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Diagnosis of Cardiovascular Disease by Digital Subtraction Angiography

Charles A. Mistretta and Andrew B. Crummy

Summary. Recent advances in real-time digital video processing have led to a practical method for intravenous arteriography. The digital subtraction technique, which detects small differences in the concentration of the iodinated contrast material injected, is relatively safe and does not usually require hospitalization of the patient. The technique can thus be used for serial evaluation of various clinical problems and for studying the natural history of certain disease processes, as well as for following therapeutic endeavors.

For several decades after the discovery of x-rays by Roentgen in 1895, medical radiography was performed with film used as the image receptor. Film provided a convenient detector, display, and archival image storage mechanism when it was used with fluorescent screens of calcium tungstate to increase x-ray detection efficiency. Dynamic fluoroscopy was performed by directly observing a fluorescent screen during continuous x-ray exposure. Because of insufficient brightness, dark adaption was required and the red-goggled radiologist was limited to the resolution of his rod vision. Within weeks of Roentgen's discovery it was recognized that blood and surrounding tissue provide similar x-ray attenuation and that studies of the cardiovascular system would require introduction of contrast materials. The first arteriogram was reported in January 1896 by Haschek and Lindenthal (*1*), who injected into the artery of a cadaver arm a medium that was largely calcium carbonate.

Iodine, an element with good biological compatibility, has become the element of choice for incorporation into angiographic contrast material. Iodine shows an abrupt increase in its x-ray attentuation coefficient at 33 kiloelectron volts, and in the energy range commonly used in diagnostic x-ray imaging it is more effective in casting x-ray shadows than lead. Zeides des Plantes (*2*) reported in 1934 that image subtraction could be used to separate iodine shadows from those produced by bone and other normal anatomical structures. By exposing a third film using light transmitted through two carefully registered films, a positive film obtained before contrast injection and a negative obtained after contrast injection, Zeides des Plantes obtained an image that showed only vascular structures, without overlying shadows from noniodinated anatomy.

In 1927 Moniz *et al.* (*3*) of Portugal reported opacification of the intracranial vasculature when iodinated contrast material was injected by means of a needle placed in a carotid artery that had been exposed surgically. In 1929, Dos Santos *et al.* (*4*) performed aortography with contrast solution injected into the aorta by way of a translumbar puncture. These workers also used one of the earliest pressure injectors to facilitate the rapid delivery of contrast agent (*4*).

In 1937 Castellanos *et al.* (*5*), and in 1939 Robb and Steinberg (*6*), reported their studies of the human heart and arterial system after intravenously injecting a contrast medium. These investi-

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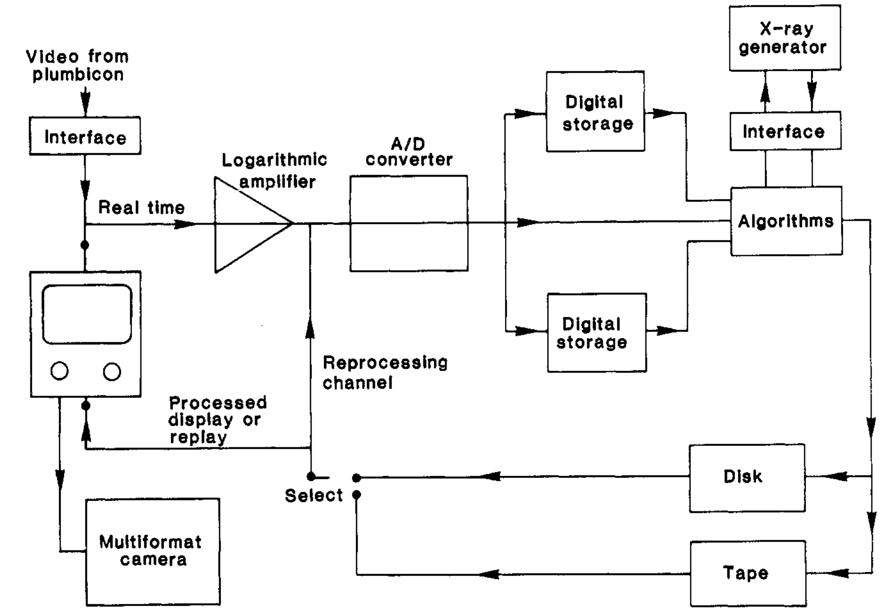

Fig. 1. Digital subtraction apparatus for medical angiography. [From C. A. Mistretta *et al.* (*31*), courtesy of *Medicamundi*]

gators used large-bore needles that they generally introduced into the veins of the antecubital fossa. Their studies were limited, however, because the contrast agents were relatively toxic, there were no devices for rapid changing of films, and the density of the images obtained after the venous injection was frequently inadequate.

