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TECHNICAL PROGRESS REPORT

NEW IMAGING SYSTEMS IN NUCLEAR MEDICINE

Gordon L. Brownell, Ph.D.

Massachusetts General Hospital
Boston, Massachusetts

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DISCLAIMER

I. Introduction

This progress report will cover four areas; instrumentation development, software development, cyclotron application, and other developments. Significant progress has been made in each of these areas over the past year. Indeed the interest in short-lived isotopes in this country and abroad has increased dramatically. In good measure, the development of the MGH positron camera has contributed to this increase. It now seems almost certain that the next decade will see this field growing to maturity and the use of cyclotron produced short-lived radionuclides take their appropriate place in medical research and diagnosis.

Modifications to the present positron camera include an extension of the arms to permit transverse section imaging. Such images are now being used in a number of areas for research purposes. Routine applications of transverse section radionuclide images will soon come into wide use.

One of the principal developments has been the randoms correct circuit which permits the instrument to be used at much higher counting rates. This circuit, although remarkably simple and straight-forward, results in a considerable improvement in the picture quality.

A new cardiac camera is under construction. This device will give even greater flexibility for transverse section imaging and for rapid dynamic imaging of heart function. This camera when completed will be a free standing unit which with its computer will be placed in operation in a myocardial infarct intensive care unit.

NUMEDICS, our computer system for nuclear medicine data processing has been expanded to include new hardware. Processing of multiple images - as in the case of motion of the positron camera - is now performed on a routine basis. Similarly the production of transverse section images is widely used.

Clinical studies with the camera have progressed in areas of heart, lung, and brain. ^{13}N as N_2 is widely used for inhalation studies and ^{15}O as O_2 and CO_2 is used to measure pulmonary ventilation, perfusion and regional lung water. ^{13}N labeled ammonia, ^{68}Ga labeled microspheres, and ^{82}Rb are used for cardiac imaging. A variety of techniques are being developed for study of blood flow and regional metabolism in the brain.

The applications of NUMEDICS with the scintillation camera have seen marked growth during the past year. Perhaps the most spectacular success has been its use to produce gated cardiac images using ^{99m}Tc labeled albumin. Gated images are produced from a sequence of heart cycles and the final images portrayed in motion picture mode using our standard data processing and display system. We are proposing a significantly increased activity in this area for the coming year.

The following sections will report briefly on progress in each of these areas. A number of papers have appeared in the past year on these topics and no attempt will be made to review all of the information in those papers in this progress report. In particular, three chapters appearing in Volume 2 of Instrumentation in Nuclear Medicine on Positron Instrumentation, Cyclotrons in Nuclear Medicine

and Scintigraphic Data Processing (8, 20, 26) cover much of the work that has been performed under this contract. A review chapter on Scintillation Scanning of the Brain (9) covers some of our work in this field.

In summary, we feel that the work performed under this contract has been productive, both in literature and in the quality and impact of the developments. The group that has been assembled for this project provides a high degree of technical ability in the theoretical and experimental development of new radionuclide techniques.

2. Summary of Research Projects

Project I - Positron Instrumentation (8, 11, 13, 16)

The original version of the positron camera, PCI, has been used extensively over the past year. A suite in the basement of the Research Building has been remodeled into a research and clinical area for more efficient use of the positron camera. The relocation of the camera required running new cables and new terminal facilities.

A random coincidence circuit has been designed and constructed. This circuit permits the collection of data giving the total number of random events. These events may then be subtracted on a point by point basis from the positron image. This circuit has worked extremely well and the resultant images are clearly superior, particularly at high count rates.

The bulk of our effort during the past year has been in the design and construction of the second positron camera, PC II, which is designed specifically for cardiac imaging and with emphasis on three-dimensional transverse section imaging. The major portion of the electronics for PC II has been completed and tested. The mechanical parts are nearing completion. We anticipate that the unit will be assembled and ready for preliminary physical testing within two months.

A number of features have been included in PC II that were not part of PC I. The arms have been extended to make transverse section imaging easier to perform. Special attention has been given to the mechanics to provide exact angles of rotation in order to improve the data for transverse section imaging.

