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Short communication

Echo planar imaging — the key to preventing acquired cardiovascular disease

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Many of those present at this Symposium have spoken with great affection about the tremendous contributions Sir Peter Mansfield has made to their careers. I am certainly grateful that I visited Nottingham in September 1976 and saw the first human magnetic resonance images produced on a home-built machine. Although in retrospect it is difficult to understand why the low spatial resolution images made such an impression, nevertheless it was the beginning of a long and special relationship during which I have received invaluable advice and scientific help: in return I have been a disciple of echo planar imaging (EPI).

The demonstration of MR almost coincided with the discovery by Sir John Vane of Prostaglandin X, later to become known as Prostacyclin, for which he was awarded a Nobel Prize. To me, these two developments meant that for the first time in the history of medicine there was a glimmer of hope for the understanding of acquired cardiovascular disease. There might be a potential method of studying the disease non-invasively and also an understanding of its mechanism.

Most cardiovascular deaths are due to a single pathological process — the formation of atheroma. Vane's work suggested that this might be an aberration of the normal clotting mechanism. Normal vessel walls secrete prostacylin in minute quantities. It has a half-life of about a minute and its purpose is to prevent the circulating blood platelets from adhering to the vessel walls and breaking down to initiate clotting. The blood platelets contain a very active substance, thromboxane A^2. Both of these substances have a common precursor, arachidonic acid. The key to the balance in life which prevents us from clotting solid is that the half-life of thromboxane A^2 in the platelets is slightly shorter than that of prostacyclin. Aspirin helps to push the balance towards prostacyclin. As the blood platelets pass through the 40 000 miles or so of vessels within us therefore, they do so without adhering. If a vessel wall is cut, the platelets streaming past detect an area which is not secreting prostacyclin and instantly adhere to the raw surface and begin to break down to form the fibrous elements of a clot and within moments the breach is plugged. What is more remarkable is that one of the breakdown products of the platelet is in an extremely powerful platelet-derived growth hormone, the platelet-derived growth factor (PDGF). Within hours of the injury the muscle layer in the vessel wall has grown to heal the breach permanently. If, for some reason, for example the inhalation of tobacco smoke, areas of the blood vessel will fail to secrete prostacyclin and circulating platelets will adhere and break down. Their breakdown product, the powerful growth hormone, causes the muscle layer in the vessel wall to overgrow. The only space it can occupy is the lumen of the vessel. Although this process is happening all the time, the majority of these overgrowths or plaques are resorbed. Some, however, become infiltrated with lipids and pose a potential hazard. If the plaque is lipid rich, containing globules of fats which are semi-liquid at body-temperature, and the cap over them is thin there is a risk that they will rupture due to the 'venturi effect' causing a pressure drop across the narrowed section of the vessel. If this happens blood platelets will be activated and there will be the rapid formation of a blood clot. If this clot occurs in a vessel supplying a vital organ, sudden death may ensue. If the blockage is in a coronary artery an area of heart muscle will be 'stunned' or infarcted and the subject may die with a coronary attack. If the blockage is in a blood vessel supplying the brain at best there may be a transient

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ischaemic attack (TIA) and at worst a debilitating stroke or sudden death. Fig. 1 shows a typical atheromatous plaque in a coronary artery.

Clearly there would be no point in trying to prevent or contain a disease which was an inescapable penalty for belonging to the species *Homo Sapiens* and growing older. Demographic evidence however shows that this is not the case. Whilst today nearly half of all deaths in the western world are from cardio-vascular disease this has not always been the case. Cardio-vascular disease

