THE IMPACT OF COMPUTERS IN NUCLEAR MEDICINE

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ABSTRACT

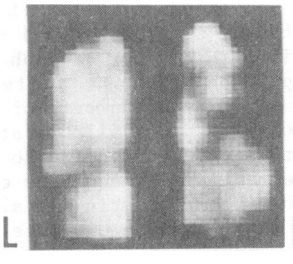
Computers have had a major impact on the development of Nuclear Medicine. Computer technology has allowed improved acquisition, display and analysis of radionuclide data and is largely responsible for the ability of radionuclide studies to accurately quantify organ physiology. In addition, computers are vital to reconstruction tomography, which has been applied to nuclear imaging. Mathematical modeling, which provides improved quantitative descriptions of complex physiologic systems investigated by radionuclides is also aided by computer technology. The role of the computer has even be extended to administrative functions like patient record keeping, automated data reporting, and programmed instruction of nuclear medicine trainees. In this review these aspects of computers in nuclear medicine will be reviewed, with emphasis on the recent improvements in nuclear imaging.

NUCLEAR IMAGING

The excellent anatomic details of central nervous system (CNS) disease provided by computerized transaxial transmission tomography emphasized the limited ability of nuclear imaging to assess morphology. Interest was thus rekindled in the basic ability of tracer techniques to investigate organ physiology. The utilization of improving computer technology has allowed these studies to provide accurate quantification of physiology and pathophysiology in patients. Region of interest capabilities have allowed computer assisted nuclear imaging studies to provide virtually the only noninvasive means for quantifying regional organ function.

Rapid acquisition of digital data is the basis for dynamic radionuclide studies of rapidly changing processes. These dynamic studies were initially applied in diagnosing CNS disease. The flow pattern of an intravenously injected radionuclide bolus is evaluated as it traverses the cerebral hemispheres. The digital data are then displayed as a hemispheric or regional time-activity curve and rates of bolus arrival, relative peak activity and lesion to background ratios are analyzed quantitatively. The advantages of such a system compared to a simple film record of analog images were summarized by Natarajan and Wagner[1]. The advantages are: (1) all original data are stored; (2) the images can be enhanced by using different levels of contrast and brightness; and (3) the data can be quantified.

Another step forward in computer processing of images was the "functional image". According to Alpert [2], a functional image is one that represents some parameter other than activity as a function of intensity. Figure 1 is an image representing pulmonary ventilation as the height (cts) at equilibrium of the washin curve divided by the area under the washout curve (H/A).



Areas with a larger H/A are areas with more rapid ventilation. The posterior lung image shows the regional H/A in varying shades of grey (the brighter areas have a larger H/A). Functional images of flow rates, clearance times, transit times, and other physiologic variables have been made using computer algorithms. This type of data compression was a forerunner of current techniques for time-compressed cinematic displays.

Cardiovascular Studies

The computer's greatest impact has been seen in cardiovascular nuclear medicine. As recently as 1970 the most commonly performed radionuclide heart study was blood pool imaging for the detection of pericardial effusion. A major advance occurred in 1971 when Strauss et al [3] showed that the left ventricular ejection fraction (LVEF), a quantitative index of LV fun-

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ction which represents the ratio of stroke volume to the end-diastole volume, could be obtained noninvasively. They used cardiac blood pool images acquired only during the end-diastolic and end-systolic portions of the cardiac cycle. The process of synchronizing the camera to the cardiac rhythm was called "gating". The process permitted the camera to record data on film only at the peak of the ECG R-wave (end-diastole) and at a specified time between successive R-waves (end-systole). Initially, the EF was calculated by projecting an end-diastolic and end-systolic blood pool image on a screen and outlining the ventricle to obtain its area and length. These dimensions were then inserted into angiographic formulae for volume determinations[4] and EF was calculated by hand. Attempts were made to analyze regional wall motion using this system, but identification of subtle changes in the LV border were often hard to visualize.

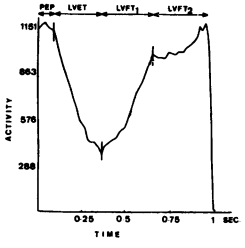
Shortly thereafter Secker-Walker et al[5,6] suggested that it would be better to calculate EF from changes in ventricular counts (EF=ED counts - ES counts/ED counts - background) than from one-plane cardiac dimensions. This new method did not use geometrical assumptions about ventricular shape which were used in the area - length approach. It also introduced the digital computer to cardiac nuclear medicine. A small, dedicated PDP-12 computer with 16K core memory was used to collect end-systolic and end-diastolic images in a 32 X 32 array. To evaluate regional wall motion the images were displayed in a rapidly alternating sequence to give the impression of motion. These images were, at best, crude representations of cardiac events. At times it was difficult to differentiate the LV from background (this may have been due in part to poor radiopharmaceuticals). The computer hardware and software to allow acquisition of greater numbers of counts at more rapid rates were not available at that time. In addition, it was time-consuming to process studies, as the machine was equipped only with LINC tapes rather than magnetic discs. This system was not by any means the ultimate methodology for noninvasive cardiac studies, but it represented an important step forward in computer applications in this area.

