Magnetic resonance imaging using ultrasmall superparamagnetic particles of iron oxide for abdominal aortic aneurysm: a risk prediction study

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Scientific summary

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Background

Abdominal aortic aneurysms (AAAs) have a prevalence of 5% in men aged 65–74 years and, when ruptured, are associated with a mortality of up to 90%. At a population level, ruptured AAAs are a major cause of death, being the 13th commonest cause of death and accounting for > 150,000 deaths in 2013. Pre-emptive elective open surgical or endovascular repair can be life-saving and is considered when the AAA diameter exceeds 55 mm, is rapidly expanding (by ≥ 10 mm/year) or causes symptoms.

Population screening has been established in some countries and is associated with a halving of the mortality associated with AAAs. Continued surveillance of aneurysms is, however, challenging, because of the non-linearity and unpredictability of expansion rates, although the best current predictor of aneurysm expansion and rupture is the baseline aneurysm diameter. Furthermore, the pathophysiological mechanisms underlying aneurysm expansion remain uncertain, and the role of cellular inflammation and macrophage infiltration has been debated. Finally, up to one-fifth of ruptured AAAs are < 55 mm in diameter and 40% of patients with aneurysm diameters between 70 and 100 mm do not experience aneurysm rupture. There is therefore an unmet clinical need to identify more reliable methods of identifying those patients at risk of AAA expansion and rupture.

Objectives

Ultrasmall superparamagnetic particles of iron oxide (USPIO) constitute a class of magnetic resonance imaging (MRI) contrast agent that is taken up by tissue-resident macrophages and can be used to identify cellular inflammation within tissues, including AAAs. In a small pilot study of 29 patients with AAAs, we have previously demonstrated that USPIO-enhanced MRI is associated with macrophage infiltration of the AAA wall and more rapid rates of AAA expansion. We therefore aimed to validate these preliminary findings in a larger, multicentre cohort of patients, and determine whether or not USPIO-enhanced MRI could predict the rate of AAA expansion and subsequent rates of rupture or surgical repair.

Methods

Study design

This was a prospective multicentre observational open-label cohort study of patients under routine ultrasonographic surveillance for AAAs.

Study population

Consecutive patients were recruited from three centres in Scotland, UK (Royal Infirmary of Edinburgh, Western Infirmary of Glasgow and Forth Valley Royal Hospital in Larbert), between 8 November 2012 and 5 December 2014. Inclusion criteria were being aged > 40 years, having a maximum anteroposterior AAA diameter of ≥ 40 mm, as confirmed by abdominal ultrasonography, and being under ultrasonographic surveillance as part of routine clinical care.

Study protocol

Participants attended for a baseline assessment within 6 weeks of the screening abdominal ultrasonography. Participant characterisation comprised full clinical assessment, USPIO-enhanced MRI and computed tomography aortography. Patients underwent a baseline 3-T MRI scan before receiving an intravenous infusion of a weight-adjusted dose of USPIO. A second MRI scan was performed 24–36 hours after USPIO

administration. To calculate the degree of USPIO enhancement, colour maps were generated to depict the percentage change in T2*, which is the decay constant for the exponential decay of signal over time. Using the predefined threshold of ≥ 71% change in T2*, each colour map was independently classified by two trained observers into patients with or without USPIO enhancement within the wall of the AAA.

Clinical follow-up

Patients were reviewed every 6 months in the research clinic for a minimum of 24 months. Structured follow-up data were collected on AAA events, hospital admissions and other relevant clinical data. Clinical events were verified independently using electronic health records and public registry data. Serial maximum anteroposterior diameters were obtained by ultrasonography performed by trained specialist vascular practitioners in dedicated AAA surveillance clinics.

Clinical end points and adjudication

Clinical data from clinic visits, research databases, electronic health records, primary care contacts and the General Register Office were reviewed and clinical end points adjudicated by an independent Clinical End Point Committee. The committee members were blinded to the MRI findings. Follow-up was censored at 21 November 2016 or at the time of event.

Statistical analysis

Categorical data are presented using counts and percentages, continuous variables presented using mean (standard deviation), median (interquartile range) deviation and absolute differences with 95% confidence intervals (CIs). Comparisons of baseline characteristics were made using either a binomial test for proportions in the case of categorical data or by two-sample *t*-test for continuous data. Aneurysm growth rate was determined from serial ultrasonographic measurements using a linear regression model that was fitted to all available data and the slope used to determine the aneurysm growth rate per year. The primary and clinical event end points were assessed by log-rank test and are presented as Kaplan–Meier curves. Cox proportional hazards models were generated to include the baseline covariates of sex, smoking, systolic blood pressure and baseline aneurysm diameter determined by ultrasonography. The additional value of USPIO enhancement was assessed by the *c*-statistic and net reclassification index. Statistical significance was taken as a two-sided *p*-value of < 0.05.