A MODCOMP II computer has been obtained for the processing of data from PC II. As an interim measure, PC I and the NUMEDICS display terminal have been interfaced with the MODCOMP for test of software to be used with PC II. The MODCOMP will provide considerably greater capability for data acquisition, processing and display.

Preliminary studies have been carried out using a physiological monitor to obtain gated heart images with the positron camera. We anticipate that this technique will become routine for heart imaging of blood pool, heart muscle and infarcted tissue.

Project II - NUMEDICS Development (5, 6, 17, 18, 22)

A. Hardware

A general purpose interface for the PDP-9 system for use in program interrupt for block tranfer of data has been constructed. This considerably enhances the transfer of data for various SPS processing routines.

The principal activity in this area has been the development of interfaces for the new MODCOMP computers to permit data acquisition and display in the same manner with the PDP-9. It is our term goal to develop a computer net employing largely MODCOMP computers to process data from a variety of nuclear medicine sources. A preliminary plan for such a computer net has been developed. We plan to put it into use over the next several years.

B. Software

Two programs have been written to facilitate the subtraction of randoms from positron camera data. The first extracts the randoms from the upper 9 bits of each 18 bit data acquisition word to form a 64 x 64 matrix of randoms. The second program allows the user to choose one of several methods to smooth the randoms matrix before subtracting it from the image.

Techniques and various algorithms for transverse section reconstruction of radionuclide data have been developed during the past year. The accuracy of the filter has been considerably improved and studies made on other aspects of absorption correction. Subsequent smoothing and sharpening of the data has been studied.

One of the most significant applications of the NUMEDICS system over the past year has been its use to simulate the design of a transverse section x-ray camera. It was used to test various algorithms and a wide variety of simulation studies have been carried out. We plan to continue this simulation to study various aspects of radionuclide transverse section reconstruction.

Project III - Cyclotron Applications (1, 2, 3, 9, 10, 12, 13, 14, 15, 19, 21, 23, 24, 25)

Table I summarizes the studies which are presently underway, using the positron camera and cyclotron-produced radiopharmaceuticals. Many of these studies have been or are being reported in current publications, as outlined in the bibliography, and may be referred to for details. Only more recent developments will be discussed here.

A. ^{11}C-Glucose Development

The development of procedures for the production of carbon-11 labeled glucose has reached the point where we are now ready to begin clinical trials using carbon-11 glucose.

The ^{11}C-glucose preparation has been shown to be sterile and pyrogen free. Organ uptake studies in tumor-bearing rats have been completed. These studies show that the brain is the only organ which retains the ^{11}C for a period of time equal to several ^{11}C half-lives. All other organs exhibit clearance of activity after approximately five minutes following administration. This indicates that ^{11}C-glucose could be used for the detection of cerebral lesions in humans using a general anesthetic to depress the uptake of label to normal brain or CO_2 inhalation to increase brain blood flow and

therefore the supply of ^{11}C-glucose to normal brain. The kinetic behavior of the label in rat brain indicates that 3-D reconstruction techniques may be used to image tomographic cross sections of the head in human studies.

B. ^{13}N- and ^{15}O-labeled Compounds

Nitrogen-13 as molecular nitrogen is routinely being used for measurement of regional lung ventilation and perfusion. The results provide a basis for assessing regional lung function in bronchiectasis, suspected pulmonary emboli, and in preoperative evaluation of patients for lung cancer resection or bulluctomy(Ahluwalia, et al, 1974). These studies have also proven useful in following the pathophysiological alteration in surrounding lung after radiation therapy for lung cancer.

Nitrogen-13, dissolved in saline and in gaseous state has also been used to quantitate the strength of the pulmonary vascular response to regional alveolar hypoxia (Hales, Ahluwalia and Kazemi, 1975). This method is being used to follow the physiological response to certain drugs. Measurement of pulmonary closing volume has been recently reported by Hales et al (1975). The measurement of extravascular lung water using C^{15}O and H$_2$^{15}O radiopharmaceuticals in an isolated lung preparation has reached a stage in which values of regional lung water are compared with wet and dry weights of lung tissue. Our collaboration with the Department of Anesthesia on positron radionuclide imaging of the circulatory distribution of an extracorporeal membrane lung has provided new methods of cannulation for better distribution of perfusion in surgical patients on the membrane lung.