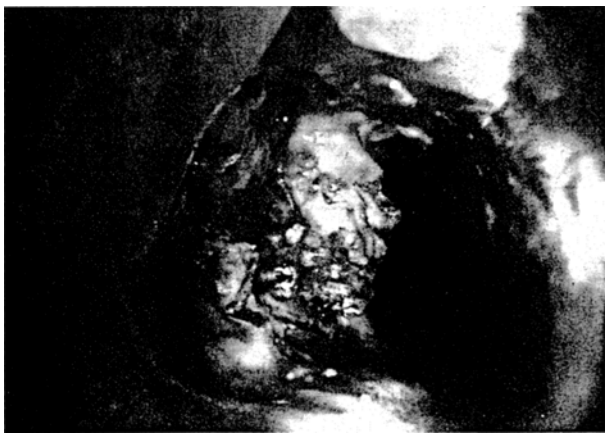

Fig. 1. An atheromatous plaque in a coronary artery. This has the typical appearance of a lipid rich plaque containing globules of fats which are liquid at body temperature and covered by very thin layers of tissue. A narrowing of this magnitude causes a considerable increase in velocity with a corresponding pressure drop due to the venturi effect making it more likely that the plaques will rupture.

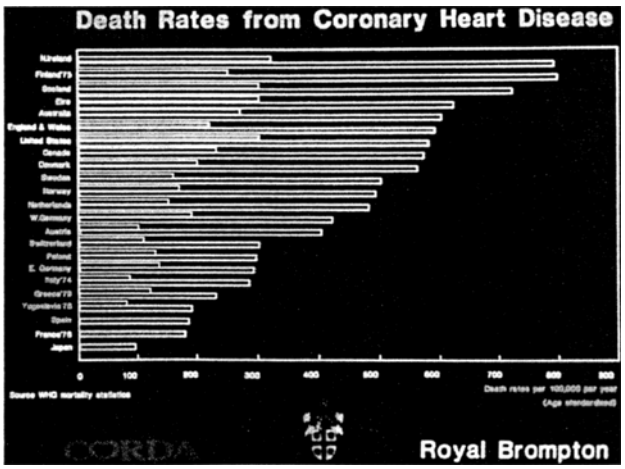

Fig. 2. This shows the death rates from coronary heart disease in different countries from which there are reliable statistics. The United States and the UK share a high incidence, whereas France and Japan have a much lower incidence. The United States spends the highest proportion of its GDP on medical care and Japan the lowest. The UK, which spends almost as little as Japan, shares bad results with the United States a very high incidence whereas France, which spends an average amount on health care, shares with Japan the lowest incidence.

was uncommon in Europe after the end of the First World War but it has increased steadily since (though the rate of increase slowed during the Second World War). The incidence of occlusive vascular disease varies from country to country. France, which is a near neighbour with an apparently genetically similar population, has a much lower incidence of occlusive vascular disease than the UK. Even when allowance is made for differences in death certification we appear to be five times as susceptible to occlusive vascular disease. Japan has an even lower incidence, whereas Finland, Northern Ireland and Canada share with the British the highest incidence. Fig. 2 shows the relative incidence in countries which have an approximately similar form of death certification and produce sound statistics.

In summary, this is a disease which varies in the same population from time to time and has a different incidence in genetically similar populations living in different parts of the world. Any disease which behaves in this way must have causative factors and for the past half century a search has been made to identify these. A number of risk factors have been identified; genetic background, a high blood cholesterol, obesity, diabetes, possibly a sedentary lifestyle and above all smoking. Many of the sudden deaths which occur however are in subjects with no obvious risk factor, whereas others with several risk factors live beyond the average normal life span. Risk factors should be regarded as multipliers of an underlying unknown pathological process.

Contemporary medical management of this disease process which focuses on end stage disease does not work. There is no correlation between the amount spent or the effort expended on the medical management of occlusive vascular disease and its incidence. The USA spends over 15% of its growth domestic product (GDP) on health care, France 7.2%, the UK 5.4% and Japan 4.4%. The US spending the largest proportion of its GDP and the UK nearly the lowest, show the highest incidence of premature death from occlusive vascular disease whereas France, a high spender and Japan the lowest spender share the lowest incidence which is of about 20% of the rate in the UK and USA. Indeed life expectancy in Japan has increased, rising by 7.5 years for men and 8 years for women during the last 25 years.