Results

We screened approximately 2000 patients attending the outpatient vascular clinics of the study centres and identified 741 potentially eligible patients, of whom ultimately 361 (48.7%) were recruited into the study. Nineteen patients were subsequently withdrawn, predominantly because they were unable to undergo repeated MRI scans because of claustrophobia. The final study population comprised 342 participants who were predominantly elderly male current or ex-smokers with hypercholesterolaemia and hypertension. There were no serious adverse events or reactions to intravenous ferumoxytol administration. It was generally well tolerated by all participants. Mild asymptomatic hypotension that was possibly related to ferumoxytol (Rienso®, Takeda) was noted in one participant but required no action or intervention.

Ultrasmall superparamagnetic particles of iron oxide enhancement of the AAA wall was identified in 146 participants (42.7%), was absent in 191 participants (55.8%) and was indeterminate in five participants (1.5%). USPIO enhancement was strongly associated with current smoking status as well as baseline AAA diameter and the presence of a common iliac aneurysm.

Aneurysm growth rate

On ultrasounds, baseline maximum AAA diameter was 49.6 [standard deviation (SD) 7.7 mm] and was slightly larger in patients with USPIO enhancement. The AAA growth rate during the trial was 2.8 mm/year (SD 2.4 mm/year) ($n = 279$) and was greater in patients with USPIO enhancement [3.1 (SD 2.5) vs. 2.5 (2.4) mm/year; difference 0.6 (95% CI 0.02 to 1.20) mm/year; $p = 0.0424$]. Current smoking status ($p = 0.0305$),

but not aneurysm diameter ($p = 0.1853$), baseline systolic blood pressure ($p = 0.6994$) or USPIO enhancement ($p = 0.1993$), was an independent predictor of aneurysm growth rate.

Clinical follow-up

All participants were followed up for a mean of 1005 days (SD 208 days). Overall, the primary end point occurred in 140 participants (40.9%) with 17 AAA ruptures and 126 AAA repairs; three participants underwent repair after rupture. There were 48 deaths (14.0%), of which one-third were AAA related [17 (35.4%)] and one-quarter were caused by other cardiovascular causes [12 (25.0%)].

Rupture or repair

The primary end point occurred more frequently in participants with USPIO enhancement of AAAs [69/146 (47.3%) vs. 68/191 (35.6%); difference 11.7%, 95% CI 1.1% to 22.2%; $p = 0.0308$] and was associated with a reduced event-free survival ($p = 0.0288$). This was consistent for both components of the end point. Baseline AAA diameter (hazard ratio 1.077, 95% CI 1.060 to 1.095; $p < 0.0001$) and current smoking habit (hazard ratio 1.473, 95% CI 1.009 to 2.149; $p = 0.0446$) were the main predictors of the primary end point. The addition of USPIO enhancement to the model did not improve the prediction of events (*c*-statistic 0.7935 to 0.7936) or the unconditional net reclassification (–13.4%, 95% CI –36.2% to 9.5%). This was true for both components of the end point: (1) aneurysm rupture [*c*-statistic 0.6318 to 0.6306 and net reclassification (29.8%, 95% CI –22.2% to 81.8%)] and (2) aneurysm repair [*c*-statistic 0.8012 to 0.8011 and net reclassification (–9.7%, 95% CI –33.3% to 13.9%)].

Discussion and conclusions

In a prospective multicentre observational cohort study, we have demonstrated that USPIO-enhanced MRI not only predicts the rate of aneurysm expansion but also the future risk of an AAA rupture or repair. This is the largest prospective clinical study of MRI in patients with AAAs, and is the first report of an imaging technique that not only identifies cellular inflammation, but also predicts disease progression and outcome. This suggests a central role of cellular inflammation in the pathophysiology, progression and outcome of AAA disease.

