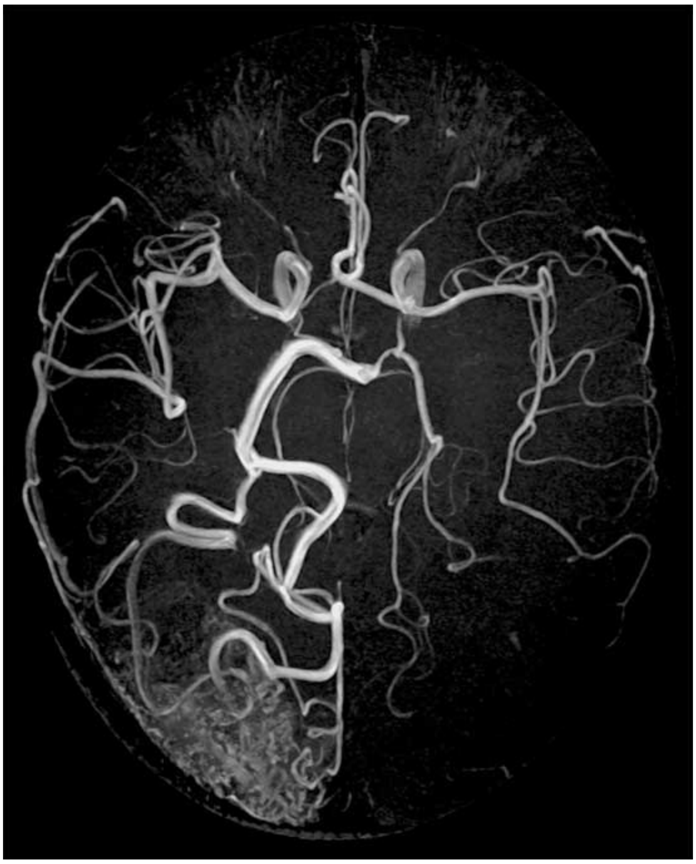
Graduate School of Biomedical Engineering

K M Dale Tan
Tutor: Chris Bertram

BIOM1001 Assignment: Angiography

Mapping the Human Body's Vascular Networks



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Cover Sheet: Assignments

Name:	Tan, Kiok Min Dale
Student Number:	
Group Number:	2
Tutor:	Chris Bertram
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Angiography

Abstract

Angiography is an ever-expanding field of diagnostic imaging crucial to the diagnosis, assessment and treatment of circulatory diseases. It involves the mapping of blood vessels and bloodflow characteristics, enabling treatment of any conditions which may affect one's quality of life. Conditions that may be examined include hypertension, atherosclerosis, and cardiomyopathy. Pre-surgical preparations might also include acquiring an angiogram to avoid accidental severing of key vessels. The concept of angiograms was conceived soon after the advent of x-rays in 1895 and has continued to develop into safer and more advanced methods, such as magnetic resonance angiography. X-ray angiography is the most common and established method which produces the sharpest images. However, the use of contrast media that includes iodine poses many problems, especially with chemotoxicity. CT angiography, although has poorer resolution, has the added ability of visualizing surrounding tissue, but still suffers the same problems with contrast media, like XRA. Magnetic resonance angiography is the new up-and-coming method set to replace XRA as the prime modality in vascular diagnosis because it does not use contrast media. Although at present, more work still needs to be done with regards to slow-flowing or non-flowing blood. Fundus fluorescein angiography, the odd one out, has also been shown to be valuable in the field of macular imaging, and will greatly benefit those suffering from macular degeneration, by aiding surgery in that field. Improvements to all these modalities now include the production of better contrast media and fusion of modalities to take advantage of each one's strengths and shortcomings.

Introduction

Angiography is the science of mapping and imaging the circulatory system. It is defined in Black's Medical Dictionary as "rendering of the blood vessels visible on an X-ray film by injecting into them a radio-paque substance… This procedure demonstrates whether there is any narrowing of the lumen (opening) of the vessel"[1]

Medical imaging has always been essential to the proper diagnosis and treatment of a patient's ailments, and angiography forms an essential portion of it. This is because the understanding of circulation is of utmost importance to a physician simply because it's everywhere in the body. Blood circulation ensures that essential nutrients are transported to wherever they are required, and toxins are removed with haste to prevent poisoning. It must therefore be recognized that the imaging of blood vessels is valuable to the correct diagnosing and therapy of many problems.

