PAPER

Comparison of the inflammatory burden of truly asymptomatic carotid atheroma with atherosclerotic plaques contralateral to symptomatic carotid stenosis: an ultra small superparamagnetic iron oxide enhanced magnetic resonance study

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Background: Inflammation is a recognised risk factor for the vulnerable atherosclerotic plaque. The aim of this study was to explore whether there is a difference in the degree of magnetic resonance (MR) defined inflammation using ultra small superparamagnetic iron oxide (USPIO) particles within carotid atheroma in completely asymptomatic individuals and the asymptomatic carotid stenosis contralateral to the symptomatic side.

Methods: 20 symptomatic patients with contralateral disease and 20 completely asymptomatic patients underwent multi-sequence MR imaging before and 36 h after USPIO infusion. Images were manually segmented into quadrants and signal change in each quadrant was calculated following USPIO administration. Mean signal change was compared across all quadrants in the two groups.

Results: The mean percentage of quadrants showing signal loss was 53% in the contralateral group compared with 31% in completely asymptomatic individuals ($p=0.025$). The mean percentages showing enhancement were 44% and 65%, respectively ($p=0.024$). The mean signal difference between the two groups was 8.6% (95% CI 1.6% to 15.6%; $p=0.017$).

Conclusions: Truly asymptomatic plaques seem to demonstrate inflammation but not to the extent of the contralateral asymptomatic stenosis to the symptomatic side. Inflammatory activity may be a significant risk factor in asymptomatic disease.

The management of asymptomatic carotid disease remains controversial despite the fact that the Asymptomatic Carotid Atherosclerosis Study¹ and the Asymptomatic Carotid Surgery Trial² have shown that carotid endarterectomy conferred a small but significant 5 year benefit over best medical therapy in asymptomatic patients. There is almost certainly a subgroup of asymptomatic patients who harbour vulnerable plaque and therefore are likely to be at increased risk of future cerebrovascular events and who may benefit from surgical intervention.

Potential clinical benefits from surgery are relatively small compared with intervention in symptomatic disease. This is perhaps due in part to the fact that these large trials assessed severity of disease purely through luminal narrowing, which may underestimate total atheroma burden caused by the process of expansive arterial remodelling.³ The value of surgical treatment remains less clear in patients with lower grades of stenosis, especially in the patient cohort with 30–69% luminal narrowing.^{2,4}

Thus identifying risk strategies to refine selection of high risk asymptomatic carotid lesions for surgery is of clinical importance. Multi-sequence MRI has been shown to be reliable in characterising carotid plaque morphology.^{5,6} Specific improvements in magnetic resonance (MR) technology have resulted in the ability to quantify plaque components with high spatial resolution,⁷ which has allowed prospective confirmation of well established findings from retrospective trials that thin or

ruptured fibrous caps and intraplaque haemorrhage are linked with future cerebrovascular events.⁸

The vulnerable carotid atheromatous plaque, considered responsible for many acute ischaemic events, not only has a thin fibrous cap, a large lipid pool but also macrophage dense inflammation on or beneath its surface.^{9,10} In contrast, stable or “safe” plaque is fibrous, with little lipid and no inflammation. Inflammation within atherosclerotic lesions increases the risk for plaque rupture and subsequent thromboembolism¹¹ and naturally presents itself for novel plaque stabilisation interventions.

It has been possible to image carotid plaque inflammation with ultra small superparamagnetic iron oxide (USPIO) enhanced MR imaging in both animal¹² and in vivo human studies.¹³ The use of a USPIO agent, Sinerem (Guerbet, Roissy, France), has allowed the direct visualisation of macrophage infiltration of carotid atheroma in vivo.^{13–15} USPIO particles are taken up by activated macrophages in vulnerable plaques and when clumped in phagolysosomes produce a strong T₂* susceptibility effect, visible on T₂* weighted sequences as magnetic susceptibility artefacts or signal voids.

In contrast, there is a predominant T₁ shortening effect at low concentrations of USPIO in tissue, allowing potentially better visualisation of the fibrous cap and suggesting that this

Abbreviations: CABG, coronary artery bypass grafting; MR, magnetic resonance; USPIO, ultra small superparamagnetic iron oxide

contrast agent could be used to detect not only inflammation within vulnerable plaque but also aid in identification of "safer" plaque with a significant fibrous component.¹⁶ While USPIO imaging relies on a decrease in signal intensity because of a T_2^* susceptibility effect, signal enhancement is predominantly a T_1 shortening phenomenon and may be related to decreased USPIO clumping within tissue and may well be unrelated to macrophage density although further work is required to more fully determine this relationship.