Subsequently, Forssmann (*7*) in Germany demonstrated the possibility of intravascular catheterization by passing a ureter catheter into the right side of his heart. He shared the Nobel Prize in 1956 with Gournand and Richards for the development of intravascular catheterization.

After the introduction of the image intensifier in 1950, techniques evolved for the selective placement of catheters in virtually all arteries of the body. These methods received great impetus from the development of better materials for the construction of catheters and from improvements in other pieces of apparatus. In addition, the method for percutaneous introduction of catheters described by Seldinger (*8*) in Sweden greatly simplified vascular access and facilitated the rapid, safe exchange of specifically shaped catheters which would allow one access to various arteries.

These methods allowed exquisite display of anatomic detail and provided functional information. Nevertheless, they had some inherent hazards, required sophisticated equipment, and usually required hospitalization of the patients, so their use had to be somewhat restricted. Subsequent developments in electronics, including digital processing techniques and their application to the isolation of the intravascular iodine signal, led to new interest in the intravenous injection of contrast agents for angiocardiography and arteriography.

With the advent of video techniques, dynamic subtraction displays were made possible by storing preinjection masks on the video tape or video disks. Whereas these were convenient to use, more definitive results were obtained by using cinefluoroscopic recording of the image intensifier output on 16- to 35-millimeter movie film that provided significantly higher spatial resolution than did the video image storage devices. Because of the limited signal-to-noise ratio of early analog video recording methods, the additional contrast detectability that was potentially available with subtraction methods was not fully realized and intra-arterial catheterization remained the method of choice for most vascular contrast studies.

Developments Leading to Digital Subtraction Angiography

During the early 1970's, researchers at the University of Wisconsin developed analog video subtraction techniques capable of isolating periodic television signals with an amplitude of less than 0.1 percent of the full-scale video signal (*9*). Periodicity was induced by x-ray spectral change that was accomplished by changes in the x-ray tube voltage; these changes were synchronized with a rotating filter wheel containing alternating segments filled with sodium iodide and cerous chloride (*10*). Later, a three-spectrum approach requiring an additional filter segment of brass was used (*11*). In principle, the three-filter approach provided a set of three transmission signals from which images corresponding to iodine, bone, and soft tissue could be isolated. The use of the large-area image intensifier coupled with a television detection system allowed an increase in data acquisition rate several orders of magnitude greater than that obtained by Jacobson (*12*) and his co-workers in Sweden. However, the image subtraction scheme with its analog storage tube made the method too complicated for widespread use. In addition, the heavy filtration required to form the quasi-monoenergetic spectra necessary for iodine isolation resulted in reduced beam intensity and images limited by the statistical fluctuations in the number of transmitted x-rays.

In 1973, the design of a real-time digital video processor was begun. When completed in early 1976, this device was used to continue the energy subtraction work that had begun with the use of analog storage tubes (*13*, *14*). The reliability of this approach proved to be far greater, but the beam intensity problem remained. With 60 filter changes per second being made at fixed x-ray tube energy, a two-spectrum technique was used successfully to image iodine flow through the canine cardiovascular system in a mode that was not affected by respiratory motion (*15*). However, beam intensity again limited the method so that it could only be used on animals with a body thickness of less than 15 centimeters.

Shortly thereafter, during studies of static energy subtraction of iodine in canine liver, we decided that time subtraction might be used to watch the flow of Cholografin, an iodinated biliary imaging agent, as it passed through the heart after being injected into a peripheral vein. A preinjection mask image was formed by averaging the x-ray transmission data over a large fraction of the cardiac cycle. This image was then subtracted, without regard for any transmission variations associated with the unopacified beating canine heart, from all subsequent cardiac video images at a rate of 60 fields of 256 by 256 picture elements per second.