Through the application of magnetic resonance imaging to the complex area of secondary and tertiary prevention there lies the potential to contain this disease process. Medical practitioners have only a limited range of options available to them and these are:

Primary prevention which involves the elimination of a known causative factor or rendering the population immune, e.g. draining mosquito swamps to prevent malaria and the irradication of poliomyelitis by vaccination. So little is known about the causative factors of atheroma that primary prevention is presently beyond reach.

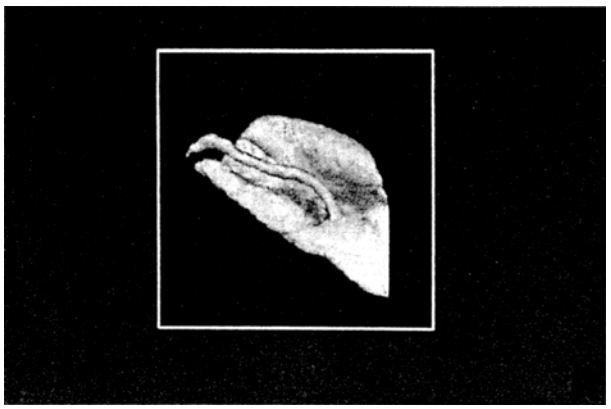

Fig. 3. This is part of a three-dimensional image of the origin and the first part of the right coronary artery. It is obtained using spiral echo planar after fat suppresion to avoid partial volume effects around the edges of the vessel. It was obtained at 0.5 T on the CORDA Royal Brompton Mobile Magnetic Resonance machine. This image is velocity encoded in order that any narrowings of the detected using velocity as a sensitive marker.

Secondary prevention is used when the causative factor or factors are unknown. It depends on detecting the disease at an early pre-symptomatic stage when it can be arrested or reversed by preventive or simple therapeutic measures, e.g. the prevention of cervical cancer by the detection of abnormal cells on a smear and the detection of microcalcification on a mammogram. To this must be added the detection of presymptomatic occlusive vascular disease by MR.

Tertiary prevention is the avoidance complications of disease by careful management, e.g. the use of insulin in diabetes to prevent blindness and peripheral gangrene. MR also has a place in tertiary prevention by defining the stages of symptomatic arterial disease.

Palliation. There is a fine dividing line between tertiary prevention and palliation which is often regarded as treatment, e.g. the coronary artery bypass graft (CABG) and angioplasty should probably be classified as palliative procedures because they do not necessarily extend life. They certainly have no effect on the incidence of the disease.

Treatment. There is a grey area between palliation and treatment. Successful treatment involves a complete cure, e.g. the removal of a septic appendix in a young person.

In the context of occlusive vascular disease three questions need to be answered; is the disease present, is it indolent or could it be associated with serious morbidity and can the efficacy of simple preventive measures and pharmaceutical agents be monitored.

Echo planar imaging provides a practical method for addressing these questions. Components of the cardiovascular system, particularly the heart walls, are moving rapidly due to a combination of muscle contraction and respiratory movement of the diaphragm. The coronary arteries which supply the heart with blood are elusive. Even if cardiac gating is applied during image acquisition the images will be blurred due to the fact that the heart is moving with respiration. Respiratory gating however does not provide a complete solution because the heart is under the control of a feedback mechanism. Anyone familiar with physiological records will be aware that there are sudden changes in heart rate and contractility due to messages from the sensory apparatus within specialised organs of the body. Echo planar imaging overcomes all of these problems because the images can be acquired in a short enough time to eliminate movement artefacts. To put this requirement in context a coronary artery may be < 3 mm in diameter yet its range of movement may be erratic and as much as 3 cm in three-dimensional space. Echo planar imaging of the cardiovascular system can be prefaced with modules to encode velocity, for fat suppression or selective fat and water imaging. Fig. 3 is an image of the right coronary artery produced on the Royal Brompton machine operating at 0.5 T using navigator pulses and spiral echo planar acquisition. Fig. 4 (A and B) show the CORDA Royal Brompton machine (CORDA is the charity which has fimded MR research over 20 years at the Royal Brompton Hospital and has favoured projects using the echo planar technique). Velocity encoding is vital because visualisation alone of the vessel does not provide sufficient diagnostic information. What matters to the downstream organ supplied by an artery is not the appearance of the vessel but the flow along it both at rest and during peak demand. Velocity mapping can provide a sensitive indicator for vessel narrowing because there is a velocity increase (and a pressure drop) across the narrowing. Fig. 5 (A and B) are amongst the first images produced where measurement of velocity along the length of a vessel has been used as markers for stenosis in the right and left coronary arteries. The angiograms are provided for comparison. At first sight the angiograms appear better suited to the Radiologist's need for good image quality but do not contain accurate functional data about for example, velocity, flow and, by inference, pressure. MR provides numbers rather than opinions. In addition MR of the coronary arteries is safer and more cost effective than angiography, being unassociated with any significant morbidity.