^{13}N-, ^{15}O-, and ^{68}Ga-labeled compounds are being used in patients to study the efficacy of these compounds to aid in differential diagnosis of brain lesions. Radiolabeled compounds currently being used are $^{13}NH_3$ (T 1/2 = 10 min) and ^{68}Ga-labeled chelating agents (T 1/2 = 68 min) given intravenously, and $^{15}O_2$ ($T_{1/2}$ = 2 min) given by inhalation.

Preliminary scintigraphic data obtained in twenty patients with a variety of intracranial abnormalities, including cerebral vascular disease and neoplasms, reveal that these agents have differing fates in the brain. Gallium-68 accumulated in two acoustic neuromas, three meningiomas but not in some other primary and metastatic tumors. $^{13}NH_3$ and $^{15}O_2$ accumulated in a meningioma but not in other tumors examined. None of the agents accumulated in regions of cerebral infarction. However, since $^{13}NH_3$ and $^{15}O_2$ readily cross the blood-brain barrier, their distribution is such that ventricles, scalp and skull are distinguishable from the brain. This feature may provide added accuracy in the localization and differential diagnosis of intracranial abnormalities.

Studies of regional myocardial oxygen utilization are being carried out using an autoperfused canine coronary circulation model and ^{15}O-labeled bloods. These studies employ bolus injection of radiolabeled bloods into the autoperfused left coronary artery of a dog, and positron scintigraphy of the clearance of activity from the heart. The aim of the studies is to examine this method of measurement of the distribution of myocardial oxygen utilization as a function of physiological changes in heart function.

C. ^{18}F Compounds

In collaboration with the Cardiac Biochemistry Unit, work is progressing on the development of ^{18}F-digitoxin and fluorodesoxyglucose. Several reaction mechanisms are currently being tested with stable fluorine.

D. Generator-Produced Positron Radiopharmaceuticals (^{68}Ga, ^{82}Rb)

We now have an extensive repertory of labeled compounds using ^{68}Ga and other labels. In collaboration with the University of California Lawrence Berkeley Laboratory (LBL) and Los Alamos Scientific Laboratory (LASL) we have undertaken to examine the utility of ^{82}Rb, a 75-sec positron-emitting daughter of 25-day ^{82}Sr. We are currently using a ^{82}Sr-^{82}Rb generator developed by LBL for myocardial scintigraphy. Studies using a canine infarct model are in progress. Preliminary results have already been reported.

The use of ^{38}K has been discontinued because of the inconvenience in producing the radionuclide under the present scheme of cyclotron activities.

Project IV - Studies with NUMEDICS and the Gamma Camera (4,7)

We have recently described an improved method for atraumatic evaluation of left ventricular (LV) function. This method is now referred to as nuclear ventriculography.

Nuclear ventriculography combines previously used electrocardiographic (ECG) gating techniques for cardiac blood pool visualization with computerized acquisition, processing and display techniques. An Anger camera, NUMEDICS computer system, and a physiological synchronizer are used to acquire a sequence of scintigrams which span the entire cardiac cycle in both the left anterior oblique (50°) and right anterior oblique (30°) projections. These images are processed on-line with a digital filter to increase definition of the cardiac borders. The sequential images are then displayed on an electronic monitor resulting in a presentation analogous to LV cineangiography.

The use of computer acquisition, processing and display techniques such as those employed in our studies result in easier identification of LV borders over previously used radionuclide methods. The display permits convenient evaluation of LV wall motion. LV time/activity curves may be derived spanning the entire cardiac cycle, and may, therefore, be correlated with other physiological measurements.

