Summary ROC analysis by diagnostic test

Summary ROC models were developed for each diagnostic test separately. In a bivariable analysis we evaluated each covariate (Table 1) to determine its explanatory value in explaining differences across studies in diagnostic performance (D) after adjustment for the used positivity criterion (S).Variables were considered explanatory in the random effects analysis if their inclusion decreased the estimate of the between-study-variance by at least 10% (which was calculated with the method-of-moments), if they had a regression coefficient of at least 1.0 for dummy variables or 1.0 over the range of the variable, or if they were statistically significant ($p<0.05$).[15] Subsequently, multivariable summary ROC models were developed for each diagnostic test separately. The explanatory variables from the bivariable analysis were evaluated in a stepwise forward selection regression model including variables one-by-one, starting with the variable that increased the adjusted R-squared the most, and keeping the variable in the model using the same selection criteria as above. S (indicating the positivity criterion) was retained in the model irrespective of its significance.

Summary ROC analysis comparing MRA and DUS

Finally, we performed a summary ROC analysis for the comparison between Duplex and MRA. The significant variables from the multivariable analysis performed for each test separately were included as test-specific covariates in the multivariable comparative model. A dummy variable was added to compare the two tests.

The regression coefficient of this dummy variable represents the difference in diagnostic performance (D) of MRA compared to DUS. A positive regression coefficient indicates better discriminatory power of MRA compared to DUS and a negative coefficient indicates reduced discriminatory ability of MRA.

Results

Overview of studies

The PUBMED search yielded a little over 900 references. After evaluating the abstracts we retrieved 151 publications for further study. Sixty-two papers met our inclusion criteria completely.[16-77] The included 62 publications yielded 85 separate study populations: 21 series on MRA and 64 series on DUS (Figure 1). Nine publications reported on both MRA and DUS results.[16,23,36,62,65,70,72-74] Five publications presented more than one study population and/or multi-center studies containing data varying from 2 to 10 institutions.[23,24,46,58,60] Forty-six authors were contacted in an attempt to obtain additional data. Three of these authors were contacted because different publications suggested the availability of data about (part of) the same study-population. The over-all response rate was 30%. Thirteen authors replied and sent us their more complete data. Two authors did answer but wrote that they could not retrieve the necessary numbers. Twenty of the remaining 31 publications were nevertheless included on the basis of the reported results only. Although several reports are now available on Gadolinium-enhanced MRA, test-results validated with DSA as the reference standard in a population larger than 15 patients were published in only 4 series.[20,23,39,41]

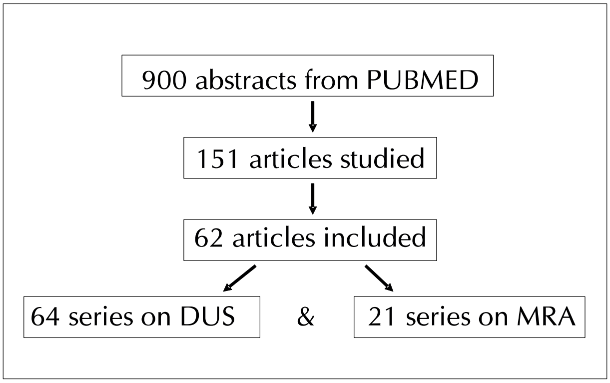

Figure 1: Flow diagram of inclusion of the patient series.

Table 2: Pooled weighted sensitivity and specificity calculated in a random effects model.

	Pooled sensitivity (%) (95% CI)		Pooled specificity (%) (95% CI)	
	MRA	DUS	MRA	DUS
70-99% vs <70%	95 (92 to 97)	86 (84 to 89)	90 (86 to 93)	87 (84 to 90)
<100% vs 100%	98 (94 to 100)	96 (94 to 98)	100 (99 to 100)	100 (99 to 100)

Pooled weighted analysis

For the diagnosis of a 70-99% vs <70% stenosis, MRA had a pooled sensitivity of 95% (CI, 92% to 97%) and a pooled specificity of 90% (CI, 86% to 93%) (Table 2). These numbers were 86% (CI, 84% to 89%) and 87% (CI, 84% to 90%) for DUS, respectively. For diagnosing occlusion (<100% vs 100%) MRA had a sensitivity of 98% (CI, 94% to 100%) and a specificity of 100% (CI, 99% to 100%), and for DUS these numbers were 96% (CI, 94% to 98%) and 100% (CI, 99% to 100%). These pooled data indicate a better discriminatory power for MRA in diagnosing severe stenosis (70-99%) whereas MRA and DUS are equally good in recognizing carotid occlusion (100%). The pooled values of D (the natural logarithm of the diagnostic odds ratio) were very similar between tests: 4.1 (CI, 3.5 to 4.8) for MRA vs 4.0 (CI, 3.5 to 4.5) for DUS in the 70-99% category and 6.5 (CI, 5.7 to 7.4) for MRA vs 6.5 (CI, 5.9 to 7.0) for DUS in diagnosing occlusion.

Summary ROC analysis by diagnostic test

In the multivariable model for the diagnosis of 70-99% stenosis type of MR scanner was a significant predictor for the diagnostic performance of MRA, whereas presence of verification bias and choice of a different cutoff to define severe stenosis were associated with a better performance of DUS. In recognizing occlusion no significant heterogeneity was demonstrated among the MRA studies. Presence of verification bias and type of DUS scanner were significant predictors for DUS.

Summary ROC analysis comparing MRA and DUS

The multivariable comparative model with adjustment for significant predictors demonstrated a regression coefficient for MRA vs DUS of 1.6 (CI, 0.37 to 2.77, p=0.01) for 70-99% vs <70% stenosis. In differentiating occlusion from <100% stenosis the regression coefficient for MRA vs DUS was 0.73 (CI, -2.06 to 3.51, p=0.51). These numbers mean that for the distinction of <70% vs 70-99% stenosis MRA discriminates significantly better than DUS, whereas for the distinction between occlusion and <100% no difference in diagnostic performance could be demonstrated. The multivariable summary ROC curves were constructed using the final comparative model, and are presented in figures 1 and 2 for both MRA and DUS for the diagnosis of severe stenosis (70-99%). The summary ROC curve for DUS was adjusted to reflect a cutoff of 70% for severe stenosis and the absence of verification bias. The summary ROC curve for MRA was adjusted to reflect the most commonly used types of MR scanners. The dots represent the original true positive and true negative rates of the individual publications.

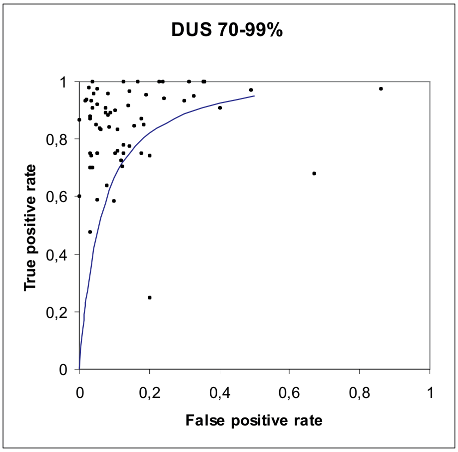

Figure2. Multivariable summary ROC model (line) for diagnosing severe stenosis on DUS, and original data from individual studies (dots). The summary ROC curve is adjusted to reflect a cutoff of 70% for severe stenosis and the absence of verification bias.

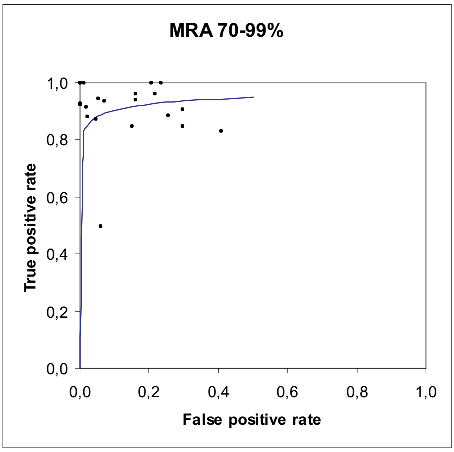

Figure 3. Multivariable summary ROC model (line) for diagnosing 70-99% vs <70% stenosis on MRA, and original data from individual studies (dots). The summary ROC curve is adjusted to reflect the most commonly used types of MR scanners.

Discussion

In this paper we systematically reviewed and compared the diagnostic value of DUS and MRA with DSA for the diagnosis of carotid artery stenosis. Our results suggest that for the distinction of <70% vs 70-99% stenosis MRA has a significantly better discriminatory power than DUS, whereas for the distinction between occlusion vs no occlusion there is no significant difference in diagnostic performance. According to our random effects model the difference between DUS results across studies for diagnosing a 70-99% stenosis can be explained (in part) by the presence of verification bias and choice of a different cutoff to define severe stenosis. For MRA the type of MR scanner was an explanatory variable. For diagnosing 100% vs <100% with DUS, presence of verification bias and type of DUS scanner were explanatory variables; for MRA no heterogeneity was found among the different studies.

An earlier meta-analysis published by Blakeley ea. in 1995 concluded that DUS and MRA had similar diagnostic performance in predicting carotid artery occlusion and ≥70% stenosis.[7] In our study we found a better discriminatory power for MRA compared with their results. In the study by Blakeley ea. the literature from 1977 to 1993 was reviewed, whereas our literature search started as of 1994. Improved MRA technology might explain an increase in diagnostic performance of MRA. Kallmes ea. reviewed MRA studies published between 1990 and 1994, and also found a lower sensitivity for MRA in recognising severe carotid artery stenosis than we did.[8] Furthermore, they discussed whether the asymptomatic arteries should be excluded from the results. Exclusion of the asymptomatic side in their analyses gave even lower sensitivities.

A limitation in the collection of our data was the fact that, to be able to perform a summary ROC analysis, we could include only those studies from which absolute numbers (TP,FP,TN and FN) for at least one defined threshold were available or derivable. Often only sensitivities and specificities were presented. When we were unable to reconstruct the absolute numbers, or when authors did not reply to our request for additional data, we needed to exclude the paper. Therefore, it was only possible to include a selection of the contemporary literature in this analysis. Furthermore, in the included papers we often found incomplete or missing data concerning population baseline characteristics, distribution of disease, and technical aspects of the imaging protocols. For some of the variables these missings precluded meaningful analysis.

In the meta-analysis we first calculated the pooled sensitivities and specificities. This method provides a relatively crude estimate of the overall diagnostic performance of the different tests. The pooled weighted analysis showed that both DUS and MRA are highly sensitive and specific for diagnosing carotid artery occlusion. For the diagnosis of occlusion only the absence of signal needs to be determined, while judgement of the severity of a stenosis is not necessary. For detecting the 70% cutoff MRA showed a better sensitivity and slightly better specificity than DUS. MRA probably gives a more precise estimate of the degree of stenosis because it provides a direct measurement of the stenotic lumen (NASCET-method), whereas DUS only allows an indirect estimate through measurement of parameters based on blood flow velocities. Therefore, DUS gives a wider dispersion in results when compared with DSA, resulting in lower sensitivities and specificities. The pooled sensitivity and specificity of 95% and 90% respectively for MRA in detecting severe stenosis are very high. This technique will probably improve even further in the near future, for example by the increased use of contrast-enhanced protocols. To date, however, only a few studies have been published reporting the results of contrast-enhanced MRA validated against DSA precluding a meaningful analysis in this study.

Apart from calculating pooled weighted sensitivities and specificities we also performed a summary ROC analysis, which is especially useful to evaluate overall diagnostic performance. The main advantage of this method is the fact that it adjusts for different positivity criteria, which cannot be achieved with pooling sensitivities and specificities. Initially we studied both a fixed and a random effects model in the summary ROC analyses. Although the random-effects model seems more elegant in a meta-analysis combining the results from diverse studies, in a diagnostic meta-analysis a fixed effects model in our opinion can also be justified. Study-populations selected for a specific test and disease often have comparable baseline characteristics which supports the assumption of a true underlying ROC curve. Because of the stricter assumptions, the fixed effects model can potentially identify additional explanatory variables. In our study the fixed and random effects model showed good consistency in finding significant variables that explain (part of) the heterogeneity of the different publications. For DUS publication year was found as an additional explanatory variable for the diagnosis of severe stenosis (70-99%) when the fixed effects model was applied. Earlier studies showed better diagnostic performance, indicating a possible effect of publication bias. Alternatively, this finding may indicate the selection bias that commonly occurs in early studies of new diagnostic technologies. In the diagnosis of occlusion a consecutive study population was found as additional significant variable for MRA.

Remarkably the type of MR scanner but not the type of DUS scanner was shown to be an explanatory variable in the diagnosis of a 70-99% stenosis. It is generally known that different DUS machines with different technologists in different institutions show variable test results, even if the same thresholds for the test parameters are used.[78] For MRA scanners this difference has not been shown previously. The type of MR scanner probably represents not only the brand of the machine but also used software and imaging protocols. This would mean that, like for DUS, in clinical practice each institution should probably validate its own machine and imaging protocol.
The fact that verification bias plays an important role in detecting 70-99% stensoses on DUS is a plausible and important finding. Verification bias may exist if the decision to perform the reference standard procedure depends on the results of the test under investigation. In the included studies DUS has often been used as a screening test to decide whether to perform DSA.

In conclusion, our results suggest that MRA has a better discriminatory power compared with DUS in recognising 70-99% stenosis, and is a sensitive and specific test compared to DSA in the evaluation of carotid artery stenosis. For detecting occlusion of the carotid artery both modalities are very accurate. To determine if non-invasive tests can replace DSA in clinical practice, however, not only the test results, but also a cost-effectiveness analysis based on the diagnostic accuracies should be taken into account.

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Chapter 3

Pre-operative diagnosis of carotid artery stenosis: accuracy of non-invasive testing

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Abstract

Background and Purpose:

Carotid endarterectomy has been shown to be beneficial in symptomatic patients with a severe stenosis (70-99%) of the internal carotid artery (ICA). Digital subtraction angiography (DSA) is the standard of reference in the diagnosis of carotid artery stenosis, but has a relatively high complication rate. In a diagnostic study we investigated whether DSA could be replaced by non-invasive testing.

Methods:

In a prospective diagnostic study we performed duplex ultrasound (DUS), magnetic resonance angiography (MRA), and DSA on 350 consecutive symptomatic patients. Stenoses were measured with the observers blinded for clinical information and other test results. Separate and combined test results of DUS and MRA were compared with the reference standard DSA. Only the stenosis measurements of the arteries on the symptomatic side were included in the analyses.

Results:

DUS analysed with previously defined criteria resulted in a sensitivity of 87.5% (95%CI, 82.1%-92.9%) and a specificity of 75.7% (95%CI, 69.3%-82.2%) in identifying severe ICA stenosis (70-99%). Stenosis measurements on MRA yielded a sensitivity of 92.2% (95%CI, 86.2%-96.2%) and a specificity of 75.7% (95%CI, 68.6%-82.5%). Combining MRA and DUS results, agreement between these two modalities (84% of patients) gave a sensitivity of 96.3% (95%CI, 90.8%-99.0%) and a specificity of 80.2% (95%CI, 73.1%-87.3%) for identifying severe stenosis.

Conclusion:

DUS and MRA seem accurate diagnostic tests to detect carotid artery stenosis. In a non-invasive diagnostic strategy, however, both tests should subsequently be performed. If DUS and MRA are in agreement, the combined test result yield a high sensitivity and specificity, making DSA redundant for the decision on carotid endarterectomy. In the event of disagreement, however, DSA should still be considered.

Introduction

Carotid endarterectomy was shown to be beneficial in symptomatic patients with a severe stenosis (70-99%) of the internal carotid artery (ICA) in two large randomised trials.[1-4] Subgroups of patients with a 50-69% stenosis may also expect a small benefit from carotid endarterectomy. The diagnosis of severe stenosis (70-99%), however, remains crucial for the majority of patients. Increasing degree of stenosis yielded increasing benefit from surgery, making precise estimation of the degree of stenosis very important. In the trials the degree of stenosis was assessed with Digital Subtraction Angiography (DSA), which consequently has become the standard of reference for selecting patients for carotid surgery. DSA, however, has a risk of morbidity and mortality, which decreases the potential overall benefit of endarterectomy. In the literature risk of 4% of transient ischemic attack (TIA) or minor stroke and 1% of major stroke, and even a small risk of death (<1%) have been reported.[5,6] More recently, a lower rate of neurologic complications due to DSA was reported: 0.5% for stroke and 0.4% for TIA.[7] However, even patients without apparent neurological complications after DSA have been shown to develop minor asymptomatic infarctions due to micro-embolisms.[8]

Over the last decade many diagnostic studies have been published in which non-invasive diagnostic tests such as Duplex Ultrasound (DUS) and Magnetic Resonance Angiography (MRA) or combinations of these tests were compared with DSA.[9-19] Two meta-analytic reviews have been published summarising the literature on the diagnostic performance of DUS and MRA from before 1996. One concluded that the actual sensitivity and specificity for MRA remain unknown, but that these are probably lower than reported in the literature because of the presence of verification bias and because frequently both carotid arteries (symptomatic and asymptomatic) were included in the analyses.[20] The other meta-analysis reported that non-invasive testing at that point did not appear to be an adequate substitute for DSA for patients about to have carotid endarterectomy.[21] Thereafter the non-invasive imaging techniques have continued to develop. A review of previous publications on this topic published between 1993 and 1998, however, criticised the design of the studies and proposed guidelines for diagnostic studies on carotid artery imaging.[22] Accordingly, a recent review summarising publications from 1990 to 1999, concluded that MRA seemed accurate for selecting patients for carotid endarterectomy, but that evidence was not very robust because of the heterogeneity of the studies included.[23] The need for a prospective diagnostic study on non-invasive testing was recently recognized in literature.[13]

The objective of this study was to obtain reliable estimates of the diagnostic accuracy of DUS, MRA, and a combination of these tests compared to DSA as reference standard to determine whether non-invasive testing can replace DSA in clinical practice.

Methods

Study population

From January 1997 to November 2000 350 consecutive symptomatic patients suspected of having carotid artery stenosis were included in a prospective diagnostic study. Patients underwent DUS, MRA, and DSA examination within a period of maximally four weeks. All patients had experienced symptoms of carotid artery disease (transient ischemic attack, minor disabling ischemic stroke, or amaurosis fugax) in the prior six months. Patients underwent complete neurological examination within 24 hours before and after DSA to establish possible deficits caused by this procedure. We excluded patients with contraindications for MRA such as claustrophobia or metal implants not suitable for MR. Medical history was recorded from all patients. The decision whether or not to perform carotid endarterectomy was made in the clinical setting on basis of the DSA examinations. The frequency of carotid endarterectomy in our study population and the complication rate within 4 weeks after surgery were recorded. Patients were enrolled in the University Medical Centre Utrecht, University Medical Centre Rotterdam and Enschede Medical Centre. Our study was approved by a medical ethical committee and all patients gave their written informed consent. We met recently published quality criteria for design and presentation of diagnostic studies on carotid artery imaging.[22]

Diagnostic tests

The degree of stenosis on DUS was determined based on the peak systolic velocity (PSV) in the proximal part of the ICA. The PSV is considered the most accurate estimator of the degree of stenosis for DUS.(24) We validated DUS results in a pilot series before the inclusion of the current study started. By means of receiver operating characteristics (ROC) curves we previously defined optimal cut-off criteria for the PSV for different stenosis categories (Table 1). In these criteria the threshold of 70% stenosis is represented by a PSV of 270 cm/sec.[25]

DSA was performed by selective positioning of an intra-arterial catheter in both common carotid arteries. From each carotid bifurcation three projections (lateral, posteroanterior, and oblique) were acquired. Additional projections of occasionally performed rotational DSA examinations were not used in the context of this study.

Table 1. DUS criteria used to estimate the degree of stenosis based on the peak systolic velocity (PSV) in the proximal internal carotid artery (ICA). The criteria were defined in a pilotseries in the University Medical Centre Utrecht before the start of the study[24].

Degree of stenosis	PSV (cm/sec)
Mild 0-29%	< 150
Mild to moderate 30-49%	< 190
Moderate 50-69%	< 270
Severe 70-99%*	≥ 270
Occlusion 100%	no detectable flow

* Slow flow in combination with visualised severe stenosis was defined as a 99% stenosis.

In all three hospitals MR angiography was performed on a 1.5-Tesla MR imaging system, using a three-dimensional time-of-flight technique. Postprocessing subvolumes were generated to visualise each carotid bifurcation and to create Maximum Intensity Projection (MIP) images. The DSA and MRA protocols have been described in detail elsewhere.[26]

Stenosis measurements

The DSA and MRA test results were read by one observer for each hospital (AFJW for Utrecht and Enschede, AvdL for Rotterdam). The observers were blinded for clinical information and for the results of the other tests. The DSA and MRA images were read independently with a period of at least 1 month between the readings. The observers read the DSA and MRA on printed hard copies. For MRA we only used MIP images. The grade of stenosis on both DSA and MRA was measured according to the NASCET criteria.[1] The degree of stenosis is defined as the remaining lumen at the stenosis as percentage of the normal lumen distal to the stenosis. For a valid comparison with DSA we only used the percentage of stenosis measured on lateral, posteroanterior, and oblique projections on MRA. The maximum of these three measurements, both on DSA and MRA, was used in the analyses.[26] To estimate the reproducibility, the percentage of stenosis was measured by two independent observers (AFJW and PCB) for a representative sample of 170 patients on both DSA and MRA.

Data analysis

Test results of DUS and MRA were first analysed separately compared to the reference standard DSA.[27] The measured stenoses were divided in categories (0-29%, 30-49%, 50-69%, 70-99%, 100%). We included for each patient only the estimate of the stenosis of the carotid artery on the symptomatic side in the analyses. Results were interpreted by calculating sensitivity, specificity and positive predictive value, defining severe stenosis (70-99%) on DSA as a positive test result. Secondly, DUS and MRA results were combined and considered as a combination test. We analysed the part in which DUS and MRA were in agreement concerning the diagnosis of severe stenosis (70-99%) as a separate group. The combined results of this group were again compared with DSA. Kappa statistics were calculated for the DSA and MRA results of the 170 patients read by two observers.

Results

Study population

Of the 350 patients included 249 patients were enrolled in Utrecht, 62 in Rotterdam and 39 in Enschede. The baseline characteristics and relevant medical history are listed in Table 2. To assess generalizability we monitored the reasons for exclusion in one hospital (Utrecht). In this hospital, during the study period, 297 patients underwent DSA to decide on carotid endarterectomy. Of this total 84% (249 patients) were included in the study. Reasons for exclusion were claustrophobia in 3.4%, metal implant not suitable for MR in 3.0% and refusal to participate in the study in 8.8%. Reasons for refusal were mostly stress for planned surgery or participation in other studies. Baseline characteristics of the 48 excluded patients did not differ significantly from the included population.

From the total of 350 patients included in the three hospitals the following numbers of stenosis measurements from the symptomatic side were interpretable and could be included in the analyses: DSA 323, DUS 330, MRA 295. Missing values were caused by the following reasons: sometimes it was not feasible to perform all three tests prior to surgery, withdrawal of patients from the study after one or two tests, and the test was not always correctly performed according to our study protocol (see methods). In DUS occasionally the PSV was not measured. Finally it was impossible to measure stenosis because of poor quality and reliability of the MRA recordings in 10 patients, of the DSA recordings in 7 patients. The complication rate of DSA in our series was 1.4% minor stroke (95%CI, 0.1-3.3%), 0.3% major stroke (95%CI, 0.0-1.6%) and 0.6% mortality (95%CI, 0.1-2.0%). Two-hundred-twenty patients underwent carotid endarterectomy (63%). The complication rate of surgery (within 4 weeks) was 3.2% minor stroke (95%CI, 1.3%-6.5%) and 0.5% major stroke (95%CI, 0.0%-2.5%).

Table 2. Baseline characteristics study population

Characteristics (N=350)	
Mean (range) age (y)	67 {39 88}
Male/Female (%)	76/24
Symptoms* (%)	
Amaurosis fugax / retinal	22
Transient ischemic attack	42
Stroke	36
Supply area (%)	
Right carotid artery	46
Left carotid artery	52
Basilar artery	1
Unknown	1
Previous carotid endarterectomy (%)	4
Hypertension (%)	49
Diabetes (%)	15
Cardiac history (%)	
Angina	18
Myocardial infarction	16
Heart failure	6
Bypass-surgery or PTCA	11
Peripheral arterial disease (%)	
Claudication	15
Surgery or PTA	8
Smoking (%)	
Smoker	49
Ex-smoker	34

* 0-6 months prior to inclusion

Diagnostic test results

In Table 3 the test results of DUS are presented with DSA as reference. DUS analysed with previously defined PSV criteria resulted in a sensitivity of 87.5% (95%CI, 82.1%-92.9%) and a specificity of 75.7% (95%CI, 69.3%-82.2%) in identifying severe ICA stenosis (70-99%). Stenosis measurements (NASCET) on MRA compared with DSA yielded a sensitivity of 92.2% (95%CI, 86.2%-96.2%) and a specificity of 75.7% (95%CI, 68.6%-82.5%) (Table 4).

