Peripheral arterial disease: gadolinium-enhanced MR angiography versus color-guided duplex US. A meta-analysis

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Authors' objectives
To summarise and compare the diagnostic performance of gadolinium-enhanced magnetic resonance (MR) angiography and colour-guided duplex ultrasonography (US) for the evaluation of arterial stenoses and occlusions in the work-up of peripheral arterial disease of the lower extremities, and to compare both methods with conventional angiography.

Searching
MEDLINE was searched; the search terms were reported. The authors also searched the bibliographies of reviews and original articles for additional studies and contacted experts in the field. Studies of duplex US published between January 1984 and November 1998, and of MR angiography published between January 1990 and November 1998, were eligible for inclusion. For the period January 1984 to June 1994, studies on duplex US from a previous meta-analysis were included. Where more than one study was identified by the same author over a brief time, the review authors contacted the study authors to ascertain whether the patient populations overlapped. Where patient populations did overlap, the studies with a research question most relevant to the review were included.

Study selection
Study designs of evaluations included in the review
The authors did not state any inclusion criteria relating to the study design. All but one of the included studies were prospective.

Specific interventions included in the review
Studies of gadolinium-enhanced MR angiography and/or colour-guided duplex US, performed to demonstrate stenoses and occlusions of the arteries in the lower extremities, were eligible for inclusion in the review.

In relation to MR angiography, the actual interventions included MR angiography with a variety of two- and three-dimensional MR parameters (further details provided in the report), using a gadolinium dose of 0.2 or 0.3 mmol/kg. The imager used was a 1 or 1.5 T body coil, 1.5 T surface coil or 1.5 T body and head coils, manufactured by Siemens Medical Systems, GE Medical Systems, Philips Medical Systems or Picker.

In relation to colour-guided duplex US, the actual interventions included the use of a peak systolic velocity (PSV) ratio of more than 2, a PSV of more than 200 cm/second, a PSV of more than 200 cm/second in iliac artery, loss of reverse flow, spectral broadening, flattening of triphasic waveform, or luminal narrowing to detect a greater than 50% or greater than 70% diameter reduction or 'severe irregularities'. The scanner used was an Ultramark 9, Model 128, QAD-1, Sonos 1000, Acuson, AU590A or AU4, Spectra or Model SSA 270A, manufactured by ATL Ultrasound, Acuson, Quantum Medical Systems, Hewlett-Packard, Esaote Biomedica, Diasonics or Toshiba.

Where reported, the maximum time between examinations ranged from 1 to 14 days in the MR angiography studies and from 0 to 61 days in the duplex US studies. Where stated, the reading of US images and reference images in the included duplex US studies was blinded.

Reference standard test against which the new test was compared
Studies that used the results of conventional angiography as the reference standard were eligible for inclusion.

Participants included in the review
The authors did not explicitly state any inclusion criteria relating to the participants. However, the review question implied that patients with peripheral arterial disease of the lower extremities were the population of interest. Where reported, the mean age of the included patients was 63 years in the MR angiography studies and 65 years in the duplex US studies, and 72% and 65%, respectively, were male. Some studies used consecutive patients while some did not, and...
Outcomes assessed in the review
Studies in which the absolute numbers of true-positive (TP), false-negative (FN), true-negative (TN) and false-positive (FP) results were provided, or could be derived for a defined cut-off criterion for angiography, were eligible for inclusion. Where studies only reported a measure of agreement between the modalities, the review authors attempted to contact the primary study authors to acquire the absolute numbers of TP, FN, TN and FP results.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assigned a quality score on the basis of whether the interpretation of the MR or US images was blinded, whether the interpretation of the reference modality results was blinded, and whether the patients were consecutive. Studies fulfilling all the criteria were given a quality score of 1; all others were given a score of 0. A published four-tiered rating of quality for diagnostic imaging studies was also determined for each study. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Both authors independently extracted data from the primary studies using a standardised spreadsheet. The level of agreement was calculated and any discrepancies were resolved by consensus. Blinding of the study characteristics was not used. Data were extracted on the study design, patient characteristics, diagnostic imaging protocol, and absolute numbers of TP, FN, TN and FP results. If multiple results for different readers were presented, the results of the first reader were used. If more than one examination technique was used in the same study, the technique advised by the study authors was used.

The natural logarithm of the diagnostic odds ratio (ln DOR) was used as a summary measure of the diagnostic performance per study; the formula for calculating ln DOR from the TP, TN, FP and FN results was given. A value of 0.5 was added to each TP, FN, TN and FP result to prevent undefined values that result from zero values. This was the measure of interest in the summary receiver operating characteristic (ROC) analysis.