TABLE I

STUDIES WITH THE MGH POSITRON CAMERA

ORGAN	STUDY	RADIOPHARMACEUTICALS	STATUS
L	Regional ventilation and perfusion	^{13}N-N_2 (gaseous and in saline)	Clinical
U		^{15}O-CO_2, ^{68}Ga- spheres	Pre-clinical and Research
N	Airway Closure	^{13}N-N_2 (gaseous)	Clinical
G	Regional distribution of interstitial lung water	^{15}O-CO_2	Pre-clinical and Research
	Pulmonary vascular response to reginal aveolar hypoxia	^{13}N-N_2 (in saline)	Pre-clinical and Research
BRAIN	Regional cerebral blood flow and oxygen distribution in cerebral neoplasms and stroke	^{15}O-H_2O, ^{15}O-O_2Hgb, ^{15}O-O_2, $^{13}NH_3$	Research
	Localization of intracranial neoplasms and stroke	^{68}Ga-chelates, $^{82}Rb^+$ ^{11}C-glucose	Clinical and Research
HEART	Localization and sizing myocardial ischemia and infarction	^{13}N-NH^+, $^{82}Rb^+$ ^{68}Ga- spheres	Clinical and Research
	Regional myocardial blood flow and oxygen utilization	^{15}O-H_2O, ^{15}O-O_2	Research

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PUBLICATIONS

1. Ahluwalia, B., Hales, C., Brownell, G.L. and Kazemi, H. Study of regional lung function using cyclotron produced $C^{15}O_2$. Fifty ninth Scientific Annual Meeting, The Radiological Society of North American, Inc. and The American Association of Physicists in Medicine, (Abstract), In press.

2. Ahluwalia, B., Hales, C., Kazemi, H. and Brownell, G.L.: Positron camera imaging for assessment of lung function. Proc. First World Congress of Nuclear Medicine, Tokyo, 1974

3. Ahluwalia, B., Kanarak, D., Jones, T., Hoop, B., Brownell, G.L., and Kazemi, H. Use of short-lived positron emitting radiopharmaceuticals for the distribution study of extravascular lung gater in the dog (abs.) J. Nucl. Med. 15:474, 1974 (Abstract).

4. Alpert, N.M., Chesler, D.A., McKusick, K.A., Potsaid, M.S., Pohost, G.M., Dinsmore, R.E. Acquisition, processing and display of gated cardiac scintigrams. Proc. 4th Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, 1974. (Abstract)

5. Alpert, N.M., Hoop, B., Jr., Chesler, D.A., Correll, J.E., Jones, T., Brownell, G.L. Dynamic studies with multiprogrammed computer system. Proc. Symposium on Dynamic Function, IAEA, Knoxville, Tenn. 1974.

6. Alpert, N.M., Burnham, C.A., Deveau, L.A., Correll, J.E., Chesler, D.A., Pizer, S.M. and Brownell, G.L. NUMEDICS - A system for on-line data processing in nuclear medicine J. Nucl. Med., in press.

7. Alpert, N.M., McKusick, K.A., Pohost, G.M., Dinsmore, R.E. and Potsaid, M.S. Non-invasive nuclear kinecardiography. J. Nucl. Med. 15:1182-1184, 1974.

8. Brownell, G.L., Burnham, C.A. Recent developments in positron scintigraphy. In Instrumentation in Nuclear Medicine, Vol. 2, Chapter 4 (G.J. Hine, J.A. Sorenson, eds.), Academic Press, New York, 1974.

9. Brownell, G.L., Correia, J.A., Hoop, B., Jr. Scintillation scanning of the brain. Annual Rev. Biophys. Bioeng. 3:365-386, 1974.

10. Brownell, G.L., Hoop, B., Jr. and Burnham, C.A. Application of Short-lived cyclotron produced isotopes in medicine, Pro. Fourth Int. Biophysics Congress, Moscow, in press.

Physics Research Laboratory

11. Brownell, G.L., Bucelewicz, W.M., Burnham, C.A., Chesler, D.A., Correll, J.E., Deveau, L.A., and Hoop, B. Positron Camera - present status and application in nuclear medicine. Proc. First World Congress of Nuclear Medicine, Tokyo, 1974

12. Brownell, G.L., Burnham, C.A., Chesler, D.A. and Hoop, B., Jr. Application of MGH positron camera with short-lived cyclotron produced radionuclides. Proc. Third Int. Conf. Medical Physics, Goteborg, Sweden, in press.