Another advance in gated blood pool imaging came when Green et al [7] at the NIH described a photographic method for displaying data collected from multiple segments of the cardiac cycle, rather than just end-diastole and end-systole. This work was subsequently extended by the NIH group [8] and workers at Johns Hopkins [9] to arrive at the current systems which provide cinematic displays of continous loop movies of the heart, high temporal resolution LV-time activity curves, and quantification of multiple parameters of LV function. One major characteristic of computer systems which can perform these studies is their large capacity relative to earlier dedicated, on-line nuclear medicine computers [10]. One such computer (Informatek Simis-3) is able to acquire 64,000 eight-bit words that can be used to generate 16 images with 4,000 picture elements at intervals as short as ten msec. This capacity facilitates cinematic display. Serial images are recycled repeatedly as a motion picture by the use of the 64,000 eight-bit word memory of the data display subsystem that is used independently of the computer's central processing unit (CPU). The image displayed on the TV screen is refreshed from a 64,000 eight-bit word memory buffer, external to the CPU. Each eight-bit memory element can accumulate 255 counts per picture element. With the separate memory buffer it is possible to display any of the following variety of images as frequently as every ten msec: one 256 X 256 picture element image; four 128 X 128 picture element images; sixteen 64 X 64 picture element images. Data can be acquired, stored and transferred from the display buffer memory to the central storage area of the computer so that image processing can be performed while images are being viewed on the television display. The most frequently used additional types of data processing are spatial and temporal averaging, field uniformity corrections, and statistical data bounding to eliminate grossly aberrant light or dark flashes. Without this additional computer-assisted data processing the high quality images obtained in clinical studies would not be possible.

The acquisition program is able to select the number of images per R-R interval, that is, whether 16, 32 or 64 frames per cycle will be acquired. The duration of each frame is calculated automatically. The mean R-R interval is measured for 16 beats. The frame time thereby is adjusted automatically for changes in average heart rate. The start of each cardiac cycle is taken as the time of the R-wave, and an input pulse from the EKG is fed into the computer with each R-wave. When the 64 frame per R-R cycle mode is used a high time-resolution activity curve demonstrating the volume changes which occur throughout the cardiac cycle is obtained. This curve allows numerous physiologic indices of ventricular function to be calculated in addition to the ejection fraction. The following indices can be obtained.

1. Pre-ejection period (PEP): period of electro-mechanical delay and isovolumic contraction.
2. Left-ventricular ejection time (LVET): period of ventricular emptying.
3. Left-ventricular rapid inflow time ($LVFT_1$): phase of rapid ventricular filling after closure of the aortic valve.
4. Left-ventricular diastasis including atrial systole ($LVFT_2$): slow phase of ventricular filling before the next systole.
5. PEP/LVET ratio
6. EF/LVET ratio: rate of left-ventricular emptying.

7. Peak rate of left ventricular emptying, filling: the peak dct/dt on the upslope or downslope of the LV curve.



The relative systolic time intervals derived from these time-activity curves have been compared with those obtained in patients by simultaneous carotid pulse tracing, phonocardiography and ECG. Significant correlations ($p<0.001$) were found ($r=0.89$ for LVET/R-R, $r=0.77$ for PEP/LVET, $n=30$). In addition, the time-activity curve indices obtained from 27 patients with either essential hypertension, myocardial infarction, idiopathic cardiomyopathy or congestive heart failure were compared with indices obtained from eight normal volunteers. Patients with congestive heart failure and cardiomyopathy showed prolongation of PEP/R-R and an increased PEP/LVET. In hypertensive patients, prolongation of $LVFT_1$/R-R and shortening of $LVFT_2$/R-R were found. Ejection fraction remained normal in hypertensive patients, was slightly decreased in myocardial infarction patients, and markedly reduced in patients with congestive heart failure and cardiomyopathy. These results suggest that display and analysis of synchronized left-ventricular time-activity curves are useful in studying patients with certain types of heart disease. The fact that this multitude of indices can be derived from a study which once yielded only an EF value demonstrates the impact of improved computer technology on nuclear cardiology. Further studies are being performed to determine the value of these indices in clinical practice.