The results obtained were more encouraging than any of the energy subtraction images we had previously produced with more effort. Furthermore, the use of a single beam in a time subtraction mode obviated the heavy filtration necessary for energy subtraction work.

Further study showed that the transmission variations associated with the beating heart were only a few percent of the transmission range associated with normal anatomical variations. Thus, the use of a simple time-averaged subtraction mask permitted an iodine signal amplification factor of 16 in the subtraction display.

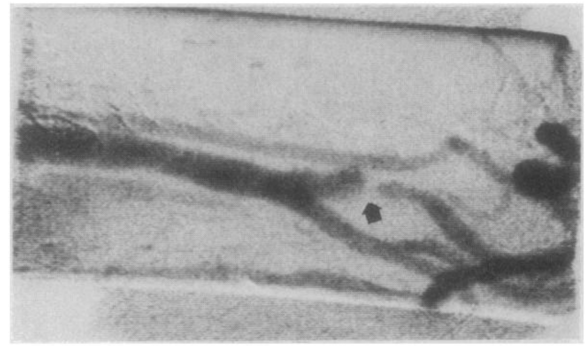

Fig. 2. Digital subtraction arteriogram obtained after injecting 40 ml of iodinated contrast agent into the superior vena cava. The arrow denotes a severe stenosis in the internal carotid artery.

Encouraged by these results, a group from our laboratory (*16*) developed several temporal subtraction algorithms. These included basic modes for continuous subtraction fluoroscopy, pulsed serial radiography, a time-derivative mode, and functional displays that transformed times to maximum or minimum opacification into gray scale displays. Videodensitometric hardware was also developed in order to investigate quantitative changes in the iodine path length associated with the observed transmission data. It soon became clear that the digital subtraction technique provided a sensitive and rapid means for utilizing the advantages achieved with greater difficulty when we used film subtraction.

All digital memories with identical specifications may be considered to be similar as far as their image transfer functions are concerned. Therefore, the digital technique, which involved the processing of all data through an identical analog channel, successfully implemented the "identical channel" subtraction imaging concept which had only been approximated with storage tube subtraction. Furthermore, unlike film subtraction, the digital technique proved to be ideal for enhancement of the small iodine signals isolated by the subtraction process.

These results suggested the possibility of returning to the use of intravenous injections for examining the cardiovascular system by digital subtraction methods. The work of Hounsfield and Cormack [see (*17*)] developing computerized tomography had already made the radiology community aware of the concept that systems which trade spatial resolution for increased detectability of small contrasts can be very useful.

After 2 years of trials with animals and with human volunteers, the digital video image processor was interfaced to an image-intensified fluoroscopy system at the University of Wisconsin Hospitals where the first 100-patient study was completed in March 1980 (*18*). During the same period, another digital video subtraction system was under study at the University of Arizona (*19*). Based on a large multipurpose computer, this system (*20*) was developed independently during the last half of the 1970's and was evaluated primarily in connection with a serial pulsed subtraction radiographic mode similar to that used by the Wisconsin workers, but differing in details of the exposure timing and data handling.

Even before the first 1000 patients had been examined with commercial prototype systems at the University of Wisconsin and the Cleveland Clinic (*21*), considerable commercial interest in subtraction methods was evident. By our count, at least 13 companies have begun development or announced their intention of becoming involved with digital video subtraction angiography.

Technical Aspects

The apparatus shown in Fig. 1 represents a simplified version of the apparatus originally used at the University of Wisconsin. It can be used to implement one quasistatic and two dynamic time-subtraction imaging modes at real-time video rates. X-rays transmitted through the patient are detected by a cesium iodide image intensifier tube, typically from 6 to 14 inches in diameter. The small intensified output image from this device is viewed by a plumbicon camera which, depending on the type used and the mode of operation, may have a signal-to-noise ratio ranging from 200:1 to 1200:1 (*22*). The output of the video camera is logarithmically processed in order to ensure that iodine subtraction residuals are displayed in a linear fashion rather than modulated by the nonuniform exponential x-ray attenuation associated with variations in patient thickness. When analog logarithmic preprocessing is used to stretch the video signals associated with regions of low x-ray transmissions, eight-bit digitization is generally sufficient for angiographic applications, especially when temporal averaging over several video frames is used. For applications not involving signal integration or in which logarithmic processing follows digitization, ten-bit analog-to-digital conversion is necessary.