Methods of synthesis
How were the studies combined?
The sensitivity, specificity and ln DOR were pooled and 95% confidence intervals (CIs) were calculated. The studies were combined using a random-effects model. MR angiography and duplex US were analysed separately, then their discriminatory power compared using a regression model. The final summary ROC model was reanalysed using a random-effects regression analysis in which inter-study variability was taken into account. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
The statistical heterogeneity of effect sizes was assessed by comparing the 95% CI of the observed values of the ln DOR with that of the predicted values of the ln DOR by using the final model. Analyses were performed to assess the effect of several variables: publication year, continent, mean age (older or younger than 65 years), prevalence of diseased segments per study, blinded interpretation of the test result, blinded interpretation of the reference test result, inclusion of consecutive patients, type of imager, and dose of gadolinium for MR angiography. Estimates of missing values were calculated with weighted means or with a best-subset regression analysis. These were then used to explore the effect of clinical variables in univariate analyses. Missing values were not estimated in the final multivariate analysis comparing MR angiography with duplex US; only studies with complete data for the selected variables were used. The selection of variables for the final model was performed by analysing each variable in turn (univariate) and considering any significant variables in a multivariate analysis; interaction terms were incorporated in the analysis to allow for differential effects, depending on the examination. Significant variables (P<0.05) were assessed in a multivariate model per examination. Variables with a P-value of 0.05 to 0.1 were retained in the model if the explanatory power of the
A 'jackknife' sensitivity analysis of the final model was carried out by performing multiple summary ROC analyses, excluding each article in turn. Sensitivity analyses were also performed in which three additional studies of duplex US, which used different definitions of disease as determined at conventional angiography, and one additional study of MR angiography, where gadolinium-based contrast material was only administered in selected patients, were included.

**Results of the review**

Nine studies of MR angiography (216 participants) and 18 studies of duplex US (1,059 participants) were included in the review.

**Weighted pooled analysis.**

The pooled sensitivity for MR angiography was 97.5% (95% CI: 95.7, 99.3), which was higher than that for duplex US (87.6%, 95% CI: 84.4, 90.8). The pooled specificity for MR angiography was 96.2% (95% CI: 94.4, 97.9), which was similar to that for duplex US (94.7%, 95% CI: 93.2, 96.2). The pooled value of the ln DOR was 6.43 (95% CI: 5.66, 7.19) for MR angiography and 4.99 (95% CI: 4.30, 5.68) for duplex US.

**Summary ROC analysis.**

No significant predictors were demonstrated in the univariate analysis for MR angiography. The univariate analysis for duplex US demonstrated that a higher number of days between duplex US and conventional angiography decreased the discriminatory power of duplex US, as did a different positivity criteria. Neither the quality scores, nor the individual quality covariates, were significant predictors of diagnostic performance for either MR angiography or duplex US.

The result of the summary ROC analysis also indicated that the discriminatory power of MR angiography was better than that of duplex US. The regression coefficients for MR angiography versus duplex US were 1.67 (95% CI: -0.23, 3.56) with adjustments for covariates and 2.11 (95% CI: 0.12, 4.09) without adjustments.

Homogeneity was present in the final model for all but three of the duplex US articles. A random-effects regression analysis was applied to the final summary ROC model, which demonstrated that the discriminatory power of MR angiography was better than that of duplex US with a regression coefficient of 1.73 (95% CI: 0.44, 3.02, P=0.009).

The 'jackknife' sensitivity analysis did not have a larger effect on the difference in discriminatory power between MR angiography and duplex US (regression coefficient range: 1.33, 2.14). The sensitivity analysis incorporating the duplex US study that used another percentage of diameter reduction as the definition of disease demonstrated better discriminatory power than the results from the other duplex US studies, but the difference was not significant (regression coefficient 2.66, 95% CI: -6.93, 12.25, P=0.56). The sensitivity analysis including two duplex US studies that used irregularities of the vessel wall and luminal narrowing seen at duplex US as positivity criteria, and severe vessel wall irregularities seen at conventional angiography as the definition of disease, demonstrated a discriminatory power lower than those of the other duplex US studies (regression coefficient -2.16, 95% CI: -3.21, -1.10, P=0.001). The sensitivity analysis incorporating the study of MR angiography in which gadolinium-based contrast material was only administered in selected patients demonstrated a discriminatory power lower than those of the other MR angiography studies (regression coefficient -2.20, 95% CI: -3.92, -0.49, P=0.02).

Overall, the discrepancies in data extraction between the authors amounted to 10%. The funnel plot had a symmetrical distribution for duplex US studies, indicating that publication bias was not present. The funnel plot also showed a symmetrical distribution for studies of MR angiography; however, a few studies had a large number of segments and publication bias could not, therefore, be properly evaluated. Statistical heterogeneity in the effect sizes was present, except for the sensitivity of MR angiography, thus a random-effects model was used.

**Authors' conclusions**

Gadolinium-enhanced MR angiography has better discriminatory power than colour-guided duplex US and is a highly sensitive and specific method, compared with conventional angiography, for the work-up for peripheral arterial disease.
CRD commentary
The review question was clearly defined in terms of the interventions, reference standard and outcomes of interest. The search was restricted to only one electronic database, supplemented by bibliographic searches and contact with experts in the field. Additional relevant studies may have been missed. Whilst attempts were made to assess publication bias, publication bias in studies of MR angiography could not be properly evaluated. Both authors independently extracted data and the level of agreement was calculated. However, the methods of selecting studies for inclusion in the review and of assessing the quality of the studies were not reported; the potential for reviewer error or bias cannot, therefore, be assessed.

Adequate details of the included studies were tabulated. The quality of the primary studies was assessed, and the quality scores and individual covariates for evaluating individual aspects of quality were assessed in the summary ROC analysis. Statistical heterogeneity was assessed and appropriate statistical methods appear to have been used to synthesise the data. No studies that directly compared MR angiography with duplex US were identified; a regression model was used to compare discriminatory power using a relatively small number of studies, but a direct comparison would have been preferable. Whilst publication bias cannot be reliably ruled out in relation to studies of MR angiography, the authors' conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors stated that their results imply that MR angiography could potentially replace duplex US and conventional angiography.

Research: The authors did not state any implications for further research.

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