Table 3. Categorised stenosis measurements of the internal carotid artery (ICA) of symptomatic patients (n=313); Duplex ultrasound (DUS) versus Digital subtraction angiography (DSA).

		Stenosis categories DSA					
		0-29%	30-49%	50-69%	70-99%	100%	Total
	0-29%	**15**	5	2			22
Stenosis	30-49%	6	**6**	7			19
Categories	50-69%	1	5	**22**	16		44
DUS	70-99%		7	30	**126**	4	167
	100%				2	**59**	61
	Total	22	23	61	144	63	**313**

For DUS the positive predictive value was 75.4% (95%CI, 68.9%-82.0%) and the negative predictive value was 87.7% (95%CI, 82.3%-93.0%). For MRA these values were 76.3% (95%CI, 69.6%-83.0%) and 92.0% (95%CI, 85.8%-96.1%). Both DUS and MRA had a tendency to overestimate the degree of stenosis compared with DSA. In 274 patients stenosis measurements from all three test results (DSA, DUS and MRA) were available. In 229 of these patients (84%) DUS and MRA were in agreement about diagnosing severe stenosis (70-99%). In this subgroup, with agreement between the two modalities, the combination of MRA and DUS results (i.e. considering them as one single test) gave a sensitivity of 96.3% (95%CI, 90.8%-99.0%) and a specificity of 80.2% (95%CI, 73.1%-87.3%) for identifying severe stenosis (Table 5).

Table 4. Categorised stenosis measurements of the internal carotid artery (ICA) of symptomatic patients (n=281); Magnetic resonance angiography versus Digital subtraction angiography (DSA).

		Stenosis categories DSA					
		0-29%	30-49%	50-69%	70-99%	100%	Total
	0-29%	**17**	3	2			22
Stenosis	30-49%	2	**5**	4	1		12
Categories	50-69%		7	**20**	6		33
MRA	70-99%		5	29	**119**	3	156
	100%				3	**55**	58
	Total	19	20	55	129	58	**281**

The positive predictive value for the combination was 81.2% (95%CI, 74.5%-88.0%), the negative predictive value was 96.0% (90.2%-98.9%). In this combination strategy there also is a tendency to overestimate the stenosis compared with the reference test DSA. In all 24 cases of overestimation in this combination strategy, based on concordant results, DSA categorised the stenosis only one category lower as 50-69%. The diagnostic test results of the single tests and combination are listed in Table 6. Interobserver variability for DSA and MRA was very good and similar for both tests (kappa 0.79 (95%CI, 0.74-0.84) for DSA and 0.79 (95%CI, 0.73-0.84) for MRA).

Table 5. Stenosis measurements of the internal carotid artery (ICA) of symptomatic patients (n=229) in which Duplex ultrasound (DUS) and Magnetic resonance angiography (MRA) were in agreement (84% of patients). The stenosis measurements are divided into two categories: 70-99% (severe stenosis) and <70% or occlusion, Digital subtraction angiography is used as standard of reference.

		Result DSA		
		<70% or 100%	70-99%	Total
Result Combination strategy MRA=DUS	<70% or 100%	**97**	4	101
	70-99%	24	**104**	128
	Total	121	108	**229**

Table 6. Diagnostic accuracies of the non-invasive tests Duplex ultrasound (DUS), Magnetic resonance angiography (MRA), and their combination strategy (DUS & MRA) in recognising severe stenosis (70-99%) in the internal carotid artery (ICA), using Digital subtraction angiography (DSA) as the standard of reference.

		Sensitivity		Specificity		Positive predictive value		Negative predictive value	
	N	%	(95%CI)	%	(95%CI)	%	(95%CI)	%	(95%CI)
DUS	313	**87.5**	(82.1-92.9)	**75.7**	(69.3-82.2)	**75.4**	(68.9-82.0)	**87.7**	(82.3-93.0)
MRA	281	**92.2**	(86.2-96.2)	**75.7**	(68.2-96.2)	**76.3**	(69.6-83.0)	**92.0**	(85.8-96.1)
DUS=MRA	229	**96.3**	(90.8-99.0)	**80.2**	(73.1-87.3)	**81.2**	(74.5-88.0)	**96.0**	(90.2-98.9)

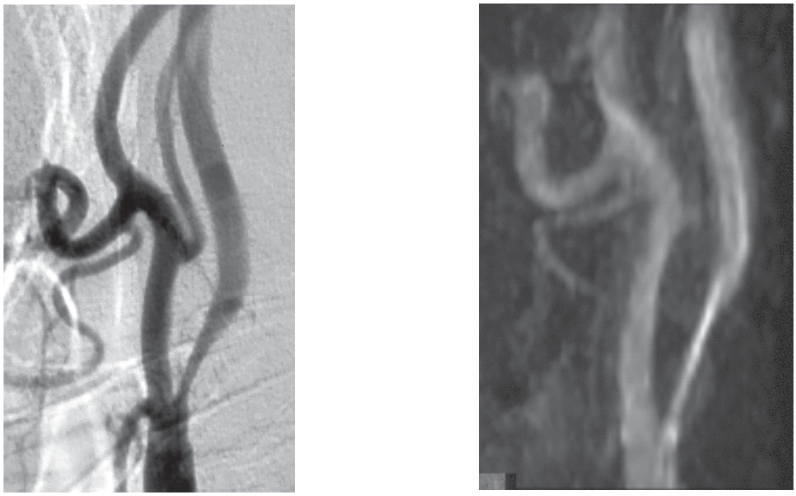

Figure 1. Male (age 64): Digital subtraction angiography on the left (DSA) and time-of-flight magnetic resonance angiography on the right (MRA) both show a moderate stenosis (50-69%) in the internal carotid artery (ICA). The peak systolic velocity (PSV) at Duplex ultrasound (DUS) examination was 250 cm/sec.

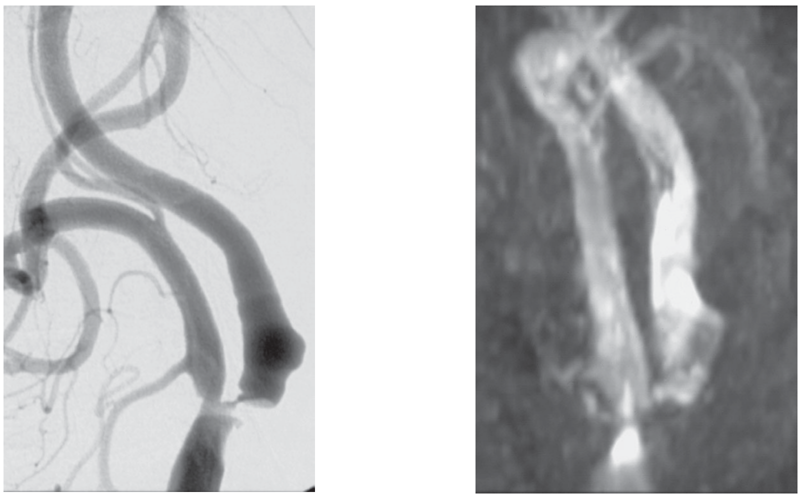

Figure 2. Male (age 74): Digital subtraction angiography on the left (DSA) and time-of-flight magnetic resonance angiography on the right (MRA) both show a severe stenosis (70-99%) in the internal carotid artery (ICA). The peak systolic velocity (PSV) at Duplex ultrasound (DUS) examination was 520 cm/sec

Discussion

Both DUS and MRA seem accurate diagnostic tests to detect carotid artery stenosis. In combining test results, agreement in diagnosing severe stenosis (70-99%) between DUS and MRA (84% of the patients) yielded a high sensitivity and specificity. Both DUS and MRA have the tendency to overestimate stenosis compared with the standard of reference DSA.

DUS is commonly used to screen patients with possible carotid artery disease,[11] but has also been suggested as the sole test to select patients for carotid endarterectomy.[12,16] This technique, however, has limitations such as variability in optimal thresholds,[25] possible effect of verification bias,[28] and limited morphological information. MRA can also be used as non-invasive test to diagnose carotid artery stenosis.[20,21] MRA provides more morphological information without exposure to the risks of DSA. At the start of our study the time-of-flight technique was the state-of-the-art technique for MRA. MRA techniques, however, have improved during the period of our study. The introduction of contrast-enhanced MRA (CE-MRA) may further add to the development.[29,30] CE-MRA provides additional morphological information about the origin of the carotid arteries and intra-cranial vessels and the effect of flow related artefacts occurring with the time-of-flight technique is diminished. To date, however, only a few studies have been published reporting the results of contrast-enhanced MRA validated against DSA in small cohorts, precluding a precise estimate of its accuracy.[23] For a valid throughout evaluation of a new imaging technique an adequately powered study is mandatory.[22] However, such a study is likely to be large, expensive and time-consuming, precluding application of the newest imaging protocols. Recently, however, we also introduced CE-MRA in our clinical setting supplemental to the time-of-flight protocol, allowing us to estimate its accuracy in a subgroup of patients.
Irrespective of the use of intravenous contrast, very good accuracies have been published for MRA if used in combination with DUS.[13,14,17,19] Most of the studies on this subject, however, did not meet all standard criteria for design and reporting of the diagnostic tests.[22] The number of patients that underwent MRA in these series was relatively small and often the data were recorded retrospectively, introducing the risk of observer bias.
Our reported accuracies of DUS and MRA might seem relatively low compared with other studies.[11-21] However, we feel that our prospective design added to valid and unbiased estimates. Another explanation is the fact that we only included the test results of the carotid artery on the symptomatic side in the analyses, yielding lower accuracies. Furthermore, since it is the symptomatic artery for which a decision

on performing endarterectomy needs to be made, excluding the asymptomatic side reflects clinical practice. Previously published reports generally also included the asymptomatic side, which was not suspected of having stenosis on DUS. The majority of the arteries on the asymptomatic side show a stenosis percentage far below the 70% threshold or no stenosis at all, making it more likely for the different tests to agree. In this way the number of true negative results inflates and thus specificity may be overestimated in those studies. In our data the specificities increased by 10.7% for DUS and 14.2% for MRA if the stenosis measurements of all arteries were included.

Furthermore, it is important to realise that diagnostic testing is limited by some general methodological limitations. In a diagnostic study a new test by definition never exactly agrees with the reference test.[27] Even if readings of the reference test itself were to be repeated there would always be certain variability in results. The aim of a diagnostic study should not be to achieve the highest possible accuracy. The more relevant question is to what degree a new test under investigation differs from the reference test and what implications this has on the outcome of clinical decisions for individual patients. For this purpose the most realistic estimate of the accuracy is requested. The results should be the guideline in deciding on diagnostic strategies in the clinical setting. Furthermore, to make the right policy decisions from a societal perspective, additionally to a valid estimate of the accuracy of non-invasive testing, a cost-effectiveness should be taken into account.

An additional point of interest is the fact that both DUS and MRA had the tendency to overestimate the degree of stenosis. In DUS verification bias may have played a role. Verification bias may exist if the decision to perform the gold standard procedure depends on the results of the test under investigation.[28] The sensitivity may be lower, and specificity higher, after adjustment for this bias. In our study, patients were often screened with DUS in the clinical setting prior to inclusion. Based on ethical grounds inclusion in the study depended on the decision of the clinician to perform DSA, if CEA was considered. Accuracy of DUS related to the 70% stenosis threshold was estimated afterwards among patients selected for DSA. The tabulations show that all categories of degree of stenosis are present, although the majority has a moderate or severe stenosis. In our opinion, however, it is precisely this selected group of patients, suspected of having ICA stenosis at DUS examination, that constitutes the right domain to answer our study objective, reflecting the population for which the decision on surgery has to be made in daily clinical practice. MRA may also overestimate stenosis in comparison with DSA. Overestimation on MRA may occur when all twelve available projections are used for the stenosis measurements, and subsequently compared with DSA where stenosis is often measured in only three directions (lateral, posteroanterior, and oblique).[26]

In our study, with regard to the endarterectomy trials, in all patients we assessed the degree of stenosis on DSA using the three standard directions, and therefore we used only the same three corresponding projections on MRA. Nevertheless, overestimation still occurred. Although we have interpreted our findings as overestimation on MRA, it is very well possible that DSA underestimates the true degree of stenosis and that new (three-dimensional) techniques can estimate the degree of stenosis more precisely.
Using the combination strategy of DUS and MRA yielded the highest accuracy. An important finding was that in all cases in which both DUS and MRA overestimated the stenosis (and agreed carotid endarterectomy was indicated) the stenosis fell into the 50-69% category according to DSA. Based on the recently published results from NASCET and ECST these patients still have limited benefit from carotid endarterectomy.[3,4] It is expected that in the near future additional evidence will come available on which patients may expect most benefit from carotid endarterectomy in the 50-69% stenosis category.[31,32]

In our opinion, in a non-invasive diagnostic strategy, both DUS and MRA should subsequently be performed. In clinical practice, based on the results of this diagnostic studie, we no longer perform DSA routinely in all symptomatic patients suspected of having a carotid artery stenosis after screening with DUS. We first perform MRA examination instead. However, DSA should still be considered in those cases where considerable doubt persists about the indication for carotid endarterectomy after DUS and MRA examination, i.e. in case of clear disagreement between these two tests, or when additional morphological information about origin of the common carotid artery or about intracranial vessels is necessary to make the right decision on performing endarterectomy. In conclusion, based on the diagnostic performance, DSA can be replaced by the combination of DUS and MRA in the majority of patients.

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Chapter 4

Diagnosing carotid artery stenosis in symptomatic patients; a cost-effectiveness analysis of diagnostic strategies

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Submitted

Abstract

Background:

Potentially hazardous Digital Subtraction Angiography (DSA) is used to decide on carotid endarterectomy in symptomatic patients, i.e., presenting with TIA, amaurosis fugax or minor stroke. The merits of non-invasive alternatives are unknown.

Objective:

To examine the cost-effectiveness of diagnostic strategies for carotid artery stenosis.

Design:

Sensitivity and specificity of Duplex UltraSound (DUS), Magnetic Resonance Angiography (MRA) or combinations were compared to the reference standard DSA in a blinded prospective consecutive cohort study. From 1997 until 2000, 350 symptomatic patients pre-selected with DUS that gave informed consent to undergo MRA and DSA were enrolled in a multi-center study with one general and two university hospitals. In parallel a study on the costs of the diagnostic tests and carotid endarterectomy was performed. Additional data on long-term costs, survival, and quality of life related to stroke were retrieved from the published literature. Long term outcomes required for cost-effectiveness analysis (CEA) were assessed by means of a Markov model. Finally, a comprehensive CEA was performed using a decision model.

Data Sources:

Clinical study results and published literature.
Target Population: Cost-effectiveness was assessed for a hypothetical cohort of 55 year old symptomatic male patients.

Time Horizon:

Lifetime.

Perspective:

Societal.

Interventions:

DUS, MRA, DSA and combinations.

Main Outcomes:

Sensitivity, specificity and incremental cost-effectiveness ratios (CE ratio) in terms of costs per quality adjusted life year (QALY) gained.

Results of Base-Case analysis:

DUS had a sensitivity of 88% and specificity of 76%. For MRA these values were 92% and 76%, respectively. Combining DUS and MRA in case of concordance yielded superior results (96% and 80%). The cost-effectiveness analysis revealed that DUS alone would be the optimal strategy. Adding MRA may marginally increase the QALY gain but costs could be considered prohibitive. DSA in cases where DUS and MRA are discordant, and DUS or MRA followed by DSA, would result in QALY loss due to complications and increased costs, i.e., were dominated strategies.

Results of Sensitivity Analyses:

Although the expected QALY gains and costs varied, the order of strategies did not change.

Conclusion:

In symptomatic patients DUS without additional imaging is the optimal diagnostic strategy to select patients for carotid endarterectomy in terms of cost-effectiveness. A combination strategy of DUS and MRA to select patients for carotid endarterectomy yields a slight benefit in terms of clinical outcome, however, at relatively high costs.

Introduction

Several large randomized trials such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have shown that patients with symptomatic carotid artery stenosis, i.e., suffering from TIA or minor stroke, may benefit from carotid endarterectomy. Particularly, patients with demonstrated severe stenosis (70-99%) of the internal carotid artery can expect beneficial effects.[1,2] More recent results show that patients with moderate stenosis (50-69%) may also benefit from surgery.[3] However, complications resulting from diagnostic testing or operation limit the margin for benefit of carotid endarterectomy as compared to medical treatment, whereas patients with low grade stenosis (<50%) are better off treated medically with aspirin therapy. Accordingly, a safe and reliable estimate of the degree of stenosis to set the indication for operation is crucial.

In the NACSET and the ECST the degree of stenosis was confirmed by means of Digital Subtraction Angiography (DSA), which has since become the standard of reference. DSA, however, is associated with a 4% risk of transient ischemic attack (TIA) or minor stroke, a 1% risk of major stroke, and even a small (<1%) risk of death.[4] Also, silent infarctions were demonstrated in patients who did not show a clear neurological deficit after DSA.[5] Exposing all patients to a hazardous diagnostic test to lower the future risk of stroke or death for a sub-group seems paradoxical. The potential benefit for symptomatic patients is certainly diminished by the invasive nature of DSA. This has increasingly been recognized over the last decade. Nowadays, non-invasive diagnostic tests are repeatedly propagated as a replacement of DSA. Recent diagnostic studies and even some reviews have appeared on Duplex ultrasound (DUS) and Magnetic Resonance Angiography (MRA). Promising results have been reported which have led to implementation of non-invasive tests to select patients for surgery in some institutions.[6-12] However, critical notes on the moderate test results of the non-invasive alternatives have also been made.[13]

Adding further to the discussion, combination strategies of DUS and MRA have been introduced. A combination of initial DUS for screening of stenosis and/or a subsequent MRA test to diagnose severe stenosis ($\geq$ 70% stenosis) may be considered sufficient to decide to operate. Also, in case of discordant results of DUS and MRA clinicians may feel compelled to perform DSA. Likewise, in accordance with recent standard practice, routine confirmation of severe stenosis by means of DSA is an option. Finally, taking into account variable cut-off points for DUS as well as MRA numerous other test strategies are conceivable.

However, despite seemingly obvious advantages of non-invasive testing the actual impact in terms of strokes prevented, life years gained or cost-effectiveness remains to be determined. Accordingly, the purpose of the current study was to assess diagnostic accuracy and long term implications in terms of longevity, quality adjusted life years (QALY), costs, and incremental cost-effectiveness ratios (CE ratio) of various non-invasive diagnostic test modalities and the current combination of DUS and subsequent DSA in case of an indication of significant stenosis in patients with symptomatic carotid artery stenosis.

Methods

Test evaluation

A blinded multi-center prospective consecutive cohort study was performed to assess the diagnostic accuracy of Duplex ultrasound (DUS) examination, Magnetic Resonance Angiography (MRA) and combinations of these tests in comparison with Digital Subtraction Angiography (DSA) in diagnosing carotid artery stenosis in symptomatic patients.[14] Briefly, 350 patients with manifest cerebrovascular symptoms, i.e., TIA or minor stroke, who gave informed consent were enrolled. Of all patients considered eligible 15% could or would not participate (3.4% had claustrophobia, 3.0% had a metal implant and 8.8% refused). Patients underwent DUS and if significant stenosis was suspected and if they were considered potential candidates for operation, MRA and DSA were subsequently performed.
Conform the results obtained in NASCET and ECST patients with 70 - 99% stenosis (NASCET criteria) were offered carotid endarterectomy.[3,15] Based on the data pertaining to the carotids ipsilateral to the symptoms sensitivity and specificity of DUS, MRA, and various combinations of these tests were calculated using DSA as the reference standard.

Cost analysis

In parallel with the clinical study the costs of the diagnostic tests, if applicable including hospitalization, and of carotid endarterectomy were estimated from a societal perspective in terms of 1998 € (€ 1 = NFL 2.20371 ~ US$ 1.11 (1998)). Actual costs were estimated which included the costs of personnel, equipment, materials, maintenance, housing, cleaning, administration and overhead.[16] Cost data were recorded in one university hospital and one general hospital. Based on the distribution of patients across various types of hospitals in the Netherlands weighted averages were calculated. Additional cost estimates for the Dutch setting were derived from existing literature.[17-20] The actual short and long term costs of minor and major stroke, including diagnostic work-up, medication, hospitalization, rehabilitation and nursing home admission were previously reported. Reports on costs pertaining to TIA or dying were not available. These were estimated with the input from experts in the field taking into account the costs of possible diagnostic testing, consultation of a general practitioner and/or specialist, diagnostic examination and emergency hospitalization.

Cost-effectiveness analysis

The cost-effectiveness outcomes of various diagnostic strategies were compared with a decision model. Both short and long term outcomes were accounted for by extrapolating to lifetime outcomes from clinical trial data.[21]

First, a comprehensive decision model was developed taking into account various diagnostic tests and combinations of tests. All tests were assessed as a stand alone subsequent to a low threshold screening DUS. Of all eligible patients, however, 11.5% did not undergo MRA because of contra-indications or claustrophobia and thus required another imaging test. For most (combination) strategies considered we assumed that these patients would instead undergo DSA. In combination strategies DUS screening and subsequent decisive MRA were evaluated, as well as relying on either one or the other test positive. We also explored relying on the results of DUS in patients unable to undergo MRA, rather than performing DSA. As DUS already has good sensitivity and specificity the latter strategy would introduce only a limited error yet would save DSA in 11.5% of the patients. Also, stand alone as well as combination strategies were considered in combination with DSA to rule in or rule out severe (≥70%) stenosis. Finally, several cut-off values for a positive result for DUS and MRA were evaluated, as well as a cut-off for endarterectomy, i.e., ≥50% or ≥70% stenosis. All in all 62 strategies were compared.

The degree of carotid artery stenosis was categorized: 0-49%, 50-69%, 70-99% stenosis and occlusion. Also, the initial symptoms (TIA or minor stroke), as well as complications occurring as a result of DSA or operation were accounted for.

Next, a Markov model was developed to extrapolate and evaluate the long-term outcome of the diagnostic work-up and subsequent treatment offered. In accordance with current Dutch guidelines time preference was accounted for using a 4% discount rate for costs and effects.[22] Multiple (Markov) health states following the initial diagnosis and treatment, i.e., reflecting degree of stenosis, treatment offered, possible stroke and vital status were modeled. Besides optimal medical care including aspirin, in symptomatic patients an operation is generally considered indicated for 70-99% stenosis. According to recent results, however, patients with a 50-69% stenosis may also expect limited benefit of operation, particularly, men with TIA or minor stroke. In lower grade stenosis (less than 50%) optimal medical care alone is recommended. In the Markov model optimal medical care as well as endarterectomy were taken into account for the four categories of stenosis.

In addition, patients with minor stroke were assumed to incur costs and experience limited disability at the onset. Therefore, the initial event, i.e., TIA or minor stroke was also distinguished in the model. Moreover, prognosis depends on the extent of the underlying vascular disorder. In symptomatic patients with low grade stenosis the risk of future events is lowest whereas in patients with high grade stenosis the risk is highest, particularly early after the initial event. The associated hazard rates used in the model were derived from the existing literature and if not reported in detail refined with the help of experts.[3] (A table presenting the hazards over time is available on request from the corresponding author.)
With regard to future cerebrovascular events carotid endarterectomy will predominantly affect the prognosis related to the symptomatic carotid artery. Accordingly, only ipsilateral cerebro-vascular events were modeled. Fatal contra-lateral cerebrovascular events and other cardiovascular mortality, however, were accounted for by adjusting age and sex specific mortality rates for the Dutch population with a disease specific rate ratio.[23]
Utility weights for the relevant health states well, minor stroke, major stroke and death were derived from the existing literature and were 1.0, 0.8, 0.2 and 0.0, respectively.[24,25] For TIA a one time disutility equivalent to 2 days with major stroke was assumed. The Markov model was used to estimate long term outcomes in terms of life years, QALYs, and costs for all possible health states assuming these would pertain to a symptomatic 55 year old male patient. The results obtained by means of the 'prognostic' Markov model were used as input for the 'diagnosis and treatment' decision model to obtain an overall comparison of the diagnostic strategies. Expected life time costs and QALYs related to the various health states resulting from the diagnostic strategies were compared using the decision model. Similarly, incremental cost-effectiveness ratios for the successive strategies were calculated. For strategies resulting in increased costs and worse outcomes in terms of QALYs compared to alternative strategies, reporting an incremental CE ratio becomes redundant, i.e., inferior strategies are so-called 'dominated'. Sensitivity analyses were performed to evaluate the impact of variability of the estimates and assumptions used in the models. Tables 1 and 2 present detailed information on the variables evaluated including the ranges over which the sensitivity analyses were conducted.