The aim of this study was to explore whether there is a difference in the degree of MR defined inflammation using USPIO particles, between truly asymptomatic carotid atheromatous plaque and asymptomatic carotid atheroma contralateral to the symptomatic disease. The hypothesis is that inflammatory atheroma is a systemic disease and that one inflamed symptomatic vascular bed is likely to increase the risk of other arterial vessels becoming inflamed.

Although both groups of patients would be classified as asymptomatic from a clinical point of view, USPIO enhanced MRI may allow improved risk stratification of the subgroup of asymptomatic patients who harbour vulnerable plaque and who are at likely increased risk of developing stroke. There is currently no literature to support the notion that the risk of stroke from asymptomatic disease contralateral to a symptomatic stenosis is any higher than 1–2%,¹⁷ which remains the predicted risk in the medically treated group from the Asymptomatic Carotid Atherosclerosis Study.¹ Numbers are however small and no proper natural history study has been published with regard to contralateral carotid disease.

PATIENTS AND METHODS

Subjects

Twenty patients with symptomatic carotid stenosis and who also had coexisting contralateral disease and 20 patients with truly asymptomatic carotid disease were recruited from a specialist neurovascular clinic. The symptomatic individuals either had a retinal or cortical transient ischaemic attack or a completed hemispheric stroke within the previous 6 months in

the designated carotid artery territory but also had asymptomatic disease on the contralateral side. These patients were scheduled for carotid endarterectomy on their symptomatic side. Truly asymptomatic patients, by definition, had no prior symptoms before imaging. This group of patients was detected as part of screening tests performed in the case of preoperative evaluation of coronary artery bypass grafting (CABG) and cervical bruits picked up by physical examination. Baseline demographic characteristics were collected prospectively.

Conduction of the MR studies did not cause a delay in surgical intervention in any of the enrolled subjects. This study was approved by the local ethics committee and all patients gave written informed consent.

Symptomatic patients who also had a contralateral stenosis on duplex ultrasound and sufficient image quality to identify the lumen wall and the outer boundary of the arterial wall were necessary requirements for inclusion. Truly asymptomatic patients were included if they had a stenosis $\geq 40\%$ on duplex imaging.

Exclusion criteria were (1) prior carotid endarterectomy; (2) prior neck irradiation and (3) contraindication for MRI.

High resolution multi-sequence MRI

Multi-spectral imaging of both the left and right internal carotid artery was acquired at 1.5 T before and 36 h after USPIO infusion, using a whole body MRI system (Signa HDx, GE Healthcare Technologies, Milwaukee, Wisconsin, USA) and custom designed four channel phased array neck coil (Flick Engineering Solutions BV, Winterswijk, the Netherlands) to improve the signal to noise ratio. Movement artefact was minimised using a dedicated vacuum based head restraint system to fix the head and neck in a comfortable position and allow close apposition of the surface coils.

After an initial coronal localiser sequence, axial two dimensional time of flight MR angiography was performed to identify the location of the carotid bifurcation and the region of maximal stenosis on each side. Axial images were acquired through the common carotid artery 12 mm (4 slices) below the carotid bifurcation to a point 12 mm (4 slices) distal to the extent of the stenosis identified on the time of flight sequence. This method ensured that the entire carotid plaque was imaged and also facilitated image coregistration.

The following two dimensional ECG gated, fat suppressed fast spin echo pulse sequences using double inversion blood suppression with a voxel size of $0.4 \times 0.4 \times 3$ mm were used in each case:

- T_1 weighted (recognition time (TR)/TEeff/ETL: 1 R–R/7.8 ms, 12),
- short T_1 inversion recovery (TR/TEeff/TI/ETL: 2 R–R/40 ms/150 ms, 24),
- intermediate T_2 weighted (TR/TEeff/ETL: 2 R–R/40 ms/24)
- two dimensional T_2^* weighted spiral acquisition using a spectral spatial excitation pulse, with a TE of 5.6 ms.