At the present time, even with a sophisticated machine such as that built by the Royal Brompton physicists and housed in a bus, there is insufficient resolution to visualise atheromatous plaques in the coronary arteries or to analyse them. There is, however, adequate resolution to study the aorta and carotid arteries.

At present the world's first trial using the mobile magnetic resonance scanner for secondary and tertiary prevention of occlusive vascular disease is underway. The trial is known as the CORDA asymptomatic

plaque assessment research (the CASPAR project). This is a longitudinal study in which 250 aymptomatic subjects have already been entered, many of them at yearly intervals. It follows a pilot study carried out on 1264 subjects which was used to develop the technology required for population studies.

The CASPAR project focuses on three areas of the body. The abdominal aorta, the carotid arteries in the neck and the right coronary artery. The first part of the study consists of a number of transverse slices of the abdominal aorta. These images are acquired as magnitude images to visualise plaques, water images and fat images. The latter two are subtracted to measure the amount of lipids in any plaques which might be present. An atheromatous plaque contains 0–28% lipids. The subtraction images can be used to provide an accurate indication of the amount of lipid present in any plaques which are detected and measured, which can then be used for comparison with studies after intervention.

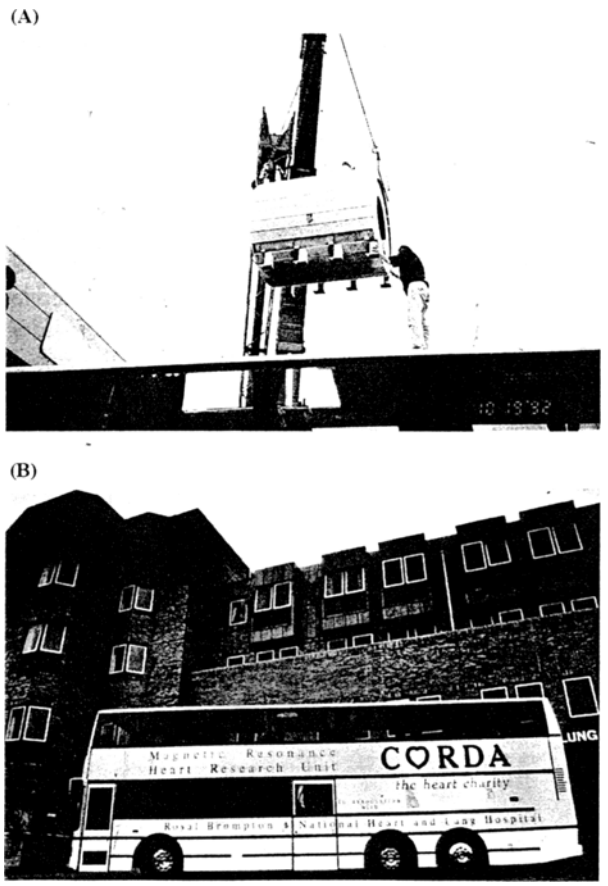

Fig. 4. This shows a passively shielded 0.5 T magnet and its gradients (Fig. 4A) being lowered into a converted motorway bus (Fig. 4B). This unit is used for secondary and tertiary prevention of cardiovascular disease in the community. It was built in-house by the Royal Brompton Magnetic Resonance Unit Staff as a total cost of £383 000.