Table 1. Variables, their point estimates and ranges used in the sensitivity analysis.

Variable	Point estimate	Range	Source
Age at diagnosis (years)	55	45 to 65	
Utility health states (major and minor	0.2 and 0.8	0.1 to 0.3 and 0.7 to 0.9	(24;25;25)
Discount rate	0.04	0.0 to 0.10	(16)
Probability stroke DSA	0.03	0.01 to 0.09	Current study,(14)
Probability dead DSA	0.001	0.0003 to 0.003	Current study,
Probability stroke carotid endarterectomy	0.055	0.015 to 0.15	Current study,
Probability dead carotid endarterectomy	0.0106	0.003 to 0.03	Current study,
Proportion MRA impossible	0.11	0.03 to 0.30	Current study
Proportion major stroke in case of stroke	0.33	0.10 to 0.66	(3;15)

Table 2. Cost estimates used in Markov and- or decision models

Cost components	Cost estimates used (€)	Range (€)	Source
Duplex ultrasound	48	24 - 96	Cost study
Digital subtraction angiography*	1,053	526 - 2,106	Cost study
Magnetic resonance angiography#	231	115 - 461	Cost study
Carotid endarterectomy	2,759	1,379 - 5,518	Cost study
Minor stroke procedure related	3,654	1,827 - 7,308	(17-20)
TIA after CEA or major stroke¶	70	35 - 140	Expert opinion
TIA in patients treated medically	1,052	526 - 2,104	Expert opinion
Minor stroke 1st year	5,092	2,546 - 10,185	(17-20)
Minor stroke subsequent years	871	436 - 1,743	(17-20)
Major stroke 1st year	29,039	14,520 - 58,078	(17-20)
Major stroke subsequent years	16,956	8,478 - 33,912	(17-20)
Dying†	2,166	1,083 - 4,332	Expert opinion

* Includes hospitalisation.
# Excludes contrast enhancement.
¶ Limited diagnostic work-up and consultation by general practitioner assumed, whereas, consultation by general practitioner, specialist and diagnostic tests were recognised in potential candidates for operation, i.e., treated medically.
† Consultation by general practitioner, specialist, and for half the patients emergency transportation and admittance to ICU or general ward and diagnostic tests were accounted for.

Results

Diagnostic performance

Compared to the standard of reference (DSA) both DUS and MRA proved to be accurate tests. At various cut-off points for peak systolic velocity,[26] the sensitivity of DUS varied between 87.5% and 98.6% and specificity between 59.2% and 75.7% for the diagnosis 70-99% carotid stenosis. Similar calculations for MRA alone yielded comparable values between 92.2% and 96.9% and 57.9% and 75.7% respectively. As expected, varying the threshold shifted the test characteristic; at lower thresholds sensitivity increased whereas specificity decreased and vice versa. The combination DUS as a low threshold screening test and MRA as a definite test, however, was superior with a sensitivity for the overall strategy of 92.1% and specificity of 78.4%. A combination considered positive either if DUS or MRA indicate a stenosis of 70-99% further improved sensitivity to 98.4%, yet the specificity was only 54.0%. Adding DSA in case of discordant test results also improved sensitivity to 98.4%. The latter, however, would imply that 16% of the patients would have to undergo DSA because of discordant results in addition to the 11.5% that were unable to undergo MRA at all. Other strategies also implied that varying proportions of the patients would have to undergo DSA, i.e., up to 75% or 100% in the reference strategy (Table 3, 4th column).

Corresponding calculations for the individual tests assuming a 50% stenosis threshold for the indication to operate resulted in small decreases in sensitivity, i.e., up to about 5%, while substantially increasing specificity by approximately 25%. For the combination strategies the effects on the test characteristics were similar but smaller, i.e., a 1% decrease in sensitivity and 10% increase in specificity.

A final finding was that all non-invasive tests, i.e., DUS, MRA and the combinations, tended to somewhat overestimate the stenosis as compared to DSA. This implies that if DSA is not used to confirm the non-invasive test results some patients (in the worst case up to about 26%) may be considered ‘overtreated’ (Table 3, right column).

Cost analysis

For DUS, MRA, DSA, and CEA the costs estimated in 1998 in the university hospital and in the general hospital did not differ substantially (Table 2). The actual costs associated with stroke and subsequent rehabilitation were retrieved from the literature. Costs incurred after TIA or dying were estimated with the help of experts (Table 2).

Table 3. Sensitivity, specificity, proportion of patients requiring DSA and proportion of patients undergoing unnecessary treatment for various diagnostic test strategies. Normal type font results pertain to a scenario with an indication for endarterectomy of ≥70% stenosis, whereas italic type font results pertain to a threshold of ≥50% stenosis.

Tests and combinations of tests evaluated	Sensitivity (range %)	Specificity (range %)	DSA (%)	Endarterectomy unnecessary (%)
DUS alone	87.5 - 98.6	59.2 - 75.7	0.0	13.1 22.0
	76.1 94.6	*84.3 89.8*	*0.0*	*3.5 5.4*
DUS, positive test operate, negative test DSA to exclude serious stenosis	100	59.2 75.7	32.6 46.6	13.1 22.0
	100	*84.4 89.8*	*32.6 46.6*	*3.5 5.4*
DUS combined with MRA, either positive operate, MRA impossible rely on DUS	96.8 98.4	51.4 65.5	0.0	18.6 26.3
	89.0 98.3	*78.5 87.1*	*0.0*	*4.4 7.3*
MRA alone, MRA impossible DSA	92.2 - 96.9	57.9 - 75.7	11.5	11.8 20.4
	80.4 94.6	*84.5 91.8*	*11.5*	*2.6 4.8*
MRA, positive test operate, negative or MRA impossible DSA to exclude serious stenosis	100	57.9 75.7	40.8 51.4	11.8 20.4
	100	*84.5 91.8*	*40.8 51.4*	*2.6 4.8*
DUS (strict cut-off) combined with DSA, positive test confirm by DSA	87.5 98.6	100	53.4 67.4	0.0
	76.1 94.6	*100*	*53.4 67.4*	*0.0*
MRA combined with DSA, impossible or positive test confirm by DSA	92.2 96.9	100	61.3 71.8	0.0
	80.4 94.6	*100*	*61.3 71.8*	*0.0*
DUS combined with MRA, MRA impossible rely on DUS, discordant tests rely on MRA*	82.5 96.8	62.8 83.8	0.0	7.7 17.7
	64.9 91.7	*88.2 93.5*	*0.0*	*1.9 3.5*
DUS combined with MRA, MRA impossible do DSA, discordant tests rely on MRA#	82.5 96.8	62.8 83.8	11.5	7.7 17.6
	64.9 91.7	*88.2 93.5*	11.5	*1.9 3.5*
DUS combined with MRA, MRA impossible do DSA, discordant test do DSA	96.3 - 98.4	58.0 80.2	18.4 27.9	7.7 - 17.6
	85.9 97.1	*86.9 93.1*	*17.5 25.8*	*1.9 3.5*
DUS combined with MRA, either positive or MRA impossible, DSA to confirm	96.8 98.4	100	60.9 67.5	0.0
	89.0 98.3	*100*	*60.9 67.5*	*0.0*
DUS combined with MRA, positive test confirm by DSA, MRA impossible or discordant do DSA	96.3 98.4	100	66.7 74.1	0.0
	85.9 97.1	*100*	*66.7 74.1*	*0.0*
DSA all (reference strategy)	100	100	100	0.0
	100	*100*	*100*	*0.0*

DUS = Duplex ultrasound, DSA = digital subtraction angiography, MRA = magnetic resonance angiography
* For patients in whom MRA is impossible relying on DUS implies somewhat higher sensitivity and lower specificity. Accordingly, the overall test characteristics will similarly change marginally. Also, proportion undergoing unnecessary operation will increase marginally. In the model this effect is accounted for. # For patients in whom MRA is impossible DSA is performed. Thus overall sensitivity and specificity will increase marginally. In the model this effect is accounted for.

Model based cost-effectiveness

First the remaining life expectancy of a 55-year-old symptomatic male patient with various degrees of carotid artery stenosis and either TIA, minor stroke or major stroke was assessed (Table 4). Similarly, by taking into account the utility weights and lifetime cost estimates for the various health states the expected QALYs and overall costs were estimated (Table 4).

Table 4. Outcomes after diagnostic work-up and initial treatment with corresponding expected life years, QALYs, and lifetime costs†.

Outcomes diagnostic work-up	Life years	QALYs	Lifetime costs (€)
Stenosis 0-49%, treated medically (ASA) after TIA	14.0	12.9	20,965
Stenosis 50-69%, treated medically (ASA) after TIA	14.0	12.5	26,646
Stenosis 70-99%, treated medically (ASA) after TIA	13.9	11.9	36,582
Occlusion, treated medically (ASA) after TIA¶	13.9	13.9	2,161
Stenosis 0-49%, treated medically (ASA) after minor stroke*	14.0	10.6	30,800
Stenosis 50-69%, treated medically (ASA) after minor stroke*	14.0	10.4	35,841
Stenosis 70-99%, treated medically (ASA) after minor stroke*	13.9	10.1	44,400
Occlusion, treated medically (ASA) after minor stroke¶	13.9	11.1	14,284
Carotid endarterectomy after TIA	14.0	13.0	18,898
Carotid endarterectomy after minor stroke*	14.0	10.7	28,923
Major stroke treated medically (ASA)#	13.9	2.8	238,162
Dead	0.0	0.0	0

†Estimates were obtained by means of the prognostic Markov model
ASA = acetyl salicylic acid, TIA = transient ischemic attack,
¶ Occlusion is assumed not to result in further ipsilateral events; contralateral events were not taken into account.
* Minor stroke as initial event or as a result of diagnostic work-up or treatment.
# Regardless of underlying stenosis no further treatment and serious prognosis assumed.

Subsequently, various diagnostic strategies were compared in terms of costs, effects (life years and QALYs) and incremental cost-effectiveness ratios (costs per LY and costs per QALY gained). In terms of costs per LY gained DUS as stand-alone test had the lowest CE ratio. The combination strategy that results from adding MRA as a definite test marginally improves longevity yet at increased costs (incremental CE ratio € 33,400/LY gained). Many other strategies had lower expected LY and higher costs, i.e., were dominated, or were dominated by subsequently more efficient strategies such as a high threshold combination of DUS and MRA without DSA, and high threshold DUS confirmed by DSA. The latter strategies, however, had quite unfavorable incremental CE ratios (respectively > € 79,000 and > 660,000 /LY gained) compared to the strategies above.

The results of the cost-effectiveness analyses in terms of costs per QALY gained had virtually similar implications (Figure 1). Again DUS as a stand-alone test was the most cost-effective test, i.e., would on average yield 11.33 QALYs at € 27,400. DUS in combination with MRA as a decisive test or relying on the initial DUS if MRA appeared impossible would result in a marginal gain in QALYs. However, having all patients undergoing MRA in addition to DUS would imply extra costs thus resulting in a prohibitive incremental cost-effectiveness ratio (> € 1,500,000 per QALY gained). All other strategies were less effective and more expensive, thus dominated. Notably, performing a DSA in patients who could not undergo MRA, or if DUS and MRA yielded discrepant results would result in QALY loss and increased costs.

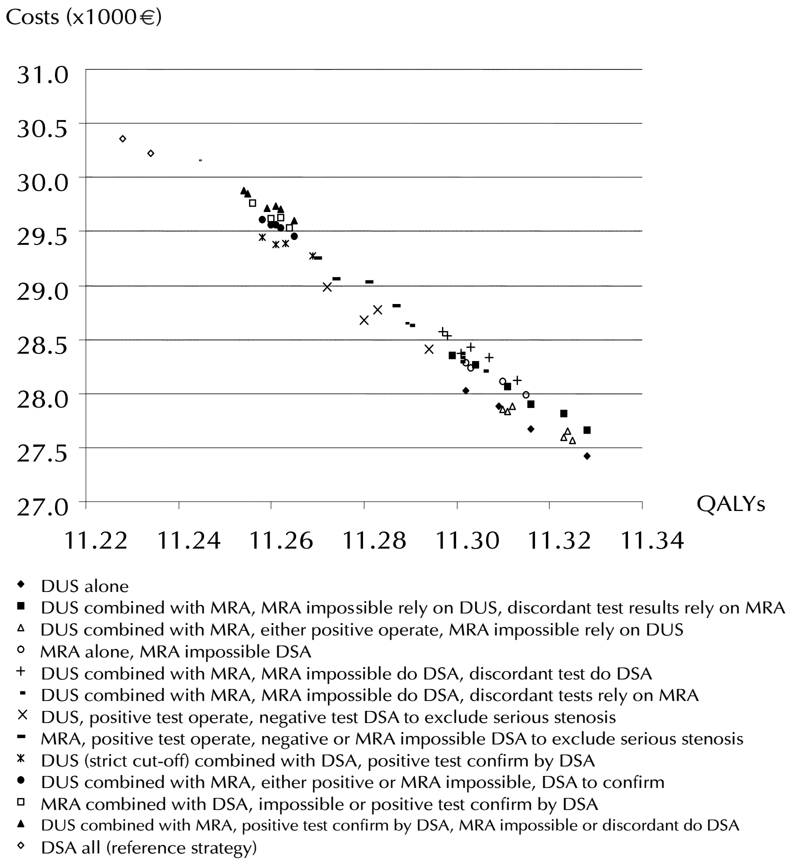

Figure 1. Expected life-time costs vs life-time QALYs.

The strategy of DUS as a screening test and subsequent DSA if a severe stenosis is suspected was also clearly dominated, i.e. would imply € 1,800 additional costs and 0.06 QALY loss as compared to DUS alone. The results of the latter analysis were clustered according to use of diagnostic tests or combinations of tests and are presented in figure 1.
The sensitivity analyses performed showed that the results were robust. We took into account various strategies at varying cut off levels for the individual tests, i.e., criteria for a positive test result, which in fact represent sensitivity analyses on matching combinations of sensitivity and specificity. This resulted in moving along the 'line' observed in figure 1 but the order of strategies remained the same. The utilities for minor and major stroke were varied by + or – 0.1 which did not alter the order of preference. Similarly, the age of symptomatic patients was varied between 45 and 65 years, and the discount rate was varied between 0 and 10%, which had no impact on the order of preference. The cost-estimates of the diagnostic tests were varied by a factor 0.5 to 2 and did not alter the order of preference among the strategies. As expected, increasing the cost of MRA resulted in even more unfavorable incremental CE ratios. Likewise, the costs of operation did not substantially alter the results. However, at high cost of operation (> € 5,900) strategies using higher threshold values for positive test results, i.e., more strict strategies implying lower sensitivity and higher specificity, became slightly more favorable. As for the likelihood of complications associated with DSA these were varied by a factor 0.3 to 3 and little effect was observed. At very low stroke rates (<0.01) the incremental CE ratio decreased substantially. The likelihood of complications arising from carotid endarterectomy were varied by a factor 0.3 to 3 and did not change the order of preference. At low peri-procedural mortality (<0.01) and stroke rates (<0.05) DUS dominated all other strategies. At high stroke rates (>0.10) strategies with high threshold values for positive test results became favorable. The proportion of patients unfit or unwilling to undergo MRA (varied over the range 0.03 to 0.3) had no impact on the order of strategies. At high values the incremental CE ratios for the combination strategies became increasingly unfavourable. Similarly, the proportion of patients suffering from major stroke had little effect. Only at implausibly high likelihood of major stroke (>0.5), however, the combination strategy reached an acceptable incremental CE ratio (< € 25,000/QALY gained).

Discussion

This study shows that for patients with symptomatic carotid artery stenosis DUS as a stand-alone test to establish a final diagnosis and treatment plan is the most cost-effective strategy. A combination strategy of DUS and MRA to select patients for carotid endarterectomy yields a slight benefit in terms of clinical outcome, however, at high additional costs. At various thresholds, i.e., sensitivities, these findings changed only marginally. At higher thresholds specificity increased thus resulting in a somewhat lower proportion that would undergo carotid endarterectomy. Under all realistic assumptions our results remained the same.

These findings emerged despite the fact that the non-invasive tests, and especially DUS, overestimated the grade of carotid stenosis. The latter is easily explained by recalling that patients with moderate stenosis may also benefit from operation, particularly men with TIA or minor stroke. Accordingly, the warnings expressed by others on the apparent misclassification and 'overtreatment' that may arise from using a non-perfect test may not be clinically relevant.[27] A further finding was that if DUS would be used as a screening test, followed by MRA as a definite test, a minimal QALY gain can be expected because some false positive cases with minor stenosis expecting minor or no benefit are likely to be 'filtered out'. However, the incremental costs appeared considerable and thus the incremental cost-effectiveness would be quite unfavorable. At various thresholds for DUS and MRA this result did not change. Also, the sensitivity analyses showed that the order in terms of efficiency was barely altered by varying the likelihood of complications resulting from DSA or operation nor by the cost estimates. The conventional approach to always use DSA as a final test after DUS was clearly dominated, i.e., the prevailing strategy implies a loss of QALYs and increased costs. Similarly, various other combinations including DSA, e.g., using DSA in case of a discrepancy between DUS and MRA, or to confirm or rule out serious stenosis, were dominated.
A comparable study by Kent et al. addressing exactly the same issue was published before results on intermediate grade stenosis and long term results of the NASCET were available.[8] They used a less complex model and assessed fewer strategies. A combination strategy of DUS and MRA including DSA in case of discordant DUS and MRA was found favourable in terms of effect with an acceptable incremental CE ratio. Some essential differences in the assumptions made for this study should, however, be mentioned. Over time a constant high risk of stroke in patients with severe stenosis was assumed. Therefore, the long-term benefits of endarterectomy were overestimated. Moreover, the benefits of operating in symptomatic patients with 50% stenosis and over, still considered 'false positives', was not taken into account. Thus, the fact that Kent et al. found an acceptable incremental CE ratio for

the combination strategy can be explained. With relatively optimistic long term benefits and underestimated benefits for patients with intermediate grade stenosis that are inadvertently operated a limited risk due to diagnostic work-up becomes acceptable and a higher specificity more relevant. In this respect our study took into account essential new information and contributes to further insight.

An interesting finding not often observed was the apparent negative correlation between costs and QALYs across the strategies. This can be explained by the high cost incurred and the strong reduction in quality of life after (major) stroke. Incident strokes are the key events driving the results. The order of diagnostic strategies is determined by the prevention of immediate and future cerebrovascular events. Expected costs decrease and QALYs increase as the diagnostic strategies are optimized in this respect. Such a clear negative correlation is not observed (results not presented) between the costs and life years. Although strokes for a major part still drive the costs incurred, the impact on longevity is not as outspoken, and a scattered non-correlated distribution of costs and effects was observed.

A point of surgical or technical interest that we can not substantiate or reject based on the available data pertains to the outcome after carotid endarterectomy. If surgeons were to decide to operate based on a stenosis diagnosed by means of DUS, i.e., a flow velocity above some threshold, they would not have detailed anatomic information available prior to the operation. Although some may argue that this information has no relevance for the operative approach or outcome, others may challenge this opinion. Fact is that in the large clinical trials all surgeons had detailed anatomic information available prior to operation because DSA was routinely performed in all patients. DUS as a stand-alone test will remain the optimal test only if the complication rate or effectiveness is not altered without anatomic information anatomic information, e.g., on the origo or intracranial part of the carotids. Surgeons uncomfortable operating without anatomic information available prior to the operation or convinced that they can not operate safely and effectively without anatomic information may insist on having an MRA image. They can still be confident that they will improve efficacy and save costs compared to using DSA. Also, at least a slight benefit for the patients may be expected compared to DUS alone, albeit at relatively high cost.

As to the reliability of the above findings and the inference made we feel that although considerable ‘extrapolation‘ occurs while using modeling techniques as explicated in the methods section, the results obtained are quite robust. The diagnostic study was performed in a large representative and consecutive sample of symptomatic patients. Also, the test characteristics were calculated based only on the findings from the ipsilateral (symptomatic) carotid artery, thus avoiding the overestimation of specificity that would have resulted from including the asymptomatic carotid arteries in the analysis.

Several limitations of our study should be recognized when interpreting the results. The population included patients pre-screened by means of DUS. The prevalence of severe stenosis and the test-characteristics estimated may have been biased because not all symptomatic patients underwent MRA and DSA. This selected verification may have resulted in an overestimate of the sensitivity of DUS and MRA and an underestimate of the specificity. However, as this applies equally to DUS (here DUS as a stringent 'final' test is considered) as well as MRA the test characteristics would very likely have changed proportionally. Accordingly, the order of preference for the diagnostic strategies in terms of clinical outcomes is not affected. With the costs of the tests unchanged no change in terms of ordering of cost-effectiveness ratios is to be expected. Similarly, the combination of DUS and MRA would still be associated with high additional costs that might well be considered unacceptable. With regard to strategies including DSA these were dominated as a result of complications occurring. Adjusting for verification bias would not have altered the results obtained in this respect. Complications would still occur and if in reality a smaller proportion of the patients undergoing DSA would be able to benefit from operation it is likely that the results would be even more extreme. Finally, we feel that although strictly speaking the test characteristics presented may not be quite correct they do apply to the domain of interest, i.e., patients pre-selected by means of a screening DUS. Accordingly, we think that in spite of the fact that the point estimates of our findings might change a little the interpretation would remain similar. Also, a recent report by a US group using data from a comparable setting corroborates our findings adding further to the credibility and robustness of the results of our study.[27]

A further limitation may be the fact that we did not take into account unrelated medical and non-medical costs, e.g., cost and effects related to non-fatal contra-lateral strokes. We think, however, that it is reasonable to assume that endarterectomy does not alter the prognosis with regard to contra-lateral strokes or other long-term cardiovascular outcomes, other than peri-procedural complications that we did take into account. Also, in an incremental comparison of strategies such outcomes would have dropped out of the equation anyhow.

Finally, we chose not to perform an extensive sensitivity analysis for the prognostic model. The results obtained in the prognostic model were used as given input for the diagnostic model. However, as the underlying estimates used in the prognostic model are based on large scale multi-center trials we think this is an acceptable simplification. Taking into account very limited uncertainty with regard to the trial results would have added substantially to the complexity of modeling, whereas one could hardly expect a change in the overall results and inference.

A point not related to validity but of potential interest is the currently used threshold for operation. The recently published results from NASCET demonstrated limited benefit for symptomatic patients with 50% to 69% carotid stenosis, particularly men with TIA or minor stroke, which is reflected in our results. The strategies with an indication threshold for carotid endarterectomy of 50% stenosis all yielded favourable CE ratios when compared to similar strategies with a 70% threshold. However, our sensitivity analyses on the complication rates of endarterectomy indicated that if peri-procedural stroke rates were to surpass approximately 10%, the high threshold for surgery would yield more favourable outcomes and should thus be upheld. This is in accordance with concerns previously expressed by various authors who emphasized that potential advantages of operating on symptomatic patients may be cancelled out or even overshadowed by complications of surgery.[3,28] Carotid endarterectomy should only be performed in centers able to maintain a stable and low complication rate. In view of the recently published results from CAVATAS, a large clinical trial comparing the results of carotid endarterectomy with angioplasty, showing around 10% major complications, we feel impelled to stress the fact that the complication rates attained should be monitored and taken into account when deciding on an optimal diagnostic and treatment strategy.[29]

A final remark should be made on contrast enhanced MRA (CE-MRA). Around the time our study commenced time-of-flight MRA was state-of-the-art for vascular imaging, whereas CE-MRA was not widely used or available. Recently we performed a small series (N=50) that shows that the images obtained by means of CE-MRA do not have the drawback of possible flow related artifacts. The latter may at times result in poor quality images and difficulties in establishing the stenosis grade precisely. Potentially contrast enhancement could contribute to an even higher accuracy of MRA, especially with regard to specificity. However, as our present analysis shows, the gain in accuracy that may be obtained as compared to DUS and especially as compared to time-of-flight MRA, is likely to result in only marginal increases in QALY gain. The increase in cost, however, will be substantial thus resulting in quite unfavourable incremental CE ratios.