After digitization, data are usually transferred at a 10-megahertz word rate into a digital memory. The first image stored is usually a "mask" image representing only noniodinated anatomy. During opacification of the heart or vessels of interest, real-time data may be integrated in a second memory in order to form a series of static images at a rate usually chosen to be about one per second. For dynamic studies, the real-time data can be subtracted at a rate of 60 fields per second prior to digital enhancement and reconverted to analog form for display on a monitor. In another commonly used algorithm, both memories alternate roles as the mask image is periodically updated in order to generate a mode in which the time derivative of the iodine distribution is displayed. This mode, as well as the straightforward continuous subtraction modes, appears useful for assessing left ventricular wall motion in the heart.

The x-ray exposures used for intravenous angiographic procedures may be tailored to the requirements of each type of study. For generating sequences of static intravenous arteriograms, exposures on the order of 1 milliroentgen at the input to the image intensifier are required. Exposure times vary from 10 to 130 milliseconds. For imaging of the extracranial carotid artery, this represents an exposure to the patient which, on an image-by-image basis, is about the same as that used for conventional catheterization angiography with x-ray film.

For examination of the motion of the left ventricle of the heart, exposures not far in excess of those used for conventional fluoroscopy (tube currents of a few milliamperes) will probably prove to be adequate for most purposes. For examinations aimed at visualization of coronary artery bypass grafts, we have used brief exposures on the order of 0.5 roentgen per second (100 to 200 mA). To facilitate such bimodal examinations, we use a dual dose mode. As the iodine passes through the right side of the heart and the lungs, a low exposure subtraction sequence is used until opacification of the left ventricle occurs. At this time, the tube current is increased and exposures are recorded on a video disk which

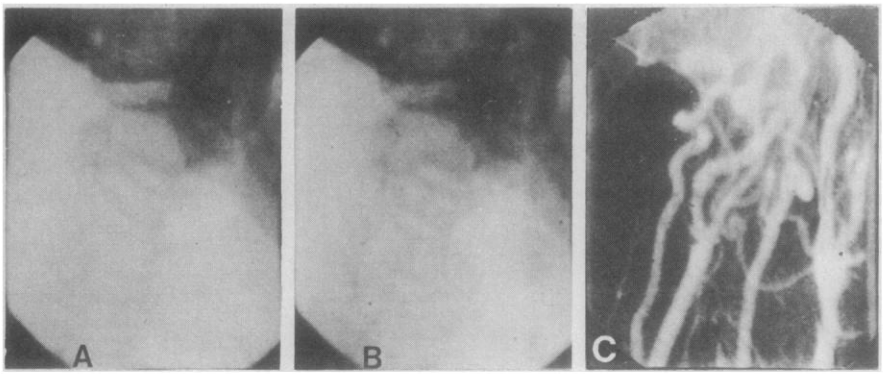

Fig. 3. (A) Preinjection mask image in the region of the extracranial carotid arteries. (B) Postinjection image. (C) Subtraction image formed by subtracting (A) from (B). [From A. B. Crummy *et al.* (*18*), courtesy of *American Journal of Roentgenology*]

is then replayed in a repetitive back-and-forth fashion to allow for extended examination of the opacified vessels.

For data storage, digital or analog techniques may be used. Although preservation of signal-to-noise ratio is best accomplished with digital storage, devices capable of the 60-millihertz rates required for real-time storage of subtracted images are prohibitively expensive. Furthermore, when the following principle is used, analog storage on tape or disk is adequate. If subtraction and amplification of iodine residuals are performed digitally in real time, the effective signal-to-noise ratio of the analog device is increased by whatever amplification factor is used. Typically, iodine isolated by time subtraction is multiplied digitally by a factor of 8 to 16 (nonintegral numbers are also possible). Because multiplication occurs before the data are reconverted to analog form and presented to the storage device, any noise associated with storage must compete with an iodine signal that is 8 to 16 times larger than it would have been if raw data were stored in unsubtracted form. Because of this, inexpensive video tape devices that have signal-to-noise ratios on the order of 100:1 produce results as good as those that would be obtained after subtraction of raw data stored on devices with signal-to-noise ratios of 1000:1 or more.

