Chemical shift magnetic resonance imaging of human atheroma

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SUMMARY Fifteen necropsy specimens of human descending aorta and from eight patients with atheromatous vascular disease were studied by magnetic resonance imaging at 0.5 T. Images were acquired in coronal and transverse planes to localised protruding lesions and then chemical shift imaging was performed by techniques described by Dixon and by Hinks. These techniques produce images in which signal strength is proportional to lipid content. The signal was expressed as a percentage of that from extravascular fat. The total lipid content and its distribution within the plaques were noted. After imaging, the postmortem specimens were examined histologically and the lipid content of the plaque was assessed on a semiquantitative scale. The distribution of lipid within the plaque and between intima and media was also noted. The findings of chemical shift imaging agreed well with histological examination both for total lipid content and for distribution within each plaque. Chemical shift imaging also provided an assessment of the lipid content of the plaques measured in living patients, but validation was more difficult. The usefulness of the technique in routine clinical practice remains to be established.

Atherosclerotic arterial disease is the commonest cause of death and disability in Europe and North America. Its pathogenesis is controversial but various lesions affect the arterial wall—from non-protruding fatty streaks to more complex lesions consisting of lipid, smooth muscle, and fibroblasts, which are occasionally calcified. A widely applicable technique for the detection and classification of atheroma will provide not only a method of detecting and monitoring the disease at an early stage, but also a method studying its development and response to intervention.

Conventional magnetic resonance imaging is able to show atheromatous lesions in postmortem human arteries, in animal models, and in patients with atherosclerosis. Most studies, however, have relied upon distortion of the arterial lumen and have not used direct visualisation of the atheroma. Those that have, have used conventional techniques that image hydrogen irrespective of the chemical environment, and have not exploited the chemical shift of resonant frequency between the hydrogen in water and that in fat (3:3 parts per million). When nuclei with only one resonant frequency are imaged rather than the entire spectrum of resonant frequencies the technique is called chemical shift imaging. With these techniques magnetic resonance should be able to detect atheroma non-invasively and to classify it according to its lipid content.

Our aim was to show the potential of magnetic resonance chemical shift imaging in postmortem specimens and in living patients. We used two different chemical shift imaging techniques. The method of Dixon gives an image in which pure water and pure fat produce no signal and tissues with a mixture of water and fat have higher signal. The method of Hinks and Quencer is a true water or fat imaging technique where only signal from water or from fat contributes to the image.

Patients and methods

METHODS

We used a Picker International Vista MR2055 machine magnetic resonance imaging at 0.5 T. To obtain conventional images we used a spin echo sequence (repeat time 1000 ms, echo time 40 ms) with two repetitions of 256 phase encoding steps for the aortic specimens.
Water. The second water precess with the same phase at the time of the echo and the signal is the sum of that from fat and water. Because the phases of fat and water protons are diametrically opposed at the time of data collection.

For the Dixon technique of chemical shift imaging two images were acquired, the first with a conventional spin echo sequence with an echo time of 40 ms, and the second with a modification of the sequence where the 180° pulse was applied 3-5 ms early (16.5 ms after the 90° pulse) but the echo time remained at 40 ms (fig 1). The first sequence gives an “in phase” image, because the protons of fat and water precess with the same phase at the time of the echo and the signal is the sum of that from fat and water. The second sequence gives an “out of phase” image because the phases of fat and water protons are diametrically opposed at the time of data collection. The signal is seen in pixels containing a high percentage of water or fat, but if there is an equal amount of each, the opposing phases lead to cancellation of signal. Subtraction of the two images gives a map of the pixels containing a mixture of fat and water while pure fat and pure water give no signal.

In the Hinks technique, a modified spin echo sequence is used and a narrow bandwidth 90° radiofrequency pulse is applied in the presence of a slice selection gradient. Since the resonant frequencies of water and fat differ, those from the excited slice of water and of fat are offset from each other in space. The offset as a fraction of slice thickness is equal to the chemical shift divided by the pulse bandwidth, and if the pulse bandwidth is less than the chemical shift the two slices do not overlap. The 180° radiofrequency pulse is applied in the presence of an opposite slice selection gradient, so that the slices of water and fat experiencing this pulse are offset in the opposite direction. The position of the slices can be adjusted so that only fat or only water

Fig 1 Diagram of pulse sequences. (a) A conventional spin echo sequence with an echo time of 40 ms gives an in phase image because fat and water precess with the same phase at the time of the echo and the signal is the sum of that from fat and water. The second sequence is a modified asymmetrical spin echo sequence that gives an out of phase image in which the signal is the difference of that from fat and water. (b) The phase of fat and water protons differs at the time of image acquisition in the “in phase” and “out of phase images”. Subtraction of the two images results in signal only from voxels containing both fat and water.
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experience both radiofrequency pulses and so only fat or only water give a signal.