In conclusion, DUS as a stand-alone test is the most cost-effective diagnostic test to select patients for CEA, provided that optimal operative outcomes can be maintained. Adding MRA to further improve the selection process or to provide additional anatomical information results in an improved efficacy, however, would still be associated with relatively high additional costs. DSA has a significant complication rate and should no longer be routinely applied in the selection process for carotid endarterectomy.

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Chapter 5

Overestimation of carotid artery stenosis by MR angiography compared to digital subtraction angiography

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Abstract

Background and purpose:

Three-dimensional time-of-flight (3D TOF) magnetic resonance angiography (MRA) is generally considered to overestimate the degree of stenosis in the internal carotid artery (ICA) in comparison with the reference standard intra-arterial digital subtraction angiography (DSA). We evaluated whether the degree of stenosis is more accurately assessed by 3D TOF MRA, if corresponding projections on MRA and DSA are compared, instead of comparing maximum stenosis at MRA with maximum stenosis at DSA.

Methods:

From February 1997 to December 1999 we included 186 symptomatic and 17 asymptomatic consecutive patients suspected of having carotid artery stenosis based on clinical presentation and screening with duplex ultrasound examination. All patients subsequently underwent DSA and MRA imaging. From each ICA 12 maximum intensity projections (MIP) by 3D TOF MRA and two or three projections by DSA were obtained. First, we compared the maximum stenosis at MRA with the maximum stenosis at DSA. Subsequently, we used the stenosis at MRA measured on the projection corresponding with the DSA projection that showed the maximum stenosis. For both strategies, the mean differences in stenosis, and sensitivity and specificity for assessing severe stenosis (70-99%) were calculated and compared.

Results:

MRA and DSA images of 354 ICAs could be compared. Sensitivity and specificity of MRA using the projection that showed the maximum stenosis were 92.6% (95% CI, 85.3% to 97.0%) and 82.7% (95% CI, 78.1% to 87.3%), respectively. Sensitivity and specificity using the MRA projection, corresponding with the DSA projection showing the maximum stenosis, were 88.3% (95% CI, 81.8% to 94.8%) and 89.6% (95% CI, 85.9% to 93.3%), respectively. The mean difference between maximum stenosis at MRA and DSA was 7.5% (95% CI, 5.2% to 9.9%). The mean difference between stenosis at MRA and DSA in corresponding projections was 0.4% (95% CI, -2.0% to 2.7%).

Conclusion:

If corresponding MR angiographic and intra-arterial DSA projections are compared, 3D TOF MR angiography does not overestimate carotid stenosis.

Introduction

Two randomized trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), both established that carotid endarterectomy is beneficial to patients with transient or non-disabling ischemic symptoms associated with severe internal carotid artery (ICA) stenosis (70-99%).[1,2] In these trials the degree of stenosis was assessed with inta-arterial digital subtraction angiography (DSA), which therefore has become the standard of reference. DSA is usually performed in two or three projections (lateral, posteroanterior, and/or oblique). The projection that shows the maximum stenosis is used to assess the degree of stenosis. However, several studies have demonstrated that the residual stenotic lumen is almost never circular and that DSA performed in a limited number of projections does not always reveal the narrowest residual lumen.[3-7] Therefore, standard DSA does not always show the maximum stenosis.
Because DSA has a relatively high complication rate, non-invasive techniques such as three-dimensional time-of-flight (3D TOF) magnetic resonance angiography (MRA) have been suggested to replace DSA.[8-10] However, studies comparing 3D TOF MRA with DSA have reported that MRA tends to overestimate the degree of stenosis.[6,7,11-15]
Flow velocity gradients, acceleration, and complex flow patterns, causing intravoxel dephasing and leading to local signal loss, as well as the used maximum intensity projection (MIP) algorithm, have been suggested to explain this overestimation.[13,16,17]
We assumed that the greater number of projection images that are obtained by MRA could also attribute to the overestimation of stenosis at MRA when compared with DSA.

In a previous study we compared lumen reduction measurements obtained with rotational angiography, which allows visualisation of the carotid bifurcation in many projections, with measurements at conventional DSA in the standard two or three projections.[18] Images provided by rotational angiography and DSA in corresponding projections showed similar degrees of stenosis. However, using additional projections, rotational angiography would have identified 16% extra carotid arteries with a severe ICA stenosis (70-99%) compared to conventional DSA. Since three-dimensional MRA usually provides 12 or more projections, this phenomenon may also explain (part of) the overestimation of this technique.
We performed a pilot study comparing the most severe ICA stenosis at twelve projections on 3D TOF MRA with the most severe stenosis at DSA in the standard two or three projections (lateral, posteroanterior, and/or oblique). Additionally, we compared MRA with the most severe stenosis at rotational angiography, providing 16 or 32 circular projections.[19] In our small study population, including 32 carotid

arteries, 3D TOF MRA overestimated the degree of maximum stenosis significantly by approximately 8% if compared with DSA performed in two or three projections, whereas this difference was reduced to about 1% if MRA was compared with rotational angiography.

In the current study we compared 3D TOF MRA with standard DSA in a large cohort. At first we compared maximum stenosis at MRA in twelve MIP projections with maximum stenosis at DSA in two or three projections. Subsequently, we compared stenosis at the MR angiographic projection, corresponding with the DSA projection showing maximum stenosis, with DSA. In addition, we compared the results. We studied the effect on the different stenosis categories and on the decision to perform carotid surgery.

Methods

From February 1997 to December 1999 we included 186 consecutive patients with symptoms of carotid disease (transient ischemic attack, stroke, or amaurosis fugax) in the past 6 months suspected of having carotid artery stenosis at duplex ultrasonography examination. Additional 17 asymptomatic patients were included who had non-specific symptoms, contralateral ICA occlusion, or symptoms more than 6 months ago. One hundred and sixty patients were men and 43 women. The mean age was 65 years (SD, 9; range, 40 to 86 years).
Patients were included if they were suspected of having carotid artery stenosis at duplex ultrasound examination and scheduled to have DSA because carotid endarterectomy was considered. After having obtained written informed consent all patients subsequently underwent MRA examination. MRA was usually performed within one week, and always within one month of the DSA. The study was approved by the hospital ethics committee.
DSA was performed with a Philips Integris V3000 angiographic unit (Philips Medical Systems, Best, The Netherlands) by selective positioning of an intra-arterial catheter in both common carotid arteries using the Seldinger technique. Two or three projections, -lateral, posteroanterior, and/or ipsilateral oblique-, were acquired from each carotid bifurcation.
MRA was performed on a 1.5-T MR imaging system (Gyroscan ACS-NT; Philips Medical Systems) using the three dimensional time-of-flight technique. Postprocessing subvolumes were generated to isolate each carotid artery and to create 12 MIP images that were radially projected at 15° increments (rotation about the long axis of the body).
DSA and MRA examinations were evaluated by a senior radiologist on different

occasions, with at least a 1-week interval. The observer was blinded for the other test results and patient data. ICA stenosis was measured on printed hard-copies according to the NASCET method (Stenosis=[1-(Minimal Residual Lumen/Distal ICA Lumen Diameter)]x100%)[1]. At DSA the percentage ICA stenosis was measured on all available projections showing the ICA without overlapping vessels. The maximum stenosis was selected and its projection was noted. From the twelve MIP images on MRA, the percentage ICA stenosis was assessed on three projections, coinciding with the vast majority of the DSA projections used (lateral, posteroanterior, and 45° ipsilateral oblique). If another projection clearly revealed a more severe stenosis, the percentage stenosis was also assessed on this projection. If an occlusion was suspected at 3D TOF MIP images, 2D TOF images were subsequently evaluated, as this technique is more sensitive to slow flow. If flow was not detectable in the expected course of the distal ICA, the vessel was regarded as occluded. If flow was detected, the vessel was considered to be patent and subtotally stenosed. MRA images of ICAs showing a flow void artefact were considered as severely stenosed (70-99%).[20] For calculations of the mean differences in ICA stenosis, these vessels as well as vessels showing a subtotal stenosis or occlusion, and normal non-stenosed vessels were excluded from analysis, since the exact percentage stenosis according to the NASCET method in these vessels can not be assessed.

The maximum stenosis at DSA was compared with the maximum stenosis that was initially assessed at MRA evaluation. Subsequently, the maximum stenosis at DSA was compared with the stenosis at MRA in a corresponding projection. The degree of stenosis was categorised as 0%-29%, 30%-49%, 50%-69%, 70%-99%, or occlusion. Sensitivity and specificity with 95% confidence intervals (CI) were calculated for assessing severe ICA stenosis (70-99%) at MRA (ie, selecting patients for carotid endarterectomy), using DSA as the reference standard. The McNemar test was used to compare the test-characteristics of MRA for selecting patients with a 70-99% ICA stenosis, in case maximum stenosis at MRA was used, with the test-characteristics of MRA, in case the stenosis at MRA was obtained on a projection corresponding with the DSA projection that showed maximum stenosis. The mean differences in ICA stenosis between maximum stenosis at MRA and maximum stenosis at DSA, and between stenosis at MRA, using the projection corresponding with the DSA projection showing maximum stenosis, and maximum stenosis at DSA were calculated with 95% CI. This analysis was performed for the total group of arteries and for the arteries divided into subgroups according to the different stenosis categories.

Results

Of the 203 included patients, three angiograms could not be retrieved and 13 MRA examinations were not performed due to claustrophobia (n=8) or lack of MRI availability (n=5). One patient refused further co-operation after inclusion in the study. Of the remaining 372 carotid arteries of 186 patients, 5 ICAs could not be assessed at DSA, because of too many overlapping vessels (n=3) or complications during the procedure (n=2). Thirteen ICAs could not be assessed at MRA, caused by movement of the patient during the test.

For the remaining 354 ICAs (Table 1 and 2), sensitivity and specificity of MRA for assessing an ICA stenosis of 70% or more using maximum stenosis at MRA were 92.6% (95% CI, 85.3% to 97.0%) and 82.7% (95% CI, 78.1% to 87.3%), respectively. Sensitivity and specificity of MRA for assessing an ICA stenosis of 70% or more using the MR angiographic projection, corresponding with the DSA projection that showed the maximum stenosis, were 88.3% (95% CI, 81.8% to 94.8%) and 89.6% (95% CI, 85.9% to 93.3%), respectively. Test-characteristics of MRA for selecting patients with severe ICA stenosis (70-99%) were significantly different ($p<0.01$) when MR angiographic projections were used that corresponded with DSA projections that showed maximum stenosis, instead of using the maximum stenosis at MRA.

Table 1. Categorised lumen reduction measurements of maximum ICA stenosis at MRA in 12 MIP projections versus those at DSA in two or three projections.

	DSA					
MRA	0%-29%	30%-49%	50%-69%	70%-99%	100%	Total
0%-29%	**66**	8	1			75
30%-49%	13	**10**	3			26
50%-69%	3	15	**23**	4		45
70%-99%	1	5	38	**87**	1	132
100%				3	**73**	76
Total	83	38	65	94	74	**354**

Table 2. Categorised lumen reduction measurements of ICA stenosis at MRA, using the projection corresponding with the DSA projection showing maximum stenosis, versus those at DSA.

	DSA					
MRA	0%-29%	30%-49%	50%-69%	70%-99%	100%	Total
0%-29%	**74**	11	2			87
30%-49%	9	**12**	11	1		33
50%-69%		12	**29**	7		48
70%-99%		3	23	**83**	1	110
100%				3	**73**	76
Total	83	38	65	94	74	**354**

Of the 354 ICAs for which MRA and DSA could be compared, 35 were normal, 59 showed a signal void at MRA, 6 showed a subtotal stenosis, and 77 were occluded at either DSA or MRA. For the remaining 177 ICAs, the mean difference in ICA stenosis between maximum stenosis at MRA and maximum stenosis at DSA was 7.5% (95% CI, 5.2% to 9.9%) (Table 3). The mean difference between stenosis at MRA, using the projection corresponding with the DSA projection showing maximum stenosis, and maximum stenosis at DSA was 0.4% (95% CI, -2.0% to 2.7%). In addition, the difference between the two calculated mean differences was 7.2% (95% CI, 5.6% to 8.7%). The results for the different subgroups of stenosis are listed in Table 3. In all subgroups the mean difference of MRA is lower if the corresponding projections with DSA are used. The effect of overestimation, however, is most apparent in the milder stenosis categories.

Table 3. Mean differences in ICA stenosis between maximum stenosis at MRA and maximum stenosis at DSA (A), and between stenosis at MRA, using the projection corresponding with the DSA projection showing maximum stenosis, and maximum stenosis at DSA (B). Additionally, the difference between the two calculated mean differences (A-B).

Category of stenosis according to DSA	A: Mean difference of maximum stenosis MRA(12 projections) and DSA (95% CI)	B: Mean difference of corresponding projections MRA and DSA (95% CI)	Difference (A-B) (95% CI)	N (number of carotids)*
0-29%	14.8% (10.0% to 19.3%)	6.1% (2.2% to 10.1%)	8.7% (5.0% to 12.3%)	47
30-49%	7.1% (0.6% to 13.7%)	-0.8% (-7.7% to 6.1%)	7.9% (4.0% to 11.9%)	37
50-69%	7.8% (4.2% to 11.3%)	0.0% (-4.1% to 4.0%)	7.8% (5.2% to 10.5%)	59
70-99%	-2.5% (-5.6% to 0.6%)	-5.6% (-9.2% to 2.0%)	3.1% (1.2% to 5.0%)	34
Total group	**7.5%** (5.2% to 9.9%)	**0.4%** (-2.0% to 2.7%)	**7.2%** (5.6% to 8.7%)	**177**

Figures 1 and 2 show the results of measurements of maximum ICA stenosis at MRA versus maximum stenosis at DSA and the results of measurements of stenosis at MRA, using the projection corresponding with the DSA projection showing maximum stenosis. In Figure 1, a substantial number of measurements are above the line of equality, indicating MRA overestimated the stenosis as compared with DSA. Figure 2, however, shows that measurements of ICA stenosis at MRA and DSA in a corresponding projection are more similar. Figures 3 and 4 illustrate how MR angiographic images in other projections than in the two or three projections obtained at DSA may reveal a more severe ICA stenosis.

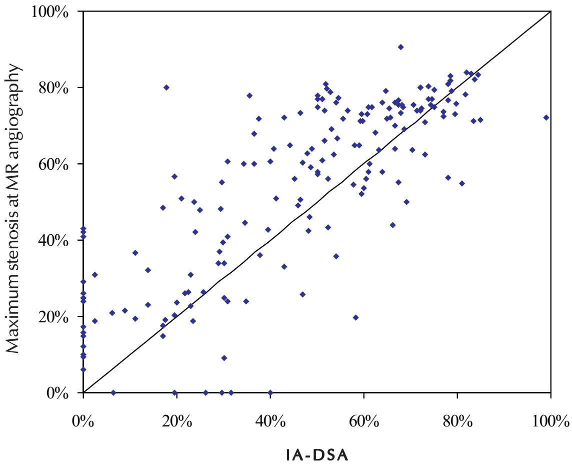

Figure 1. Scatter plots show measurements of maximum ICA stenosis obtained at MRA versus maximum stenosis obtained at DSA. Normal vessels and carotid arteries showing a signal void, subtotal stenosis or occlusion are excluded. A substantial number of measurements are above the line of equality, indicating that measuring maximum stenosis at MRA results in more severe estimates of ICA stenoses than measuring maximum stenosis at DSA.

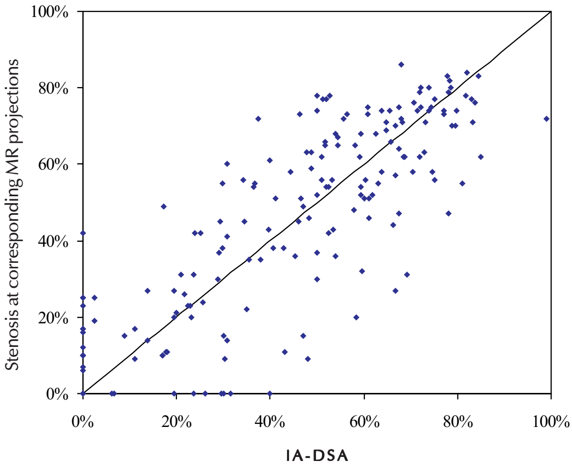

Figure 2. Scatter plots show measurements of ICA stenosis obtained at MRA, using the projection corresponding with the DSA projection showing maximum stenosis, versus maximum stenosis obtained at DSA. Normal vessels and carotid arteries showing a signal void, subtotal stenosis or occlusion are excluded. Compared with Figure 1, more measurements are at or around the line of equality, indicating that measurements of ICA stenosis at MRA and DSA in a corresponding projection showed more agreement.

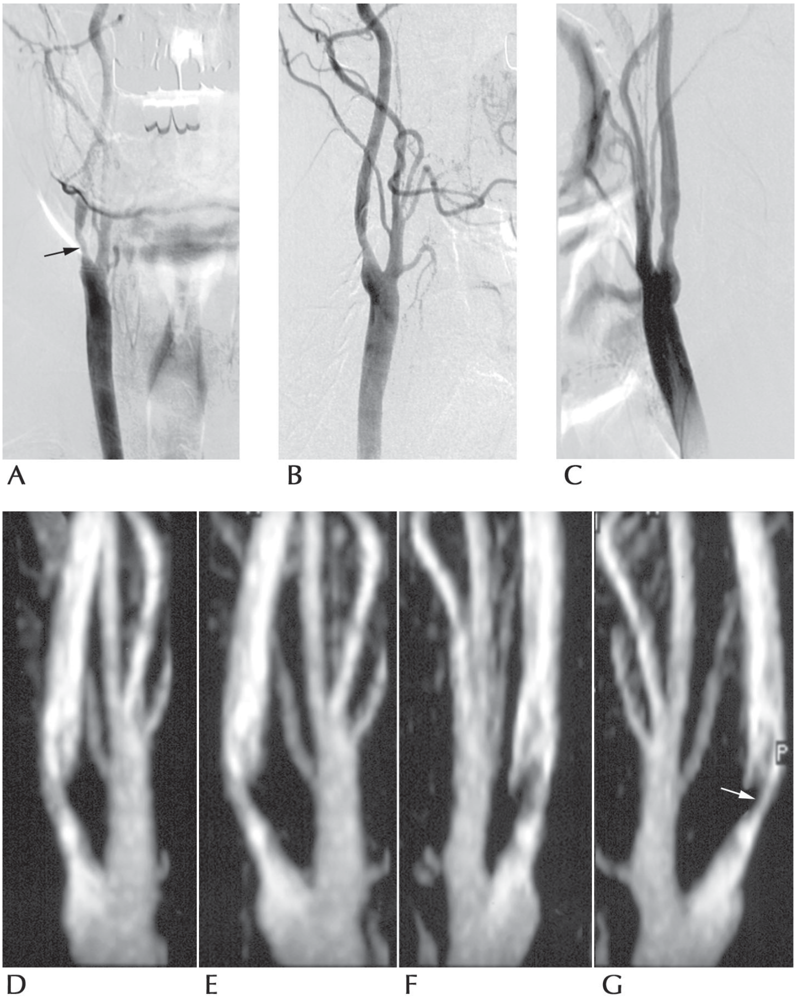

Figure 3. From the **A**. posteroanterior, **B**. 45° ipsilateral oblique, and **C**. lateral digital subtraction angiographic projections of the carotid bifurcation, the posteroanterior projection reveals the maximum ICA stenosis (a moderate 50%-69% stenosis, arrow in **A**.). The corresponding three MR angiographic MIP images (**D**., **E**., and **F**.) show the same configuration of the ICA as DSA. An additional MR angiographic MIP image (**G**.), however, depicts the ICA as a 70%-99% stenosis (arrow).

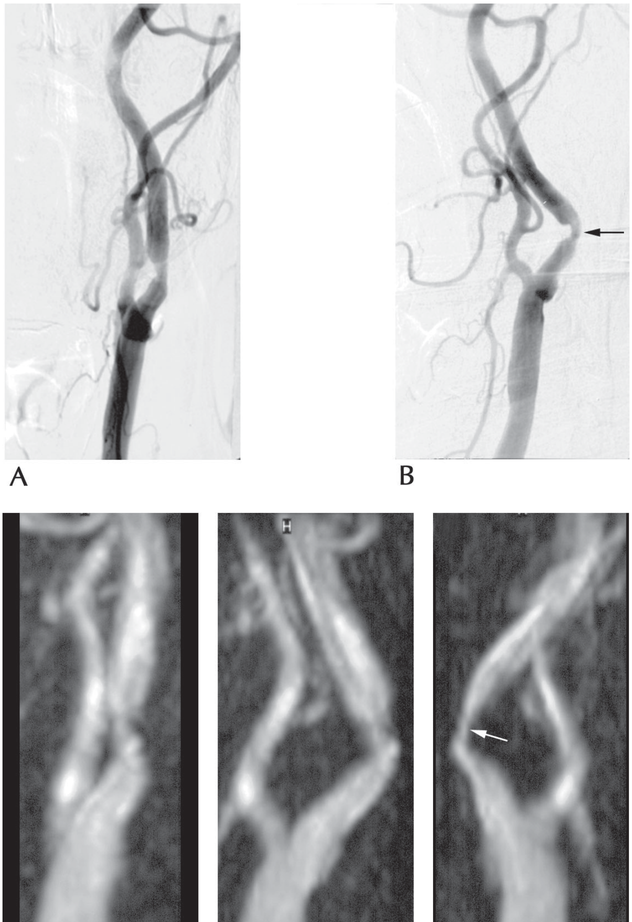

Figure 4. Digital subtraction angiographic projections (**A**. posteroanterior and **B**. 45° ipsilateral oblique) reveal a moderately stenosed ICA (arrow in **B**.), which was estimated similarly at the corresponding MR angiographic MIP images (**C**. and **D**.). However, according to another MR angiographic projection (**E**. contralateral oblique), which reveals a severe stenosis (arrow), the ICA should be operated.

Discussion

3D TOF MR angiography overestimated carotid stenosis when the most severe stenosis at MR angiography from the 12 MIP images available was used and compared with the most severe stenosis at intra-arterial DSA, performed in two or three projections. This finding was consistent with results of other studies. [6,7,11-15] In our study, MRA overestimated ICA stenosis with one category or more in 22% and underestimated stenosis in 5% of the arteries. Additionally, the mean difference in stenosis (7,5%) was statistically significant. However, using MRA projections that corresponded with DSA projections did not systematically overestimate ICA stenosis. Using this approach MRA overestimated ICA stenosis in only 14% and underestimated ICA stenosis in 9% of the cases and no significant mean difference in percentage stenosis between MRA and DSA was found. This indicates that corresponding projections should be used for the most accurate comparison of a new imaging technique with the reference standard DSA, which results from the fact that residual stenotic lumen is almost never circular.

We realise, however, that 3D TOF MRA in our study still misclassified 23% of the carotid stenoses. From these incorrectly classified stenoses 42% had clinical relevance i.e. would result in a different decision with view on carotid endarterectomy.
In the categories with milder degree of stenosis there was a reasonable amount of over and underestimation (i.e. misclassification as compared to the reference test). Other factors than using different projections of the vessel must account for this effect. First, it is important to realise that in a diagnostic study a new test by definition never exactly agrees with the reference test, and that a certain variation in the observed test results will always occur.[21] Secondly, the stenosis can be missclassified, because measurements on MIP images of MRA can be complicated by signal loss due to intravoxel dephasing in the stenotic area. Signal loss might depend on the MRA technique used (3D TOF is less susceptible to flow related artefacts than 2D TOF because of the smaller voxel size), gradient moments and echo times of the imaging protocol, and the complexity of the blood flow in and beyond the stenosis.[16] Complexity of blood flow depends on the velocity proximal to the stenosis, on the severity of stenosis, and on the configuration of the stenosis (ie, ulceration and irregular plaque cause irregular flow patterns and, hence, signal loss).[22] Therefore, whether or to what extent intrastenotic signal loss affects lumen reduction measurements will vary for each specific carotid stenosis.

In table 3 the mean differences in stenosis measurements between MRA, for both described methods, and DSA, are lined out for the different categories of stenosis. In all subgroups the mean difference is lower if the corresponding projections at DSA are used. Remarkably, in the 70-99% group the mean difference of MRA with DSA is negative also if the maximum stenosis of 12 projections is assessed. However, this subgroup is relatively small and the CIs of the mean differences of the two methods overlap and the differences are therefore not significant. Nevertheless, a possible explanation might be that the residual lumen of the stenosis in this subgroup is very small in absolute sense. With stenosis measurement according to NASCET, the diameter of the residual lumen is divided by the diameter of the normal lumen distal to the stenosis. Therefore, a possible effect of overestimation decreases as the percentage of stenosis increases.