In the ensuing report, the pathology of the blood vessels will be discussed, followed by some history of angiography. Each modality above will then be looked into with more detail, and an investigation of potential developments in this field will then wrap up this report.

The Need to Examine Blood Flow…

A great deal of problems can occur in the circulation of blood, many of which would threaten a person's life. The need for the imaging of the vessels can never be over-emphasized. Being able to see the way blood flows gives medical practitioners the ability to anticipate possible problems, investigate their effects and plan intervention, if required.

Any narrowing of the lumen will reduce blood flow to all points downstream from the point of stenosis (or occlusion), and therefore reduce the ability of the blood to transport material in and out of the tissue. Stenosis may occur in a variety of ways. Sometimes, the vessels were simply malformed from the beginning. The network of blood vessels evolves all the time. They develop when the need for them arises and degenerate when that need no longer exists. Sometimes, malformations occur spontaneously during formation of these vessels, and anomalies such as kinkage, irregular lumen diameters, and blockage occurs.

More often than not, stenosis is an effect of old age, where there has been a prolonged buildup of cholesterol, fats and other deposits. The vessel effectively hardens with the formation of plaque in the walls, especially in arteries due to their muscular nature. As buildup occurs, the walls of the vessel thicken and the lumen begins to shrink due to that process. While these problems pose no immediate threat to a person, a host of other problems may develop.

For example, a blood clot traveling through a narrowed region may be trapped, thereby cutting off blood supply to a region of tissue, resulting in the death of the tissue there. The most well-known of this effects being myocardial infarction, or heart attack. This is when oxygen is cut off from the coronary arteries, depriving the heart muscles of much required oxygen, resulting in the stoppage of contractions and most certainly death. If this occurred in say, the carotid artery in the neck, it would have been described as a stroke instead.

The hardening of the blood vessels (arteriosclerosis) may also reduce the ability of the arteries to regulate some of the blood pressure, because of the reduction in flexibility. Because arteries mostly assist in the movement of blood to the extremities, hindrance of those pulsatile abilities results in an increase in blood pressure to satisfy demand. This is commonly termed as ischaemic heart disease.

Arteriosclerosis, in more advance stages, can also result in the formation of aneurysms due to the inflexibility of the vessels. Their inability to stretch causes differences in blood pressure on the vessel walls, and the high pressure (also a result of arteriosclerosis) exploits any weaknesses in the vessels walls. Deformation of the vessel then occurs, and points of weakness start stretching outwards. These bulbous formations stretch the vessel wall to almost the point of breakage, with the potential of causing internal hemorrhages, and therefore, death.

Other cardiac indications for angiography include the diagnosis of "obscure or confusing problems in heart disease"[2]. For example, cardiomyopathy (the death of the heart muscle) carries similar, if not identical symptoms to occlusive coronary vessel diseases, and the patency of the vessels on the heart would clearly differentiate the two diseases.

Beyond the realm of cardiovascular diseases, problematic blood vessels also affect other important regions of the body. In the central nervous system (CNS), circulation problems affect the supply of oxygen and glucose to tissue, which impairs the function of the nerves. Motor and thought processes are therefore impaired, leading to more serious problems of retardation.

Other areas subjected to possible impairment when blood supply is affected include (most notably) the retina, the kidneys, the liver, the lungs and the limbs. Other than being affected by poor blood supply, organs may also be affected by larger-scale, systemic diseases such as hypertension, high blood pressure, diabetes, and the like.

In essence, potentially every portion of the human body is affected by circulation problems, and it is therefore important that we are able to map out affected vessels and therefore be able to intervene if necessary.

Getting the Angiogram Done...

Introduction to the modalities

There are many possible ways in which an angiogram can be acquired, each with their own benefits and shortcomings.

The major modalities of X-Ray, Computed-Tomography (CT), Magnetic Resonance (MR) and Fundus Fluorescein angiography will be covered in this section of the report. These methods produce an image normally involve a contrast media to differentiate between the vessels and the surrounding tissue.

The basic principles behind each method will be covered first, followed by any considerations that are involved in the use of that modality. A comparison of the modalities will then wrap up the entire section.