Experimental calibration of the chemical shift images was performed by scanning a tube containing unmixed oil and water with a 20 mm thick slice parallel to the interface between the two. The proportion of oil and water was varied by moving the slice to contain more or less oil. The signal produced by the chemical shift imaging techniques could therefore be studied as a function of the proportion of oil present.

Patients
Specimens of the descending aorta obtained at necropsy were distended with air at 80 mm Hg pressure and scanned in a chamber maintained at 37°C. A surface coil was used and a coronal image was first obtained followed by transverse images through areas with suspected atheroma. The Dixon method was used and signal strength in the subtraction image was expressed as a percentage of signal strength from extravascular fat.

After the scan, the aorta was opened to confirm the presence of atheroma and histological examination was performed with haematoxylin and eosin, elastic Van Gieson, and oil red O stains. Lipid deposition within the plaque was assessed by a pathologist, who was unaware of the magnetic resonance findings, using a semiquantitative scale from 0 to 3, where 0 corresponded to no lipid deposition and 3 to heavy deposition.

We also studied two patients with coronary artery disease and six with peripheral vascular disease. Atheromatous plaques within the thoracic and abdominal descending aorta were located by spin echo imaging. The Dixon method of chemical shift imaging was used to measure the proportion of lipid within the plaques by comparison of the signal strength with that from extravascular fat.

Results

Figure 2 shows the results of the experimental calibration of the Dixon method of chemical shift imaging. The signal strength in the subtraction image was plotted as a function of the proportion of oil, and a maximum signal was obtained with a 50% mixture of water and fat as expected. Pure water and pure fat gave a relatively low signal.

The table shows the correlation between histological grading of lipid within 10 atheromatous lesions and the signal intensity in the lesions in the Dixon subtraction image. There is a relation between the two, with the three plaques with lowest signal (8%, 8%, and 14%) having absent or little lipid (grade 0 and 1), and the other plaques with signal intensity >25% having moderate or high lipid content (grade 2 and 3).

Figure 3 shows a lipid rich atheromatous plaque in a postmortem aorta. The in phase magnetic resonance image shows both the plaque and an area of extravascular fat. The subtraction image shows relatively high signal within the plaque (45% of signal from extravascular fat), indicating a high lipid content. This was confirmed histologically by grade 3 lipid deposition.

Lipid deposition within the plaques was not uniform. Figure 4 shows a plaque with mainly intimal lipid. This was shown by the magnetic resonance images and confirmed histologically.

Figure 5 shows a lipid deficient plaque. There is very low signal in the subtraction image within the plaque, and the histological grading was 0.

Figure 6 shows an oblique section perpendicular to

![Graph](image_url)

**Table** Signal strength from the area of atheroma in the subtraction image of the Dixon technique (expressed as a percentage of signal from extravascular fat) compared with the histological grading of lipid deposition with the plaque

<table>
<thead>
<tr>
<th>Plaque number</th>
<th>Signal (%)</th>
<th>Histology</th>
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<tr>
<td>1</td>
<td>8</td>
<td>0</td>
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<td>2</td>
<td>8</td>
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<tr>
<td>3</td>
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Fig 3  (a) Postmortem aortic specimen imaged by a conventional spin echo sequence together with a phantom containing oil floating on water. Atheroma affected approximately half of the circumference of the vessel and the largest accumulation is arrowed. (b) The subtraction image shows high signal in extravascular fat and in the lesion. The ratio of signal intensity compared with extravascular fat is 45%. The oil and water in the phantom give low signal as expected. (c) Histology of the same plaque (oil red O stain) showing grade 3 lipid deposition (red) within the intima (I) and media (M).
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Fig 4  (a) Atheroma affected 70% of the circumference of this aortic specimen. (b) The subtraction image shows high signal (33% of extravascular fat) limited to the intima in one location (arrowed). (c) Histology of the same plaque showing grade 3 lipid deposition (red) limited to the intima (I).

The descending abdominal aorta in a 60 year old man with peripheral vascular disease. The circular lumen is distorted by thickening of the wall corresponding to an atheromatous plaque. The subtraction image shows a low signal within the plaque indicating a low lipid content. End diastolic images were found to be more useful than systolic images for definition of the vessel wall, because at this phase of the cardiac cycle blood is moving relatively slowly and gives high signal and good contrast with the wall.