Because of this effective signal-to-noise ratio transformation made possible by digital preprocessing, stored analog data may be redigitized for further processing without significant loss of quality. An example of such reprocessing is the "remasking" operation which is often used to help eliminate misregistration artifacts associated with movement of the patient. By subtracting two subtraction images, both of which were formed with the original mask, this mask cancels out and the first of the two images serves as a new mask for the second.

In principle, logarithmically processed x-ray transmission data should provide quantitative information about the amount of iodine—in grams per square centimeter—along the path length associated with each picture element in the video image. However, considerable care must be taken (*23*) to correct for the effects of the x-ray scatter and light scattering within the image intensifier. These effects produce nonzero video signals behind radiopaque objects. These signals add a nonuniform error to the video signal which leads to underestimation of the amount of iodine in the subtraction image. When these effects are properly taken into account, it should be possible to use digital videoangiography to measure a variety of important physiological quantities.

Clinical Aspects

We estimate that more than 3000 patients have been evaluated with digital angiocardiography and arteriographic techniques at the universities of Wisconsin and Arizona, the Cleveland Clinic, and the Kinderklinik in Kiel. The exact role of digital subtraction arteriography and angiocardiography is yet to be determined. However, the results obtained to date indicate that there will be numerous clinical applications. For example, digital subtraction arteriography will have utility as a screening test, as an alternative to standard arteriography, and as a method of obtaining arteriographic information not provided by conventional arteriograms. Digital subtraction arteriography will also aid in the performance of certain interventional radiological procedures. The group at the Cleveland Clinic (*24*) has reported a study of carotid artery bifurcation arteriography in which the digital subtraction technique was compared with the conventional method. The results obtained with digital subtraction were bilaterally good to excellent in 60 percent and unilaterally good to excellent in 23 percent of the patients. There was excellent correlation of the digital subtraction results with those obtained by conventional studies (sensitivity 95 percent, specificity 99 percent, and accuracy 97 percent).

Using digital subtraction arteriography for the evaluation of renal arteries in patients with a variety of renal related problems, Hillman *et al.* (*25*) at the Univeristy of Arizona reported a satisfactory examination rate of 92 percent with a high degree of diagnostic accuracy. We have had similarly good results in the examination of patients with a spectrum of peripheral vascular problems (*26*).

Because the digital subtraction technique requires that the patient not move between the time the mask and the iodine image are obtained, it will be restricted to patients who are able to cooperate. In addition, the digital technique has less spatial resolution than standard film techniques. However, this disadvantage is counterbalanced by the better contrast recognition of the digital technique, which means that when detection of low contrast is paramount the digital method will generally be the procedure of choice.

Digital subtraction arteriography can demonstrate obstructive as well as ulcerated lesions in the extracranial carotid and vertebral arteries. A typical examination is illustrated in Fig. 2. Potentially the digital method can detect surgically correctable lesions in patients at risk for stroke. Detailed studies to define exactly the advantages and inherent limitations of digital subtraction arteriography in this area are under way. Preliminary studies indicate that digital subtraction arteriography is very satisfactory in the evaluation of the thoracic aorta for anomalies such as right aortic arch, coarctation of the aorta, and vascular rings. The vessels are large, can be densely opacified, and are very suitable for this method. There is very little inherent motion of the vessel so that subtraction images can be exquisite.

Arteriographic opacification of vessels distal to severe obstructions has been a clinical problem. It is necessary to determine whether these vessels are open if bypass surgery is to succeed. Because of the increased contrast resolution of the digital subtraction, vessels can be identified with the digital method that cannot be seen with the standard arteriographic technique. Also, because an arteriographic image can be maintained on the television screen and then subsequent motion of a catheter within a vessel be displayed, the placement of balloon catheters for dilatation of obstructing lesions or the placement of catheters for embolization of tumors or other arterial abnormalities can be greatly facilitated (*26*).