X-Ray Angiography (XRA)

A Bit of History…

X-ray angiography is the oldest, most established method of angiography involving the use of x-rays and an iodine-based contrast media in creating an image of the blood vessel.

As early as 1844, Claude Bernard used a catheter to inject the contrast media into a horse for the purpose of examining the jugular vein, the carotid arteries and both ventricles of the heart. The first recorded angiogram done on a person was acquired by Werner Forssmann, who, in 1929, passed a catheter up his own forearm and into his right atrium. He did it by guiding it under fluoroscopy (a nurse held up a mirror to show him the fluoroscopic screen), then walked to Radiology (on a different level) and was subsequently documented. Following this, angiography via catheterization was rapidly researched and many techniques. The most notable was developed by Seldinger, who envisaged the use of the percutaneous method by which needles were used to puncture the skin and guidewires inserted, to guide the catheter[2].

Today's digital angiography system is a far cry from the first catheterization and now involves the use of computers and digital storage systems. But in general, the principles, however, have not changed. The process of acquiring an angiogram still involves the use of an iodine-based contrast media, injected into the blood vessels, and photographed using x-rays.

The most common form of X-ray angiographic systems are the Digital Subtraction and Computed Tomographic (CT) systems. CT scanning methods are, however, rather different, and will be covered in a subsection of its own later on in this report.

Digital Subtraction Angiography – an Introduction

The Digital Subtraction Angiography (DSA) System of today has 3 general portions. The first of which is the acquisition system, involving an X-ray source and image intensifier. This hands the data over to the image processing computer via an analogue-digital converter. The image, with artifacts (imaging flaws) subtracted using computer, is then stored in the storage portion of the system, which retains the data via computer hard disks, or in older systems, film.[3]

In this system, the first step to acquiring the angiogram is patient preparation. Lignocaine, a local anesthetic is injected into the selected puncture site, which is normally the inner thigh where the femoral artery is, to reduce pain. Other preparatory drugs may also be used, such as antibiotics (to reduce possibility of infection) and vasodilators (when difficulty in maneuvering the catheter is anticipated).

A skin puncture is then made using a scalpel, followed by a Seldinger needle which is inserted into the artery. A guidewire is then run into artery, and guided to the target site using a feedback system by which a monitor shows what the image-intensifier is currently "seeing". A catheter then follows the guidewire down to the target area and the wire is retrieved. Contrast is injected along the way to ascertain the whereabouts of the tip of the catheter, and finally to ensure that it is in the right location.

More contrast media is then injected down the catheter, normally under fixed pressure and flow rate, and the image of the moving bolus is then captured by the system.

The reason for the term Digital Subtraction is that a "mask" of the tissue in the region in first acquired before the entry of the contrast. This image is then digitally subtracted from the actual image to remove all other imagery with the exception of the contrast. This enhances viewing by removing all other distracting features which might be in the area, leaving an image of the vessels only.

The Contrast Media in DSA

An important aspect of DSA is the use of iodine-based contrast media. A list of contrast agents and their osmolality (the number of charge particles of solute per kg of water) is shown below:

Compound	Osmolality (mol kg^{-1})
Conray 280	1.5
Iopamidol 280	0.47
Ioxaglate 280	0.49
Iohexol 300	0.64
Iopromide 300	0.61
Iopromide 370	0.77

The main consideration in the choice of chemical for contrast media is the chemotoxicity of the chemical, its osmolality, and possible allergic, anaphylactic (hypersensitive) reactions. The ideal contrast media should be able to travel through the body without altering systems in any way.

Most of the contrast media above are large organic molecules with an iodide group attached to it, and are relatively unable to diffuse thru the capillary beds into the tissue fluids, which is what makes them good for use as contrast.

However, a problem that persists is that they are still slightly ionic, which enables it to bond (if only temporary) to the other molecules in the blood plasma, and in this way, may affect the pH balance, amongst other factors.

A Discussion on XRA

XRA, being the oldest and most established method of angiography, is the most commonly used at this point in time.

The process produces a high quality image of target areas, no matter the conditions of the blood vessels there. Occlusions and slow-flowing blood prove no problem to image, and image quality is crisp, even when zoomed in on small areas. Furthermore, its selectiveness (only the flow downstream is captured) is a boon when an area is heavily populated with vessels, thereby affecting non-selective imaging.