13. Brownell, G.L., Burnham, C.A. and Hoop, B., Jr. Recent advances in applications in positron instrumentation. Trans. Amer. Nuclear Soc. 19:40-41, 1974 (Abstract)

14. Budinger, T.F., Yano, Y., and Hoop, B., Jr. A comparison of $^{82}Rb^{+}$ and $^{13}NH_3$ for myocardial positron scintigraphy. J. Nucl. Med., in press.

15. Chesler, D.A., Hales, C., Hnatowich, D.J. and Hoop, B., Jr., Three-dimensional reconstruction of lung perfusion images with positron detection. J. Nucl. Med., in press.

16. Chesler, D.A. Positron tomography and three-dimensional reconstruction In Tomographic Imaging in Nuclear Medicine (Freedman, G.S., Ed.) New York, Society of Nuclear Medicine, 1974.

17. Chesler, D.A. and Correia, J.A. Statistical accuracy of transverse section tomography. Proc. Third Int. Symposium on Image Processing in Scintigraphy, in press.

18. Correia, J.A., Hoop, B., and Brownell, G.L. Scintillation scanning of the brain. Annual Review of Biophysics and Bioengineering, Annual Review, Inc., Calif., 1974

19. Hales, C.A., Ahluwalia, B.D., Kazemi, H. Strength of the hypoxic pulmonary vascular response. American Thoracic Society, 1974 (abs.).

20. Hoop, B., Jr., Laughlin, J.S., Tilbury, R.S. Cyclotrons in nuclear medicine. In Instrumentation in Nuclear Medicine, Vol. 2 (G.J. Hine, J.A. Sorenson, eds.), Academic Press, New York, Chapt. 12, 1974.

21. Hoop, B., Jr., Beller, G.A., Hnatowich, D.J., Bucelewicz, W.M., Burnham, C.A., Chesler, D.A., Conroy, J., Correll, J.E., Deveau, L.A., Kaufman, D.E., Brownell, G.L. and Smith, T.M. Techniques for positron scintigraphy of the myocardium. Proc. First World Congress of Nuclear Medicine, Tokyo, 1974.

22. Hoop, B., Jr., Brownell, G.L., Burnham, C.A., Alpert, N.M., Chesler, D.A., Correll, J.E., Deveau, L.A. and Pizer, S.M. A large computer system. Proc. Symposium on Regional Use of Computers in Radiology, Webster, E.W., Ed. New England Radiological Physics Organization, Boston, in press.

23. Hoop, B., Beller, G.A., Brownell, G.L., Budinger, T.F., Chesler, D.A. and Smith, T.W. Techniques for positron scintigraphy of the myocardium Radiology, in press.

Physics Research Laboratory

25. Kanarek, D., Zapol, W., Ahluwalis, B.D., et al: Radionuclide imaging of the circulatory distribution of membrane lung perfusion. Artificial Internal Organ Proc., 1974.

26. Pizer, S.M., Brownell, G.L., and Chesler, D.A. Scintigraphic Data Processing. In Instrumentation in Nuclear Medicine (G.J. Hine and J.A. Sorenson, eds.) Academic Press, New York, Chap. 7., 1974.

27. Hales, C.A., Gibbins, R., Burnham, C.A., Kazemi, H., and Greene, R. Federation Proceedings, Vol 34, 402, 1975.

28. Hales, C.A., Ahluwalia, B., and Kazemi, H. Strength of pulmonary vascular response to regional alveolar hypoxia. Accepted for publication in J. App. Physiology..

29. Hoop, B., Jr., Hnatowich, D.J., Chesler, D.A., McKusick, K.A., Parker, J.A., Subramanyam, R., Brownell, G.L., Ojemann, R.G. and Taveras, J.M. Positron scintigraphy of cerebral function in man. J. Nucl. Med. 17, 1975 (in press).

30. Hnatowich, D.J., ^{68}Ga-labelled radiopharmaceuticals. J. Nucl. Med. 17, 1975 (in press).

31. Hoop, B., Jr., Hnatowich, D.J., Brownell, G.L., Ojemann, R.G., Techniques for Positron scintigraphy of cerebral function Stroke 5, 1975 (in press).