Digital subtraction arteriography is well accepted by patients. The minor discomfort of examinations by this method will be further decreased when nonionic contrast agents are available. Nonionic agents will not cause the sensation of heat which some people find disturbing. Since hospitalization of the patient is not essential, and since the safety of the digital procedure will allow serial evaluation of various clinical problems, digital subtraction arteriography will be useful for studying the natural history of various disease processes as well as for following therapeutic endeavors.

Digital subtraction techniques are now under investigation for applications in the diagnosis of cardiac disease. The most promising applications include analysis of ventricular wall motion, calculation of cardiac ejection fraction, and evaluation of coronary bypass graft patency (*26*). Thus far, coronary arteries have not been adequately visualized when intravenous injections have been used. However, encouraging results have been obtained with aortic root injections in dogs (*27*).

Left ventricular ejection fractions obtained by using the area-length method with digital subtraction angiocardiography have correlated well with conventional cineangiographic determinations of this quantity (*28*). Videodensitometric methods are under study but are complicated somewhat by the presence of x-ray scatter and nonuniformities in the image intensifiers (*29*). However, it seems reasonable to expect that it will soon be possible to make quantitative assessments of the left ventricle without having to make the assumptions regarding its shape that are required with conventional angiography. Physiological background problems involving opacified pulmonary structures and myocardium are similar to the problems inherent in nuclear medicine techniques. However, border recognition should be improved with the use of digital x-ray data.

Several improvements in digital subtraction angiography are anticipated. In the case of cardiac imaging, electrocardiographic labeling of a sequence of preinjection mask images will lead to better subtraction of noniodinated anatomy. For pediatric applications where suspension of respiration may not be achieved readily, dynamic energy subtraction techniques (*15*) may be useful. Recently, the use of digital subtraction in conjunction with nonselective arterial catheterization has suggested the need for higher digital matrix densities so that spatial resolution comparable to that of film may be obtained. Larger memory arrays will also be needed to maintain spatial resolution when large-area image intensifiers are used.

Conclusion

We believe that the principal advantage of digital subtraction angiography is its ability to aid visual perception of small differences in iodine concentration. Perception is probably aided somewhat by the increased image signal-to-noise ratio which, although it is degraded by subtraction, may be increased beyond what is achievable with film techniques because of the possibility of amplification of the signal before display. However, the most important element in the imaging process is the subtraction, which isolates a clinically relevant subset of the signals present in an unsubtracted image. The digital implementation of subtraction, because of its speed and simplicity relative to film, has simply provided a practical means of utilizing the previously known advantages of subtraction in a wide variety of static and dynamic imaging situations.

The perceptual advantages of subtraction are difficult to quantitate. Because of this, attention has focused on the signal-to-noise ratio, a necessary but not sufficient condition for visualization of low contrast structures in an x-ray image. In unsubtracted arteriography, the faint opacification of vessels achieved by intravenous injection of contrast material does not permit separation of vascular shadows from those produced by noniodinated anatomy. Even in the presence of an arbitrarily high signal-to-noise ratio, there may be no basis for resolving ambiguities.

The main advantage of the subtraction technique is that it increases the conspicuity (*30*) of vascular structures relative to their surroundings. Quantitation of the degree of conspicuity is not possible because it would require complete knowledge of the perception process. Nevertheless, we believe that conspicuity is often the most important property enhanced in digital subtraction angiography. The limited role of signal-to-noise ratio is illustrated in Fig. 3, where the advantages of the image in (C) relative to that in (B), which has a higher signal-to-noise ratio, are obvious.

One measure of what is provided by the subtraction technique is the ratio of the vascular iodine signal (S) to the complete range of background signals (B) associated with nonvascular anatomy. This quantity, which might typically be 1/20 in an unsubtracted intravenous angiogram, is increased to values on the order of 10 or more, depending on the degree of motion-related anatomical misregistration in the subtraction image. In this example the S/B ratio is increased by a factor of 200. We believe that this effect will prove to be one of the main advantages of digital subtraction angiography. Small increases in contrast resolution as determined by signal-to-noise ratio considerations will continue to be of importance in determining the limits of detectability in situations not involving the ambiguities of overlying anatomy or the problems of pattern recognition in the short times usually available for image examination. However, the isolation and amplification of vascular signals are probably the most important advantages of the digital subtraction techniques.

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