The main disadvantages of using this method lie in the use of ionizing radiation and the invasive nature of the process. The patients, together with the medical stuff, are normally subjected to large doses of radiation. The contrast media doesn't help very much either because of their normally chemo-toxic natures.

The fact that the catheter has to be inserted into the patient is also a very discouraging factor. Blood loss, needles and incisions frequently scare the patients. Sedation and the use of drugs may also pose problems, especially if there is some form of allergy to the drug used.

All the above factors have led to a low (but still present) morbidity rate of 1.5% and mortality rate of 0.1%[4].

Computed Tomography Angiography

Some History…

Practical Computed Tomography (CT) scanning was developed in the early 1970s by Dr G. N. Hounsfeld in England. This first instrument was used to image the brain and the data took about 5 minutes to acquire. Since then, the scan timing for a CT image has been significantly reduced to about 1 second, and reconstruction of image takes another 3 to 5 seconds.[5]

Basic Principles

Computed Tomography Angiography (CTA), as it was mentioned above, is very much similar to X-Ray Angiography in the sense that it is a contrast-and-X-Ray based way of imaging. Everything else about it, however, is different.

In CTA, the image is obtained by using a CT-Scanner in conjunction with contrast as well. The major difference between CTA and XRA is the way the contrast is delivered into the bloodstream. In XRA, the contrast is delivered into the target area directly using a catheter. While that is possible in CTA as well, the most common method is injecting the bolus of contrast into the veins and tracking it.

The contrast is delivered using a pressure-regulated syringe, possibly automated to time it with the scanner, and a CT-Scan is taken of the target site depending on when the bolus of iodinated contrast is expected to reach the site.

The CT scanner operates in very much the same way as it normally does – in a spiral manner. While the patient table is constantly in motion, the platform on which the sensors are mounted rotates, thereby producing a 3D image of the entire area, contrast media together with the surrounding organs.

Contrast Media

The contrast media in CTA is no different from the ones used in XRA, even though the method of delivery.

Unlike XRA, however, a much larger dose of contrast is required to acquire the same image. The contrast has to be injected throughout the 'run' for it to be effective. If not, it runs the risk of being too diffused to produce a clear image by the time it reaches the target area.[6]

Use of large amounts of contrast has been known to endanger patients[7], especially those with renal complications. This is because the patients must have the ability to excrete the excessive iodine before nephrotoxicity sets in. Also, it is generally advised that the contrast media in use is a non-iodinated version so as to minimize the effects it has on the bloodstream.

Fortunately, some areas, such as the pulmonary arteries require little or no contrast, due to the great difference between the air and the tissue.[8]

CTA in Summary

CTA's main strengths lie in the fact that it is able to (natively) acquire the image in 3-dmiensional form, without the need for further processing. This allows the imaging of large swaths of area and visualization of entire circulatory networks.

Furthermore, there is no subtraction involved most of the time, and this allows the surrounding region to be mapped. Organs and other tissue which are near the vessels are included in the image, and may provide more information for diagnosis. This also overcomes the problem of understanding the nature of a stenosis, especially when there is a blood clot involved. Neither of the other 2 methods can overcome this problem due to the fact that they a deference towards viewing of the lumen.

It's less invasive nature is also a boon for those adverse to XRA's catheters, as contrast is normally injected into the veins, rather than the arteries.

The problems with the contrast are no different from those of XRA. However, the magnitude of the problems are the likelihood of morbidity increases with the large amount of contrast used.

Furthermore, the resolution of the image is sadly lacking, even in mapping the fast flowing coronary arteries.[9]

Magnetic Resonance Angiography (MRA)

The Principles behind Magnetic Resonance Angiography

MRA has roughly the same principles as MRI. The patient is placed in a very strong magnetic field of up to 3T, and the magnetic moments of the molecules in the body are aligned with the rest of the field.

This magnetic moment is then tipped over by a radio frequency pulse. When the pulse is stopped, the molecule will attempt to return to it's alignment with the rest of the field. However, the axis of the moment does not return directly to its original position, but rather takes a certain path back.