The multi-shot spiral sequence involved the acquisition of 22 spiral interleaves, each of 4096 data points, resulting in an effective inplane pixel size of 0.42×0.42 mm, two signal averages were performed and a quadruple inversion preparation was utilised to null the signal from blood before and after administration of USPIO. Slices were acquired sequentially with a 3 mm thickness and no interslice gap.

MR contrast agent

The USPIO agent, Sinerem (Guerbet, Roissy, France), was supplied as a dry powder and initially made up to a volume of 10 ml with normal saline. The contrast agent was further

Figure 1 Carotid artery showing the cross hairs dividing the vessel into quadrants labelled Q1–Q4. Signal underneath the coloured areas is considered in the analysis, eliminating any artefact from extravascular structures or the luminal blood pool.

Table 1 Baseline characteristics

Group	Contralateral asymptomatic	Truly asymptomatic	p Value*
No of patients	20	20	
Age (y) (median (range))	72 (53–84)	76 (62–83)	
Male (%)	11 (55)	14 (70)	0.5145
Per cent luminal stenosis (mean (SD))	46 (6)	63 (11)	<0.0001
Normalised wall index (mean (SD))	0.789 (0.09)	0.827 (0.07)	0.1587
Hypertension (%)	18 (90)	15 (75)	0.4075
Diabetes (%)	6 (30)	5 (25)	1.0000
PTCA/CABG (%)	5 (25)	3 (15)	0.6948
Peripheral vascular operations (%)	3 (15)	2 (10)	1.0000
Current or ex-smoker (%)	18 (90)	12 (60)	0.0648
Hypercholesterolaemia (%)	15 (75)	9 (45)	0.1053
Cholesterol (mmol/l) (mean (SD))	4.3 (1.6)	4.5 (2.1)	0.7368
HDL cholesterol (mmol/l) (mean (SD))	1.2 (0.45)	1.3 (0.34)	0.3707
Statin use (%)	19 (95)	16 (80)	0.3416
Antiplatelet agent (%)	18 (90)	15 (75)	0.4075

CABG, coronary artery bypass graft; PTCA, percutaneous coronary angioplasty.

*p Values are presented to provide an indication as to the degree of difference between the two groups. p values greater than 0.05 should not be interpreted as evidence of "no difference".

diluted in 100 ml of normal saline and given as a slow infusion through an indwelling large bore intravenous cannula over 30 min. The dose used was 2.6 mg/kg. Safety data for this contrast agent have been published previously and the optimal time window for MR imaging post USPIO infusion has been previously determined to be 36 h.¹⁵

Quantitative image analysis

MR images before and after administration of USPIO were manually coregistered according to plaque morphology and distance from the carotid bifurcation at the time of imaging. Following this, images were manually segmented into quadrants and excluding the luminal blood pool using predefined rules in an effort to reduce interobserver error (CMR Tools, London, UK). A horizontal line was constructed across each image and through the lumen centre. Likewise, a perpendicular line was constructed at right angles to this ensuring that the "cross hairs" were centred through the lumen (fig 1).

Surface coil positions differ slightly between imaging sessions and therefore signal intensities in each quadrant were normalised to the adjacent sternocleidomastoid muscle before and after USPIO. It was assumed that the muscle signal would not change following USPIO infusion. Signal change was then calculated as the difference in these normalised quantities. (Note that as a result of this calculation, signal change is expressed as a percentage, but this is a percentage of the adjacent muscle signal, not a percentage of the pre-USPIO signal). This was accomplished by manual delineation of each

quadrant as a region of interest and mean signal before and after infusion of USPIO was calculated (CMR Tools).

To avoid misclassifying plaque calcification, which can give similar appearances to USPIO on T₁ and T₂ weighted sequences, we attributed only new areas of signal loss to USPIO accumulation.

Positive USPIO enhanced MRI of carotid plaque was defined as a signal decrease of $\geq 10\%$ in two or more quadrants between pre and 36 h post USPIO imaging. This was determined by two experienced independent readers (TT, SPSH) and confirmed by a consultant neuroradiologist (JHG), who were all blinded to the patient groups and patient demographics at the time of analysis.