NASCET recently concluded that patients with a symptomatic carotid stenosis of 70% or more benefit substantially from carotid endarterectomy for at least 5 years.[1] The beneficial effect of carotid endarterectomy is far less and only marginal significant for patients with a 50% to 69% stenosis. In fact, only men, patients with recent stroke, and patients with hemispheric symptoms really benefit, provided that the risk of stroke or death due to the operation does not exceed 2%. Because of the apparent beneficial effect for all symptomatic patients with a 70% or more carotid stenosis, we choose a threshold of 70% for selecting patients eligible for carotid endarterectomy. Using this threshold, sensitivity and specificity of 3D TOF MR angiography were about 90%. If we had chosen a threshold of 50%, sensitivity and specificity of 3D TOF MR angiography would have been better, although one has to take into account that the initial duplex screening may affect these data. Sensitivity and specificity would have been 95.6% and 87.7%, respectively, if maximum stenosis at MR angiography was compared with maximum stenosis at IA-DSA, and 89.3% and 91.8%, respectively, if corresponding projections of MR angiography and IA-DSA were compared.

Contrast-enhanced MRA (CE-MRA) becomes more frequently used for imaging of the carotid arteries.[23,24] This technique provides additional morphological information about the origin of the carotid arteries and intra-cranial vessels, and the effect of flow related artifacts occurring with the time-of-flight technique is diminished. The use of intravenous contrast results in a stronger signal with better background suppression, and less signal saturation. However, suppression of signal from the jugular vein overlapping the carotid bifurcation is one of the drawbacks of this technique. Suppression can be achieved by scanning the carotid arteries within 10 seconds after enhancement (before venous return). Until recently, however,

the poor resolution of three-dimensional methods, even on high-gradient hardware, did not yet allow accurate measurements of carotid stenosis.[25]
More recent studies have used other methods for venous signal suppression, allowing longer scanning time and, hence, better spatial resolution and seem very promising.[15,24,26,27] To date, however, only a few studies, with relatively small study populations, have been published reporting the results of contrast-enhanced MRA validated against DSA.

In conclusion, we believe that 3D TOF MRA is a thoroughly validated technique in selecting patients for carotid endarterectomy. MRA overestimated carotid stenosis when the most severe stenosis at MR angiography from the 12 MIP images available was used and compared with the most severe stenosis at DSA, performed in two or three projections. However, using MRA projections that corresponded with DSA projections did not systematically overestimate ICA stenosis. When new techniques, e.g. gadolinium-enhanced three-dimensional MR angiography, are validated, using conventional DSA as standard of reference, we recommend the use of identical projections of the ICA. Otherwise, the greater number of projections of the ICA on MRA will most certainly cause overestimation of carotid stenosis. With regard to NASCET findings the diagnosis of the most severe stenosis at the standard three projections remains the essential clinical criterion for the decision on carotid endarterectomy.

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Chapter 6

Time-of-flight MR angiography of carotid artery stenosis: does a flow void represent severe (70-99%) stenosis?

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Abstract

Background and Purpose

The time-of-flight technique (TOF) is a commonly used magnetic resonance angiography (MRA) technique to visualise the carotid arteries. However, the appearance of flow void artefacts is one of the drawbacks of this modality. Most diagnostic studies on MRA use the assumption that a flow void represents severe stenosis (70-99%), based on technical explanations. Correct estimation of the degree of stenosis is of crucial importance with regard to the decision on carotid endarterectomy. Therefore, we validated flow voids in a clinical study, using digital subtraction angiography (DSA) as the reference test.

Methods

390 consecutive patients suspected of having carotid artery stenosis at Duplex ultrasound (DUS) examination were included in this study over the period 1997-2000. All patients subsequently underwent 3D-TOF MRA and conventional DSA. We determined the frequency of flow void artefacts in this population on 3D-TOF MRA imaging and compared them with stenosis measurements on DSA.

Results

We recorded 107 flow voids (16%) on the 3D TOF MRA examinations of 662 carotid arteries. DSA images for comparison were available in 102 of these 107 cases. The median percentage of stenosis in this subgroup of flow voids on MRA was 80% when compared with stenosis measurement on DSA according to the NASCET criteria. The stenoses ranged from 36% to 100% (occlusion). Three flow voids (2,9%) fell into the 0-49% range of stenosis, 11 (10,8%) in the 50-69% range, 86 (84,3%) in the 70-99% range and 2 (2,0%) represented an occlusion (100%). The positive predictive value of a flow void artefact for the presence of severe stenosis (70-99%) was 84,3% (95%CI, 77,3%-91,4%).

Conclusion

In this clinical study flow void artefacts represent severe stenosis in the vast majority of the arteries. According to our data, the assumption that a flow void on 3D TOF MRA represents severe stenosis is justified.

Introduction

Traditionally Digital subtraction angiography (DSA) has been widely used to visualise the carotid arteries. On the basis of randomised trials it became the gold standard to select patients for carotid endarterectomy.[1-4] DSA, however, has a relatively high risk of morbidity and mortality.[5,6] Non-invasive tests such as Duplex ultrasound (DUS) and Magnetic resonance angiography (MRA) are therefore increasingly used in the diagnosis of carotid artery stenosis avoiding the risks associated with DSA.[7-11] The most commonly used MRA technique is time-of-flight (TOF) MRA. Although new techniques such as contrast-enhanced MRA are promising for the future, this technique is not yet commonly used and mostly restricted to specialised centres.[12,13]
One of the main problems in imaging carotid arteries with TOF MRA is the possibility of flow void artefacts (signal loss near to the stenosis).[14] This phenomenon is believed to occur particularly in stenosed lumen of arteries due to turbulence of the blood flow. In imaging carotid arteries the frequency of flow voids might be 10 to 20%. Most diagnostic studies on MRA therefore use the assumption that a flow void represents severe stenosis (70-99%).[15-18] This assumption is mostly based on technical explanations rather than clinical studies.
One publication studied the appearance of flow void artefacts using DSA as the reference standard in a series of 50 patients, and concluded a very good accuracy of concordant DUS findings and the presence of a void on MRA in recognising severe stenosis.[19]
In our opinion correct interpretation and estimation of the degree of stenosis of a flow void artefact is of crucial importance with view on the decision on carotid endarterectomy in clinical practice. In the present paper we studied the frequency and diagnostic meaning of flow voids on patient data, as part of a larger study in which MRA was compared with the reference standard DSA.

Time-of-flight MRA

The time-of-flight (TOF) MRA method is a gradient echo technique in which contrast is obtained by the inflow of fresh, unsaturated blood through an image section with (pre)saturated static tissue. This makes visualisation of the lumen of an artery possible. Both two-dimensional (2D) and three-dimensional (3D) techniques are applied. 2D TOF MRA uses very thin slices as scan volumes. The signal of blood is very high, making the technique very sensitive to distinguish slow flow from occlusions. The scanned volume in 3D TOF MRA is larger. 3D techniques has a higher spatial resolution, a greater signal-to-noise-ratio and is less sensitive for voids then 2D TOF MRA due to smaller voxels and shorter echo time. With 3D TOF MRA the degree of stenosis of the carotid artery can be measured according to the NASCET[1] using post processing maximum intensity projections of the bifurcation of the carotid artery.

Flow voids

In carotid artery imaging the frequency of flow voids on TOF MRA might be 10 to 20%. Flow voids are considered to be caused by blood flow disturbances near to a stenosis. Based on technical explanations, however, exact estimation of the degree of stenosis remains impossible. When reading TOF MRA scans, one should realise that this technique does not provide purely morphological images, but relies on the signal created by flowing blood. For this reason, direct comparison of DSA and TOF MRA is not at all straightforward. A problem commonly observed with 2D and 3D TOF MRA is local reduction of signal or even total signal loss due to spin dephasing caused by the presence of complex flow patterns distal to high-grade stenoses.[20] It has been shown that the severity of such dephasing artefacts depends on the gradient wave forms of the imaging sequence used[21] and on many parameters related to the hemodynamics of the stenosis, like its geometry, the average blood flow velocity, the Reynolds number, the turbulence intensity and the turbulent fluctuation velocity.[22] Because of the complex nature of the post-stenotic signal appearance (PSA) on TOF MR angiograms, and especially the hemodynamic aspects involved, accurate grading of stenoses on MR images from a technical point of view remains very difficult, even with knowledge of the present flow rate. Still, flow-induced signal loss, also called flow void, distal to a stenosis in the internal carotid artery on TOF angiograms is assumed to reflect the presence of a severe stenosis (70-99%).

In this study we will test if classification as severe stenosis (70-99%) is appropriate when a flow void is observed with TOF MRA examination on patient data. Because of the clinical relevance of selecting the right patients for carotid endarterectomy, we studied the incidence of this phenomenon and validated the appearance of flow void in relation to stenosis measurements on DSA.

Methods

Study population

From January 1997 to November 2000, 390 consecutive patients suspected of having carotid artery stenosis at DUS examination and scheduled to have DSA prior to possible carotid endarterectomy were included in a prospective diagnostic study. Subsequently, all patients underwent MRA examination. Ninety-one percent of the patients had experienced symptoms of carotid artery disease (transient ischemic attack, minor disabling ischemic stroke, or amaurosis fugax) in the prior six months, nine percent was asymptomatic. We excluded patients who had contraindications for MRA such as metal implants not suitable for MR or claustrophobia. All patients gave their written informed consent. Our study was approved by the medical ethical committees of the participating hospitals. The baseline characteristics of the patients are listed in table 1. The accuracies of MRA and DUS in comparison with DSA from the total study population will be published elsewhere.[23]

Diagnostic tests

All patients underwent DUS, DSA and MRA within a period of one month. The degree of stenosis on DUS was determined based on the peak systolic velocity (PSV) in the proximal part of the internal carotid artery, which is the most accurate estimator of the degree of stenosis for DUS.[24] We used a PSV of 270 cm/sec as threshold representing 70% stenosis and 210 cm/sec representing 50% stenosis according to DSA.[25]

DSA was performed by selective positioning of an intra-arterial catheter in both common carotid arteries using the Seldinger technique. Two or three projections, lateral, posteroanterior, and/or ipsilateral oblique, were acquired from each carotid bifurcation.

MRA was performed on a 1.5-T MR imaging system using the three dimensional time-of-flight technique. A 3D spoiled gradient echo acquisition was applied using the following parameters: repetition time (TR) 30 ms, echo time (TE) 6.9 ms, excitation angle 15 degrees, field of view 96x120, acquisition matrix 147x256, 50 slices with a thickness 1.0 mm, reconstructed to 100 slices of 0.5 mm. The number of signal averages was 3 and a quadrature head coil was used as receiving coil. The scan duration was about 9 minutes. Postprocessing subvolumes were generated to isolate each carotid artery and to create 12 MIP images that were radially projected at 15° increments (rotation about the long axis of the body).

The DSA and MRA test results were read by one observer in each hospital (AFJW; AvdL). The observer was blinded for clinical information and for the results of the other tests. The DSA and MRA results were read independently with a period of at least one month between the readings. The observers examined DSA and MRA on printed hard copies. The stenoses were measured on both DSA and MRA according to the NASCET criteria.[1] Flow voids on MRA were defined as complete loss of signal in the internal carotid artery for a minimal length of 1 mm on the MIP images of both 2D and 3D TOF MRA images. Per definition signal had to reoccur distal from the flow void signal in the ICA. To assess the inter-observer variability in recognising a flow void artefact a second observer read the tests of a sub-series of 200 consecutive patients.

In addition, the quality of all DSA examinations was assessed by using a score ranging from 1 to 3 (1: good, 2: moderate, 3: inferior quality). In this score the overall quality of the examination as well as more detailed items such as overprojection and applicability to measure the degree of stenosis are incorporated.

Analysis

The frequency of flow void on MRA was calculated in the total study population. From the flow voids observed on MRA the corresponding estimated stenosis on DSA and DUS was recorded. Proportions from the voids divided over the different categories of stenosis (0-49%, 50-69%, 70-99%, 100%) were calculated. The positive predictive value of flow void for presence of severe stenosis using DSA as the gold standard was estimated. Inter-observer variability in recognising a flow void was assessed by estimating the kappa. Additionally, we studied whether the degree of stenosis on DSA (in case of a flow void on MRA) was related to the quality of the test, using the Chi-squared test.

Table 1. Baseline characteristics study population.

Characteristics (N=390)	
Age (years) {range}	67 {39 88}
Male/Female (%)	76/24
Symptoms* (%)	
Amaurosis fugax / retinal	20
Transient ischemic attack	38
Stroke	33
Asymptomatic	9
Hypertension (%)	48
Diabetes (%)	14
Cardiac history (%)	
Angina	18
Myocardial infarction	16
Heart failure	6
Bypass-surgery or PTCA	11
Peripheral arterial disease (%)	
Claudication	15
Surgery or PTA	8
Smoking (%)	
Smoker	49
Ex-smoker	34

Results

In total 390 consecutive patients were included in the study (76% male). The mean age of our study population was 67 years (range 39-88 years). Ninety-one percent of the patients had experienced neurological symptoms in the 6 months prior to the date of inclusion (Table 1).

Table 2. Degree of stenosis according to DSA from 102 flow voids occurring with time-of-flight MRA.

Stenosis according to DSA	N flow voids (%)
0-49%	3 (2,9%)
50-69%	11 (10,8%)
70-99%*	86 (84,3%)
Occlusion (100%)	2 (2,0%)
Total	102 (100%)

TOF MRA examinations of sufficient quality were available of 662 carotid arteries. During the readings of the examinations of these 662 carotid arteries 107 flow voids (16,2%) were recorded. Stenosis measurements of the DSA examinations were available in 102 of the 107 arteries. The median percentage of stenosis from the flow voids was 80% with a range of 36% to 100% (occlusion), when they were compared with stenosis measurements on DSA according to the NASCET criteria. In comparison with DSA 3 flow voids (2,9%) fell in the 0-49% range of stenosis, 11 (10,8%) in the 50-69% range, 86 (84,3%) in the 70-99% range and 2 (2,0%) represented an occlusion (Table 2). In the group of severe stenosis (70-99%) nine cases of slow flow or string sign were recorded according to DSA and were graded as 99% stenosis.

Table 3. Categorised degree of stenosis on DUS and DSA. All 98 carotid arteries in this table were recognised as flow voids on MRA.

		Stenosis categories DSA				
		0-49%	50-69%	70-99%	100%	Total
	0-49%					
Stenosis	50-69%		**1**	2		3
Categories	70-99%	3	10	**79**	1	93
DUS	100%			1	**1**	2
	Total	3	11	82	2	**98**

The positive predictive value of a flow void artefact for presence of severe stenosis (70-99%) according to DSA was 84,3% (95%CI, 77,3%-91,4%). The kappa statistic for the inter-observer variability in recognising a flow void was 0,81 (95%CI, 0,76-0,83).

MRA, DUS and DSA results were all three assessed in 98 of the total number of 107 carotid arteries in which MRA showed a flow void artefact. Table 3 illustrates the concordant and discordant findings by tabulating DUS versus DSA results. DSA did not conclude severe stenosis (70-99%) in 16 cases were MRA showed a flow void. In 10 out of the 14 arteries in which DSA showed <70% stenosis, DUS did show severe stenosis.

There was a trend between the better quality of DSA and the larger proportion of the carotids in which the angiogram showed severe stenosis. This proportion was 87,5% in the group of DSA examinations with good quality and declined to 78,3% in the group with moderate quality to 71,4% in the group with inferior quality (Table 4). However, this trend was not significant (Chi-squared test: p=0,15).

Table 4. Proportion of DSA examinations showing severe stenosis (70-99%) and not showing severe stenosis (<70% or 100%) versus the quality score of the tests. All 102 carotid arteries in this table were recognised as flow voids on MRA.

	No of arteries (%)		
Quality score DSA	<70% or 100%	70-99%*	Total
1: good	9 (12,5%)	63 (87,5%)	72 (100%)
2: moderate	5 (21,7%)	18 (78,3%)	23 (100%)
3: inferior	2 (28,6%)	5 (71,4%)	7 (100%)

* Non-significant linear-by-linear association (Chi-squared: p=0,15).

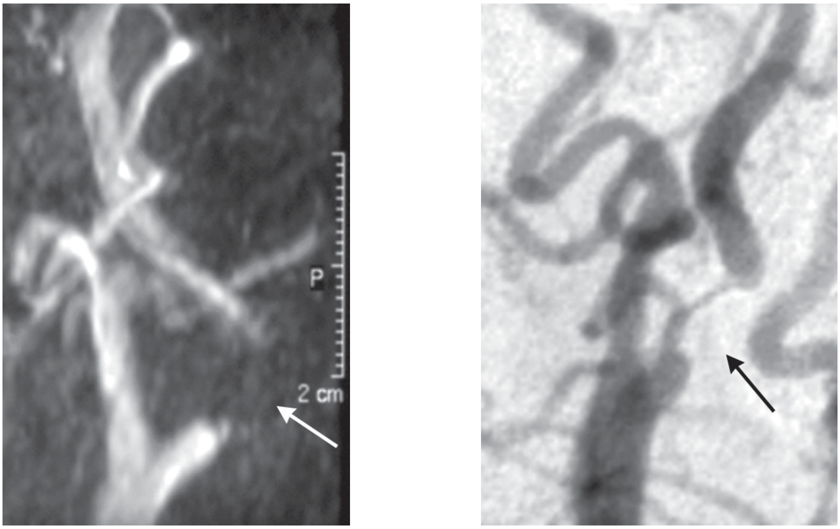

Figure 1. Example: male, age 70 (minor stroke of the right hemisphere). MRA (left) showed a long flow void artefact (arrow). DSA (right) clearly showed a severe stenosis (70-99%) in the internal carotid artery (arrow).

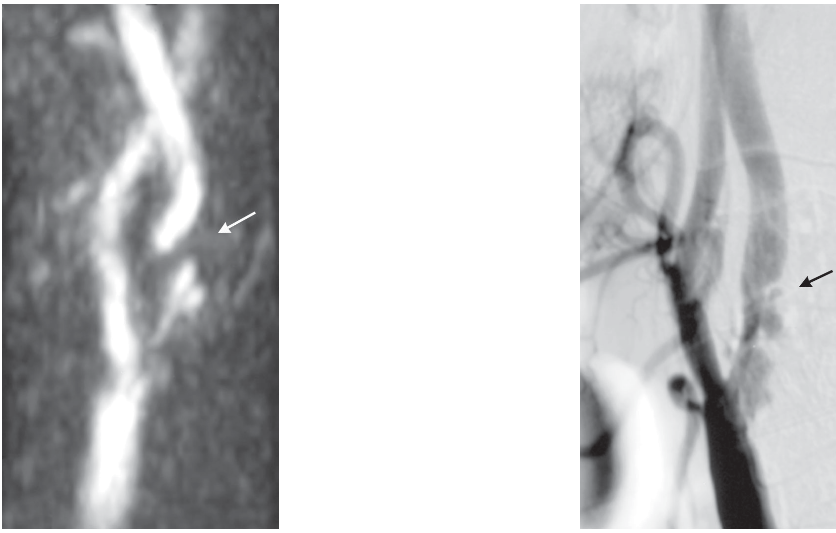

Figure 2. Example: male, age 64 (TIA of the right hemisphere). MRA (left) showed a short flow void artefact distal to a visible irregular plaque in the internal carotid artery (arrow). On all other available projections on 3D TOF MRA, (12 in total, except for two directions with overprojection making the internal carotid artery invisible), there was an interruption of the blood flow signal. The flow void was confirmed on the transversal 2D TOF MRA images. DSA (right) also showed the irregular stenosis with an ulcerated plaque in the internal carotid artery. The measurement of the most severe stenosis on DSA, however, resulted in a moderate stenosis (50-69%) (arrow).

Discussion

In visualising carotid arteries with 3D TOF MRA we found a frequency of 16% of flow void artefacts near by the stensoses. Flow voids are often considered to represent severe stenosis (70-99%), based on technical explanations. In the present clinical study the positive predictive value of a flow void artefact for presence of severe stenosis (70-99%) was 84,3% according to the reference standard DSA. The median percentage of stenosis was 80%, with a range of 36% to 100%. In this clinical study flow void artefacts represent severe stenosis in the vast majority of the arteries.

According to randomised trials patients with a symptomatic severe stenosis of the ICA (70-99%) benefit from carotid endarterectomy. Patients with a 50-69% stenosis have smaller benefit and it is expected that in the near future more determinants will be published selecting the right subpopulation for surgical treatment.[3] Diagnosis of 70-99% stenosis therefore remains crucial in the work-up of patients with carotid artery disease. DSA traditionally has been the gold standard for estimating the degree of stenosis of the ICA on basis of the trials. Because DSA has a relative high risk on complications, non-invasive techniques such as MRA and DUS are increasingly used. A commonly applied technique is time-of-flight (TOF) MRA. If DSA were to be abandoned patients have to be selected for surgery on basis of MRA, most likely after screening with DUS. Occurrence of flow related artefacts is one of the drawbacks of the time-of-flight technique. However, correct interpretation is very important with view on the decision on carotid endarterectomy. In the current study patients suspected of having carotid artery stenosis at DUS were examined with TOF MRA. Flow void artefacts appeared in 16% of the observed arteries, which we think is relatively often. Although the population was selected, because patients were initially screened with DUS before undergoing DSA and MRA examination, this population exactly reflects the domain in which MRA would be performed if DSA were to be abandoned.
New developments such as contrast-enhanced MRA (CE-MRA) might decrease the problem of flow related artefacts in the near future.[12,13,17] The frequency of voids is expected to be lower but the problem of artefacts has not yet disappeared with the introduction of this technique. Furthermore, the exact causes of artefacts in CE-MRA remain unknown. CE-MRA has not yet been validated in very large series using DSA as the reference test. Moreover, this technique is not yet generally accepted and its use is still mostly restricted to specialised centres.
The assumption that a flow void on TOF MRA represents a severe stenosis is confirmed by our data. In 84% of the voids that appeared in our study the reference standard DSA concluded 70-99% stenosis. The voids ranged from 36% to 100%. In 14% of the cases (14 arteries) stenosis was < 70%. Important is the fact, however, that 11 of

these 14 arteries fell into the 50-69% category. The remaining 3 represented a 0-49% stenosis according to DSA. The quality of the DSA examinations in the group, in which this test did not show severe stenosis, seemed lower than in the group in which it did show severe stenosis. Although this difference was not statistically significant, we feel this strengthens our conclusion that a flow void can be considered as severe stenosis in the work up of patient prior to possible carotid endarterectomy. In all 16 cases in which a flow void on MRA did not represent a severe stenosis (70-99%) on DSA, the DUS and DSA examinations were retrospectively re-evaluated by a senior radiologist (WPThM) and a senior vascular surgeon (BCE). In 7 examinations this non-blinded re-evaluation showed inferior quality of DSA, making adequate measurement of the stenosis difficult. In these cases they could not decide on carotid endarterectomy on basis of the presented DSA only. In 4 cases the stenosis or atherosclerotic disease seemed worse then the stenosis measurement according to the protocol indicated, and together with the DUS results they tended to advise on carotid endarterectomy. In 5 cases there was no comment on DSA or DUS examination. The total number of cases of flow void in the presented series with the gold standard available is relatively large. In most cases of flow void on MRA where DSA had not concluded severe stenosis, the quality of the reference test was inferior and/or the stenosis seemed worse than only the measurement of stenosis percentage could indicate. The conclusion that the DSA examinations of the group showing <70% had shortcomings in establishing the severity of the disease, was supported by the fact that DUS did show severe stenosis (PSV≥270 cm/sec) in 10 out of the 14 arteries.

In conclusion, flow voids, appearing in 16% of the carotid arteries with TOF MRA imaging, in our opinion need to be assessed with care with view on the clinical decision on carotid endarterectomy. In our patient series flow void artefacts represent severe stenosis in the vast majority of the arteries. We feel that this finding is strengthened by the fact that the quality of DSA tended to be worse and the fact DUS showed severe stenosis in most of the arteries in the group in which DSA did show <70% stenosis. In general we think the assumption that a flow void on 3D TOF MRA represents severe stenosis is justified.

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Chapter 7

Diagnostic value of contrast-enhanced MR angiography in carotid artery stenosis

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Submitted

Abstract

Background and Purpose:

On the basis of large randomised trials conventional intra-arterial digital subtraction angiography (DSA) is the standard of reference in the decision on performing carotid endarterectomy. Contrast-enhanced MR angiography (CE-MRA), a promising non-invasive imaging test, is increasingly used in the assessment of carotid artery stenosis. The technique yields possible advantages such as diminishment of flow related artefacts and allows visualisation of a long tract of the carotid artery from origin to intra-cranial siphon. In the present paper we introduce a 3D CE-MRA technique visualising the carotid artery from the origin to the intra-cranial siphon. The aim of this study was to assess the accuracy and reproducibility of CE-MRA in diagnosing carotid artery stenosis compared with 3D time-of-flight MRA and the reference standard DSA.