The path of the axis, or precession, and the rate at which it returns to its original position is dependent on the chemical in question. The frequency at which the precession is commonly called the Larmor Frequency. The change in this magnetic moment as the precession is in progress induces a current in the coil that originally produced the RF signal, thereby allowing the area to be imaged.[10]

In MR angiography, there are two main methods of imaging, and they are Time-Of-Flight (TOF) and Phase-Contrast Angiography (PCA).

Time-Of-Flight

The TOF method of imaging portrays the size of the tissue magnetic moment. The stationary tissue is repeatedly pulsed and is saturated, whereas the moving blood is fully relaxed and has relatively larger magnetic moment.

This method requires the target vessels to have rather large volumes of blood flowing through them, so as to be able to produce a reasonable signal. These vessels include the aorta, the vena cava and the carotids.

Phase-Contrast Angiography

Phase-Contrast Angiography utilizes a magnetic field gradient to image the subject. The gradient is created using the gradient coils in the MRI scanner and the causes the precess in the spin of the magnetic vectors to be faster on one side than the other.

The gradient is then reversed and the tissue that stays stationary will have their magnetic moments restored. However, if the tissue is moving, as in the case of blood, their magnetic moments will not experience the same restoring fields, and will therefore have a net spin that is different from that of the stationary tissue. It is this difference that enables the tissues to be differentiated.[11]

While this method still requires the blood to be flowing, the range of velocities that can be mapped out are relatively larger, and slower regions, such as the peripheral circulation, can also be mapped out.

Contrast in MRA

Contrast in MRA is produced by differentiating the relaxation and signal decay rates (T1 and T2 times respectively), and for most part, MRA can do without the use of injected contrast media. If and when contrast required, it is normally employed in a region where blood flow is very slow.

The contrast of choice is gadolinium-DTPA (diethylenetriamine penta-acetic acid), which is the only approved contrast agent for human use.

This contrast agent can be employed in both TOF and PCA, to some limited degree. It is known to be able to reduce the T1 relaxation rate, thereby increasing the signal strength from the tissue. However, this method is not effective in recovering a signal from areas of turbulence[11].

Moreover, Gd-DTPA does not stay in the vascular areas too long, and has a tendency to diffuse out into the tissue fluids. This reduces the amount of contrast that reaches the target region. To give a significant change in signal intensity, a high concentration of gadolinium is required, and this is only achievable if the molecules are non-ionic. Current concentrations used are 0.1 mM/kg, whereas a 03.mM/kg dose has been shown to increase the signal intensity by about 100%[11].

A Review of MRA

MRA's major edge over the rest of the methods is its totally non-invasive nature. It is able to do almost all the imaging with no ionizing radiation, little need for contrast media and no incision whatsoever, making it a lot safer[7]. Its non-selective nature allows the imaging of collateral flow (a result of vessel occlusion) and if focus on key areas is required, the image may be 'sliced' to show key areas as with all MRI images. Relatively speaking, this method is also faster than XRA, though less so compared to CTA.

MRA also does functional imaging rather than anatomical imaging, which allows stenosis or occlusions to be more clearly visualized.

Its main disadvantage however, is the MRI scanner's inability to pick up slow-flowing or turbulent blood. This is only marginally improved by the use of contrast media, but improvements are limited. Resolution is also never quite as good as XRA for the peripherals as well.

Furthermore, the strong magnetic field use makes it contraindicative to patients with pacemakers and artificial joint replacements.

Fundus Fluorescein Angiography

Introduction

Fundus Fluorescein Angiography, unlike the other modalities discussed above, is a very much more 'visible' form of it. It is the mapping of the circulation in the retina, instead of some obscure, unseen portion of one's body, and is therefore normally employed for the investigation of vision problems.

The first time fluorescein dye was employed for such purposes were in 1954 when Dr. Edward Maumanee used fluorescein to differentiate choroidal hemangioma and melanoma.[12]

From then on, the techniques were refined include colour in 1968, and to include the use of indocyanine green dye and black and white infrared film in 1972. Further refinements continue to be made to filters for the emitters and barriers in the equipment.

Principles and Technique

The basic principle behind fluorescence is that the chemical involved receives light from one source, absorbs it, and then re-emits it at a different frequency (due to the 2nd law of thermodynamics : emitted energy must be less than absorbed energy.