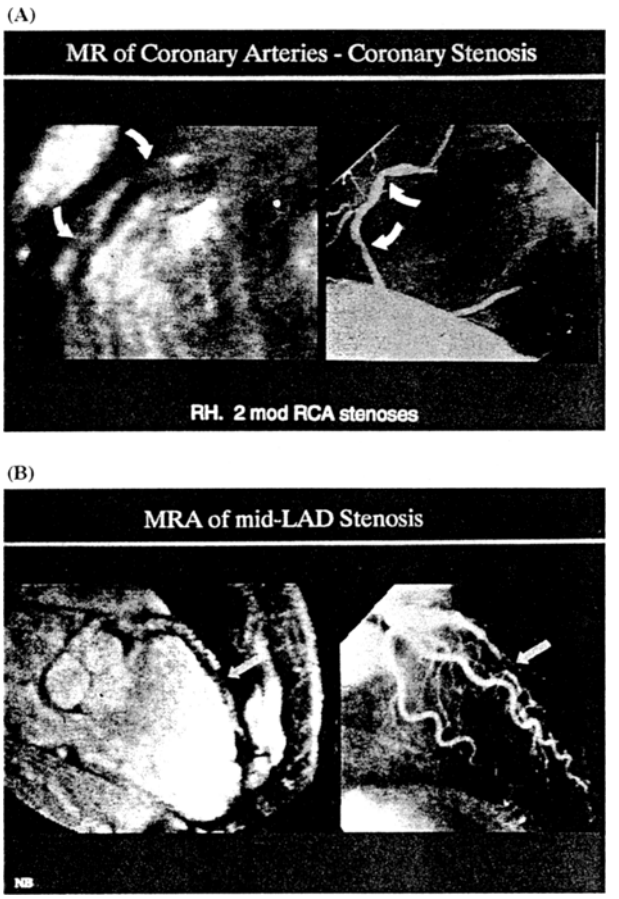

Fig. 5. (A) This is a comparison between a magnetic resonance velocity encoded angiogram of the right coronary artery and a conventional X-ray angiogram. Although the image quality of the magnetic resonance image appears to be not as good as the angiogram the reality of the situation is that it contains far more diagnostic information. The velocity encoding enables assessment of the energy loss across the plaque and the pressure drop. (B) This is a similar comparison for the Left Anterior Descending coronary artery (LAD). The left coronary artery is more difficult to study than the right because it is more deeply placed lying behind the heart. The MR angiogram shown in (A) and (B) are cheaper to produce than the conventional angiograms and are produced without risk to the patient.

The second part of the study focuses on the carotid arteries in the neck in the region of their bifurcation. A similar triad of images are acquired to study the anatomy and lipid content of any plaques. If there is any doubt about the presence or not of a plaque, velocity encoding is used as a marker.

The final part of the study uses a velocity encoded spiral EPI following fat suppression to detect narrowings in the coronary artery.

The advantage of the CASPAR study is that it is a longitudinal study fulfilling the requirement of observation over a period of time. The detection of plaques answers the first important question as to whether the disease is present; chemical shift analysis answers the second question as to whether the plaque is indolent or