Methods:

In a prospective diagnostic study we performed CE-MRA, 3D TOF MRA, and DSA on 51 consecutive patients suspected of having carotid artery stenosis at duplex ultrasound examination. Stenoses were measured by two independent observers using the NASCET method. The observers were blinded for clinical information and other test results.

Results:

CE-MRA, 3D TOF MRA, and DSA yielded comparable test results. The Pearson's correlation coefficients were 0.94 ($p<0.01$) for CE-MRA compared with DSA, 0.92 ($p<0.01$) for 3D TOF MRA compared with DSA, and 0.93 ($p<0.01$) for CE-MRA compared with 3D TOF MRA. The kappa statistics reflecting the inter-observer variability were 0.81 for CE-MRA, 0.79 for 3D TOF MRA, and 0.78 for DSA. Stenosis measurements of the first observer on CE-MRA, with inclusion of the carotid arteries on the symptomatic side only, compared with the reference standard DSA, yielded a sensitivity of 90% (95%CI, 68%-99%) and a specificity of 77% (95%CI, 55%-92%) in the diagnosis of severe stenosis (70-99%). 3D TOF MRA yielded a sensitivity of 86% (95%CI, 67%-97%) and a specificity of 73% (95%CI, 50%-89%) compared with DSA.

Conclusion:

CE-MRA showed promising preliminary results. The diagnostic accuracy of CE-MRA in the diagnosis of severe stenosis (70-99%) is similar to 3D TOF MRA. CE-MRA allows visualisation of a long tract of the carotid artery, from origin to siphon. Furthermore, compared to 3D TOF MRA, CE-MRA diminishes occurrence of flow related artefacts.

Introduction

Two large randomised clinical trials, The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), have proven the benefit of carotid endarterectomy in patients with severe symptomatic carotid artery stenosis (70-99%).[1,2] Recent publications have shown that subgroups of patients with a 50-69% stenosis may also expect a small benefit from carotid endarterectomy.[3,4] The diagnosis of severe stenosis (70-99%), however, remains crucial for the majority of patients.
The degree of stenosis in the endarterectomy trials was established by conventional intra-arterial digital subtraction angiography (DSA), which has become the standard of reference for selecting patients for carotid surgery. DSA in patients with atherosclerosis, however, has a relatively high risk of morbidity and mortality. In the literature a risk of 4% of transient ischemic attack (TIA) or minor stroke and 1% of major stroke, and even a small risk of death (<1%) have been reported.[5,6] Even patients without apparent neurological complications after DSA have been shown to develop minor asymptomatic infarctions due to micro-embolisms.[7]
Therefore, non- or minimal-invasive techniques such as 3D time-of-flight (TOF) MR angiography (MRA) and contrast-enhanced magnetic resonance angiography (CE-MRA) are increasingly used supplementary to duplex ultrasound in the diagnosis of carotid artery stenosis. In the last decade 3D TOF MRA was the most commonly applied MR technique. Several studies have proven good diagnostic performance in the selection of patients for carotid surgery.[8-13] More recently, CE-MRA has been introduced, enabling visualisation of a longer tract of the carotid artery compared to 3D TOF MRA, including origin and intra-cranial parts.[14-16] Furthermore, CE-MRA diminishes the possibility of flow related artefacts, one of the drawbacks of the TOF technique. To date, however, only few studies have been published reporting the results of contrast-enhanced MRA validated against the reference standard DSA.[17] A recently published review concluded that MRA is highly sensitive and specific in diagnosing severe carotid artery stenosis (70-99%), however, that included studies were of poor and heterogeneous quality.[18] More importantly, they concluded that further research was essential to assess the diagnostic value of contrast-enhanced MRA. We recently developed a 3D CE-MRA technique that visualises the complete tract of the carotid artery from origin to the siphon within 10 seconds before venous return. The high resolution of 0.75 x 0.75 x 1.0 mm should potentially allow good visualisation of near-occlusions with high flow velocities in the internal carotid artery and decrease the effect of flow related artefacts.[19-21]
The aim of this study was to assess the accuracy and reproducibility of CE-MRA compared with 3D TOF MRA and the reference standard DSA in the diagnosis of carotid artery stenosis.

Methods

Study population

From June 1999 to May 2000, 51 consecutive patients were included in this prospective diagnostic study. All patients were suspected of having carotid artery stenosis and were screened with duplex ultrasound. If carotid endarterectomy was considered, patients subsequently underwent CE-MRA, 3D TOF MRA, and DSA examination within a period of maximum two weeks. Forty-nine patients had experienced symptoms of carotid artery disease (transient ischemic attack, minor disabling ischemic stroke, or amaurosis fugax) in the prior six months. The remaining 2 patients were asymptomatic: one was evaluated because of vertigo with a progressive stenosis on duplex examination, the other because of a stenosis found on duplex during work-up after endarterectomy of the anonyma. We excluded patients who had contraindications for MRA such as metal implants not suitable for MR or claustrophobia. All patients gave their written informed consent. Our study was approved by the medical ethical committee. The baseline characteristics of the patients are listed in Table 1.

Diagnostic tests and stenosis measurements

CE-MRA and 3D TOF MRA were performed on a 1.5-T MR imaging system (Gyroscan ACS-NT; Philips Medical Systems, Best, the Netherlands). For CE-MRA Bolus trak technology (Philips Medical Systems) was applied to determine the arrival of the contrast bolus in the carotid artery. This scan-protocol included an optimised centric profile order and a variable scan matrix. The scan parameters were: repetition time (TR) = 4.5 ms, echo time (TE) = 1.5 ms, flip angle = 40°, 70 slices, slice thickness = 0.4 mm, a variable scan matrix (reconstructed matrix 320 x 512) and a 256 x 140-mm^2 rectangular field of view. The contrast material used was a 5-mM solution of gadopentate dimeglumine (Magnevist, Schering). Imaging time was approximately 44 seconds. The actual resolution was 0.75 x 0.75 x 1.0 mm.
In the TOF protocol first a sagittal scout two-dimensional phase-contrast image with 30 cms^{-1} velocity encoding and two-dimensional TOF images (30 consecutive 4-mm-thick transverse sections) were acquired for localising the carotid arterial bifurcation and for planning the 3D TOF acquisition. A carefully planned 3D TOF MR angiographic acquisition was performed by using a radio-frequency spoiled gradient-echo sequence with 50 1-mm-thick transverse sections (interpolated to 100 sections), a superior saturation band, 31/6.9 (repetition time ms/echo time ms), a flip angle of 15°, flow compensation, a field of view of 120 x 80 mm, an imaging matrix of 256 x 256, and three signals acquired. Imaging time was approximately 9 minutes.

The TOF MRA protocol was always performed prior to the CE-MRA protocol, to avoid image disturbances due to remaining contrast. In both 3D TOF MRA and CE-MRA postprocessing subvolumes were generated to isolate each carotid artery and to create 12 MIP images that were radially projected at 15° increments (rotation about the long axis of the body).
Intra-arterial DSA was performed with a Philips Integris V3000 angiographic unit (Philips Medical Systems) with an image intensifier matrix of 1024 x 1024. By using the Seldinger technique, the tip of a 5-F catheter was guided from the common femoral artery to the ascending aorta and positioned in the right and, subsequently, in the left common carotid artery. Two or three projections (lateral, posteroanterior, and/or ipsilateral oblique) were acquired from each carotid bifurcation. For each projection 6 ml of contrast agent (Ultravist [300 mg of iodine per ml]; Schering) was injected at a flow rate of 3 ml/s.

The 3D TOF MRA, CE-MRA, and DSA results were read independently by two observers (O.E.E. and P.J.N.), with a period of at least one month between the readings. The tests were read with the observers blinded for clinical information and for the results of the other tests. ICA stenosis was measured on printed hard-copies according to the NASCET method (Stenosis=[1-(Minimal Residual Lumen/Distal ICA Lumen Diameter)] x 100%) by using a mechanical calliper with a digital display. On DSA the percentage ICA stenosis was measured on all available projections showing the ICA without overlapping vessels. From the twelve MR angiographic MIP images, the percentage ICA stenosis was assessed on three projections, coinciding with the vast majority of the IA-DSA projections used (lateral, posteroanterior, and 45° ipsilateral oblique). Flow void artefacts on 3D TOF MRA were defined as 85% stenosis.

Analysis

First, the data was analysed including two arteries per patient, i.e. both carotid arteries, to compare all stensosis measurements of CE-MRA and 3D TOF MRA with the reference standard DSA and of CE-MRA with 3D TOF MRA. Scatterplots were constructed and Pearson's correlation coefficients were calculated, according to the measurements of the first observer. Subsequently, for all three imaging tests the inter-observer variability was calculated using kappa statistics with categorised stenosis measurements: 0-29%, 30-49%, 50-69%, 70-99% and 100% (occlusion). In the second part of the analyses, to assess the accuracy of CE-MRA and 3D TOF MRA compared with the reference test DSA in the diagnosis of severe stenosis (70-99%), with regard to the decision making on carotid endarterectomy, we included only one carotid artery per patient, i.e. the symptomatic side, in the analyses. In the two asymptomatic patients that side was included on which carotid endarterectomy

was considered. We calculated the sensitivity and specificity with 95% confidence intervals (CIs) for the diagnosis of severe (70-99%) stenosis of CE-MRA and of 3D TOF MRA compared to DSA for both observers.
Finally, we recorded the frequency of flow related artefacts on 3D TOF MRA, and of possible tandem lesions on DSA and CE-MRA; i.e.stenosis >50% in the origin, in the siphon, or else in the tract of the carotid artery.

Results

Fifty-one consecutive symptomatic patients were included in the study (44 male, 7 female). The mean age of the study population was 64 years (range 39-88 years, SD 9.6). Baseline characteristics are summarised in Table 1. CE-MRA was of non-diagnostic quality in five patients. These cases were excluded from the analyses. Reasons for non-diagnostic quality were failure in the timing of contrast arrival and start of the scan, causing too much venous over-projection of the jugular vein for an adequate assessment of the degree of stenosis of the internal carotid artery. The 5 non-diagnostic CE-MRA procedures were performed in the first period of the study. After the first phase of our study failure in timing no longer occurred. The test results of the remaining 46 patients (92 arteries) could be included in the analyses.

Table 1. Baseline characteristics study population.

Characteristics (N=51)	
Age (years {range})	64 {39 88}
Male/Female (n)	44/7
Symptoms (%)*	
Amaurosis fugax / retinal	17
Transient ischemic attack	44
Stroke	35
Asymptomatic	4
Hypertension (%)	38
Cardiac history (%)	
Angina	18
Myocardial infarction	18
Bypass-surgery or PTCA	12
Peripheral arterial disease (%)	
Claudication	8
Surgery or PTA	13
Smoking (%)	
Smoker	58
Ex-smoker	18

* 0-6 months prior to inclusion

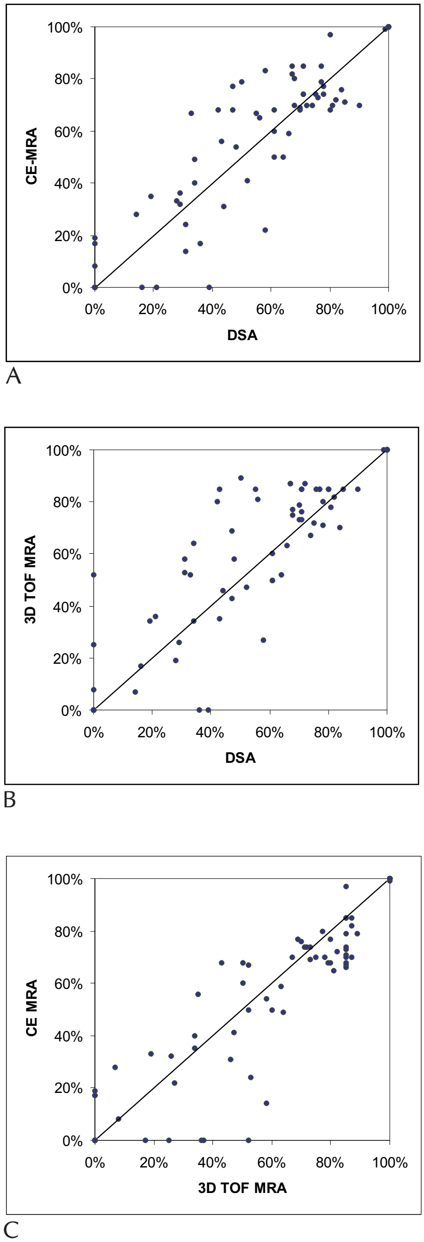

Figure 1. Scatterplots of the measured percentage of stenosis of all arteries by the first observer on CE-MRA versus on DSA (**A**), on 3D TOF MRA versus on DSA (**B**), and on CE-MRA versus on 3D TOF MRA (**C**). The Pearson's correlation coefficients were 0.94 ($p<0.01$), 0.92 ($p<0.01$), and 0.93 ($p<0.01$) respectively.

Figures 1 shows the scatterplots of the measured percentage of stenosis of all arteries by the first observer on CE-MRA versus DSA (Figure 1A), on 3D TOF MRA versus DSA (figure 1B), and on CE-MRA versus 3D TOF MRA (Figure 1C). The Pearson's correlation coefficients were 0.94 ($p<0.01$), 0.92 ($p<0.01$), and 0.93 ($p<0.01$) respectively. The kappa statistics reflecting the inter-observer variability between observer 1 and observer 2 were very good and similar for the three tests: 0.81 for CE-MRA, 0.79 for 3D TOF MRA, and 0.78 for DSA.

Table 2. Accuracies of CE-MRA and 3D TOF MRA compared with the reference test DSA in the diagnosis of severe stenosis (70-99%). Only the carotid arteries of the symptomatic are included (n=46).

Test	Observer 1				Observer 2			
	Sensitivity		Specificity		Sensitivity		Specificity	
	%	(95%CI)	%	(95%CI)	%	(95%CI)	%	(95%CI)
CE-MRA	**90**	(68-95)	**77**	(55-92)	**91**	(70-99)	**76**	(52-91)
3D TOF MRA	**86**	(67-97)	**73**	(50-89)	**90**	(68-99)	**77**	(51-92)

Stenosis measurements on CE-MRA compared with the reference standard DSA, with inclusion of the carotid arteries of symptomatic side only, yielded a sensitivity of 90% (95%CI, 68%-95%) and a specificity of 77% (95%CI, 55%-92%) in the diagnosis of severe stenosis (70-99%) for the first observer (Table 2). For 3D TOF MRA sensitivity and specificity were 86% (95%CI, 67%-97%) and 73% (95%CI, 50%-89%), respectively. The results of observer 2 were in a similar range and are listed in Table 2.

On 3D TOF MRA 6 flow voids were recorded, whereas on CE-MRA a flow related artefact near by the stenosis occurred in only one case. On DSA once we recorded a stenosis of >50% in the right common carotid artery in one patient, and once a stenosis of >50% in the left siphon in another patient. The diagnosis of both stenoses could be confirmed on CE-MRA, whereas the limited field of view of 3D TOF MRA did not allow visualisation of these parts of the carotid artery.

Discussion

Although we studied a relatively small study population of consecutive patients, CE-MRA shows promising preliminary results and appears an accurate test in the diagnosis of carotid artery stenosis. In our study CE-MRA yielded a sensitivity and specificity comparable to 3D TOF MRA in recognising severe stenosis (70-99%) compared to the reference test DSA.
MRA is increasingly used in imaging of carotid artery stenosis. In the last decade several studies have been published comparing MRA with DSA.[8-13] The most commonly applied technique in these studies was TOF MRA. In the last few years implementation of CE-MRA has been repeatedly suggested in the diagnosis of carotid artery stenosis.[14-16] CE-MRA of the carotid arteries is a recent development that could minimise signal loss and motion artefacts. By using an intravenous contrast bolus this technique allows shortening of T1 and a longer flip angle, generating a stronger signal with better background suppression and less signal saturation. Suppression of signal from the jugular vein overlapping the carotid bifurcation, however, has been one of the main drawbacks. Suppression can be achieved by scanning the carotid arteries within 10 seconds after enhancement (before venous return). Until recently, the poor resolution of three-dimensional methods, however, even on high-gradient hardware, did not allow accurate measurements of carotid stenosis.[19] Nowadays other methods for venous signal suppression, allowing longer scanning time and, hence, better spatial resolution are available.[22-24]

To date, however, only few studies have been published comparing CE-MRA with the reference test DSA in sufficient large populations.[17,19-21] In 1998 Slosman et al introduced a non-breath-hold 3D gadolinium enhanced MRA technique, but concluded after comparison with 3D TOF MRA and DSA in 50 patients that the technique could not yet be recommended in the diagnosis of carotid artery stenosis.[19] The main limitation was the difficulty with the timing of contrast arrival, and consequently the overprojection of the jugular veins, in about 30% of the carotids. Serfaty et al (2000) found a sensitivity and specificity of 94% and 85% respectively for 3D CE-MRA in a population of 48 patients. In their study 90% of the tests yielded good image quality. They concluded, however, that CE-MRA should not be used as stand alone but only in combination with duplex ultrasound instead of DSA.[17] Randoux ea. (2001) compared CE-MRA and DSA in 22 patients and found a sensitivity and specificity of 93% and 100% respectively.[20] Their conclusion was that CE-MRA could be an adequate substitute for DSA. In their series they found only 2 CE-MRA less than adequate for diagnosis. Recently Remonda (2002) compared first-pass CE-MRA with DSA in 120 patients and found agreement between both tests in 93%

in the detection of severe stenosis (70-99%).[21] The quality of CE-MRA images of all patients was graded as adequate for diagnosis.

We have recently developed a 3D CE-MRA technique that visualises the complete tract of the carotid artery from origin to the siphon. The technique uses an optimised centric profile ordering of the k-space, allowing data acquisition during the uptake of the arterial contrast media, ensuring improved resolution by exploiting the tail of the contrast signal and longer scanning, improved venous suppression and improved robustness to errors in timing. The high resolution of 0.75 x 0.75 x 1.0 mm and the use of optimised profile ordering should potentially allow good visualisation of near-occlusions with high flow velocities in the internal carotid artery and decrease the effect of flow related artefacts. As in other studies, the timing of arrival of the contrast bolus and start of the scan was the most crucial part in the introduction of this new procedure. With the implementation of a new technique the MR technologists, however, experience a learning curve. The 5 non-diagnostic CE-MRA procedures were performed in the first period of the study. After the first phase of our study failure in timing no longer occurred.

Our reported accuracies in the diagnosis of severe stenosis (70-99%) might seem relatively low compared with literature. However, one should realise that we included only the symptomatic arteries (i.e. one carotid per patient) in this part of our analysis, in contrary the cited studies in literature.[17,19-21] Including all arteries yields a higher specificity, due to the fact that the asymptomatic artery often shows a stenosis far beyond the cut-off point of 70%, and therefore will be often classified correctly by both tests in the comparisons. Including stenosis measurements of all arteries (both asymptomatic and symptomatic sides) in our data (observer 1) would result in a sensitivity of 90% and a specificity of 89% for CE-MRA. These numbers are in line with literature, and we can conclude that we found a similar accuracy for CE-MRA. It is preferable to investigate a larger population. Earlier, however, we performed a diagnostic study comparing 3D TOF MRA with DSA in 350 patients.[25] On basis of the results of this study we do not perform DSA routinely anymore in all patients in whom carotid endarterectomy is considered. Therefore, we no longer have the reference standard to our disposal in a consecutive patient series. This implies an important limitation in the validation of CE-MRA, and of any new technique in carotid artery imaging, with regard to the endarterectomy trials.
In our relatively small study-population, we could not find a significant difference in accuracy between 3D TOF MRA and CE-MRA. However, even if a larger population was to be investigated, it remains uncertain if possible advantages of CE-MRA over 3D TOF MRA can be reflected in a significantly different accuracy. For example,

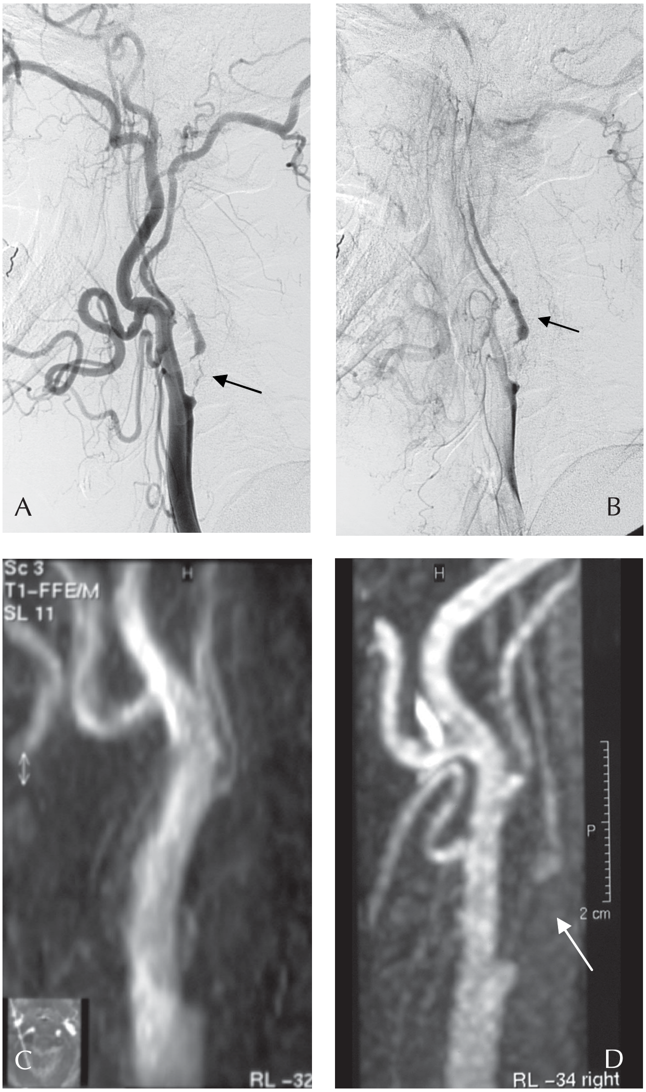

Figure 2. Example of a near-occlusion. **A)** Early DSA image of a right carotid artery. Distal to the bifurcation the nearly occluded lumen of the internal carotid artery (ICA) is visible. **B)** Late DSA image. More contrast appears in the remaining lumen of the ICA. **C)** 3D TOF MRA: ICA was diagnosed as occluded (with scoring blinded for the other test results). Retrospectively, a very low signal could perhaps have been recognised. **D)** Remaining lumen visible on CE-MRA near by and distal to the near-occlusion.

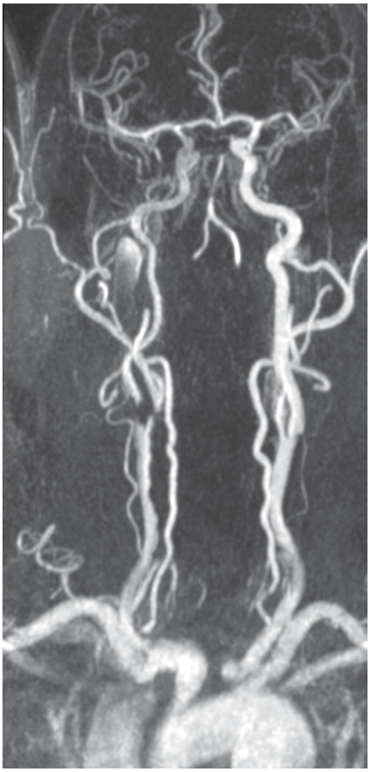

Figure 3. Visualisation of origin and intra-cranial part of the carotid arteries on CE-MRA.

with CE-MRA the occurrence of flow void artefacts strongly diminishes. Because flow voids on 3D TOF MRA occur in approximately 15% of the imaged arteries, and are classified correctly as severe stenosis (70-99%) in 85% of the cases, the number of patients needed to find a significant difference between the two techniques would be more that one thousand.[26] However, there certainly is a clinical advantage in the availability of good morphology of severely stenosed arteries provided CE-MRA. Furthermore, in our study CE-MRA correctly classified all occlusions. Figure 2 represents a case in which 3D TOF MRA yielded a false positive occlusion, whereas CE-MRA visualised the nearly occluded lumen of the internal carotid artery similarly to the images of the reference test DSA. Finally, as DSA, CE-MRA allows visualisation of a long tract of the carotid artery from origin to siphon (Figure 3). In a preliminary evaluation, the two additional lesions diagnosed with DSA (one in the carotid origin and the other in the intra-cranial siphon), could be confirmed with CE-MRA. The accuracy of CE-MRA in recognising tandem-lesions was not studied properly yet. Although the effect of additional morphological information of tandem lesions on the results of carotid endarterectomy has not yet been entirely studied, it is certainly often taken into account in the decision on carotid endarterectomy in individual cases.[27]

In conclusion, CE-MRA seems a promising new technique in the imaging of carotid arteries. First results show a similar accuracy to 3D TOF MRA in diagnosing severe stenosis. Our reported diagnostic accuracy is comparable with recent literature. Preferably CE-MRA should be compared with DSA in a larger study population. To date, however, DSA is often not performed routinely anymore in all patients in whom carotid endarterectomy is considered. Therefore, an exact estimate of the accuracy of CE-MRA compared with DSA, with regard to the results of the carotid surgery trials, remains unsolved.