Fluorescein is injected intravenously, normally via the forearm, and is allowed sometime to reach the retina. Blue light is flashed into the eyes thru a cobalt blue filter, and this causes the fluorescein to start emitting green light in response. The excess blue light from the initial flash is filtered out using a light filter and an image is formed by the re-emitted green light. These images are then recorded, mostly on film cameras, forming a sequence of images that show the path of the blood through the vessels.

Contrast Media

The contrast media in fundus fluorescein angiography, as stated earlier, is a fluorescent dye. The most commonly used variant up-to-date is sodium fluorescein ($C_{20}H_{12}O_5Na$).

The spectrum at which it absorbs the most energy is 465-490nm, and the peak emission frequencies lie between 520-530nm. This allows the light filtering to differentiate between reflected light from the emitted light.

It also has a low molecular weight, enabling it to infiltrate the capillary beds of the retina, allowing a great amount of detail for diagnosis. It is also because of this same reason that the chemical diffuses rather easily into the intra and intervascular compartments, staining practically everything in the body yellow. A discoloration of the urine also occurs as the chemical is slowly eliminated over 2-3 days.

On and above those factors, it must also be noted that sodium fluorescein suffers a reduction in its ability to absorb light when bound to protein (50%), which it does rather readily. Up to 80% of the fluorescent dye is bound to albumin during each procedure.[10]

A Comparison of Major Modalities

	XRA	CTA	MRA
Advantages	• Specific • Clear • Mature technology • Works in slow moving peripheral networks as well	• "Slicing" • Less invasive than XRA • Other surrounding tissue visible • Fast	• Faster • No contrast medium used • Non-specific • Functional view (as opposed to anatomical) • No irradiation
Disadvantages	• Invasive • Sedation used • Patient receives large doses of radiation • Complications plenty	• Image is very low-res, not adequate for smaller vessels • Large radiation dose • Contrast used	• Noisy • Claustrophobic • Unable to detect low velocity blood flow or still blood (clotting) • Magnetic field strength

Possible Future Developments

Right now, most of the known research projects with impact on angiography, deal with the reduction of radiation dosage, improvement of contrast, and fusion or improvement of techniques.

Dosage reduction will be made possible through the use of new gadolinium compounds. For example, experiments are being carried out to produce Gd-DTPA-cholesterol, which is a compound more likely to stay within the confines of the vascular spaces, rather than diffuse out. The new compounds also enable the iodine concentrations to b much higher, therefore providing better contrast[13]

Processing techniques may also reduce contrast usage. Dual K-edge subtraction focuses on the attenuation jump in iodine at certain excitation frequencies, and can therefore produce a better XRA image with less concentrated iodine contrast media[4].

Image acquisition techniques have also improved. For example, the rotation of the C-arm while performing an XRA (similar to a CT-scan) has reduced contrast usage by a third and also allowed the production of 3-dimensional images from XRA 2D ones thru the use of multiple frames[14]. Computer projections are also slowly being worked on to reconstruct vascular networks from existing data, without having to actually see the finer vessels.[15]

Finally, the next major step in angiography is the fusion of techniques to better perform certain functions. For example, biplane angiograms and Doppler ultrasound are combined for 3D coronary artery reconstruction will enable a very accurate reconstruction of the turbulent area, which is relatively difficult to image due to constant movement.[16]

Siemens has also put together a combined angiography-CT system which will enable not only imaging, but interventional therapy to be carried out with better precision and speed. It is said the system is especially adept at conducting percutaneous biopsies of the spine, where safety cannot be risked.[17]

Conclusion

Since its inception in the late 1800s, angiography has continually provided the medical world with vascular imaging, with the sole goal of providing better, more affordable healthcare.

X-ray angiography now continues to provide excellent, high resolution images of the vascular networks, in an although invasive, but relatively safe method. CT-scanning as a method of angiography continues to be developed as more applications continue to be explored. Magnetic resonance angiography, being the newest of modalities, will need to continue to evolve into the replacement of x-ray angiography as the new, non-invasive method of imaging.

Angiography has finally reached maturity as a diagnostic method. It can now comfortably image many vascular systems with its many modalities, thereby assisting healthcare in innumerable indispensable ways, and it will continue doing so in ever-improving ways in the future.

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