Figure 7 shows another plaque in a 57 year old man with peripheral vascular disease. There is high signal
Fig 5  (a) Conventional image of a lipid deficient plaque in a postmortem aortic specimen (arrowed). (b) The subtraction image shows very low signal (8%) compared with that from the extravascular fat. (c) Elastic Van Gieson stain of the same plaque indicates a predominantly smooth muscle and fibrous plaque. Lipid deposition would appear as vacuoles in this alcohol treated stain, but there are none.
in the subtraction image, indicating a high lipid content.

Figure 8 shows an example of the Hinks method of chemical shift imaging. A postmortem aortic specimen with atheromatous lesions was scanned together with a phantom of oil and water. The technique produces true fat and true water images, in contrast with the Dixon technique which produces high signal from mixtures of fat and water. This is apparent from the phantom. In the specimen, a high signal is seen in the extravascular fat in the fat image but almost no signal from lipid within the vessel wall.

Discussion

We showed that it is possible to use the chemical shift between protons in lipid and in water to acquire magnetic resonance images in which signal strength depends upon lipid content. Theory predicts that, with the use of the Dixon technique, a maximum signal will be obtained in the subtraction image from an equal mixture of lipid and water, and that low signal will be obtained from pure water and from pure fat. The theory is complex, however, and it is difficult to predict the exact shape of the curve because the signal strength is strongly dependent upon the imaging variables and upon the relaxation times of water, fat, and their mixtures. Nevertheless, we showed a maximum signal from an equal mixture of oil and water, and we were able to use the signal strength from extravascular fat as a standard. An unexpected finding was that extravascular fat gave a high signal, implying that there was a mixture of fat and water in "pure" fat. This may be explained by the presence of connective tissue and other non-lipid cellular components.

Since the shape of the relation between signal strength and fat content has a maximum, any single measurement of signal could correspond to two proportions of fat. It might therefore be difficult to know whether a plaque with low signal contains either pure fat or pure water, and unless the proportion of lipid is always either one side or other of the maximum, ambiguities could arise. In practice this is not the case because even the most lipid rich plaques have a relatively low fat content. The percentage of intimal and medial lipid in atheroma varies with different types of lesions; in the fatty streak, for example, it is 8% while in the porridge type it is
Fig 7 (a) Spin echo image perpendicular to the descending aorta of a 57 year man with peripheral vascular disease. The wall is irregularly thickened with atheroma and the main accumulation is arrowed. The subtraction image (b) shows high signal within the lesion indicating high lipid content (similar to the marrow in the lumbar vertebral body (double arrow)).

18%, but it is reasonable to equate an increasing signal with increasing lipid content.

The shape and composition of arterial segments containing atheroma are of considerable importance. Plaques of different shape (concentric or eccentric for example) have different effects on the arterial wall in terms of their potential for thrombosis and arterial spasm. The lipid content may also affect the propensity for fissuring, ulceration, and thrombosis. Other properties of atheroma that may be affected by the lipid content are the short term and long term outcome of angioplasty and the potential for regression. Although little is known of these areas it is possible that there is a link between the composition of atheroma and its susceptibility to mechanical or chemical intervention. There is certainly evidence of regression in laboratory animals and that it may be possible to alter the rate of progression in man.

Although most of our studies were in postmortem specimens we showed the feasibility of using chemical shift imaging to study atheroma in living patients. This application is difficult and there are several factors which need careful attention. Motion artefact could be a problem and if a signal is obtained from moving blood it may produce noise on the image and either mimic or obscure areas of atheroma. We did not find this to be an important problem and we preferred to acquire images at end diastole, when the relatively slowly moving blood gave a high signal that aided the delineation of the vessel wall. A second problem is that accurate registration is important in any technique that uses subtraction of images. The patient must not move between acquisition of the two images of the Dixon technique, although with suitable modifications to the scanner it should be possible to interleave acquisition of the two images so that they are acquired at the same time.

Another factor influencing the ease of chemical shift imaging is magnetic field strength. The absolute chemical shift (in Hz) depends upon the field strength and in the Hinks technique greater separation is obtained between the water and fat slices at
higher field strengths. High field strength would therefore make the technique more reliable for static specimens, but it may produce more motion artefact in patients.

Magnetic resonance imaging provides a method of assessing the site, size, and shape, as well as the lipid content of atheromatous plaques. Validation in vivo is more difficult than in vitro but images were obtained. The utility of the technique in routine clinical practice remains to be established.

We thank the Arabian Gulf University, the board of Governors of the National Heart and Chest Hospitals, the Coronary Artery Disease Association (CORDA), and Picker International Ltd, for financial support. We thank Professor Michael Davies and Professor Colin Berry for providing us with specimens, and also Miss Elisabeth Burman, Mr Karl Lotey, and Miss Marjorie Watson for their assistance.

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*Br Heart J* 1989 62: 81-89
doi: 10.1136/hrt.62.2.81

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