CE-MRA shows possible clinical advantages over 3D TOF MRA. The technique provides additional morphological information about the origin and intra-cranial part of the carotid artery. Flow related artefacts are strongly diminished. Slow blood flow in nearly occluded lumen still provides recognisable signal. The distinction between occluded and nearly occluded vessels remains of crucial importance with regard to the decision to perform carotid endarterectomy.

Acknowledgement

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Chapter 8

Patient preferences for duplex ultrasound, MR angiography and digital subtraction angiography in carotid artery imaging: a short report

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Submitted

Introduction

Non-invasive tests, such as duplex ultrasound (DUS) and magnetic resonance angiography (MRA) are increasingly used in the work-up of patients suspected of having carotid artery stenosis in replacement of, or in addition to digital subtraction angiography (DSA).[1,2] The decision on which test or which combination of tests is applied is predominantly made on basis of the diagnostic accuracy, possible complication rate, and cost-effectiveness considerations.[3,4] When forming study-cohorts for diagnostic studies, selection due to absolute contra-indications of patients for a particular test have to be taken into account. For example, claustrophobic patients, or patients with other contra-indications such as metal implants, will not undergo MRA examination. Thus, considering these absolute contra-indications, the analyses and the results of a diagnostic study should reflect a setting consistent with daily clinical practice. However, discomfort of particular modalities that do not necessarily preclude performing the imaging test, and, subsequently, patients' possible preference for other imaging tests, are generally not taken into account in the interpretation of the results of a diagnostic study. In clinical practice, discomforts such as for example confined space for MR imaging, hospitalisation for DSA, or the time a patient is confined to bed after DSA, might be decisive factors for the decision for a particular imaging modality in individual cases. Two earlier studies showed that patients undergoing imaging for peripheral arterial disease experienced more discomfort due to DSA than to MRA.[5,6] As part of a diagnostic study, including nearly 400 patients who all underwent DUS, MRA, and DSA imaging, to asses the diagnostic accuracy of non-invasive testing, patients received a questionnaire about their experiences with the particular imaging tests. The aim of this paper is to present patient preferences and test related discomforts for DUS, MRA, and DSA.

Patients, Methods and Results

From January 1998 to November 2000, a consecutive sub-population of 215 patients, part of a larger study-cohort, received a questionnaire on their preferences for and possible discomforts due to DUS, MRA, and DSA. In the study, after initial screening with DUS, all patients subsequently underwent MRA and DSA examination if carotid endarterectomy was considered. Patients with contra-indications for MRA such as claustrophobia or metal implants not suitable for MR were excluded. DUS, MRA and DSA were performed within a period of maximum four weeks.Unless patients were hospitalised for planned carotid surgery, DUS and MRA imaging were performed on an outpatient basis. For DSA the patients were always hospitalised for at least one night. Imaging protocols are described in detail elsewhere.[7] The patients filled in the questionnaire at home after all imaging tests were performed and returned them by mail.

The questionnaire was completed and returned by 134 patients (response rate 63%). On the question 'which test is most bothersome?' 71% (95/134) of the patients answered DSA, 25% (33/134) MRA, none (0/134) DUS, and 4% (6/134) gave no answer. On the question 'which test is least bothersome?' 84% (113/134) of the patients answered DUS, 10% (14/134) MRA, 2% (2/134) DSA, and 4% (5/134) gave no answer. On a continuous scale from 0 (not bothersome at all) to 60 (very bothersome), patients median grade for DUS was 0 (SD 5.2), for MRA 10 (SD 15.5), and for DSA 20 (SD 18.7) (figure 1). The three ratings were all significantly different from each other (Wilcoxon signed-rank test: p<0.001). Subsequently, patients were asked to rate possible test related discomforts on the same continuous scale from 0 to 60. Generally, possible discomforts of DUS were ranked lower than for MRA and/or DSA. The results of the mean rating of the different variables are listed in Table 1. Of each variable, the Spearman's correlation coefficient is listed, indicating the relation of possible discomforts with the overall rating score of the test. All relations were significant (p<0.01).

Table 1. Experienced test related discomforts and correlation with the overall rating score of DUS, MRA and DSA.

	N	Mean rating (0-60) !	SD	Sp-r
DUS				
Endurance	133	2.7	6.5	0.57*
Painful or discomforting sensations	131	1.7	4.2	0.55*
Enclosed feeling	131	2.6	7.8	0.50*
MRA				
Endurance	131	9.1	12.0	0.58*
Noise	132	15.2	16.6	0.61*
Enclosed feeling	132	13.3	16.5	0.55*
DSA				
Endurance	134	15.2	17.0	0.57*
Warm and/or painful sensations	133	17.3	16.7	0.65*
Hospitalisation	133	12.6	16.6	0.33*
Confined to bed for several hours afterwards	134	23.9	21.1	0.58*
Enclosed feeling	131	9.3	14.8	0.40*

SD = standard deviation
† Number of respondents on particular question
‡ Continuous scale from 0 (not bothersome at all) to 60 (very bothersome)
¶ Spearman□s relation coefficient, indicating correlation with overall rating score of the particular test.
* Statistically significant (p<0.01).

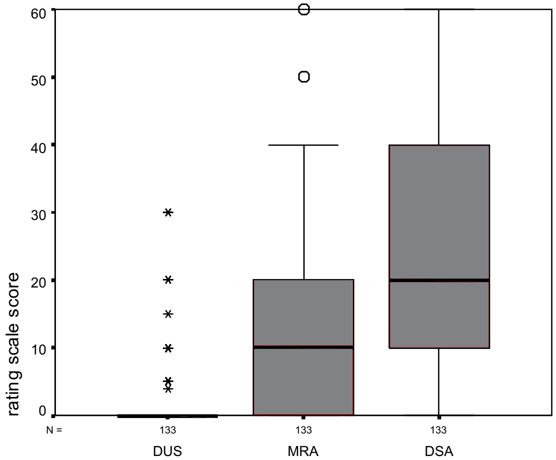

Figure 1. Box and whisker plot for the overall rating score for DUS, MRA and DSA. Patients (N=134) graded the imaging tests on a continuous scale from 0 (not bothersome at all) to 60 (very bothersome).

The lower and upper lines of the box correspond with the first and third quartiles. The bold line corresponds with the median. The vertical line represents less than 1.5 times the interquartile range from the first and the third quartiles. Outliers (O) are defined as more tan 1.5 times and extremes (*) are defined as more than 3 times the interquartile range outside the box.

Comment

We found a statistically significant order in patients' preference for the particular tests in carotid artery imaging. Patients that underwent all three imaging modalities reported hardly any burden of DUS. DSA was graded more bothersome than MRA. Variables explaining possible discomforts for each of the three tests were significantly related to the overall rating scores. Our findings are consistent with two earlier studies reporting that patients undergoing imaging for peripheral artery disease experienced more discomfort due to DSA than to MRA.[5,6] In the latter (Visser ea.), DUS was also evaluated, however, was graded more bothersome than MRA.
The main limitation of our study is the fact that patients with claustrophobia as contra-indication for MRA (3%), were excluded from our diagnostic study. The burden of MRA, therefore, was underestimated. However, the difference with DSA was large and we have reason to believe that patients still experience DSA as more bothersome, even after taking this selection bias into account. Furthermore, still 25% of the included patients answered that they found MRA the most bothersome test, i.e. more bothersome than DSA.

In DUS and MRA the reported test related discomforts are comparable. In MRA, particularly the noise was reported to be bothersome. In DSA, as we expected, the overall rating was related to the warm and painful sensations during the contrast injections. However, the confinement to bed for several hours after performing DSA was also reported as bothersome. The latter is recognised by clinicians as an important factor explaining discomfort. Remarkably, discomfort due to hospitalisation, showed the lowest correlation coefficient.

In our previous work we concluded, based on diagnostic accuracies of non-invasive tests and on cost-effectiveness considerations, that DSA should not be performed routinely anymore in all patients suspected of having carotid artery stenosis.[4,7] The current analysis of patient preferences supports this conclusion.

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Chapter 9

General discussion

The aim of this thesis was to evaluate whether non-invasive tests could replace intra-arterial digital subtraction angiography (DSA) in the diagnosis of carotid artery stenosis. To obtain reliable estimates of the diagnostic accuracy of duplex ultrasound (DUS), magnetic resonance angiography (MRA), and a combination of these tests, we performed a diagnostic study with DSA as reference, including nearly 400 patients in the period from 1997 to 2000. Subsequently, we performed a comprehensive cost-effectiveness analysis.

In the literature very good accuracies of non-invasive tests such as DUS and MRA have repeatedly been reported. In our systematic review, summarising literature published between 1994 and 2000 (Chapter 2), we reported a pooled weighted estimate of the sensitivity and specificity in the diagnosis of severe stenosis (70-99%) for DUS of 86% and 87% respectively. For MRA the pooled sensitivity was 95%, the specificity 90%. As we concluded in Chapter 3, the accuracies for non-invasive testing obtained from our own diagnostic study (Table 1) might seem relatively low compared to the literature. We found the highest diagnostic performance for a combination strategy of DUS and MRA, which yielded a sensitivity of 96% and a specificity of 80%. However, the results of this strategy apply only for a sub-population in which DUS and MRA show agreement (85% of the patients), implying that in approximately 15% of the patients DSA should still be considered. Sensitivity and specificity for DUS as sole tests were 88% and 76%, and for MRA 92% and 76%, respectively.

Table 1. Diagnostic accuracies of the non-invasive tests DUS, MRA, and the combination strategy (DUS=MRA) in recognising severe stenosis (70-99%) in the internal carotid artery (ICA), using DSA as the standard of reference.

	Sensitivity		Specificity		Positive predictive value		Negative predictive value	
	%	(95%CI)	%	(95%CI)	%	(95%CI)	%	(95%CI)
DUS	87.5	(82.1-92.9)	75.7	(69.3-82.2)	75.4	(68.9-82.0)	87.7	(82.3-93.0)
MRA	92.2	(86.2-96.2)	75.7	(68.2-96.2)	76.3	(69.6-83.0)	92.0	(85.8-96.1)
DUS&MRA	96.3	(90.8-99.0)	80.2	(73.1-87.3)	81.2	(74.5-88.0)	96.0	(90.2-98.9)

The presented results give rise to two important questions: why did we find a lower diagnostic performance than previously reported in the literature, and what does this mean for clinical practice? In our opinion, the accuracies we reported can be considered valid and realistic for three reasons. First, for a thorough evaluation of a diagnostic test an adequately powered study, using a prospective design and a consecutive study-population, is mandatory. Such a study is likely to be large and time-consuming. Recently a review of 132 previous publications of diagnostic studies on carotid artery imaging published between 1993 and 1998 criticised the design of the majority of these studies.[1] Particularly, the number of patients included in those studies often was too small to justify the conclusions about the diagnostic performance. While collecting the data for our meta-analysis (Chapter 2) we could confirm this finding. We think that including a large consecutive population and collecting the data prospectively provides realistic results.

Another explanation is that we report on the test results of the carotid artery on the symptomatic side in the analyses. Since it is the symptomatic artery for which a decision on performing endarterectomy has to be made, excluding the asymptomatic side reflects clinical practice. Only few studies in literature have presented their diagnostic data similarly. Previously published reports generally also included the asymptomatic carotids of the contralateral side. The majority of the arteries on the asymptomatic side show a stenosis percentage far below the 70% threshold or no stenosis at all, making it more likely for the different tests to agree. In this way the number of true negative results inflates and thus the specificity may be overestimated in those studies. For example, in our data the specificities increased by 10.7% for DUS and 14.2% for MRA if the stenosis measurements of all arteries were included.

Finally, it is very important to realise that in a diagnostic study a new test by definition never exactly agrees with the reference test.[2] If measurements of DSA examinations of the same group of patients were to be repeated by the same observer, we would still certainly find variability in results. In other words, even a theoretically perfect test will never yield perfect test results. The aim of a diagnostic study should not be to achieve the highest possible accuracy. The more relevant question is to what extent a new test under investigation differs from the reference test and what implications this has on the outcome of clinical decisions for individual patients.

If we assume that the accuracies we reported are valid and realistic, what do they mean for clinical practice? In other words, do the results allow replacement of DSA by non-invasive testing? It is not easy to answer this question unambiguously. Reporting the false positive and false negative rates only is, in our opinion, not sufficient to completely understand the consequences of implementing a new test in clinical practice. Additionally, the results of a cost-effectiveness analysis should be taken into account to understand the true implications of introducing non-invasive testing. From the limited published evidence available, the cost-effectiveness of carotid endarterectomy and of the preoperative investigations remained unclear.[3] We found (Chapter 4) that the expected lifetime costs and quality adjusted life

years (QALYs) were almost equal for DUS and MRA, as well as for the combination strategy. The traditionally used strategy of DSA implies higher costs and a small loss of QALYs (Table 2). Although the difference with the non-invasive strategies appears limited, DSA results in a small but significant number of additional complications (i.e. strokes or deaths). Compared to the total number of evaluated patients the number of complications is relatively small. However, the reported loss in QALYs is substantial if the results are extrapolated to the total patient population. In the three non-invasive strategies additional costs are incurred because selection for carotid endarterectomy is assumed to be sub-optimal, i.e. the number of outcome events in the follow-up increases due to the false-positive and false-negative test results. The tests themselves, however, are less expensive and do not carry the risk of complications. In the combination strategy the assumption is made that patients undergo DSA in case of disagreement, giving a small complication rate as well.
From the societal perspective, based on our models, DUS alone would be the strategy of choice. From the perspective of an individual patient, however, the differences between the non-invasive strategies are small, and it could be justifiable to select the most accurate one. From the clinical point of view it seems attractive to add MRA to DUS. As said before the combination strategy provides a higher diagnostic performance and therefore is the most accurate replacement for DSA for an individual case. In addition, MRA provides more morphological information. Surgery results might very well improve if additional information about possible tandem lesions is available, however, this has never been investigated. Furthermore, DUS test results are operator dependent and not all laboratories will achieve the same level of diagnostic performance. Finally, we should realize that if DUS would be used as stand alone, unlike MRA or the combination of DUS and MRA, its test results as presented in this thesis suffer from verification bias.

Table 2. Cost-effectiveness of the four clinically most relevant test strategies.

Strategy	Costs (Euro)	QALYs (Quality Adjusted Life Years)
DUS	28,040	11.30
MRA	28,270	11.30
Combination DUS & MRA	28,540	11.29
DSA	30,360	11.22

Verification bias may exist if the decision to perform the reference standard procedure depends on the results of the test under investigation.[4] In our study, patients were often screened with DUS in the clinical setting prior to inclusion. Based on ethical grounds, inclusion in the study depended on the decision of the clinician to perform DSA if CEA was considered. Accuracy of DUS related to the 70% stenosis threshold was estimated afterwards among patients selected for DSA. The tabulations show that all categories of degree of stenosis are present, although the majority has a moderate or severe stenosis. The sensitivity may be lower, and specificity higher, after adjustment for this bias.
If subsequently MRA is performed in all patients, however, it is precisely this selected group of patients, suspected of having ICA stenosis at DUS examination, that constitutes the right domain to answer our study objective, reflecting the population for which the decision on surgery has to be made in daily clinical practice. Therefore, the accuracy of MRA, as described in Chapter 2, is not biased. However, it is important to realise that if DUS would be performed as sole test in clinical practice, the calculated sensitivity and specificity are influenced by verification bias and do not reflect the best estimate.
At the start of our study the time-of-flight technique was the state-of-the-art technique for MRA for imaging of the carotid arteries. The introduction of contrast-enhanced MRA (CE-MRA) was an important step in the development of MRA techniques during our study.[5] Imaging techniques and protocols develop continuously. While performing a study of a diagnostic test over a period of several years, the state-of-the-art imaging protocol most certainly changes. In diagnostic studies it is tempting to switch to a novelty and publication of preliminary results of a new technique often is appealing. However, if new protocols were to be adapted within the period of the study, the size of the study cohort undergoing one and the same test diminishes, which is a limitation in the assessment of valid test results. If multiple changes are adapted successively, even if they are small, a summarised estimate of the accuracy of a test could become invalid. Development of new techniques should not tempt the investigators to abandon their initially defined imaging protocol. In our opinion the only correct solution is to maintain the initial protocol, and eventually to add new protocols or tests to the standard protocol. This allows an evaluation of the improved protocol in a sub-population, while maintaining the possibility of a more precise estimate of the initial technique.

One of the limitations of the 3D TOF technique was the occurrence of flow void artefacts, particularly in severely stenosed carotids (Chapter 6). We reported a frequency of 16% of flow void artefacts in imaging carotid arteries with 3D TOF MRA. CE-MRA shows possible clinical advantages over 3D TOF MRA. The technique provides additional morphological information about the origin and intra-cranial part of the carotid artery. Flow related artefacts are strongly diminished. Slow blood flow in nearly occluded lumen still provides recognisable signal. The distinction between occluded and nearly occluded vessels remains of crucial importance with regard to the decision to perform carotid endarterectomy. After a learning period we added CE-MRA to our standard MRA protocol in the last period of our study instead of replacing it. We were therefore able to assess a preliminary estimate of the accuracy of CE-MRA in a subgroup of 40 patients (Chapter 7). However, we realise that a cohort of this size only allows preliminary results. Although we certainly experienced advantages of CE-MRA compared with 3D TOF MRA, such as decrease of flow related artefacts and possibility of visualising the aortic arch and intra-cranial vessels, the estimates of the sensitivity and specificity yielded relatively large confidence intervals. Only DUS, 3D TOF MRA, and their combination could be investigated elaborately in the time-span of our study. Because we do not perform DSA routinely anymore in all patients in whom carotid endarterectomy is considered, based of the results of the main study, we will no longer have the reference standard to our disposal in a consecutive patient series. This implies an important limitation in the validation of CE-MRA, and of any new technique in carotid artery imaging, with regard to the endarterectomy trials.

Other techniques that were not investigated in this thesis may also play a more important role in the near future. The use of computer tomographic angiography (CTA), for example, could increase.[6] We chose not to investigate this technique in a large cohort, because of its limitations compared with MRA, such as problems in assessing the exact degree of stenosis due to plaque calcifications. New developments, however, such as the use of multi-detector CT scanners, might improve this technique. Limitations in validation of this technique as with CE-MRA, due to absence of the reference test in a consecutive population, will remain.
It is difficult to predict the future role of DUS. In the future more patient related characteristics, for example infarct size or location, or presence of collateral blood flow, could play an additional role, besides the assessment of the degree of stenosis of the carotid artery, in the decision to perform carotid surgery. Consequently, it is conceivable that MR protocols further expand and that symptomatic patients will directly undergo an even more extensive program including MR imaging of the brain and MR angiography of the cerebral circulation. Furthermore, recent publications have shown that subgroups of patients with a 50-69% stenosis may also expect a small benefit from carotid endarterectomy.[7] Although the diagnosis of severe stenosis (70-99%) will remain crucial for the majority of patients, we expect that in the future more patients with a moderate (50-69%) stenosis will be operated. The question will be whether it will still be useful to perform preceding DUS examination, if additional imaging would be requested for a larger part of the patient

population. On the other hand, DUS is an inexpensive and widely available test for initial screening in patients suspected of having carotid artery stenosis. In addition, patients prefer DUS examination to other tests and they experience little discomfort (Chapter 8).

A final point of interest is that the decision on surgery, based on the results of the carotid endarterectomy trials, is mainly made on basis of the degree of stenosis. Moreover, the cut-off points for stenosis, obtained from the trials, are strictly defined. Unfortunately, this precludes a meaningful analysis of the percentage of stenosis as a continuous variable. Theoretically, the percentage of stenosis could be included in a model as a risk factor, together with the other patient characteristics, that nowadays become increasingly important in the decision on carotid surgery and should be taken into account. Furthermore, in such a model the time-span between the test and the symptoms could also be included, and by doing so the strict distinction between asymptomatic and symptomatic patients could possible be abandoned. To date, a patient is considered symptomatic if neurological symptoms were experienced strictly within six months prior to the evaluation. The effect of carotid surgery on asymptomatic patients according to this definition remains unclear, but ongoing trials will present their results on this topic in the near future.

In clinical practice, based on the results of this study, we no longer perform DSA routinely in symptomatic patients suspected of having a carotid artery stenosis after screening with DUS. Particularly with knowledge of the results of the cost-effectiveness analysis, and with regard to the limitations of a diagnostic study, the presented results, in our opinion, yield enough evidence to decide not to perform DSA routinely anymore in all patients. To date, after initial screening with DUS, we always perform MRA in our non-invasive strategy. In our opinion patients should now only undergo DSA in those cases where considerable doubt persists about the indication for carotid endarterectomy after DUS and MRA examination, for example in case of clear disagreement between these two tests, or when additional morphological information about origin of the common carotid artery or about intra-cranial vessels is necessary to make the right decision on performing endarterectomy. In the majority of patients, however, DSA can safely be replaced by the combination of DUS and MRA.

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Chapter 10

Summary

The aim of this thesis was to determine if digital subtraction angiography (DSA) could be replaced by non-invasive testing. *Chapter 1* gives a general introduction, illustrating the background of this objective. Carotid endarterectomy was shown to be beneficial in symptomatic patients with a severe stenosis (70-99%) of the internal carotid artery (ICA) in two large randomised trials. Increasing degree of stenosis yielded increasing benefit from surgery, making precise estimation of the degree of stenosis very important. In the trials the degree of stenosis was assessed with DSA, which consequently has become the standard of reference in the selection of patients for carotid endarterectomy. DSA, however, has a relatively high risk of morbidity and mortality, which decreases the potential overall benefit of endarterectomy. To date, non-invasive tests, such as duplex ultrasound (DUS) and magnetic resonance angiography (MRA), are increasingly used in the diagnosis of carotid artery stenosis. These tests do not carry the potential risk of complications. However, with regard to the results of the carotid surgery trials, it remains very important that the correct group of patients is selected by new test strategies. In a diagnostic study and a cost-effectiveness analysis we investigated the consequences of implementation of non-invasive testing for individual patients and from a societal perspective.

In *Chapter 2* the published data in the literature from 1994 to 2001 on the diagnostic value of DUS and MRA in the diagnosis of carotid artery stenosis is systematically reviewed. Publications were only included in this meta-analysis if DSA was used as the reference test in the presented study. For the diagnosis of severe stenosis (70-99%), MRA had a pooled sensitivity of 95% and a pooled specificity of 90%. For DUS these numbers were 86% and 87%, respectively. A multivariable summary ROC analysis demonstrated that the type of MR scanner and the type of DUS scanner predicted the diagnostic performance. For DUS this phenomenon is known, whereas for MRA this finding has not been described before. Furthermore, for DUS the presence of verification bias predicted the diagnostic performance. Verification bias may exist if the decision to perform the reference test depends on the results of the test under investigation. The results suggest that MRA has a better discriminatory power compared with DUS in diagnosing 70-99% stenosis and is a sensitive and specific test compared to DSA in the evaluation of carotid artery stenosis.