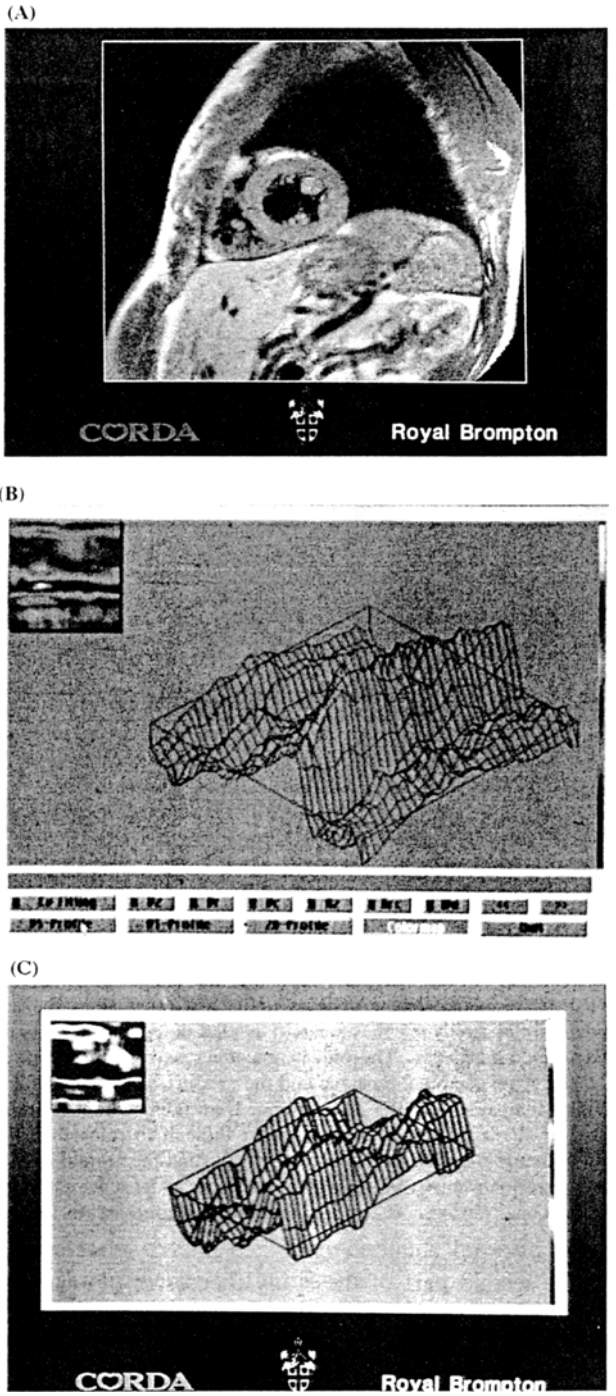

Fig. 6. (A) This is a double oblique image across the heart looking from the apex towards the base up the 'barrels' of the two ventricles. Velocity encoding in and out of plane can be plotted at a number of points round the ventricles against time making it possible to study ventricular contraction and more importantly ventricular filling. (B) This shows a normal heart. (C) This shows an area of abnormal filling and contraction. There is no other method by which these important measurements could be made.

not and overall the methodology can answer the third question to assess the efficacy of simple preventative measures and monitor therapeutic agents.

The shortcomings of the study are that it cannot detect all plaques in the aorta. Technically it could, but the time taken for multislice imaging and chemical shift imaging along the length of the aorta renders it impractical at this stage. There is no evidence as yet that the presence of benign plaques in the aorta and the carotid arteries excludes the possibility of a malignant plaque in the coronary arteries.In conclusion, now that the advantages of EPI have now been widely recognised and increasing number of scanners with this capability are being installed around the world, this will facilitate clinical and research studies in the cardio-vascular system. The questions which we have a responsibility to answer are clear; indeed can there be any more important structural and functional information to be acquired other than that relating to the disease process which is responsible for approximately half of all deaths through its impact on cardio-vascular function. High speed imaging strategies can provide information which cannot reliably be obtained by any other method. Fig. 6 (A, B and C): Fig. 6A shows a short axis view of the heart looking from the apex up the lumen of the ventricles. Fig. 6B shows an analysis of the contraction and relaxation of the heart muscle as it moves in and out of plane against time in a normal heart. Fig. 6C shows abnormal relaxation and contraction which could not reliably be demonstrated by any other technique. EPI will undoubtedly play an increasing role both in the clinically management of disorders of the cardio-vascular system and more importantly in fundamental research.