The rate of AAA growth has previously been shown to be predicted by (1) smoking status, (2) aneurysm size and (3) the presence of common iliac aneurysms. Indeed, smoking habit is the principal modifiable risk factor for AAA progression and rupture, and is the main focus of lifestyle modification in these patients. It is demonstrated here that USPIO-enhanced MRI is associated with all three risk factors. In particular, current smoking was an independent risk factor for AAA growth and, intriguingly, USPIO enhancement was twice as frequent in current smokers. This suggests a potential mechanistic link between smoking and macrophage-driven AAA inflammation. Indeed, components of cigarette smoke, such as 3,4-benzopyrene, promote macrophage infiltration of AAAs, leading to increased matrix metalloproteinase expression and vascular smooth muscle apoptosis. Using adoptive transfer experiments, Jin *et al.* (Jin J, Arif B, Garcia-Fernandez F, Ennis TL, Davis EC, Thompson RW, Curci JA. Novel mechanism of aortic aneurysm development in mice associated with smoking and leukocytes. *Arterioscler Thromb Vasc Biol* 2012;**32**:2901–9) have further shown that in vivo exposure of leucocytes to smoke can accelerate the progression of aneurysm disease in smoke-free animals. Taken together, these findings suggest that macrophage-mediated inflammation may be the mechanistic link to explain the association between smoking and disease progression in patients with an AAA.

The primary end point of the study was the rate of AAA rupture or repair, and although this was higher in patients with USPIO-enhanced MRI, it was not independent of known predictors of outcome, including baseline AAA diameter and smoking habit. Indeed, incorporation of USPIO-enhanced MRI did not improve the discrimination of a model incorporating these known clinical risk factors. This most probably reflects the mutual interdependence and potential causal association of these factors, namely that smoking induces

cellular inflammation within the aneurysm, which causes more rapid expansion and increase in the aneurysm diameter leading to aneurysm rupture or triggering of the threshold for repair.

Ultrasonographic measurements of AAA diameter are the mainstay of clinical management and the principal determinant of the timing of elective surgical repair. Their dominant effect on the primary end point is therefore perhaps not surprising, especially as most events were caused by elective surgical repair. Given that the clinicians were blind to the results of the USPIO-enhanced MRI, it would be challenging to demonstrate that it could lead to any changes in the rate of elective surgical repair. We therefore explored other measures of outcome that were independent of elective surgical repair. We found that USPIO enhancement appeared to be greater in those with emergent AAA-related events, including AAA rupture and AAA-related mortality, although the absolute number of events was small and fell just short of achieving statistical significance. Given the small number of emergent events, our study did not have sufficient power to determine whether or not USPIO enhancement could provide clinically useful information that could independently predict emergent events.

Although USPIO-enhanced MRI was not an independent predictor of outcome across the whole study population, it did identify aneurysm disease activity, correlate with rates of aneurysm expansion and appear to predict clinical outcomes, including rupture and death. For some patients, treatment decisions are not straightforward. For example, abdominal pain in a patient with an AAA may be caused by other abdominal pathology and not the aneurysm itself. Urgent repair may be unhelpful in such circumstances and associated with considerable risk. Furthermore, decisions to undertake surgical repair can be challenging in those with high-risk or morphologically atypical aneurysms of < 55 mm in size those with borderline aneurysm sizes of 50–55 mm (especially in women) and those with larger aneurysms in which the balance of risk and benefit is uncertain. Additional information regarding disease activity that is tied to disease progression and adverse clinical outcome may be helpful in guiding such decisions. Although not directly tested here, USPIO-enhanced MRI may assist the clinician in making these difficult management decisions that are associated with significant potential benefits and hazards. This requires further investigation.

Our study has a number of strengths. It was a multicentre prospective observational cohort study that ensured blinding of the USPIO-enhanced MRI findings from the patients and attending clinicians, and was therefore independent of clinical decision-making. It was an adequately sized Phase II proof-of-concept trial that was ≈10-fold larger than previous studies in this area. The study also achieved its predicted event rates and met its primary end point, although not independent of known clinical predictors. However, the inclusion of elective surgical repair in the primary end point generates some challenges in interpretation because of the ultrasonography and diameter-guided decision-making for elective surgical repair. The prediction of emergent events appears promising but will require a much larger study with greater power to confirm these findings. Finally, USPIO-enhanced MRI is resource intensive and was not possible in a small number of patients because of contraindications or claustrophobia. However, it was a feasible, safe and deliverable clinical technique that was well tolerated in the vast majority of patients with no serious adverse effects from the MRI or contrast agent.

In conclusion, in a multicentre prospective observational cohort study, we have demonstrated that USPIO-enhanced MRI predicts the rate of aneurysm expansion, and the risk of AAA rupture and repair. This is the first demonstration of a cellular imaging technique that can predict clinical events in patients with an AAA. Whether or not clinical outcomes can be improved by treatment decisions based on this novel imaging approach remains to be established. Larger trials are now needed to explore the prediction of emergent aneurysm events to establish the added benefit of USPIO-enhanced MRI. Comparative outcome studies should determine whether or not using other imaging biomarkers that track alternative disease processes have better predictive capability than USPIO-enhanced MRI.

Trial registration

This trial is registered as ISRCTN76413758.

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This report

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