In *Chapter 3* the diagnostic study we performed is described. From January 1997 to November 2000, 350 consecutive symptomatic patients suspected of having carotid artery stenosis were included. After initial screening with DUS, the patients underwent both MRA and DSA examination. All patients in this study had experienced symptoms of carotid artery disease (transient ischemic attack, minor disabling ischemic stroke,

or amaurosis fugax) in the six months prior to inclusion. Both DUS and MRA seemed accurate diagnostic tests to detect carotid artery stenosis. In combining test results, agreement in diagnosing severe stenosis (70-99%) between DUS and MRA (84% of the patients) yielded a high sensitivity and specificity. Both DUS and MRA had the tendency to overestimate stenosis compared with the standard of reference DSA. Our reported accuracies of DUS and MRA might seem relatively low compared with other studies. However, we feel that our prospective design and inclusion of a relatively large study population added to valid and unbiased estimates. Another explanation is the fact that we only included the test results of the carotid artery on the symptomatic side in the analyses, yielding lower accuracies. In literature often test results of both carotid arteries are included in the analyses. However, since it is the symptomatic artery for which a decision on performing endarterectomy needs to be made, excluding the asymptomatic side reflects clinical practice. In clinical practice, based on the results of the diagnostic study, we no longer perform DSA routinely in symptomatic patients suspected of having a carotid artery stenosis after screening with DUS.

To be able to understand the consequences of implementation of non-invasive imaging strategies from a societal perspective, a valid estimate of the diagnostic value is not sufficient. Additionally to the diagnostic study, a cost-effectiveness analysis was performed, which is presented in *Chapter 4*. First, an all including calculation on the costs of the diagnostic tests and carotid endarterectomy was carried out. Additional data on long-term costs, survival, and quality of life related to stroke were retrieved from the published literature. Secondly, the long term outcomes required for the cost-effectiveness analysis were assessed by means of a Markov model. Finally, a comprehensive analysis was performed using a decision model, in which all the different combinations of the diagnostic tests could be compared. We concluded that, from a societal perspective, DUS without additional imaging is the optimal diagnostic strategy to select patients for carotid endarterectomy in terms of cost-effectiveness. The results of DUS, however, could be influenced by verification bias. A combination strategy of DUS and MRA to select patients for carotid endarterectomy yields a slight benefit in terms of clinical outcome, however, at relatively high additional costs. DSA was more expensive and less effective than all evaluated non-invasive strategies.

In *Chapter 5* a possible explanation for the overestimation of MRA compared to DSA was investigated. Three-dimensional time-of-flight (3D TOF) MRA is generally considered to overestimate the degree of stenosis in the ICA in comparison with the reference standard DSA. Several mostly technical explanations have been described in literature. Often, the shape of the stenosed lumen of the artery, however, is not circular. DSA, the reference test based on the carotid surgery trials, is according to their protocol performed in two or three projections (lateral, posteroanterior, and/or oblique). In MR imaging of the carotid artery, however, often 12 directions of the vessels are reconstructed and available for the assessment of the stenosis. We found that if corresponding MR angiographic and intra-arterial DSA projections are compared, instead of comparing maximum stenosis at MRA on 12 projections with maximum stenosis at DSA on the standard three projections, 3D TOF MR angiography did not overestimate carotid stenosis. The effect of overestimation decreased when the degree of stenosis increased.

The time-of-flight MRA technique (TOF) was commonly used to visualise the carotid arteries at the start of our study. As described in *Chapter 6*, the appearance of flow void artefacts, especially in severely stenosed arteries, is one of the drawbacks of this modality. Most diagnostic studies on MRA use the assumption that a flow void represents severe stenosis (70-99%), based on technical explanations. In the patient data we validated the occurrence of this kind of artefact. We found a frequency of 16% of flow void artefacts in visualising carotid arteries with 3D TOF MRA. The positive predictive value of a flow void artefact for presence of severe stenosis (70-99%) was 84,3% according to the reference standard DSA. The median percentage of stenosis was 80%, with a range of 36% to 100%. In this clinical study flow void artefacts represented severe stenosis in the vast majority of the arteries.

For a valid throughout evaluation of a new imaging technique an adequately powered study is mandatory. However, such a study is likely to be large, expensive and time-consuming, precluding application of the newest imaging protocols. Recently, however, we also introduced CE-MRA supplemental to the time-of-flight protocol, allowing us to estimate its accuracy in a subgroup of patients and preliminary findings are presented in *Chapter 7*. CE-MRA seems a promising new technique in the imaging of carotid arteries. First results show a similar accuracy to 3D TOF MRA in diagnosing severe stenosis. CE-MRA shows possible clinical advantages over 3D TOF MRA. The technique provides additional morphological information about the origin and intra-cranial part of the carotid artery. Flow related artefacts are strongly diminished. Slow blood flow in nearly occluded lumen still provides recognisable signal. The distinction between occluded and nearly occluded vessels remains of crucial importance with regard to the decision to perform carotid endarterectomy. Preferably, CE-MRA should be compared with DSA in a larger study population. To date, however, DSA is often not performed routinely anymore in all patients in whom carotid endarterectomy is considered. Therefore, an exact estimate of the accuracy of CE-MRA compared with DSA, with regard to the results of the carotid surgery trials, remains unsolved.

Finally, in *Chapter 8*, we investigated patients' preferences for DUS, MRA, and DSA. As part of the diagnostic study, patients received a questionnaire about their experiences with the particular imaging tests. Patients that underwent all three imaging modalities reported hardly any burden of DUS. DSA was graded more bothersome than MRA. Variables explaining possible discomforts for each of the three tests were significantly related to the overall rating scores. In DUS and MRA the reported test related discomforts are comparable. In MRA, particularly the noise was reported to be bothersome. In DSA, as we expected, the overall rating was related to the warm and painful sensations during the contrast injections. However, the confinement to bed for several hours after performing DSA was also reported as bothersome. The latter is recognised by clinicians as an important factor explaining discomfort. Remarkably, discomfort due to the hospitalisation with DSA, showed the lowest correlation coefficient.

In *Chapter 9* the methodological limitations of a diagnostic study are discussed, as for example the consequences of inclusions of the carotids of the symptomatic side in the analysis only, or the effect of verification bias on DUS results. The expected further developments in carotid artery imaging are discussed, as well as the fact that other patient characteristics than the degree of stenosis only might play a more important role in the future in the decision on carotid endarterectomy. In clinical practice, based on the results of this study, we no longer perform DSA routinely in symptomatic patients suspected of having a carotid artery stenosis after screening with DUS. Particularly with knowledge of the results of the cost-effectiveness analysis, and with regard to the limitations of a diagnostic study, the presented results, in our opinion, yield enough evidence to replace DSA by the combination of DUS and MRA as standard evaluation. In our opinion patients should now only undergo DSA in those cases where considerable doubt persists about the indication for carotid endarterectomy after DUS and MRA examination, for example in case of clear disagreement between these two tests, or when additional morphological information about origin of the common carotid artery or about intra-cranial vessels is necessary to make the right decision on performing endarterectomy. In conclusion, in the majority of patients, DSA can safely be replaced by the combination of DUS and MRA.

Chapter 11

Nederlandse samenvatting

Hoofdstuk 1 geeft een introductie van de achtergrond bij de vraagstelling van dit proefschrift. In het verleden is in twee grote gerandomiseerde onderzoeken aangetoond dat een operatie van de halsslagader (arteria carotis interna) waarbij de atherosclerotische plak wordt verwijderd nuttig is bij patiënten met een vernauwing (stenose) van meer dan zeventig procent. Tevens dienen de patiënten neurologische symptomen gehad te hebben passend bij de stenose. Van patiënten met een carotis stenose die daarvan geen symptomen hebben ondervonden is nog niet goed bekend of ze baat hebben bij een operatie. Dit wordt momenteel nog bestudeerd. Als zo'n carotis desobstructie operatie plaatsvindt bij een patiënt met een stenose van meer dan zeventig procent is in de jaren daarna zijn risico op het krijgen van een beroerte verminderd. Digitale subtractie angiografie (DSA) is de gouden standaard of referentie test voor het diagnosticeren van zo'n stenose. Bij dit onderzoek wordt er een katheter via een kleine snee in de lies via de lichaamsslagader naar de halsslagader opgevoerd en er wordt contrast vloeistof ingespoten. Echter, omdat dit een invasief onderzoek is, waarbij noodgedwongen met de katheter in de halsslagader wordt gemanipuleerd, geeft het zelf een geringe kans op het krijgen van neurologische complicaties. Al langer werd duplex geluids-onderzoek (DUS) gebruikt voor een eerste screening op de aanwezigheid van een carotis stenose. Intussen werd het ook mogelijk om met een MRI scanner een MR angiografie (MRA) te verrichten. Deze beide testen zijn niet invasief en hebben daarom niet zoals DSA het risico op complicaties. Het doel van dit proefschrift was om aan de hand van de resultaten van een diagnostische studie met daaraan gekoppeld een kosteneffectiviteit studie te bepalen of DSA vervangen kon worden door DUS, MRA of een combinatie van deze testen.

In *Hoofdstuk 2* wordt de reeds bestaande literatuur over dit onderwerp uit de periode van 1994 tot 2001 samengevat. In een meta-analyse werden alle artikelen bestudeerd met een studiepopulatie van meer dan 15 patiënten waarin MRA of DUS werden vergeleken met de referentie test DSA. Zodoende konden de gemiddelde diagnostische waarden voor de diagnose van de carotis stenose van de niet invasieve testen worden geschat. Voor DUS werden een gepoolde sensitiviteit van 86% en een gepoolde specificiteit van 87% gevonden. Een sensitiviteit van 86% betekent dat DUS van de 100 ernstige vernauwingen er 86 opspoort. Van de 100 slagaders die niet ernstig vernauwd zijn wijst DUS er 87 als zodanig aan (specificiteit). Voor MRA waren deze waarden respectievelijk 95% en 90%. Deze getallen geven aan dat beide testen geschikt lijken te zijn voor de diagnose van een ernstige carotis stenose (70-99%). In een aanvullende analyse werd aangetoond dat voor DUS de resultaten uit de literatuur mogelijk beïnvloed zijn door verificatie bias. Verificatie bias speelt in diagnostische studies een rol als alleen patiënten met een positieve testuitslag voor aanvullende diagnostiek in aanmerking komen. Dit is een bekend probleem als DUS met de invasieve angiografie wordt vergeleken, omdat men patiënten met een kleine kans op een ernstige afwijking niet wil blootstellen aan een invasieve test. De diagnostische waarden in de verschillende studies werden zowel bij DUS als bij MRA ook veroorzaakt door het type apparaat waarmee het onderzoek was uitgevoerd. Voor DUS was dit een bekend fenomeen, maar voor MRA is deze bevinding in de literatuur nooit eerder gerapporteerd.

Hoofdstuk 3 beschrijft de hoofdstudie van dit proefschrift. In de periode van 1997 tot en met 2000 werden 350 opeenvolgende patiënten geïncludeerd die op basis van een screenend DUS onderzoek verdacht waren voor het hebben van een carotis stenose. Alle patiënten hadden in de zes maanden voorafgaand aan de inclusie in de studie neurologische symptomen ondervonden welke kunnen passen bij een stenose in de arteria carotis. De patiënten ondergingen na de DUS ook een MRA en een DSA onderzoek van de carotis. Zowel DUS als MRA bleken na berekening van de resultaten over deze hele groep adequate testen voor het diagnosticeren van een carotis stenose in vergelijking met de referentie test DSA. DUS en MRA bleken met name erg betrouwbaar wanneer ze hetzelfde testresultaat lieten zien. Echter, wanneer op die manier naar de resultaten wordt gekeken, blijft er een kleine groep patiënten over (ca. 15%) waarbij DUS en MRA niet hetzelfde testresultaat laten zien. In die gevallen dient alsnog een DSA overwogen te worden. De gevonden sensitiviteit en specificiteit van de niet invasieve testen lagen in onze studie wat lager dan de gemiddelde waarden uit de literatuur. Dit is te verklaren doordat we een relatief grote en prospectieve studie uitvoerden, maar met name ook door het feit dat we in plaats van alle beschikbare vaten (twee carotiden per patiënt) alleen de symptomatische vaten waarbij een desobstructie-operatie werd overwogen includeerden in onze analyses. In studies waarbij beide carotiden in de analyses worden meegenomen wordt met name de specificiteit overschat, omdat er dan veel vaten zonder een stenose zijn waardoor de overeenstemming tussen de technieken hoger is.
In de diagnostische studie komen we tot de eindconclusie dat DSA in de meerderheid van de patiënten die verdacht worden van het hebben van een carotis stenose, en bij wie een operatie wordt overwogen, niet meer als routine onderzoek dient te worden uitgevoerd. DSA dient alleen te worden verricht bij speciale indicaties, bijvoorbeeld bij duidelijke discrepantie tussen DUS en MRA resultaten, of in individuele gevallen waarbij nog andere delen van de vaten bekeken moeten worden om de beslissing te kunnen nemen.

In *Hoofdstuk 4* wordt de kosteneffectiviteit berekend van het eventueel invoeren van niet invasieve testen. Met het niet uitvoeren van DSA wordt geld bespaard en het aantal complicaties ten gevolge van de diagnostiek vermindert. Vergeleken met de referentie test DSA zal met DUS en/of MRA echter een iets andere patiënten groep voor operatie worden geselecteerd. Dit komt omdat nieuwe testen als gevolg van een toevallige variatie nooit precies hetzelfde meten als de referentie test. Dientengevolge zullen de percentages complicaties na afloop van de operatie ook iets anders liggen. In een besliskundig model werden de consequenties van die verschillen doorgerekend voor het hele verdere leven van alle patiënten. Hierbij werden alle mogelijke kosten meegenomen, zoals de kosten van de diagnostische onderzoeken, van een opname in het ziekenhuis en van het benodigde personeel, maar ook alle kosten in het verdere verloop zoals bijvoorbeeld revalidatiekosten na een complicatie of opname in een verpleegtehuis in het geval van een ernstige beroerte. Berekend over de hele populatie zullen niet invasieve testen gemiddeld een iets betere levensverwachting geven en zullen tevens iets goedkoper zullen zijn dan DSA, zelfs met de aanname dat met DSA precies de goede patiënten worden geselecteerd. Volgens het model zou het uitvoeren van alleen DUS (zonder MRA) nog het meest gunstig zijn, echter, de resultaten van DUS zijn waarschijnlijk weer beïnvloed door verificatie bias. Omdat wij niet goed weten hoe groot de invloed hiervan is kunnen we de exacte diagnostische waarde niet berekenen.

In de analyses bleek dat MRA de stenosegraad enigszins overschat in vergelijking met DSA. In *Hoofdstuk 5* werd onderzocht of dit verschijnsel te verklaren was doordat bij MRA gebruik wordt gemaakt van meer projectierichtingen van het te onderzoeken vat dan bij DSA. Bij routine DSA onderzoek van de carotiden wordt in drie richtingen naar het vat gekeken, terwijl bij MRA de beschikking is over 12 verschillende projectie richtingen. Inderdaad bleek dat MRA de stenosegraad niet meer overschat wanneer niet alle twaalf, maar alleen de drie richtingen die met DSA overeenkomen werden gebruikt. De overschatting was ernstiger naarmate het vat een minder ernstige stenose vertoonde. Bij de evaluatie van een nieuwe techniek moet rekening worden gehouden met het feit dat het aantal projectierichtingen kan verschillen van de referentie test.

De gangbare techniek voor MRA, bij aanvang van onze studie, was de time-of-flight (TOF) techniek. Dit is een MR techniek waarmee stromend bloed afgebeeld kan worden. Op die manier wordt de omvang van een bloedvat, en dus ook eventuele stenosen, in beeld gebracht. *Hoofdstuk 6* beschrijft echter een van de beperkingen. De techniek is erg gevoelig voor wervelingen van het bloed, en omdat die juist bij een stenose vaak optreden, kunnen in de gereconstrueerde beelden artefacten ontstaan. Dat wil zeggen dat ter hoogte van de stenose in plaats van het lumen een zwart defect in het beeld ontstaat (flow void artefact). Op basis van de bovengenoemde technische verklaring, en op basis van ervaringen in de praktijk, werd in de literatuur algemeen aangenomen dat bij de aanwezigheid van een flow void artefact er sprake moest zijn van een ernstige stenose (70-99%). In onze studie hadden we de kans om alle opgetreden flow voids te vergelijken met de precieze afbeelding op de DSA. In de MRA onderzoeken van onze patiëntengroep kwam in 16% van de in beeld gebrachte vaten een flow void voor. Hoewel de stenosegraad volgens DSA kon variëren van 37% tot 100% (occlusie), bleek de aanname dat een flow void een ernstige stenose representeert in het merendeel van de gevallen gerechtvaardigd (85%) in de klinische praktijk.

Een diagnostische studie neemt noodgedwongen een aantal jaren in beslag. Dit is onvermijdelijk voor het verzamelen van de gegevens van een patiëntengroep die groot genoeg is om een precieze schatting te kunnen maken van de diagnostische waarde van de te onderzoeken test, in ons geval DUS en met name MRA. Het is echter zeer waarschijnlijk dat in zo'n relatief lange periode de techniek verandert. Bij aanvang van onze studie was TOF MRA 'state-of-the-art' MR techniek in het afbeelden van bloedvaten. Gedurende onze studie kwam contrast-enhanced MRA (CE-MRA) steeds meer in opkomst, een techniek die in andere delen van het lichaam al langer werd toegepast. Hierbij wordt een kleine hoeveelheid intraveneus contrast toegediend. In tegenstelling tot bij DSA is er geen risico op complicaties bekend. Na een leerperiode hebben we in het laatste deel van onze studie in een serie van iets meer dan vijftig patiënten deze techniek toegevoegd aan het studie protocol. Zodoende hadden we de mogelijkheid, hetzij in een relatief kleine populatie, om ook deze nieuwe techniek te vergelijken met de referentie test DSA. In *hoofdstuk 7* worden de resultaten hiervan beschreven. De diagnostische waarde van CE-MRA was in deze sub-populatie ongeveer gelijk aan die van TOF MRA, echter, de populatie was te klein om hierover een nauwkeurige uitspraak te kunnen doen. Daarnaast lijkt CE-MRA een aantal praktische voordelen te bieden boven TOF MRA. Het optreden van flow void artefacten lijkt sterk te verminderen, en met deze nieuwe techniek blijkt het mogelijk om, net als bij DSA, een veel langer traject van de carotis te visualiseren, van de oorsprong bij de aortaboog tot en met de intra-craniële siphon. Er is niet bewezen of een aangetoonde afwijking elders in het traject de resultaten van chirurgie aan de arteria carotis beïnvloedt, echter, in individuele gevallen weegt een dergelijke bevinding zeker in de overweging mee.

In *Hoofdstuk 8*, tenslotte, onderzochten we wat de patiënten, los van de genoemde risico's, zelf vinden van en ervaren bij de drie testen, DUS, MRA en DSA. Zoals we verwacht hadden werd DSA als meest belastend ervaren, gevolgd door MRA. Van DUS onderzoek werd weinig hinder ondervonden. Hierbij dient wel te worden vermeld dat de resultaten mogelijk beïnvloed zijn door het feit dat patiënten met claustrofobie, of patiënten met metalen implantaten zoals bepaalde vaatclips, niet deelnamen aan het MRA onderzoek. Bij DSA werden zoals verwacht de vervelende en/of pijnlijke sensaties van het katheter onderzoek als belastend ervaren. Opvallend was echter dat de opname in het ziekenhuis die voor DSA, in tegenstelling tot DUS en MRA, noodzakelijk is, niet als erg belastend werd ervaren. Het lange stilliggen na het DSA onderzoek, nodig om de snee in de liesslagader goed te laten genezen, werd als meest belastend gerapporteerd. Ook opvallend was dat 25% van de patiënten een MRA minder belastend vond dan een DSA.

In de algemene discussie in *Hoofdstuk 9* wordt een aantal methodologische beperkingen besproken van het uitvoeren en analyseren van diagnostisch onderzoek, zoals de gevolgen van het uitsluitend betrekken van de carotis aan de symptomatische zijde in de analyses, en het effect van de verificatie bias op de resultaten van het DUS onderzoek. Vervolgens wordt kort ingegaan op de toekomst, waarbij door de ontwikkeling van de techniek een toenemende rol van het MR onderzoek wordt verwacht. Tenslotte wordt besproken dat in de toekomst waarschijnlijk meer dan nu het geval is in plaats van alleen de stenosegraad ook andere karakteristieken van de patiënt, zoals leeftijd, geslacht, en bijvoorbeeld de tijd sinds het optreden van de symptomen, mee gaan bepalen of een patiënt al dan niet een operatie geadviseerd moet worden.

De conclusie van dit proefschrift is dat DSA niet meer routinematig dient te worden uitgevoerd bij alle patiënten die verdacht zijn voor het hebben van een carotis stenose en bij wie een desobstructie operatie wordt overwogen. DUS alleen is niet voldoende maar dient altijd gevolgd te worden door MRA onderzoek. Met name de combinatie van DUS en MRA onderzoek is een veilige en kosteneffectieve niet invasieve strategie, die de DSA kan vervangen in het merendeel van de patiënten. DSA dient allen nog te worden verricht op speciale indicatie, bijvoorbeeld wanneer er een duidelijke discrepantie bestaat tussen de bevindingen van DUS en MRA onderzoek, of wanneer er aanvullende informatie nodig is van andere vaten voor de beslissing of een operatie de voorkeur verdient.

List of publications

PJ Nederkoorn, Y van der Graaf, MGM Hunink. Duplex ultrasound and MR angiography compared to digital subtraction angiography in carotid artery stenosis: a systematic review. *Submitted.*

PJ Nederkoorn, WPThM Mali, BC Eikelboom, OEH Elgersma, E Buskens, MGM Hunink, LJ Kappelle, PC Buijs, AFJ Wust, A van der Lugt, Y van der Graaf. Pre-operative diagnosis of carotid artery stenosis: replacing digital subtraction angiography by non-invasive testing. *Accepted for publication Stroke.*

E Buskens, PJ Nederkoorn, T Buijs-van der Woude, WPThM Mali, LJ Kappelle, BC Eikelboom, Y van der Graaf, MGM Hunink. Diagnosing carotid artery stenosis in symptomatic patients; A cost-effectiveness analysis of diagnostic strategies. *Submitted.*

PJ Nederkoorn, OEH Elgersma, WPThM Mali, BC Eikelboom, LJ Kappelle, Y van der Graaf. Overestimation of carotid artery stenosis by MR angiography compared to digital subtraction angiography. *Accepted for publication J Vasc Surg.*

PJ Nederkoorn, Y van der Graaf, BC Eikelboom, A van der Lugt, LW Bartels, WPThM Mali. Time-of-flight MR Angiography of carotid artery stenosis: does a flow void represent severe stenosis? *Accepted for publication ANJR Am J Neuroradiol.*

PJ Nederkoorn, OEH Elgersma, Y van der Graaf, BC Eikelboom, LJ Kappelle, WPThM Mali. Diagnostic value of contrast-enhanced MR angiography in carotid artery stenosis. *Submitted.*

PJ Nederkoorn, MGM Hunink, Y vander Graaf. Patient preferences for duplex ultrasound, Mr angiography and digital subtraction angiography in carotid artery imaging: a short report. *Submitted.*

DM Somford, PJ Nederkoorn, DR Rutgers, LJ Kappelle, WPThM Mali, J van der Grond. Different prognostic implications of proximal and distal hyperdense middle cerebral artery sign on CT. *Radiology,* 2002;223:667-671.

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C Jongen, JPW, Pluim, PJ Nederkoorn, MA Viergever, WJ Niessen. Construction of an Average CT Brain Image as a Reference Frame for Intersubject Registration. *Submitted.*

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Curriculum vitae

Paul Nederkoorn werd op 3 februari 1969 te Haarlem geboren. In 1987 behaalde hij zijn VWO diploma aan het 'Kruisheren Kollege' te Uden. In 1987 ging hij werktuigbouwkunde studeren in Delft, waar hij in 1989 zijn propaedeuse behaalde. In 1989 startte hij met de geneeskunde opleiding in Brussel, die hij in 1990 vervolgde in Rotterdam. In zijn doctoraalfase, in 1994, ging hij voor een klinische stage in de neurologie en neurochirurgie naar Odense, Denemarken (Prof. P. Bjerre). In 1997 legde hij met goed gevolg zijn artsexamen af. Aansluitend werkte hij een jaar als agnio neurologie in het 'Drechtsteden' ziekenhuis te Dordrecht (Mw. C. Oppelaar en Dhr. R. de Waal). In 1999 begon hij zijn promotieonderzoek aan het Julius Centrum in het Universitair Medisch Centrum Utrecht. (Prof. dr. Y. van der Graaf, Prof. dr. M.G.M. Hunink en Prof. dr. W.P.Th.M. Mali). Tevens startte hij de opleiding tot MSc in de richting 'Clinical Epidemiology' aan the Netherlands Institute of Health Sciences. In mei 2002 is hij begonnen op de afdeling Neurologie in het Academisch Medisch Centrum te Amsterdam (Prof. dr. J. Stam, Prof. dr. M. Vermeulen).