Area measurements of the lumen and total vessel area of the carotid artery were obtained using CMR Tools. The total vessel area included the lumen, intima, media and adventitia. Wall area was calculated as the difference between total vessel area and lumen area. The normalised wall index was calculated by dividing the wall area by the total vessel area.

Statistical methods

A statistical model has been previously developed which explicitly models the correlation between signal loss in different quadrants within a slice and different slices within a plaque, and also accounts for any dependence or correlation between multiple measurements made on a single patient.¹⁶ Furthermore, this model allowed quantification of the mean signal drop and provided a method for testing for differences between groups and controlling the type I error rate. A model

Figure 2 Imaging before (A) and after (B) administration of ultra small superparamagnetic iron oxide, showing significant signal loss in the post imaging (yellow arrows) of a patient with a contralateral carotid stenosis to the symptomatic side.

Figure 3 Comparison of percentage of quadrants showing signal loss between the two groups. Boxes show quartiles and median across quadrants for each group. Whiskers show minimum and maximum values.

was required in order to take into consideration the interdependence of the signal in adjacent quadrants. Each quadrant signal change recorded will not contribute as much statistical information as one truly independent observation but will nonetheless add some information to the overall whole that would be lost if a simple summary statistic were used.

Note that as a result of this calculation, signal change is expressed as a percentage, but this is a percentage of the adjacent muscle signal, not a percentage of the pre-USPIO signal, in contrast with our previous publication.¹⁶

USPIO enhanced MRI signal change was analysed using a repeated measures model with USPIO enhanced MRI signal drop as the outcome variable. The group in question (asymptomatic contralateral/truly asymptomatic) was fitted as a fixed effect and patient as a random effect. No other covariates were considered. Slice and quadrant were used to define the within patient correlation within each side. Estimates of signal change within each side were calculated with appropriate 95% confidence intervals adjusting for the correlation between measurements made on the same subject. An estimate of the difference between sides with appropriate 95% confidence interval was also calculated, together with a p value testing the hypothesis of no difference between sides. Model assumptions regarding homogeneity of variance were verified by inspection of residual plots. Distributional assumptions regarding normality were verified by assessment of normal probability plots. The analysis was carried out using PROC MIXED in SAS for Windows version 8.2 (SAS Institute, Cary, North Carolina, USA).

Fisher's exact test was calculated for frequency counts, and unequal variance t test for continuous measurements.

RESULTS

The analysis included 20 symptomatic patients with contralateral disease and 20 truly asymptomatic patients. All patients had risk factors consistent with severe atherosclerotic disease. Baseline characteristics are presented in table 1.

Figure 4 (A) T1 weighted imaging of an asymptomatic atheroma (left side) before (1) and 36 h after (2) infusion of ultra small superparamagnetic iron oxide (USPIO). Obvious fibrous cap enhancement suggesting plaque stability and/or thick fibrous cap can be seen in the post imaging (yellow arrow). (B) Pre and post USPIO imaging at the same level. T2* weighted spiral sequence with quadruple inversion recovery preparation to null the luminal blood pool. Enhancement can be seen in the post imaging (yellow arrows).

Mean stenosis in the contralateral plaques was lower than for those that were completely asymptomatic (46% compared with 63%; $p = 0.001$), as measured by conventional angiography and according to NASCET criteria.¹⁸

Patients had 1–6 MRI slices, providing sectional images of the carotid plaque. This resulted in a mean of 14.2 quadrants per symptomatic patient with contralateral disease (range 4–24), and 15 quadrants per truly asymptomatic patient (range 4–24).

Twelve (60%) contralateral patients showed USPIO signal loss ($\geq 10\%$ in two or more quadrants between the pre and post Sinerem MRI scans), compared with six (30%) truly asymptomatic patients ($p = 0.111$) (fig 2).

For contralateral patients, the mean percentage of quadrants showing any signal loss was 53%, compared with a mean percentage of quadrants from truly asymptomatic patients of 31% showing signal loss ($p = 0.025$) (fig 3). The mean percentages showing enhancement were 44% and 65%, respectively ($p = 0.024$) (fig 4).

According to the repeated measures model described previously, the contralateral plaques showed a significant mean signal intensity decrease of 1.4% after USPIO infusion (95% CI 6.4% decrease to 3.5% increase). The asymptomatic plaques showed a mean signal intensity increase (ie, enhancement) after USPIO infusion of 7.1% (95% CI 2.2% to 12.2% increase). The mean signal difference between the two groups was 8.6% (95% CI 1.6% to 15.6%; $p = 0.017$) (fig 5).