Other Cinematic Studies

Although the improved imaging and data analysis systems were initially applied to heart disease, the techniques have now been extended to other organ systems (8). Minicomputers and television display of images make "fast motion" pictures of a variety of physiological processes, from the cerebral circulation to the kidneys. Using these techniques physiological data obtained over periods of minutes, hours or even days are compressed into 16 images that can be viewed at a rate that is matched to the perceptive ability of the viewer. These "compressed-time" images are shown over and over on a television screen to improve perception of regional dysfunction. The hypothesis that cinematic display improves perception of regional function remains to be proved, but initial experiences have been encouraging. Reports of experiences with cinematic display of ^{201}Tl myocardial images [12] and pulmonary perfusion images [13] have been published. The cinematic ^{201}Tl technique provided detection of regional wall motion abnormalities and improved distinction of cardiac borders without losing perception of perfusion defects. The pulmonary cinematic imaging technique provided modestly improved sensitivity for detecting defects caused by pulmonary emboli. Based on these initial experiences, Wagner [11] has predicted that motion pictures of regional function, displayed at variable rates on a TV screen, will become routine in nuclear medicine.

Emission Reconstruction Tomography

The introduction of computerized transaxial tomography (CT) for radiographic systems in the mid-1970's had an enormous impact on the practice of nuclear medicine. The demand for radionuclide brain scanning fell drastically in most hospitals. Nuclear medicine physicians realized that they could not continue using two-dimensional Anger camera images as primary tools for morphologic diagnosis. This led to a reviewed emphasis on physiologic studies and on improved systems to acquire and display radionuclide data in ways similar to those used in transmission CT. The computer played a central role in these developments, as these images are reconstructed by solving thousands of simultaneous differential equations. These computations are possible only if sophistocated, dedicated computer systems are available.

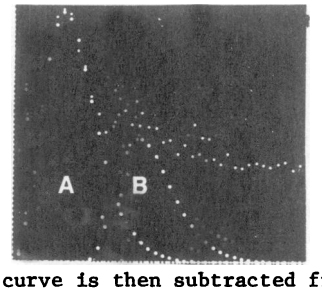
Reconstruction tomography of radionuclide images (emission CT) was first applied by Kuhl and his associates [14] in the early 1960's. They used a comparatively simple backprojection technique to produce single section tomographs of gamma emitting radionuclides. Modern analytical alogrithms can produce better quality tomographs from gamma emitters and can also be applied to reconstruction tomography with positron emitting radionuclides. The introduction of the positron emission transaxial tomography (PETT) by Ter Pergossian, Phelps and their colleagues [15] represented a unique step forward in nuclear imaging. For the first time high quality tomographic images of ^{15}O, ^{13}N and ^{11}C could be obtained in vivo. These basic "building blocks" of nature can be synthetically incorporated into a multitude of physiologically important compounds, and images of regional organ metabolism can be obtained. In addition, the activity distribution in the images can be quantified. The potential of this technology is enormous. Unfortunately, it does require the use of ultra-short lived cyclotron produced radionuclides. Emission reconstruction tomography is likely to be an increasingly important part of nuclear medicine. Whether single photon or positron reconstruction techniques will dominate is not yet clear. However, it is clear that improved computer technology has formed the common base for the advancement of these techniques and will be a key factor in their continued improvement.

CURVE FITTING AND MATHEMATICAL MODELING

The effects of improved computer algorithms have had an impact on analysis of data obtained from numerous radioisotope studies. This is especially obvious in radionuclide quantitation of left-to-right (L-R) cardiac shunts. Until about five years ago the only radionuclide method available for quantitating shunts was the C_2/C_1 count ratio technique [16,17]. In this method shunt size was measured by the ratio between the counts of two specified data points on a pulmonary transit curve. Recently, more sophisticated techniques which use mathematical curve fitting to analyze areas under the curve rather than points on the curve have been used. These area ratio techniques have two theoretical advantages over count-ratio techniques: (1) since they use mathematical functions which are fit to the pulmonary transit curve, results are altered by the shape of the first transit curve, and (2) they make use of multiple data points from the transit curve (rather then just two points) and are less affected by point-to-point statistical data flucuations. Thus, these methods yield more accurate quantitation and fewer false positives.

The most widely used area ratio technique for measuring L-R cardiac shunts is the gamma function method of Maltz and Treves [18]. Using a least squares technique the first transit pulmonary activity curve is fit with a gamma variate function of the form: $C(t_i) = Kt_i^{\alpha} e^{-t_i/\beta}$.

The limits of the first transit fit are from 10% maximum activity on the upslope to 70% maximum activity on the downslope. The area under this fitted curve (A) is felt to represent a normal first pulmonary transit (Fig 3).