DISCUSSION

USPIO enhanced MR imaging is a promising non-invasive method to identify high risk atheromatous plaque inflammation in vivo in humans, in which areas of focal signal loss on MR imaging have been shown to correspond to accumulation of iron particles in ex vivo specimens.^{13 15} USPIO is thought to accumulate predominantly in activated macrophages either at the shoulders or in the necrotic lipid core of ruptured and rupture prone human atherosclerotic lesions. Signal loss on T_2^* weighted imaging as a result of USPIO uptake may be

considered to be a surrogate measure of the extent of inflammation within the plaque.^{16 19}

The thrust of this study was to explore whether there was a difference in the degree of MR defined inflammation between asymptomatic plaques in patients with known contralateral symptomatic disease and completely asymptomatic ones. The primary findings were as follows:

- (1) Patients with contralateral asymptomatic disease showed more inflammatory activity than did the completely asymptomatic cohort, as demonstrated by normalised signal loss in significantly more quadrants and a significant decrease in mean signal intensity after USPIO infusion, despite a mean lower grade of luminal stenosis (46% vs 63%).
- (2) Completely asymptomatic individuals had significantly more quadrants with signal enhancement (possibly implying a larger fibrous cap component and hence possibly greater plaque stability) but there was also a subset of quadrants showing signal loss.

The results of this study support the idea that USPIO may be useful in the assessment of inflammatory activity in asymptomatic carotid atherosclerotic plaques. We have previously shown that almost 100% of symptomatic carotid plaques demonstrated USPIO uptake in contrast with decreased uptake in any asymptomatic contralateral lesions.¹⁶ In turn, the contralateral side to the symptomatic stenosis showed more USPIO enhanced MR defined inflammation than the truly asymptomatic plaques. These findings are consistent with the hypothesis that inflammatory atheroma is a systemic disease and suggests that one inflamed symptomatic vascular bed is likely to increase the risk of other arterial vessels to become inflamed.

However, this assumption can only be validated from large scale prospective natural history studies of both contralateral disease and truly asymptomatic disease. Unfortunately, at the time of writing no such study exists and therefore although this

Figure 5 Ultra small superparamagnetic iron oxide enhanced MRI signal change for 20 truly asymptomatic and 20 contralateral patients. Boxes show quartiles and median across quadrants for each patient. Whiskers show minimum and maximum values. Horizontal reference lines show group means from the repeated measures model (solid for asymptomatic, broken for contralateral).

study represents interesting preliminary work, it requires validation not only in terms of larger number of patients but also corroborative natural history data. Were such validation to be possible, there may be a strong argument in the future for following these two patient groups prospectively in a future USPIO study to determine the number of cerebrovascular events that occur. An interesting question is whether or not there is a correlation between the degree of USPIO uptake and the development of symptoms over time, and only a large longitudinal study would be able to answer this question.

Of the truly asymptomatic carotid patients, three were recruited from a cardiovascular clinic prior to CABG and as such had a symptomatic coronary vasculature territory, albeit not carotid. It may be expected that these patients would have a higher degree of inflammation than those who had no symptomatic vasculature lesion. Numbers were obviously too small to perform a meaningful subgroup analysis although this is an interesting question that needs to be addressed in the future. It is highly clinically relevant as patients awaiting coronary revascularisation who are found to have a degree of carotid artery stenosis may still be offered carotid endarterectomy prior to CABG. It remains unclear whether this is clinically appropriate.

For the purposes of this study, the patients were deemed to be truly asymptomatic if they had no symptoms whatsoever in the relevant carotid territory. Since a great deal of interest has been voiced in the literature concerning the systemic nature of inflammatory atheroma, it may be argued that a patient with symptoms in another vascular territory, for instance angina or myocardial infarction in the cardiovascular system and intermittent claudication in the peripheral vascular system, would likely have a higher systemic inflammatory burden in their atheroma than a truly asymptomatic individual. Thus differences found between these two groups may well be greater than this study would suggest as the truly asymptomatic group was perhaps slightly diluted with cases that were symptomatic in other vascular territories.

The role of surveillance of both contralateral disease and truly asymptomatic carotid stenoses remains unclear. It has been previously argued that the onset of symptoms preceded recognition of disease progression on each occasion and that none of the observed strokes could have been prevented by postoperative surveillance.^{17–20} However, contralateral surveillance in these studies was performed using either duplex ultrasonography or conventional angiography, which are unable to look at plaque morphology in detail and may underestimate atheroma burden because of the process of arterial remodelling.³ Natural history suggests that contralateral plaques have a 1–2% risk of ischaemic sequelae per annum.^{1–17} This is not in keeping with the degree of inflammatory burden detected (95%) but subclinical microembolic phenomena could be occurring. Furthermore, the significance of cerebral white matter lesions best imaged on FLAIR MRI sequences, which have been shown to be an independent predictor of future stroke risk in several CT and MR based studies,^{21–23} remains controversial. Although the long term risk of stroke in the non-operated internal carotid artery territory appears to be small, progression of the carotid stenosis was detected in 7–26% of patients.^{24–25} Today, with improved imaging techniques and with a better understanding of the atherosclerotic process, disease progression could be better monitored and the risk of stroke predicted. It is worth noting that in these older studies, there were a substantial number of patients who were lost to follow-up because they were either too frail, had too far to travel or died from one of their other comorbidities, most often as a result of myocardial infarction, underlining the truly systemic nature of the atherosclerotic process.

The completely asymptomatic plaques showed an overall normalised mean signal enhancement. Enhancement may be related to low concentrations of USPIO within the plaque²⁶ (as T_1 shortens at low concentrations before a T_2^* susceptibility effect produces an exponential drop in signal at higher concentrations). As there is a lack of phagocytic activity in these plaques, it is likely that USPIO concentrations locally will be reduced and little clumping of particles will occur in phagolysosomes and hence reduced number of signal voids will be seen on T_2^* weighted MR imaging. Asymptomatic enhancement may therefore be related to plaque stability. It is possible that this may go some way to understanding the relatively low event rate from the asymptomatic contralateral side as well as from a truly asymptomatic carotid stenosis.

At first glance, statistical analysis of the patient baseline data reveals a significant difference between the degree of stenosis between the contralateral and truly asymptomatic groups (46% v 63%, respectively). Thus it should naturally follow that the higher the stenosis the greater the inflammation and therefore the higher the risk. This was in fact not the case as the group with the least amount of stenosis (ie, the contralateral group) had the highest degree of USPIO defined inflammation, quite contrary to conventional expectations.

Limitations of the study include, by design, there was no corroborative evidence with histology although Trivedi *et al* have shown that there is good correlation and colocalisation of USPIO uptake on MRI and USPIO staining of activated macrophages within carotid plaques.¹³ Studies have suggested that calcification may affect overall inflammatory burden²⁷ and this may be a confounding factor. We noticed no obvious difference between the calcification observed in the imaging of the two patient cohorts although MRI is not the modality of choice for quantification of calcification within atheromas. However, new advances in imaging of ultra short T_2 species²⁸ may facilitate such quantification using MR in the future.

The results indicated that there was a significant difference between the degree of stenosis in truly asymptomatic patients and the symptomatic individuals with contralateral asymptomatic disease. However, the relationship between stenosis and USPIO uptake is interesting. At least in these cohorts, USPIO attributable signal loss was found to be greater in the contralateral asymptomatic plaques than in the completely asymptomatic ones, despite the fact that the atheroma on the contralateral side producing a significantly lower degree of stenosis than truly asymptomatic atheroma according to NASCET criteria. Thus USPIO uptake is likely to enhance risk stratification compared with luminal stenosis alone.

Despite this interesting observation, quantification of macrophage burden by USPIO signal change remains unclear and the technique described in this study in quantifying signal change is by no means definitive as numbers are still small who have had USPIO infusions. This study has also not directly addressed the inflammatory load in patients with bilateral asymptomatic disease who are generally thought to have a higher risk of stroke than patients with a unilateral asymptomatic carotid stenosis.²⁹

CONCLUSIONS

Truly asymptomatic plaques seem to demonstrate inflammation but not to the extent of the contralateral asymptomatic stenosis to the symptomatic side. Inflammatory activity may be a significant risk factor in asymptomatic disease.

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