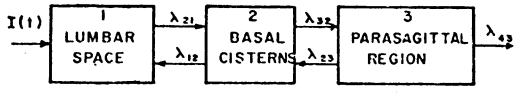
This fitted curve is then subtracted from the real data to obtain the difference of the real and fitted curves. A second curve is fit to this difference data by finding the maximum point in the difference curve (defined as the last point on the upslope whose value is greater than 105% of the previous point). Then a gamma function is fit from 10% on the upslope of the difference curve to its maximum. This second derived histogram represents the time-activity plot of the shunted blood. The area under this curve (B) is then calculated. The ratio $\left(\frac{A}{A-B}\right)$ is a direct representation of the QP/QS ratio. This method has provided accurate and reproducible determinations of L-R shunt size in experimental [19] and clinical [20,21] studies and represents a significant improvement in accuracy when compared to the count ratio approach.

Deconvolution Analysis

One of the practical problems encountered during quantitative radionuclide angiocardiography is inability to inject a sharp, short bolus. The shape of the pulmonary time-activity curve depends on the shape of the input bolus, and will accurately measure shunt size only if the input bolus is good. Thus, if the bolus is prolonged (>2.5 sec) or fragmented the study must be repeated. The frequency of bad injections varies, but in our experience [21] the injection is unacceptable in nearly 20% of patients. Thus, it would be useful if the dependence of the pulmonary time-activity curve on the shape of the bolus could be minimized. One way to accomplish this is to mathematically alter the frequency distribution of the output function (the pulmonary curve) to compensate for the frequency distribution in the input function (the bolus). This technique requires use of Fourier transform algorithms and is known as deconvolution analysis. We have recently been using deconvolution techniques in an attempt to correct bad injections purposely given to dogs with experimental ASDs and shunts of known size [22]. Our initial results suggest that deconvolution will be useful for preventing false-positive studies due to a bad bolus and for improving quantitation of studies obtained after a prolonged bolus injection. Fragmented boluses are the hardest to deconvolute. We are now attempting to improve the results with fragmented bolus injections. These computer-assisted deconvolution techniques have also been applied to aid analysis of quantitative renal perfusion and function studies in nuclear medicine [23].

Compartmental Analysis

Computers have been useful in developing and testing mathematical models to describe biological systems. These systems are often described in terms of compartmental models. These compartments may represent distinct anatomic structures or simply a different series of physiologic reactions in a single anatomic region. The most common reason for constructing a model in nuclear medicine is to derive an accurate mathematical description of input-output relationships so a system response can be predicted. An example of this type of study is provided by the mathematical models of cerebrospinal fluid (CSF) kinetics developed by Partain and his colleagues [24,25]. Normal volunteers received a 500 uCi lumbar intrathecal injection of ^{111}In-DTPA and frequent serial images of the lumbar region and head were obtained. The data were then used to develop a compartmental model of CSF kinetics. Initially a unidirectional two-compartment model was constructed. Better data fits were obtained using the bidirectional three compartment model shown in figure 4.



Rate constants for each of the system responses were calculated using a simple iterative algorithm. Eventually an extended eight-compartment model with multidirectional flow at each level was proposed. Solutions for this latter complex model require a complex, iterative algorithm (SAAM) not available on most dedicated nuclear medicine computers. This model was developed to allow more accurate prediction of CSF kinetics in a brief imaging time, to provide more accurate prognosis for response to CSF shunting in demented patients, and to yield improved CSF radiation dosimetry calculations. At present, this and other mathematical models have not been widely applied in nuclear medicine.

OTHER COMPUTER FUNCTIONS

Computers have also been used in nuclear medicine to perform administrative functions, like data reporting and retrieval. The NUMEDICON system developed at the University of Cincinnati [26] is an excellent example. The data organization and retrieval functions of computers are also quite useful for in vitro operations where hundreds of samples are counted in close proximity. Computers have also been used for programmed instruction of nuclear medicine technologist and physician trainees [27], and have even been used to "interpret" digital organ images [28]. However, computerized image interpretation has not become widely used in nuclear medicine.

CONCLUSION

Computers have had a major influence in the recent development of nuclear medicine, and this influence is not limited to teaching hospitals and referral centers. Many community hospitals have, or are in the process of obtaining, a small dedicated digital computer. A flourishing industry has developed to supply these demands. The most frequently asked question in nuclear medicine today is not "should I buy a computer", but "which computer should I buy?" With the increasing interest in quantification of regional organ physiology, cinematic display of dynamic studies, and localization of chemical reactions by positron emission reconstruction tomography, it seems likely that computers will become increasingly important in the future of nuclear medicine.

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